PhD Research

Age Differences in The Factors Affecting Baseline Assessment and Systemic Treatment Allocation for Breast Cancer Females in Kuwait

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ABSTRACT

Introduction: Breast cancer is the most common cancer occurring in females, and it accounts for 25.1% of all cancers. Worldwide statistics highlight that around 40% of breast cancer cases occur in patients aged 65 years and above, with expectations that this will increase as the population gets older. Cancer management in older patients is still unclear and depends primarily on individual oncologist decisions. The literature suggests that older breast cancer patients receive less intensive chemotherapy compared to younger patients, which is mainly attributed to a lack of effective individualized assessment. The current study investigated and compared the differences in the factors affecting baseline assessments and systemic treatment allocation and outcomes between younger and older breast cancer patients in Kuwait.

Methods: In a comparative prospective population-based observational cohort study, a total of 180 patients with breast cancer were included and subdivided into two age categories (<60 or ≥60 years). Data were collected manually from the breast cancer new-case clinics at the Kuwait Cancer Control Center (KCCC) between April 2016 and April 2019. The correlation between baseline factors (age, performance status, comorbidities, polypharmacy, BMI, and disease stage) and treatment allocation (intensive versus less intensive protocols) was investigated using multivariate logistic regression analysis. Factors contributing to less intensive treatment were identified and compared between the two age cohorts.

Results: A higher prevalence of less intensive treatment allocation was observed in patients aged ≥60 years than younger patients [41.2% vs 4.9%, OR 0.16 (CI 0.049-0.52), p-value 0.001]. Unlike younger patients, older patients with PS=0 and two comorbidities were 83% and 50% less likely to receive intensive treatment. The correlation between the co-existence of diabetes and hypertension and intensive treatment allocation was negatively affected by age due to the risk of cardiotoxicity. However, older and younger patients having ≥3 comorbidities were 86% less likely to receive intensive treatment. Besides, patient interference with the treatment plan occurred in 15% and 0.3% of older and younger patients.

Overall, significantly increased neurotoxicity was observed among older patients than younger patients (33.3% and 19.2%), and increased nausea was observed among younger patients than older patients (56.7% and 38.3%). Intensive treatment toxicities and subsequent dose modifications were comparable between older and younger patients.

In subgroup analyses of the older age cohort, intensive treatment contributed to increased nausea (57% vs 12%), vomiting (11% vs 0%), and mucositis (26% vs 8%) than less intensive treatment, while less intensive treatment contributed to increased depression (28% vs 6%). Cardiotoxicity, defined as ≥10% decline in the left ventricular ejection fraction (LVEF), occurred in 86.7% and 55.6% of older and younger patients. Factors contributing to increased cardiotoxicity were an age of ≥60 years [OR 4 (CI 1.35-18.6), p-value 0.012] and baseline LVEF <60 [OR 2.1, CI (0.73-7.99), p-value 0.15].

Conclusion: An age of 60 years and above was associated with a higher prevalence of less intensive treatment allocation compared to younger age among breast cancer patients in Kuwait. Factors contributing to less intensive treatment allocation included increased comorbidity burden, advanced performance status, and risk of treatment-induced cardiotoxicity. The lack of effective standardized baseline assessments contributed to differences in the factors correlated with less intensive treatment by age cohort due to toxicity concerns.

CHAPTER 1

INTRODUCTION

1. INTRODUCTION

Age is considered a strong risk factor for cancer in the literature. Unfortunately, there is a current lack of evidence-based information about treating older patients with cancer in general. This is often due to an under-representation of the elderly in clinical trials. Older age is associated with different physiological changes, comorbidities, and increased medication use. These unfavorable baseline characteristics may not fit into cancer management guidelines categories because the guidelines are designed for treating 'fit' adults with normal body function and do not provide guidance on treating patients with multiple comorbidities or advanced age. Consequently, treatment allocation remains unclear, and selection primarily resides with individual oncologists. Breast cancer is the most commonly occurring cancer in females and affects both older and younger patients. During the past 20 years, exploring histological and molecular characteristics has led to the introduction of more classifications and breast tumours subtypes in the guidelines and emerged the concept of targeted therapies and individualized treatment protocols. Treating older breast cancer patients remains challenging due to the wide range of toxicity risks associated with standard management protocols (mainly cardiotoxicity). Advanced comorbidity and performance status scores are considered unfavorable baseline characteristics that limit treatment options and may lead to offering suboptimal treatment. It is still unclear whether this concept is also applied to younger patients. Also, it is unclear whether older and younger patients with similar performance status and comorbidities scores are allocated to similar or different treatment protocols.

This chapter will introduce a review of breast cancer epidemiology, breast tumour characteristics, and age-related characteristics manifested by physiological changes,

comorbidities, polypharmacy, and drug-related problems. In addition, this chapter will discuss landmark studies for breast cancer management. Also, it will demonstrate different aspects of the breast cancer management dilemma in clinical practice. These topics will lay the foundation for understanding baseline assessment and treatment allocation of breast cancer patients in clinical practice.

1.1 Breast cancer epidemiology

1.1.1 Breast cancer incidence and death rates globally

According to the International Agency for Research on Cancer (IARC), it has been estimated that around 19.3 million new cancer cases (combining all cancer types) were diagnosed globally in 2020, with 10.0 million cancer-associated deaths recorded for the same year [GLOBOCAN 2020].[1] Breast cancer was the most common type of cancer diagnosed in females, accounting for 11.7% of all cancers worldwide. Approximately 2.3 million breast cancer cases were diagnosed globally in 2020, with 684,996 deaths due to breast cancer recorded for the same year. Cancer incidence data has been continuously collected from the early 1960s from many countries. Results show that breast cancer has the highest incidence rate and lung cancer has the highest mortality worldwide, followed by female breast cancer.[2, 3] Table 1.1 presents the most common cancers occurring worldwide, combining both sexes and the corresponding death rates. While Table 1.2 shows the most commonly occurring cancers by sex.

Table 1.1 Cancer incidence and mortality worldwide combining both sexes (2020)[1]

Cancer type	Incidence n (%)	Death rate n (%)
Breast cancer	2,261,419 (11.7%)	684,996 (6.9%)
Lung cancer	2,206,771 (11.4%)	1,796,144 (18%)
Prostate cancer	1,414,259 (7.3%)	375,304 (3.8%)
Non melanoma skin cancer	1,198,073(6.2%)	63,731 (0.6%)
Colon cancer	1,148,515 (6%)	576,858 (5.8%)
Stomach cancer	1,089,103 (5.6%)	768,793 (87.7%)
Liver cancer	905,677 (4.7%)	830,180 (8.3%)
Rectum cancer	732,210 (3.8%)	339,022 (3.4%)
Cervical cancer	604,127 (3.1%)	341,831 (3.4%)
Esophagus cancer	604,100 (3.1%)	544,076 (5.5%)

Table 1.2 The most commonly occurring cancers worldwide by sex (2020)[1]

Males (%)	Females (%)
Lung cancer (13.4%)	Breast cancer (24.5%)
Prostate cancer (14.1%)	Colorectal (9.4%)
Colorectal cancer (10.6%)	Lung cancer (8.4%)
Stomach cancer (7.1%)	Cervical cancer (6.5%)
Liver cancer (6.3%)	Thyroid cancer (4.9%)
Other cancers (48.5%)	Other cancers (45.3%)

1.1.2 Breast cancer incidence and death rates in the UK

In the UK, more than 375,000 cancer cases were diagnosed yearly (2016-2018).[4] Breast cancer accounted for approximately 15% of newly diagnosed cancer cases and 7% of all cancer mortalities.[4] According to Cancer Research UK, the UK registered more than 55,900 breast cancer cases and 11,500 deaths between 2016 and 2018. Over the last decade, breast cancer incidence has increased by 24% in the UK with anticipated further increases over the coming decade, while in the same period, breast cancer mortality has decreased by 19%.[4]

In Scotland, the Scottish Cancer Registry has been collecting cancer data since 1958. Statistics show that around 55,000 cancer cases are diagnosed yearly from all cancer types.[5] Breast cancer is the most common cancer in females and accounts for 15% of all cancers, which is comparable with the wider UK statistics. Annually, more than 4700 breast cancer cases are diagnosed in Scotland.[6] Over the last decade, breast cancer incidence has increased by 6%. Similar to the UK figures, breast cancer mortality has decreased by 21% over the last decade despite increasing the incidence rate.[7]

1.1.3 Breast cancer incidence and death rates in Kuwait

The Kuwait population currently stands at more than four million, of which around 1,337,000 are Kuwaiti nationals.[8] During the last 40 years, the Kuwait Cancer Control Centre (KCCC) has registered 48,000 cancer cases of all cancer types.[9, 10] Around 2000 cancer cases are diagnosed yearly, with a continuous year-on-year rise observed. Cancer incidence occurs at the same rate among Kuwaiti and non-Kuwaiti populations. Breast cancer is the most common type of cancer, accounting for 23% of all cancers and 40% of all females cancers (2014).[9] The estimated annual breast cancer mortality rate is 25.4% of cases (2015).[11]

1.2 Breast cancer incidence and death rates by age

Age is considered a strong risk factor for cancer.[12, 13] Worldwide, more than 40% of breast cancer cases occur in patients aged 65 years and above, and the median age at diagnosis is around 60 years.[14] Table 1.3 compares breast cancer incidence rate by age group from authorized cancer registries and databases.

Table 1.3 Breast cancer incidence by age group (years)[5, 9, 15, 16]

		<50	50-59	60-69	≥70
Cancer Research UK 2015		18.7%	21.7%	25.6%	34%
The Scottish Cancer Registry 2016		16.4%	25.5%	25.6%	32.5%
SEER Cancer Statistics 2011-2015* By NCI**		12.5%	14.8%	23%	49.8%
Kuwait Cancer Registry	**National**	37%	28%	35%	
	Non-National	54%	27%	19%	

*The Surveillance. Epidemiology and End Results (SEER)
** National Cancer Institute (NCI), US

Different cancer registries show a correlation between cancer incidence and age at diagnosis. For example, the US, UK, and Scottish statistical data show a significant increase in breast cancer incidence, especially after the age of 70 years.

In Kuwait, the mean age at breast cancer diagnosis is 54.4 (CI 95%: 52.9-55.8) years for Kuwaiti patients, and 49.1 (CI 95%: 52.9-55.8) years for non-Kuwaiti patients.[9] Patients, regardless of nationality, experience a higher incidence of breast cancer at an earlier age, with the incidence being less at age 60 years and over compared to the US, UK, and Scotland (Table 1.3). The causes of earlier cancer onset in Kuwait are not well established but have been partly attributed to the massive environmental pollution that resulted from the Gulf War in the early nineties since the number of cancer cases has risen from then.[17]

Table 1.4 below compares breast cancer mortality rate by age group (Table 1.4). Generally, older age is associated with higher mortality rates than younger age, with dramatically higher mortality rates reported in patients aged 70 years and above.

Table 1.4 Breast cancer mortality by age group (years). [5, 9, 15, 16, 18]

	<50	50-59	60-69	≥70
Cancer Research UK 2014-2016	9.7%	14.6%	18.2%	57.5%
The Scottish Cancer Registry- 2017	7.6%	16.9%	19.5%	56%
SEER Cancer Statistics 2011-2015* By NCI**	6.1%	9.9%	16.4%	67.5%

*The Surveillance. Epidemiology and End Results (SEER)
** National Cancer Institute (NCI), US

This trend in breast cancer mortality among older patients has been the subject of much clinical debate, and many questions have arisen relating to cancer treatment allocation and tolerability among different age groups. The high mortality rate in older cancer patients was attributed to the patients receiving less intensive treatment (under treatment) protocols and/or intolerability to intensive standard treatment.[19] Also, poor therapeutic outcomes may be attributed to the existence of comorbidities and organ dysfunction. More details about breast cancer treatment patterns in older patients will be discussed in section (1.4.4).

In clinical practice, the management of older breast cancer patients is still considered challenging. Section 1.3 will address an overview of old age and discuss critical physiological changes that potentially impact cancer treatment allocation and outcomes among older patients.

1.3 An overview of old age

According to the World Health Organisation (WHO), older age is considered 65 years and above.[20] It has been estimated that there are around 617 million (8.5%) people aged 65 years and above worldwide, and 126 million of this population are aged 80 years and above (2015).[20] The WHO reported a significant increase in life

expectancy over the past decades. The older population is projected to grow dramatically from around 524 million in 2010 to 1.5 billion in 2050.[20] This significant change in demographics has raised concerns about the global health of aging populations and emphasized raising awareness about their heterogeneity among clinicians and healthcare providers. [21]

1.3.1 Age-related physiological changes and comorbidities

Adult patients of older age have different pharmacokinetic and pharmacodynamic responses to medication compared to younger adults due to physiological changes in body organs function and regulatory systems with age.[22] This includes changed in the cardiovascular, renal, hepatic, and gastrointestinal systems (Table1.5).

Table 1.5 Age-related physiological changes.[21-24]

Organ function/ system	Physiological Changes
Cardiovascular	• Reduced elasticity of the aorta and increased pressure. • Left ventricular hypertrophy
Renal	• Decreased renal mass • Reduced glomerular filtration rate • Reduced secretion
Hepatic	• Decreased hepatic blood flow • Decreased hepatic volume
Gastro-intestinal	• Reduced absorption

The ability of organs to maintain their normal physiological state during stress or added workload is referred to as “functional reserve”.[25] Normally, the reserve in organ function starts to decline by the age of 65 years, and a marked decline is noticed after the age of 70 years.[26] People aged 85 years and above appear to have noticeable clinical signs and symptoms of this type of organ decline, e.g. fatigue, general weakness, and cognitive changes.[26, 27] The existence of age-related multi-organ dysfunction is often referred to as frailty or geriatric syndrome.[27, 28] Frailty is also

associated with changes in body composition manifested by a decrease in body water and increased body fat.[29] Besides, body mass decreases with advanced age. These changes can significantly impact the volume of distribution and bioavailability of many drugs, which consequently changes their efficacy and/or safety profiles.[27] This is manifested by decreased therapeutic efficacy and/or prolonged toxicity of many drugs such as diuretics, angiotensin converting enzyme inhibitors (ACEI), nonsteroidal anti-inflammatory drugs (NSAIDs), benzodiazepines, and tricyclic antidepressants (TCA).[30-32] Examples of chemotherapeutic agents will be discussed in section 1.4.4.3.2. It is critically important to emphasise that these changes are not uniform (heterogeneous), and a high individualization in functional reserve is seen within the population.

In addition, older age is associated with a higher prevalence of disabilities and common chronic comorbidities, including hypertension, diabetes, congestive heart failure, strokes, osteoporosis, cardiac dysfunction, and renal/hepatic dysfunction.[33, 34] Decreased cognition, dementia, and malnutrition are also noticed, especially in patients who are aged 80 years and above.[35, 36] Some reports suggest that these conditions contribute to poor quality of life and poorer therapeutic outcomes in older patients.[37-39] These complicated healthcare issues with the older population have a significant impact on healthcare service expenditure.[40] According to the UK National Health Service (NHS), increased age is associated with a sharp increase in the total healthcare costs (Figure 1.1).[40]

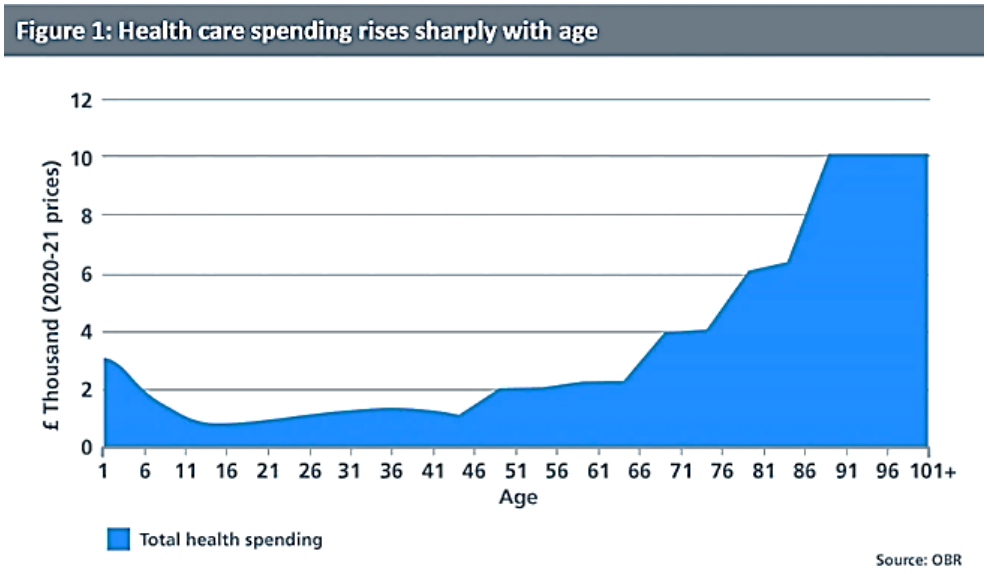

Figure 1.1 Healthcare spending by age (2017).[40]

1.3.2 Polypharmacy burden and drug-related problems in older patients

Comorbidities in the older adult population correlate with prescribing multiple medications.[41] This is referred to as 'polypharmacy'.[42, 43] Polypharmacy can be either defined according to the number of medications prescribed concomitantly (ranging from two to 11 medications) or the inappropriateness of the medications regardless of their number.[44] The most commonly used definition of polypharmacy is using at least five medications daily.[44]

A prospective cohort study estimated that 40 - 50% of older (>65 yrs old) patients take one or more medications in Sweden.[45] On the other hand, large data analysis of a database involving more than 10,000 patients in the US showed that six or more medications are prescribed for 29.4% of the patients.[46] In Kuwait, 58.4% and 10.2% of patients aged above 65 years are using 5-8 medications and more than eight medications, respectively.[47]

Generally, increasing the medication burden increases the risk of drug-drug interactions and adverse effects.[48, 49] Therefore, the risk of drug-related problems increases with age.[48, 50] Approximately, 15.7% of older patients are being prescribed medications that fall in one or more of the categories of drug-related problems (Table 1.6).[48]

Table 1.6 Drug-related problems.[48]

Drug-related care issue	Categories
Indication	- Unnecessary drug(s) - Needs additional drug(s)
Effectiveness	- Ineffective drug(s) - Ineffective (low) dose(s)
Safety	- Adverse drug reaction - High dose
Compliance	- Non-compliance

Non-compliance to prescribed medications is also a common drug-related problem in the elderly and is considered a major challenge in managing their comorbidities. It may occur due to multiple medical and/or personal causes, including dementia, poor cognition, physical disability, or preference to omit doses.[51, 52] In addition to the prescribed medications, elderly patients may also use non-prescribed (over the counter) medications, which can potentially interact with prescribed medicines and become unsafe.[53, 54]

In order to ensure appropriate medication utilization in older patients, standardized assessment tools were developed, such as the STOPP/START criteria, Beers criteria, and Hyperpharmacotherapy Assessment Tool (HAT).[48, 54, 55] These criteria are evidence-based tools used by clinicians to identify drug-related problems in older patients. Regular follow up and medication review are critical to identify actual and

potential drug-related care issues and design a suitable management plan that maximizes the therapeutic effect and minimizes the undesirable side effects.

The impact of comorbidities and polypharmacy burden on the management and outcomes of breast cancer in older patients will be discussed in greater detail in sections 1.4.4.4 and 1.4.4.5. Comorbidities and polypharmacy create many difficulties and challenges in managing older patients and have emerged as the crucial need for pharmacotherapy guidelines.

1.3.3 Elderly pharmacotherapy guidelines

There is a current lack of effective treatment protocols being adopted into guidelines for older populations in general. Typically, clinical practice guidelines are designed for treating healthy, fit adults with normal body function. Treatment of frail/older patients with multiple comorbidities is still variable and depends primarily on individual doctors. Shamsher *et al.* (2014) conducted a qualitative study to review and analyse 20 Australian clinical practice guidelines to investigate how elderly populations are defined and considered for pharmacotherapy. [56] This study found that 85% (n=17) of guidelines did not define or describe "elderly" clearly, while 15% (n=3) used chronological age to define elderly. In parallel with the WHO guidelines, only two guidelines considered being 65-years old as a cut-off for describing the elderly, while one guideline considered 75-years as a cut-off.[56] In Kuwait, older age is considered 60 years and above due to the early onset of chronic comorbidities, including hypertension, diabetes, cardiovascular diseases, and cancer. Clinical practice guidelines in Kuwait include medication adjustment in case of organ dysfunction but do not provide recommendations for managing older patients.

The chronological-age-based guidelines do not provide an actual description of the elderly functional status of individual characteristics such as physical abilities, comorbidities, polypharmacy, and cognitive status.[56] This limits their usefulness for clinicians in clinical practice since there is a wide variation of older patients' characteristics and physical/functional abilities. Even though this study limited the analysis in Australian guidelines, these results can potentially be compared and applied to other national guidelines since they are derived from international clinical practice guidelines.

1.4 Breast cancer management

Breast cancer management can generally be sub-divided into curative and palliative treatment plans. The main available management protocols include different combinations of surgical intervention, radiation therapy, and chemotherapy.[57] The most commonly used systemic chemotherapeutic agents in breast cancers are anthracyclines (doxorubicin and epirubicin), taxanes (paclitaxel and docetaxel), cyclophosphamide, and carboplatin.[58, 59] Besides traditional chemotherapy, hormonal therapy and targeted therapy are indicated in specific histological subtypes of breast cancer tumours based on the hormonal status and growth factor receptors expression (this will be discussed in section 1.4.2).[60, 61]

Physicians are directed by international and national guidelines [such as The European Society for Medical Oncology (ESMO) and The National Comprehensive Cancer Network (NCCN)] to categorize patients into appropriate evidence-based treatment protocols. Patients are categorized based on standardized classifications of malignant tumours by assessing the tumour size (T), lymph nodes involvement (N), and disease

metastasis (M); which is referred to as the TNM scoring system.[62, 63] In clinical practice, treatment protocols are adjusted based on factors that are expected to influence the baseline assessment, including individual patient functional status, quality of life, individual patient beliefs, and life expectancy.[64-67]

1.4.1 Baseline assessment

In clinical practice, most oncologists apply simple traditional methods to assess patients' physical and functional status to predict their eligibility for intensive cytotoxic chemotherapy, which is the first-line chemotherapy (standard protocol) recommended by the guidelines. [68, 69] The Eastern Cooperative Oncology Group (ECOG) performance status (PS) scale is the most commonly used method in medical oncology practice and clinical studies because it is easy to apply and not time-consuming. [68, 70] The PS scale categorizes patients based on their ability to carrying out daily activities (Table 1.7). The literature demonstrated a significant correlation between advanced PS scores and poor cancer prognosis. [213]

Table 1.7 ECOG Performance Status (PS) scale. [68, 70]

Grade	ECOG PS
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework and office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Dead

Besides the PS assessment method, geriatric assessment tools have been developed to evaluate the general condition of older patients and predict their tolerance to cytotoxic

treatment.[193] The American Society of Clinical Oncology (ASCO) conducted a systematic review of the medical literature to develop guidelines that aim to provide a validated decision-making models and standardized clinical geriatric assessment (GA) tools to enhance treatment outcomes in older cancer patients.[71] Their multi-disciplinary Expert Panel provided recommendations and listed multiple validated tools for measuring and managing specific factors (domains) known to have a potential negative impact on cancer therapeutic outcomes and patients' quality of life. This includes comorbidities and polypharmacy, cognition, functional status, physical performance status, depression, and nutrition.[71] These tools are rarely applied in oncology clinics because of time constraints and the effort required to produce a final comprehensive evaluation of an older patient's status.[71] Otherwise, they are occasionally applied in clinical trials and studies. Unlike geriatric assessment tools, international oncology practice guidelines consider the PS score a crucial factor in the decision-making process of treating patients with different types of tumours.[72-74] While patients with PS= 0 are considered eligible for intensive cytotoxic chemotherapy, patients with PS ≥ 1 are expected to have poorer tolerance to chemotherapy and require further evaluation and most likely less intensive treatment allocation.

Cancer management guidelines are regularly updated underpinned by emerging evidence-based clinical research outcomes. Clinical trials significantly contribute to enhancing the clinical decision-making of cancer management and the consequent treatment outcomes.[75] A dramatic increase in breast cancer survival has been achieved during the last decade because of the continuous research in understanding

the biological heterogeneity of breast cancer tumours, and introducing the concept of individualized treatment approaches.[76]

1.4.2 The era of individualized treatment

During the past 20 years, there has been a growing interest in exploring the biological heterogeneity of breast tumours. Understanding histological and molecular characteristics has led to introducing more classifications and subtypes of breast tumours in the guidelines and changing aspects of treating patients from applying standardized treatment protocols to tailoring individualized treatment protocols.[77, 78] This advancement was accompanied by the discovery of targeted therapies based on specific tumour characteristics and expressions. Currently, targeted therapies are being prescribed as a standard of care for both metastatic and non-metastatic eligible breast cancer patients besides classic cytotoxic chemotherapy.[79]

Sections 1.4.2.1 and 1.4.2.2 will briefly discuss breast tumours classification to understand the scope of targeted therapies.

1.4.2.1 Histological classifications of breast tumours

Breast cancer is a very heterogeneous disease that exhibits different responses to therapeutic agents, and hence different prognosis and survival rates among patients. Based on the morphological characteristics of breast tumours, more than 95% are adenocarcinomas and can be either *in situ* (without penetration to surrounding tissues) or invasive (with penetration).[80] Both *in situ* and invasive breast adenocarcinomas are divided into histological subtypes based on the tumour origin. The most common histological subtype of breast tumours is invasive ductal carcinoma (IDC), accounting for more than 63% of cases.[81] Less common subtypes include invasive lobular

carcinoma, mixed ductal and lobular carcinoma, invasive mammary carcinoma, invasive papillary carcinoma and others.

Besides histological classifications, breast tumours are also classified according to their grade of cell differentiation and proliferation into well-differentiated, moderately differentiated and poorly differentiated tumours.[82] The histological grading of tumour cells differentiation is highly correlated with disease prognosis.[82] Poorly differentiated breast tumours have lower survival rates when compared to well-differentiated tumours. In addition, Ki67% is a commonly measured biomarker in breast tumours to assess tumour cells division and proliferation. Previous studies showed that Ki67% is associated with poor disease prognosis and survival.

1.4.2.2 Molecular classification of breast tumours

The breast tumours classification system has further improved after establishing additional subtypes of molecular classifications based on tumour cell biology rather than morphology. These differences in molecular behaviours paved the way for the development of targeted therapies that can exploit specific molecular expressions. The main molecular subtypes are hormonal receptor expression and Human Epidermal Growth Factor-2 (HER-2) receptor overexpression, and each will be discussed briefly.

1.4.2.2.1 Hormonal positive tumours

Hormonal receptor expression is considered a major criterion for evaluating tumour cells because it determines the treatment decision and predicts disease prognosis.[83] Oestrogen (ER) and/or progesterone (PR) receptor expression is detected in more than 70% of breast tumours, which are referred to as hormonal positive tumours.[83, 84] These tumours are associated with a better prognosis when compared to receptor negative tumours.[83, 84] This is because multiple targeted therapies can be prescribed

to inhibit hormonal expression and consequently inhibit tumour proliferation and growth.[85] Higher hormonal expression in tumours is associated with a better response to hormonal therapies when compared to lower hormonal expression tumours. As a result, better survival is realised.[86]

The association between androgen (AR) hormonal receptor status and survival was investigated in the Nurses Health Study (NHS), which included 121,700 post-menopausal patients with stage I-III breast cancer between 1976 and 1997, and followed them until January 2008 or death.[87] A significant reduction in breast cancer mortality and overall mortality was documented in patients with ER and AR positive receptors when compared to other expression statuses (p value= 0.0004) (Figure 1.2).[87] However, the survival benefit of patients with AR positive tumours was highly dependent on the ER receptor status. Among ER positive patients, a 30% reduction of breast cancer mortality was reported in AR positive patients. While in ER negative patients, AR status was not associated with better survival. Unlike ER and AR receptors, PR receptor status was not considered an independent prognostic factor of breast cancer mortality.

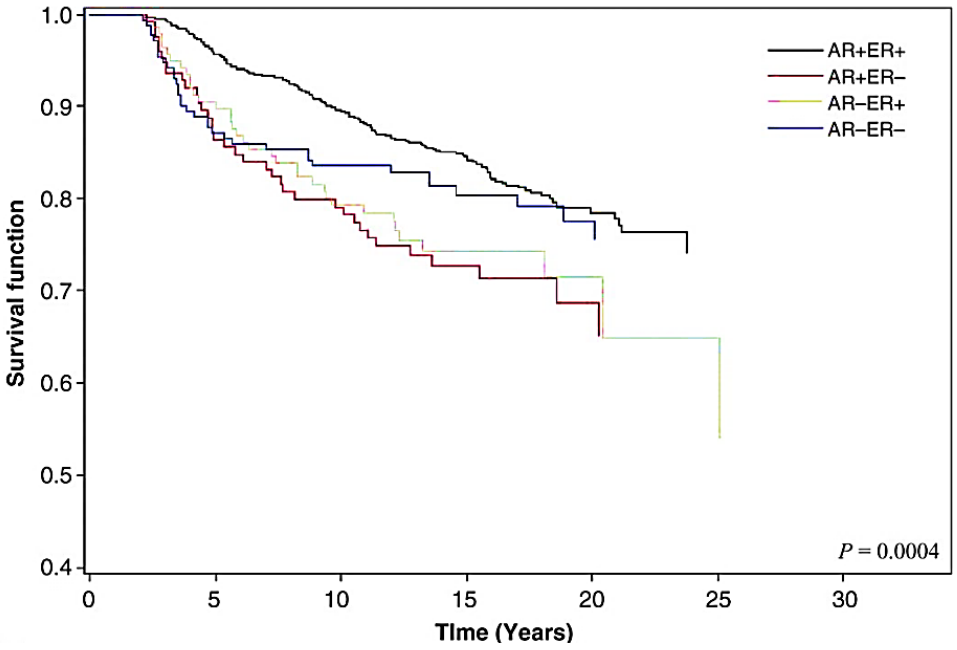

Figure 1.2 Comparing the survival rate (years) based on the hormonal status of breast tumours.[87]
http://clincancerres.aacrjournals.org/content/17/7/1867.figures-only

Tamoxifen is considered a gold standard adjuvant therapy in the management of hormonal breast tumours. [88] Tamoxifen is classified as a Selective Estrogen Receptor Modulators (SERMs) that competitively displaces oestradiol from oestrogen receptors, which blocks the role of oestradiol in the proliferation of hormonal breast tumours.[88, 89] Tamoxifen was approved by the Food and Drug Administration (FDA) in the 1970s. Over 40 years of clinical usage demonstrated that tamoxifen administration has a significant clinical impact in reducing breast tumours recurrence and mortality. [88] In addition to tamoxifen, aromatase inhibitors such as letrozole, anastrazole, and exemestane, are other hormonal therapies usually prescribed in post-menopausal patients.[90] These drugs suppress oestrogen production by inhibiting the aromatase (cytochrome P450) enzyme, which is responsible for converting androgen precursors to oestrogen.[90]

Fulvestrant is another alternative for adjuvant hormonal therapy and is classified as a selective estrogen receptor down-regulator.[91] Fulvestrant was approved by the FDA

in 2002 to be prescribed in advanced cases after previous hormonal therapy failure. [92, 93] In 2017, the FDA approved the expanded use of fulvestrant as initial therapy for post-menopausal patients with advanced hormonal breast tumours after the publication of the phase III FALCON trial that showed a 20% reduction in disease progression when compared to anastrazole.[94]

Recently, the detection of gene mutations in hormonal breast tumours has led to the discovery of newer targeted therapies, including palbociclib and ribociclib (CDK4/6 inhibitors), pictilisib and buparlisib (PI3K/AKT/mTOR inhibitor).[95] It is important to mention that these mutations are not detected in all patients (20-50%), meaning that not all hormonal positive breast cancer patients are considered eligible for these targeted therapies.[96, 97] Discovering these pathways of disease control is very promising and will encourage conducting more clinical trials that may further change breast cancer management in the future.

The present research did not include hormonal therapy outcomes because project data collection was limited to 36 months, whereas hormonal therapy outcomes require a treatment duration of five to ten years to appreciate their value. This has been highlighted in the ATLAS and aTTom landmark trials.[98, 99] Since the eighties, offering hormonal treatment for less than five years was considered a definite sub-optimal duration. The ATLAS trial was conducted between 1995-2010 to evaluate the outcomes of extending the hormonal treatment beyond five years. Findings showed that 10 years provided more favorable outcomes than 5 years. The aTTom trial confirmed the findings. Accordingly, the ASCO updated the guidelines in 2013.

1.4.2.2.2 HER-2 positive tumours

Another receptor that is overexpressed in more than 25% of breast cancer patients is the Human Epidermal Growth Factor-2 (HER-2).[100] HER-2 receptor overexpression is associated with more aggressive breast tumours and considered an independent prognostic factor. Since 1998, the survival rate of HER-2 positive tumours has improved after the introduction of HER-2 targeted therapies.[101] Trastuzumab is a monoclonal antibody that interferes with HER-2 receptor overexpression through different mechanisms of action. The main role of trastuzumab is binding to the tumour sites that overexpress HER-2 receptors and attracting the immune cells to the binding sites, which triggers antibody-dependent cellular toxicity (ADCC).[102] Also, trastuzumab inhibits MAPK and PI3K/Akt pathways, which have an essential role in suppressing the growth of breast tumours, proliferation, and survival signaling pathways (Figure 1.3).[94] These mechanisms induce cell arrest in breast tumours. Previous studies reported a 24-58% improvement in the 4-year disease-free survival and 23-35% in the 5-year overall survival among eligible non-metastatic breast cancer patients receiving trastuzumab therapy; as a result, it became the standard of care in HER-2 positive breast cancer management.[103, 104]

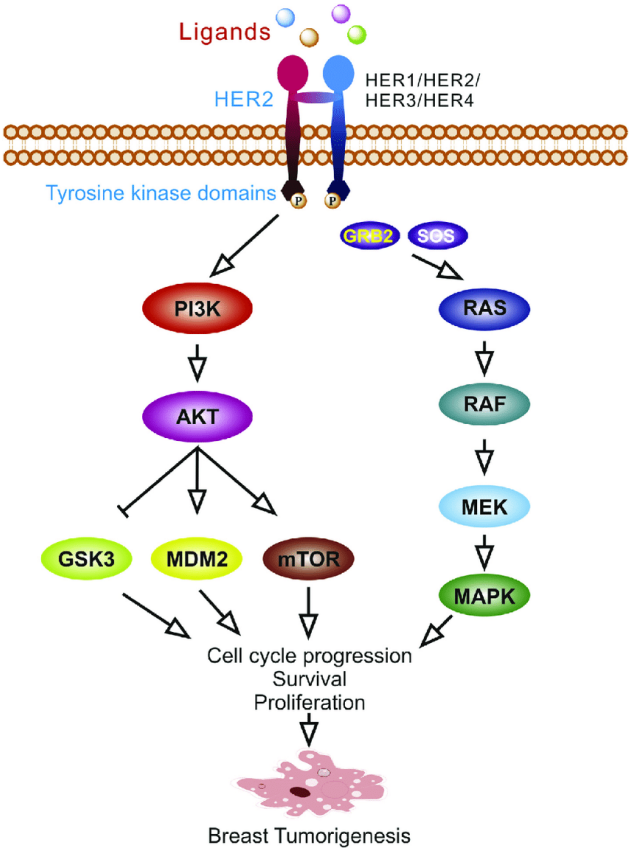

Figure 1.3 Different anti HER-2 pathways for breast cancer management [105]

Feng Y, Spezia M, Huang S, Yuan C, et al. Breast cancer development and progression: Risk factors, cancer stem cells, signaling pathways, genomics, and molecular pathogenesis. Genes Dis. 2018 May 12;5(2):77-106. doi: 10.1016/j.gendis.2018.05.001.

Following the introduction of trastuzumab, pertuzumab and lapatinib HER-2 targeted therapies were developed.[106] Combining HER-2 targeted agents with cytotoxic chemotherapy added significant survival benefits, especially in advanced cases of eligible aggressive breast tumours.[107] The first targeted-cytotoxic conjugate, trastuzumab-emtansine (T-DM1) combination, was approved in 2013 to be prescribed in advanced breast tumours overexpressing HER-2 after previous trastuzumab-taxane combination failure.[108] According to the EMILIA trial, trastuzumab-emtansine conjugate significantly improved progression-free and overall survival and decreased toxicity profiles in eligible patients compared to lapatinib/capecitabine combination.[109]

1.4.2.2.3 Triple negative tumours

Tumours with both hormonal and HER-2 overexpression are referred to as "triple positive" tumours, while tumours that are neither hormonal positive nor HER-2 positive are referred to as "triple negative" tumours, and account for approximately 15% of all breast tumours.[110] This subtype of breast tumours is associated with a lower survival rate when compared to "non-triple negative" tumours due to the lack of targeted therapies available for this aggressive tumour (Figure 1.4).[111, 112] Therefore, cytotoxic chemotherapy is the only available option for this group of patients.

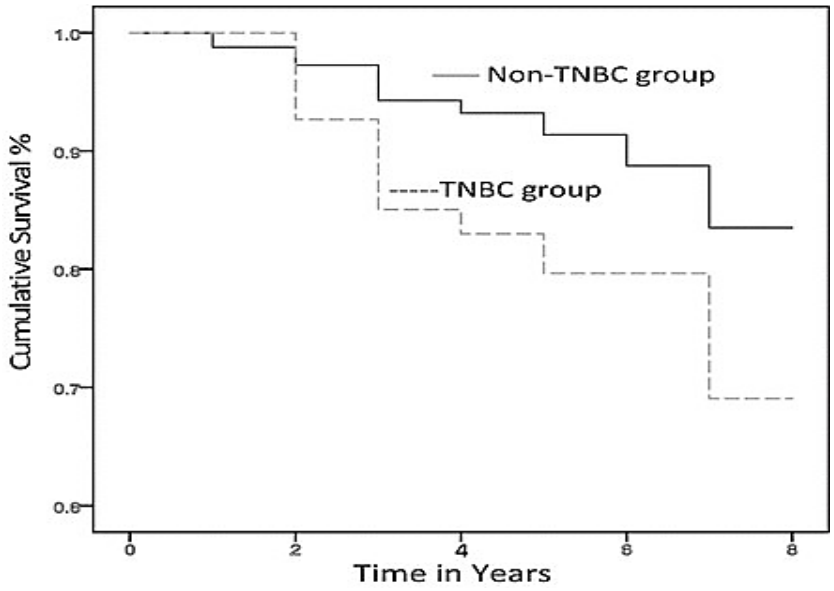

Figure 1.4 Comparing 5-year survival rate (years) between triple negative breast cancer (TNBC) and non-triple negative breast cancer (Non-TNBC).[112]
https://current-oncology.com/index.php/oncology/article/view/815/712

None of the previously discussed classifications are considered entirely independent for predicting the therapeutic response and disease prognosis.[112] Combining the hormonal status and HER-2 receptor status exhibits a specific pattern of overall survival among patients with breast tumours. The lowest survival rate is detected in triple negative tumours followed by hormonal negative patients and HER-2 positive tumours.[113] On the other hand, a high survival rate is detected in hormonal positive

patients, especially in the absence of HER-2 overexpression. Aggressive tumours are associated with a high grade of cell proliferation (poorly differentiated) and lower survival rates.[113]

1.4.2.3 Histological/ molecular changes and age

Diversity in breast tumour biology has raised questions regarding the impact of age on histological and molecular changes of tumour cells and the corresponding disease prognosis. A review of the literature suggested that age was associated with favorable histological characteristics of breast tumours. Poltinnikov *et al*. (2006) found that age 70 years and above was associated with less HER-2 expression as 78% of patients had HER-2 negative breast tumours.[114] Besides, different studies concluded that older age was associated with a higher prevalence of hormonal receptor expression indicating less aggressive tumours and a better prognosis. [115, 116]

1.4.3 Breast cancer management dilemma

Breast cancer affects young as well as older females. Many concerns are always raised regarding the side effects of aggressive anti-cancer treatment, mainly including breast surgeries and chemotherapy-induced hair loss. Sections 1.4.3 and 1.4.4 will address essential psychological and behavioural aspects of breast cancer management in the clinical practice of oncology and clinical trials.

In the early stages of breast cancer, both doctors and patients usually aim to select the most potent anti-cancer treatments recommended by the guidelines, despite their aggressiveness, to minimize the risk of relapse and prolong patient survival.[117] Unfortunately, patients then have to cope with the side effects that negatively impact their femininity and quality of life.[118] In reality, this is not always the case as some patients refuse intensive treatment to avoid collateral destruction to their bodies despite

the increased risk of relapse.[119] For example, patients may refuse mastectomy even if indicated to allow breast reconstruction surgery during or following breast conserving surgery.[119, 120] This contributes to significantly better cosmetic results and hence a better quality of life.[121] On the other hand, some patients from all age groups may reject the recommended treatment by their oncologists and refuse standard intensive, which is the first-line treatment according to the guidelines, chemotherapy that causes hair loss and a myriad of other side effects, including nausea, vomiting, and nail and skin changes. In such cases, oncologists explain the options and risks before offering any alternative treatment.

Unlike early-stage breast cancer, advanced breast cancer (relapsed/metastatic) management may be influenced by both doctors' and patients' communication and beliefs manifested by "not accepting death" and "never give up" agreement.[122] Historically, palliative cytotoxic treatment was continued in relapsed/ metastatic cases to prolong survival. Besides, continuing treatment even at terminal stages of the disease reflected doctors' support to patients with poor prognosis. However, evidence was published in JAMA oncology in 2015 showed that palliative chemotherapy worsens the quality of life in progressive metastatic cancer without any therapeutic benefits, even in patients with good performance status.[72] This derived doctors to terminate treatment earlier to minimize suffering at the end of life regardless of patients' age.[72]

It is essential to understand that these barriers make breast cancer management more challenging compared to other chronic comorbidities or types of cancers. For example, the management of breast cancer is more sensitive and influenced by patients' opinions of refusing intensive treatment or surgical intervention when compared to other types

of cancers.[123] Also, it may be accompanied by gender-biased decisions to maintain an acceptable quality of life for females, which is not detected in other common conditions and comorbidities, including diabetes or hypertension. [124, 125]

1.4.4 Breast cancer management in older patients

There is a current lack of evidence-based information about the treatment of older patients with cancer. This is often due to an under-representation of the elderly in clinical trials (section 1.4.4.1).[126-128] Cancer management guidelines are designed for treating 'fit' adults with normal body function. Treatment adjustment is occasionally recommended based on clinical evidence in some conditions (regardless of age), such as renal/liver dysfunction or heart failure. However, optimal treatment of older cancer patients with comorbidities, such as hypertension and diabetes, is still unclear, and selection primarily resides with individual oncologists.

In this research, allocating patients to receive first-line chemotherapy recommended by the oncology clinical practice guidelines is referred to as "standard/ intensive protocol". While allocating patients to receive treatment protocols other than the first-line is referred to as "non-standard/ less intensive protocol".

1.4.4.1 Participation in clinical trials

Elderly patients are usually excluded from clinical trials, which has a negative impact on cancer management due to a lack of effective treatment protocols being adopted into guidelines.[128] Unfortunately, only 25% of cancer patients aged 65 years and above participate in clinical trials.[126] This has raised the question of whether older patients were not offered clinical trials as commonly as their younger counterparts or older patients were unwilling to participate despite being offered clinical trials by their treating doctors. Townsley *et al.* (2006) studied the attitudes of 94 older cancer patients

towards their participation in clinical trials through a self-administered questionnaire and semi-structured interview.[129] Data showed that three-quarters of patients were willing to participate in clinical trials if offered the opportunity. Kemeny *et al*. (2003) aimed to investigate whether age bias was a significant factor in offering clinical trials to older patients. He collected data from 154 breast cancer patients eligible for open clinical trials from 10 different Cancer and Leukaemia Group B institutions.[130] Patients were divided into two age groups (<65 and ≥65 years old) and matched (77 pairs) by disease stage and treating oncologist to be compared. Self-administered questionnaires were given to the treating oncologists to explain their reasons for either offering or not offering clinical trials for the patients. Results showed that younger patients were significantly offered more clinical trials than elderly patients (68% versus 34%; p= 0.0004) despite matched patients' and disease characteristics.[130] The most commonly reported reasons for not offering clinical trials for older patients by their treating oncologists were toxicity concerns (33%), required treatments were not included in the trials (27%), and comorbidity burden concerns even when patients were considered eligible for the clinical trial (18%).[130]

In order to demystify the barriers of recruiting older patients into clinical trials, Denson and Mahipal (2014) classified them into three categories: physician barriers, patient barriers, and trial barriers.[131] The main physician-related barrier was a lack of evidence about possible treatment toxicity and tolerance among older populations. Physicians believed that comorbidities and polypharmacy contribute to increased cancer treatment-related toxicity (Figure 1.5). Also, older patients are anticipated by physicians to show poorer therapeutic outcomes due to physiological and

psychological changes, which are common but not uniform within this population, as mentioned earlier.[131]

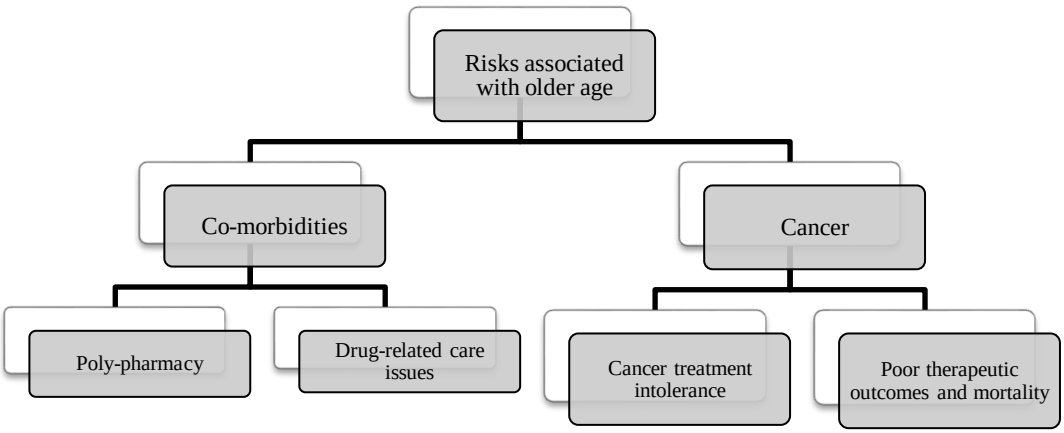

Figure 1.5 The complexity of older cancer patients' management

The requirement to prescribe less intensive treatment and deviate from standard treatment protocols usually does not fit the clinical trials' criteria, which is considered a trial-related barrier.[131] Besides treatment allocation barriers, multiple comorbidities and decreased functional reserve are usually listed as exclusion criteria of cancer clinical trials. On the other hand, common patient-related barriers include poor access to clinical trials, toxicity-related concerns, and lack of autonomy.[131] This complexity in the treatment of older patients led to less intensive treatment allocation for elderly cancer patients.

1.4.4.2 Under treatment

Treating older cancer patients is challenging due to the lack of evidence-based standard management protocols. In the literature, different population-based studies show that older breast cancer patients are less likely to receive optimal cancer management, including surgical therapy, radiotherapy, chemotherapy, or hormonal therapy, compared to younger adults with the same type and stage of cancer who receive a full

dose of intensive standardized treatment protocols.[132-135] Indeed this leads to poor therapeutic outcomes in older breast cancer patients and lower survival rates. Allocating older patients for a less intensive therapy is mainly attributed to the lack of effective individualized assessment for each patient despite chronological age.[136, 137] For example, Yood *et al.* (2008) indicated that older patients are offered breast-conserving surgery instead of either mastectomy or a combination of breast-conserving surgery and radiation therapy, which doubled the mortality rate in this group of patients.[138] Also, older patients with positive hormone receptor expression are more likely to be offered either hormonal therapy alone (for a suboptimal duration), or breast-conserving surgery alone compared to younger patients who receive both surgical and hormonal therapy. Similarly, this significantly worsened the therapeutic outcomes and survival.

Bouchardy *et al.* (2003) studied the impact of breast cancer treatment patterns on cancer-specific survival in 407 patients aged 80 years and above.[139] Clinical data showed that age was significantly associated with less intensive treatment allocation and poorer five-year survival (Table 1.8).

Table 1.8 Treatment allocation for breast cancer patients who were aged 80 years and above.[139]

Rate of treatment allocation	
No treatment	12%
Tamoxifen only	32%
Breast conserving surgery only	7%
Mastectomy only	33%
Breast conserving surgery + adjuvant treatment	14%
Miscellaneous treatments	2%

The five-year breast cancer mortality was 46%, 51%, 82%, and 90% for patients who had no treatment, tamoxifen only, mastectomy only, and breast conserving surgery

with adjuvant treatment, respectively.[139] This study showed that omitting cytotoxic chemotherapy was correlated with poor survival rates among older patients. The general health status was reviewed for all patients to correlate the treatment decision with the general health condition of patients. Surprisingly, results showed that 40% of patients had good health, and 42% had either no comorbidities or chronic controlled conditions (data was not available for 26% of patients), indicating that prescribing less intensive therapy was not always attributable to the existence of multiple comorbidities.[139]

Schonberg *et al.* (2010) collected data from 49,616 breast cancer patients aged 67 years and above from the Surveillance Epidemiology and End Results (SEER) Medicare data set to investigate the impact of tumour characteristics and comorbidities on cancer treatment allocation and survival in older breast cancer patients.[140] Patients were divided into two age cohorts (between 67-79 years) and (80 years and above). Data analysis showed that among patients aged 80 years and above and without comorbidities, 26% received either no surgery or breast-conserving surgery alone (non-standard protocol) despite being clinically eligible.[140] This treatment allocation precipitated lower survival rates observed in this age group compared to younger patients. It is worth mentioning that no significant differences were noticed in tumour characteristics in terms of grade and hormone receptor status between the two older age cohorts in this study. This could be attributed to the shorter life expectancy anticipated for the oldest age group rather than the number of comorbidities that led oncologists to offer less intensive treatments. Therefore, oncologists preferred less aggressive treatments to maintain a good quality of life among older patients.

These studies showed that the older adult populations are heterogeneous, and less intensive treatment protocols cannot be readily standardized based on age alone. A significant decrease in the survival outcomes among older patients with breast cancer was noticed due to undertreating eligible older patients. Since most of the published papers are retrospective reviews, the actual causes of treating elderly patients with less intensive treatment protocols are not always stated and remain unclear. However, age bias and comorbidities could affect treatment decisions.

The present research discusses only chemotherapy allocation and does not include other treatment modalities (surgical intervention and radiotherapy) because not all chemotherapy candidates are eligible for combined treatment modalities. In addition, combined treatment modalities require being involved in different oncology departments and a more extended timeframe for data collection than what is allowed for this study. In addition, multiple obstacles in the healthcare system in the Kuwait Control Cancer Centre (KCCC) made data collection from different departments very complicated; this will be illustrated in the methodology (section 2.2.1).

1.4.4.3 Chemotherapy allocation guidelines and outcomes in older patients

Clinical practice guidelines are designed and updated based on landmark studies and research outcomes. Lack of evidence-based guidelines for managing older patients with cancer raised treatment efficacy and safety concerns in this population.[141-143] Patients aged 70 years and above are more likely to receive modified doses of chemotherapy, which is referred to as 'elderly-friendly' or 'elderly-adapted' regardless of their comorbidities and daily living capabilities.[140] This section will discuss

landmark studies comparing the efficacy and safety of different chemotherapy protocols in the management of breast cancer.

1.4.4.3.1 Chemotherapy efficacy

Trials and clinical studies have compared the tolerance and therapeutic outcomes of different chemotherapy protocols between elderly cancer patients and their younger counterparts.[144, 145] Landmark studies included in Table 1.9 demonstrate that standard doublet anthracycline-based chemotherapy is considered the standard of care in managing breast cancer patients because it improves the response rate and disease progression regardless of patients' age. However, it is associated with a wide range of toxicity that can be tolerable in selected patients (Table 1.9). On the other hand, less intensive single agent taxane chemotherapy is not associated with improved survival outcomes or quality of life compared to classic chemotherapeutic combinations. Besides chemotherapy combinations, doublet anti HER-2 targeted treatment combination improves the survival outcomes in eligible breast cancer patients despite age without increasing the haematological toxicities among patients aged 65 years and above.

Table 1.9 Main meta-analysis & randomized controlled trials.[146-148]

Authors/ group	Cohort (Sample size)	Chemotherapy regimen	Primary endpoint	Outcomes
Early Breast Cancer Trialists' Collaborative Group **EBCTCG Meta-analysis**	Comparisons between different polychemotherapy regimens for early breast cancer: meta-analyses of long-term outcome among 100 000 women in 123 randomised trials	* Standard CMF 6 cycles of C100×14 M40×2 F500×2, given 4-weekly; widely studied Near-standard CMF 6–12 cycles with same doses as Standard CMF and/or C600×2 replacing C100×14	Breast cancer mortality and 10-year overall mortality	- Trials with CMF-treated controls showed that standard 4AC and standard CMF were equivalent (RR 0·98, SE 0·05, 2p=0·67). - Higher than standard cumulative doses of anthracycline-based-regimens 4AC (eg, CAF or CEF) were superior to standard CMF (RR 0·78, SE 0·06, 2p=0·0004).

		** Standard 4AC 4 cycles of A60 C600, given iv 3-weekly *** Standard 4EC 4 cycles of E90 C600, given iv 3-weekly **** CAF 6 cycles of C100×14 A30×2 F500×2, given 4-weekly ***** CEF 6 cycles of C75×14 E60×2 F500×2, given 4-weekly		- Trials versus no chemotherapy showed greater mortality reductions with CAF (RR 0·64, SE 0·09, 2p<0·0001) than with standard 4AC (RR 0·78, SE 0·09, 2p=0·01) or standard CMF (RR 0·76, SE 0·05, 2p<0·0001) - Taxane-plus-anthracycline-based or higher-cumulative-dosage anthracycline-based regimens reduced breast cancer mortality by, on average, about one-third.
Perrone F, Nuzzo F, Di Rella F, Gravina A, Iodice G, Labonia V, Landi G, Pacilio C, Rossi E, De Laurentiis M, D'Aiuto M, Botti G, Forestieri V, Lauria R, De Placido S, Tinessa V, Daniele B, Gori S, Colantuoni G, Barni S, Riccardi F, De Maio E, Montanino A, Morabito A, Daniele G, Di Maio M, Piccirillo MC, Signoriello S, Gallo C, and de Matteis A. **(ELDA) Trial**	Women aged 65-79, and operated for breast cancer, with average to high risk of recurrence. (n=299)	Patients were allocated 1: 1 to CMF (cyclophosphamide 600 mg/m², methotrexate 40 mg/m², fluorouracil 600 mg/m², days 1, 8) Or docetaxel (35 mg/ m²) days 1, 8, 15) every 4 weeks.	Disease-free survival (DFS), toxicity profile and quality of life.	- Unadjusted hazard ratio (HR) of DFS for docetaxel versus CMF was 1.21 [95% confidence interval (CI) 0.83-1.76, P = 0.32]; DFS estimate at 5 years was 0.69 with CMF and 0.65 with - Hematological toxicity, mucositis and nausea were worse with CMF. - Allergy, fatigue, hair loss, onychopathy, dysgeusia, diarrhea, abdominal pain, neuropathy, cardiac and skin toxicity were worse with docetaxel (resulted in worse quality of life).
Swain SM[1], Baselga J, Kim SB, Ro J, Semiglazov V, Campone M, Ciruelos E, Ferrero JM, Schneeweiss A, Heeson S, Clark E, Ross G, Benyunes MC, Cortés J; CLEOPATRA Study Group. **(CLEOPATRA) Trial**	Patients with HER2-positive locally recurrent, unresectable, or metastatic breast cancer who had not received prior chemotherapy or biological therapy for their advanced disease were eligible. Patients were divided into two age groups (<65 years vs ≥65 years) (n=127 elderly patients)	A randomized, double-blind, placebo-controlled phase III trial designed with two treatment arms: placebo, trastuzumab and docetaxel (referred to as placebo arm); trastuzumab and pertuzumab and docetaxel (referred to as pertuzumab arm)	Progression-free survival, overall survival, objective response rate and safety	-Progression-free survival benefit with treatment in the pertuzumab arm. -Diarrhoea, fatigue, asthenia, decreased appetite, vomiting, and dysgeusia were reported more frequently in patients 65 years of age or older. -Neutropenia and febrile neutropenia were reported less frequently in the older age group

* CMF: Cyclophosphamide + Methotrexate + Fluorouracil
** AC: Doxorubicin (Adriamycin) + Cyclophosphamide
*** EC: Epirubicin + Cyclophosphamide
**** CAF: Cyclophosphamide+ Doxorubicin (Adriamycin) + Fluorouracil
***** CEF: Cyclophosphamide+ Epirubicin + Fluorouracil

Anthracycline-based chemotherapy is a gold standard of care for breast cancer patients. It is the first-recommended treatment line by the clinical practice guidelines in high-risk breast cancer patients, including patients with family history, BRCA1 gene mutation, advanced stage (III), and aggressive tumour subtypes (HER-2 positive and Triple negative tumours).[149] Anthracyclines are generally have good tolerance; however, it is associated with a high risk of cardiotoxicity among all patients despite age.[150] Anthracycline-induced cardiotoxicity is still a major concern, especially in older patients, and often drives oncologists to prescribe a non-anthracycline-based (non-standard) chemotherapy (will be discussed in greater details in section 1.4.4.3.2.1).

Cyclophosphamide, methotrexate, and fluorouracil (CMF) in combination is a historically gold standard chemotherapy regimen mainly indicated as adjuvant therapy (post-surgical chemotherapy) for limited-stage tumours. This regimen is an option for patients who are not suitable for anthracycline-based chemotherapy. Questions about safety and efficacy differences between these two chemotherapy regimens in elderly patients have been consistently raised. A large meta-analysis was conducted by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) to assess the 10-year outcomes of different chemotherapeutic combinations in patients with early breast cancer (Table 5).[146] Results show a 36% reduction in breast cancer mortality with either anthracycline-based chemotherapy or CMF versus no chemotherapy. Standard doses of anthracycline-based chemotherapy and CMF combination have comparable

10-year clinical outcomes. However, significantly less than standard doses of each regimen are associated with compromised efficacy. Superior survival with a further proportional 15-20% reduction in breast cancer mortality has been achieved by adding at least four cycles of a taxane to anthracycline-based chemotherapy.[146] This large meta-analysis concludes that combining a taxane with anthracycline-based chemotherapy or offering higher than standard cumulative doses of anthracycline-based regimens reduces the 10-year breast cancer mortality by one-third, regardless of tumour characteristic or patient's age.[146] Accordingly, treating older adult breast cancer patients with standard intensive protocols improves the response rate and disease-specific survival to a similar extent to their younger counterparts compared to less intensive (non-standard) chemotherapy protocols.

The main challenge in treating older cancer patients is not only allocating patients to receive chemotherapy protocols with the maximum benefits but also with minimal toxicities. As mentioned, non-anthracycline-based chemotherapy, such as CMF, is usually offered for older patients to avoid the risk of cardiotoxicity.[151] However, the CMF regimen is associated with increased risks of nausea, leukopenia, and neutropenia in elderly patients and sometimes leads to poor compliance compared to other regimens.[152] In order to decrease the risk of chemotherapy toxicity and the consequent requirement for discontinuation in older patients, oncologists considered prescribing taxane monotherapy in patients with possible poor tolerance to intensive doublet chemotherapy. The ELDA trial compared the therapeutic outcomes between adjuvant CMF and docetaxel (taxane monotherapy) in older breast cancer patients, and results highlighted that docetaxel did not result in better efficacy or survival.[131] Furthermore, taxane monotherapy did not improve tolerance. A higher toxicity rate

was reported, including fatigue, hair loss, dysgeusia, diarrhoea, abdominal pain, and neuropathy that significantly worsened individual patients' quality of life. Besides these side effects, taxane monotherapy precipitated more cardiac and skin toxicities when compared to CMF. This trial, therefore, supported treating older breast cancer patients with classic CMF combination therapy instead of taxane monotherapy if they were ineligible for anthracycline-based therapy.[147]

Besides traditional chemotherapy, different targeted therapies have entered the marketplace during the last 20 years.[153] Even though targeted therapies became a standard of care in treating specific subtypes of breast tumours, there is a lack of evidence-based knowledge about their utilization in older patients. Trastuzumab is currently considered a standard of care in HER-2 positive patients.[154] Pertuzumab is also approved to be combined with trastuzumab in selected cases.[155] The safety of this combination has not been extensively studied in the literature. The CLEOPATRA trial (phase III) compared the tolerance and response of triple chemotherapeutic agents' combination (pertuzumab, trastuzumab, and docetaxel) between two eligible age cohorts (≥65 and <65 years).[148] Results showed that patients from both age cohorts have comparable tolerance and a progression-free survival benefit. As expected, patients from the older age cohort experience more frequent but tolerable non-haematologic side effects, including diarrhoea, vomiting, and decreased appetite. However, the older age cohort had less incidence of neutropenia and febrile neutropenia.[148] Based on this trial, eligible older adult patients appear to tolerate the combination of targeted therapies to a similar extent as younger adult patients.

The literature provides evidence-based knowledge about the superior therapeutic and survival outcomes of intensive doublet anthracycline-based chemotherapy. However,

they are not always prescribed in clinical practice because of toxicity concerns. In patients who are not eligible for anthracycline-based chemotherapy, oncologists prescribe single agent taxane monotherapy to minimize the toxicity outcomes among older patients, but this contributes to worse quality of life compared to the CMF combination. This means that less intensive treatment is not always associated with better tolerance among older patients. Besides chemotherapy, doublet anti HER-2 targeted treatment improves the survival outcomes of breast cancer patients despite age and can be safely prescribed for selected older patients.

1.4.4.3.1.1 The clinical practice of oncology guidelines in Kuwait

The clinical practice of oncology guidelines in Kuwait follows standardized international guidelines, such as the European Society for Medical Oncology (ESMO) and National Comprehensive Cancer Network (NCCN) guidelines. Consistent with the international guidelines, systemic treatment allocation for breast cancer management in Kuwait should be based on the intrinsic tumour subtype, predicted benefits, predicted side effects, and patient preference.[156] The performance status is assessed at baseline to evaluate patients' tolerability and eligibility for intensive (first line) treatment, while comprehensive geriatric assessments are not applied in clinical practice. In accordance with the previously discussed evidence in section 1.4.4.3.1, doublet intensive anthracycline-based chemotherapy [Anthracycline + Cyclophosphamide (AC) / Taxane (T)] is considered a gold standard of care and first-line treatment in managing breast cancer patients regardless of age.[156] Carboplatin is occasionally added to taxane in case of BRACA gene mutation and triple negative tumours. The guidelines consider patients with a history of cardiac disease

contraindicated for anthracycline treatment.[156] On the other hand, anthracyclines should be used with caution in patients aged 60 years and above, patients with reduced left ventricular ejection fraction (LVEF), and patients with significantly increased blood pressure (BP). However, the guidelines do not provide guidance on cardiotoxicity risk assessment or borderline values for LVEF and BP to determine the eligibility for anthracycline utilization. Accordingly, assessing patients' eligibility or predicting the tolerance for anthracycline treatment resides on individual oncologists. Baseides cardiotoxicity, intensive treatment is associated with a high risk of gastrointestinal toxicities (nausea and vomiting), haematological toxicities (anemia, neutropenia and thrombocytopenia), and risk of infection. If patients are considered at toxicity risk, they should be allocated for taxane-based (non-anthracycline) chemotherapy, considered nonstandard chemotherapy. This includes [Taxane + Cyclophosphamide (TC)] or [Taxane + Carboplatin] for aggressive tumours. Lack of guidance on assessing patients' eligibility and tolerability for intensive treatment is detected in Kuwait and standardized international guidelines, such as the (ESMO) and (NCCN) guidelines.

1.4.4.3.2 Chemotherapy organ toxicity

Chemotherapy-induced organ toxicity is a major concern in treating older cancer patients, especially if patients have multiple comorbidities. This section will briefly discuss critical risks that may limit chemotherapy utilization: cardiotoxicity, nephrotoxicity, and hepatotoxicity.

1.4.4.3.2.1 Cardiotoxicity

A recently published population-based study of cardiovascular disease (CVD) mortality risk among 3,234,256 patients with 28 cancer types in the US between 1973-2012 showed that 38% and 11% mortality cases occurred during this period due to cancers and cardiovascular diseases, respectively.[157] This study raised concerns about the increased prevalence of CVD-related mortality among cancer patients. In 2012, around 61% of CVD-related mortality cases were diagnosed with breast, prostate, or bladder cancer. Data showed that the first year after cancer diagnosis was associated with the highest risk of CVD mortality, and the risk reached more than 10-fold in cancer patients compared to the general population during longer follow-up. Besides, the risk of CVD mortality was higher among survivors diagnosed with cancer when younger than 35 years of age.

Among breast cancer patients, cardiotoxicity is considered one of the main challenges in clinical practice.[140] This is because the main chemotherapeutic agents prescribed in managing metastatic and non-metastatic breast cancer are associated with an increased risk of cardiotoxicity.[158] The mechanism of chemotherapy-induced cardiotoxicity is not fully understood; however, it results from direct injury to cardiomyocytes.[159, 160] In clinical practice, cardiotoxicity is detected using cardiac ultrasound. There is no evidence of routine monitoring of cardiac biomarkers such as troponins and brain natriuretic peptides (BNP) to predict cardiotoxicity in asymptomatic patients; however, these markers are requested if a significant decline in the Left Ventricular Ejection Fraction (LVEF) or CHF symptoms occur. Cardiotoxicity signs and symptoms can range from transient changes, such as arrhythmias, to permanent cardiomyopathy characterized by clinical signs and

symptoms of congestive heart failure.[161] Decreased left ventricular function can be precipitated either during chemotherapy (early-onset) leading to discontinuation of the treatment or many years after completing the treatment (late-onset).[162]

Consensus on the definition of cardiotoxicity has not been reached. However, the assessment is based on the percentage LVEF decline from the baseline value and the existence of signs and symptoms of heart failure; According to the ESMO clinical practice guidelines, the lower limit of acceptable LVEF function during anti-cancer treatment is 50%.[160] Reaching LVEF values below 50% is considered cardiotoxicity even in the absence of cardiac symptoms. On the other hand, developing cardiac symptoms, such as chest pain or shortness of breath, is considered cardiotoxicity even if the LVEF is above 50%.

During the last 20 years, a dramatic change occurred in the era of individualized HER-2 breast tumours management and the introduction of trastuzumab (section 1.4.2).[163] According to the HERA (Herceptin Adjuvant), BCIRG-006 (Breast Cancer International Research Group 006), NSABP B-31 (National Surgical Adjuvant Breast and Bowel Project B-31), Intergroup N9831 (The North Central Cancer Treatment Group Intergroup N9831, and FinHer (Finland Herceptin) trials, patients who received trastuzumab were at a 2.45-fold higher risk of cardiotoxicity when compared to patients who did not receive trastuzumab.[164] Previous exposure to cardiotoxic chemotherapy is considered one of the major factors that increase the risk of trastuzumab-induced cardiotoxicity. According to the Cardiac Review and Evaluation Committee (CREC), the risk of trastuzumab-induced cardiotoxicity increases from 8% to 27% and 30% with concomitant administration of cyclophosphamide and previous exposure to anthracycline treatment, respectively.[165] On the other hand, concomitant

administration of trastuzumab and taxanes results in a 13% risk of cardiotoxicity. Among patients aged more tha 65 years, cardiotoxicity occurred in 29.4% of patients receiving trastuzumab and in 18.9% in patients receiving different chemotherapy protocols not including trastuzumab.[166] Trastuzumab-induced cardiotoxicity differs from other chemotherapeutic agents-induced cardiotoxicity in that it is usually reversible, not dose-related, and re-challenge is usually well tolerated.[167]

In contrast to trastuzumab, the risk of anthracycline-induced cardiotoxicity is highly dose-related.[168] For example, 400 mg/m^2 of doxorubicin is associated with a 3-5% risk of cardiotoxicity, while the risk increases to 18-48% at 700 mg/m^2 of doxorubicin.[168] Besides, the potentially cardiotoxic dose is not consistent across the anthracyclines (Table 1.10). It is strongly advised not to prescribe anthracyclines and trastuzumab concomitantly.[169]

Table 1.10 Potential cardiotoxic cumulative doses of anthracyclines (ESMO)[168]

Drug	**Dose (mg/m^2)**
Doxorubicin	>500
Liposomal doxorubicin	>900
Epirubicin	>750
Idarubicin	< 90

Besides anthracyclines and trastuzumab, taxanes such as paclitaxel and docetaxel are associated with 0.5-5% and 7% risk of cardiotoxicity, respectively, mainly manifested by bradycardia.[161] Also, cyclophosphamide causes dose-related cardiotoxicity in 7-28% of patients with occasional reports of myopericarditis and pericardial effusion.[170] Other cardiotoxicity risks depend upon individual patient characteristics, such as advanced age, comorbidities, especially hypertension and coronary artery disease, and previous cumulative exposure to cardiotoxic treatments, such as radiation.[168, 171]

1.4.4.3.2.2 Nephrotoxicity

Unlike younger patients, older cancer patients are at a high risk of organ dysfunction due to normal physiological changes associated with the typical aging processes as previously mentioned and/or cancer management complications. Renal dysfunction decreases the elimination of some chemotherapeutic agents that are mainly excreted via the kidneys.[172] This increases drugs level in the blood, with subsequently increased toxicity risks. For example, in the literature, the CMF regimen has been shown to cause bone marrow toxicity in older adult patients with renal dysfunction even at standard doses.[173] This toxicity is significantly related to the degree of kidney dysfunction but not chronological age. With CMF combination dosage adjustment (75% of standard dose), better tolerance is seen without compromising the anti-tumour effects of the therapy.[173] In case of significant kidney dysfunction, further reduction in methotrexate dose is indicated. The risk of nephrotoxicity is also observed with other chemotherapeutic agents, such as cisplatin, gemcitabine, and pemetrexed. However, these agents are not indicated for the management of breast cancer. [174, 175] Furthermore, another major risk of renal dysfunction in older patients undergoing chemotherapy is volume depletion.[154] This can be precipitated by chemotherapy-induced vomiting and diarrhoea.[176, 177] Besides, the risk of acute renal dysfunction is also increased in older patients with comorbidities such as diabetes and/or receiving nephrotoxic medications concomitantly e.g. non-steroidal anti-inflammatory drugs (NSAIDs) or angiotensin converting enzyme inhibitors (ACEI).[178-181] Such cases require regular monitoring of the renal function and plasma electrolytes.

1.4.4.3.2.3 Hepatotoxicity

Unlike chemotherapy-induced nephrotoxicity, hepatotoxicity is infrequently reported in the medical literature and rarely detected in breast cancer patients.[182] Identifying the cause of liver abnormalities during chemotherapy may necessitate multiple investigations, including blood tests, liver ultrasound, or scans if required because it can be attributed to underlying liver diseases (e.g. cirrhosis), metastases, viral hepatitis, or chemotherapy-induced.[183]

Sinusoidal obstruction syndrome and chemotherapy-associated steatohepatitis are uncommon induced liver abnormalities in patients receiving oxaliplatin-based chemotherapy, a platinum anti-cancer agent primarily licensed for colorectal cancer; however, it is rarely used off-label in metastatic breast cancer. [184, 185] These hepatic conditions are reported mainly in patients with liver metastasis and/or undergoing liver resections. Liver function assessment among elderly patients receiving chronic medications that could potentially elevate liver enzymes, such as statins, is critical to identify patients at possible risk of developing liver dysfunction during potential hepatotoxic chemotherapy or in case of liver metastases.[186] In such situations, a baseline assessment of the liver function test (LFT) helps in the treatment decision-making of considering a full starting dose of chemotherapy or dose escalation. Regular monitoring of liver function enzymes during cancer treatment helps predict liver abnormalities and apply appropriate intervention (with-holding hepatotoxic treatment) if dramatic elevation in hepatic enzymes is detected (more than three-fold).[187] Chemotherapy-induced elevation in liver enzymes is usually transient and without clinical symptoms. Therefore, re-challenge with dose escalation is usually indicated after reaching normal ranges of LFT. [183, 188] Balancing chemotherapy benefits and

risks in older cancer patients is always recommended to avoid organ dysfunction that may lead to treatment discontinuation.

1.4.4.4 The impact of comorbidities on treatment tolerance and outcomes

The co-existence of multiple comorbidities limits cancer treatment options for older patients and may lead to offering suboptimal treatment. This section will briefly discuss the controversial debate about the impact of comorbidities on breast cancer treatment tolerance and therapeutic outcomes.

The most commonly reported chronic comorbidities among breast cancer patients are cardiovascular diseases and diabetes, contributing to unfavorable therapeutic outcomes.[189] Statistics show that diabetes is associated with poor quality of life.[190] However, the impact of diabetes on overall survival is controversial. On the other hand, cardiovascular diseases precipitate multiple complications leading to breast cancer treatment intolerance and therapeutic failure (section 1.4.4.3.2.1). According to Yancik *et al.* (2001), 17% of mortality cases in post-menopausal breast cancer patients are due to heart disease rather than cancer itself.[191] Besides cardiovascular diseases, other critical comorbidities, including stroke, renal failure, and hepatic disease, are considered predictors of early mortality in older cancer patients.[191]

The Alliance trial (CALGB 49907 and CALGB 361004) studied the impact of chronic comorbidities in non-metastatic breast cancer patients aged 65 years and above with good performance status (0-2).[192] The median number of comorbidities was two with arthritis (58%) and hypertension (55%) the most prevalent. Other common comorbidities, including diabetes, osteoporosis, history of myocardial infarction, and chronic lung disease, presented in 20-30% of patients. This trial demonstrated that

comorbidities are not associated with increased treatment-related toxicity or relapse in older breast cancer patients but significantly decreased the overall survival rate. The coexistence of four or more comorbidities increased the mortality rate by 18% for each comorbidity (p value= 0.002).[192] Unlike diabetes, cardiovascular diseases, and lung diseases, limited data support the link of hypertension and arthritis to poorer cancer treatment outcomes in the wider literature.

In contrast to the Alliance trial, the OMEGA study correlated the number of comorbidities with increased treatment intolerance (toxicity) and poor survival in metastatic breast cancer patients aged 65 years and above and receiving single-agent chemotherapy.[193] This study applied the Comprehensive Geriatric Assessment (CGA) at baseline to identify age-related (geriatric) conditions and vulnerabilities. The CGA included Charlson's Comorbidity Index (CCI), Instrumental Activities of Daily Living (IADL), Mini-Mental State Examination (MMSE), Geriatric Depression Scale (GDS), polypharmacy, and nutritional status reflected by the Body Mass Index (BMI). Results of the OMEGA study demonstrated that the number of geriatric conditions was associated with a higher rate of grade 3-4 chemotherapy-related toxicity; the incidence was 19% in patients without comorbidities, 32% in patients with only one comorbidity, 56% in patients with two comorbidities, and 80% in patients with three or more comorbidities (p=0.002).[193] However, the number of comorbidities was not correlated with overall survival.

The disagreement in the Alliance trial and OMEGA study could be attributed to differences in the disease stage among recruited patients. The Alliance study recruited patients aged ≥ 65 years old with stages I-III breast cancer. On the other hand, the OMEGA study recruited patients aged ≥ 65 years old with stage IV (metastatic) breast

cancer. Non-metastatic patients receive scheduled chemotherapy to prevent or delay tumour relapse. In comparison, metastatic patients receive chemotherapy until disease progression or intolerable toxicity.[194] In such cases, cumulative doses of chemotherapy are expected to precipitate a higher rate or grade of toxicity in metastatic patients who are anticipated to have poorer quality of life compared to non-metastatic patients.[194] An older patient with metastatic cancer exhibits poorer chemotherapy tolerance than an older patient with non-metastatic cancer and a similar number of comorbidities.

1.4.4.5 The impact of polypharmacy on cancer treatment outcomes

Cancer management is associated with prescribing multiple medications that include anti-cancer agents and palliative medications to manage the collateral side effects, such as nausea and vomiting or pain.[195] Therefore, older adult cancer patients are at a higher risk of drug-related care issues when compared to the general older population.[196] The influence of polypharmacy on cancer treatment outcomes has not been extensively studied in the literature. This likely reflects the general ideology that treating cancer is a clinical priority as long as other comorbidities are considered manageable. Unfortunately, oncologists occasionally prefer not to modify medications other than chemotherapeutic agents unless there are actual (instead of potential) drug-related care issues.[197]

There is a lack of published articles investigating polypharmacy among breast cancer patients in the literature. A recently published study showed that 50% and 74% of younger and older (aged 65 years and above) patients with breast cancer are using five medications or more.[198] In addition, the previously discussed OMEGA study

confirms that polypharmacy is associated with a significantly increased risk of chemotherapy-related toxicity.[193] Statistics show that 57% and 17% of older patients using five medications or more and four medications or less, respectively, experience grade 3-4 chemotherapy-related toxicity (p-value= 0.001).[193]

Besides, older cancer patients are at potential risk of drug-drug interactions between chemotherapeutic agents and other chronic medications.[199] For example, the anticoagulant effect of warfarin may increase if co-administered with paclitaxel, necessitating regular monitoring of INR and dose adjustment of warfarin as needed.[199] Also, cyclophosphamide may decrease digoxin absorption, compromising its efficacy in managing heart failure or atrial fibrillation.[200] Besides, methotrexate is associated with a wide range of drug-drug interactions, including commonly prescribed drugs such as amoxicillin, aspirin, esomeprazole, and diclofenac.[200-204]

To overcome the previously discussed polypharmacy-related care issues, oncologists and pharmacists can identify and evaluate potentially inappropriate medication in older patients using STOP/START, Beers, or MAI (Medication Assessment Index) criteria.[205-207] Also, online computer softwares, such as LexiComp, are available to predict drug-drug interactions.[208] This enhances medications utilization and modification during cancer treatment.

1.5 The rationale for conducting this research in Kuwait

The literature suggests that intensive treatment protocols are associated with superior survival outcomes among breast cancer patients despite age. However, intensive protocols precipitate a wide range of toxicity, including gastrointestinal, haematological, and cardiotoxicity. This raises concerns about treatment tolerance and

compliance among patients with comorbidities or poor performance status. The guidelines recommend against allocating patients at toxicity risk for intensive treatment regardless of age but do not provide standardized guidance to assess the toxicity risk in the clinical practice.[156] Treating older patients remains challenging because advanced age is associated with physiological changes and comorbidities that are not uniform among the elderly. While selected older patients look fit and can tolerate intensive treatment to a similar to their younger counterparts, other patients may seem vulnerable. The oncology practice guidelines recommend assessing individual performance status to predict patients' eligibility for intensive treatment. However, information on allocating patients with advanced age or comorbidities is not clearly stated. As a result, allocating such cases resides on individual oncologists' decisions.

There is an ongoing debate about the feasibility of assessing cancer patients based on their performance status score alone. This is because it does not provide comprehensive information about patients' functional status, leading to over-estimate or under-estimate patients' eligibility for intensive treatment. Besides the performance status score, oncologists consider increased comorbidity burden and polypharmacy unfavorable factors contributing to intensive treatment intolerance, increasing the requirements for treatment modifications and discontinuation. Differences in the prevalence of less intensive systemic treatment allocation and the contributing factors between younger and older patients remain unclear and may vary across different cancer centres around the world.

There is a general lack of information about managing cancer patients in Kuwait. This is the first research aiming to investigate systemic treatment allocation patterns among

breast cancer patients and establish the differences in baseline patients' and tumour characteristics between patients aged 60 years and above and younger patients. It is crucial to identify the factors contributing to less intensive treatment allocation and understand the difference by age to provide a representation of breast cancer patients' baseline assessments and management in the clinical practice in Kuwait.

1.6 Present research study

1.6.1 Aim

This research aims to investigate the differences in the baseline assessment factors contributing to less intensive systemic treatment allocation between patients aged 60 years and above and younger patients with breast cancer in Kuwait.

1.6.2 Objectives

- Investigate the differences in the baseline patients' characteristics (performance status, comorbidity burden scores, polypharmacy, and BMI) and tumour histological and molecular characteristics between patients aged 60 years and above and younger patients (Figure 1.6).

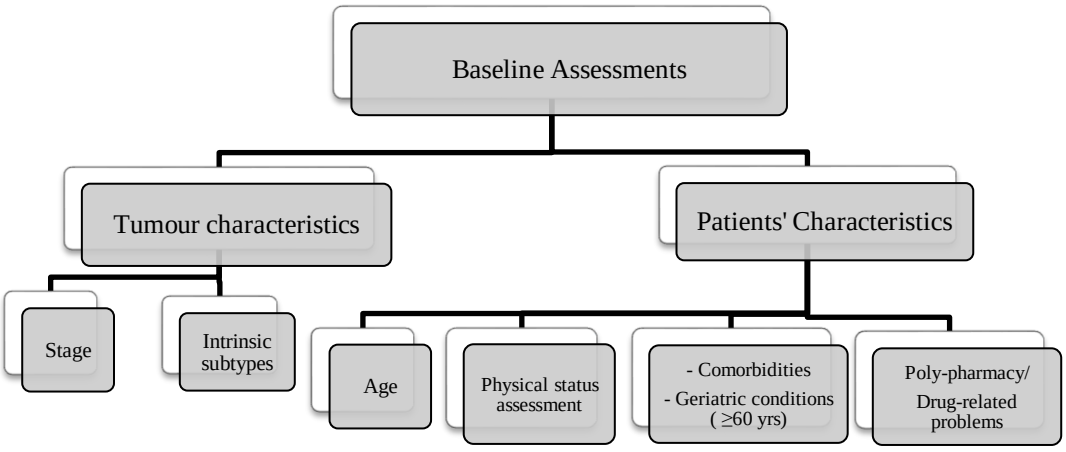

Figure 1.6 Baseline assessment of potential factors that may impact the decision-making process of treating breast cancer patients.

- Identify the baseline factors contributing to less intensive treatment allocation in clinical practice.
- Compare the baseline factors contributing to less intensive treatment allocation between patients aged 60 years and above and younger patients.
- Quantify and compare the consequent requirements for treatment modification and deviation between the two age cohorts.
- Quantify and compare the consequent outcomes (toxicity profile and disease control) between the two age cohorts.
- Conduct a subgroup analysis within the older age cohort to compare the outcomes of receiving intensive versus less-intensive chemotherapy protocols.
- Quantify the prevalence of patients' interference, manifested by rejecting or delaying chemotherapy, with the the treatment plan.
- Explore and document the causes of patients' interfering and requesting less intensive treatment through a short semi-structured interview.

CHAPTER 2

METHODS

2. METHODS

2.1 Study design and patients' criteria

In a comparative population-based observational prospective cohort study, a total of 180 breast cancer patients were randomly selected, included and divided into two cohorts according to their age (<60 yrs or ≥60 yrs). Patients aged 60 years and above were considered elderly according to the Ministry of Health (MOH) of Kuwait criteria and Kuwait Cancer Control Centre (KCCC) guidelines. Principle characteristics of patients included were: newly diagnosed stage II-IV breast cancer patients aged 21 years and above and candidates for chemotherapy (did not receive chemotherapy before) who could communicate in either Arabic or English. All patients provided written informed consent to allow retrieving their medical notes during the study period (Appendix 1). On the other hand, patients excluded were: those not eligible for chemotherapy, refused chemotherapy, received chemotherapy before, or preferred to be treated abroad. Besides, patients with a previous history of tumours and pregnant patients were excluded.

Patients from each age cohort were grouped based on the treating oncologists' decision of receiving either intensive first-line chemotherapy (standard protocol) or less intensive/ other than first-line chemotherapy (non-standard protocol) according to Kuwait cancer guidelines, which follow standardized international guidelines recommendations (ESMO and NCCN guidelines; Figure 2.1).

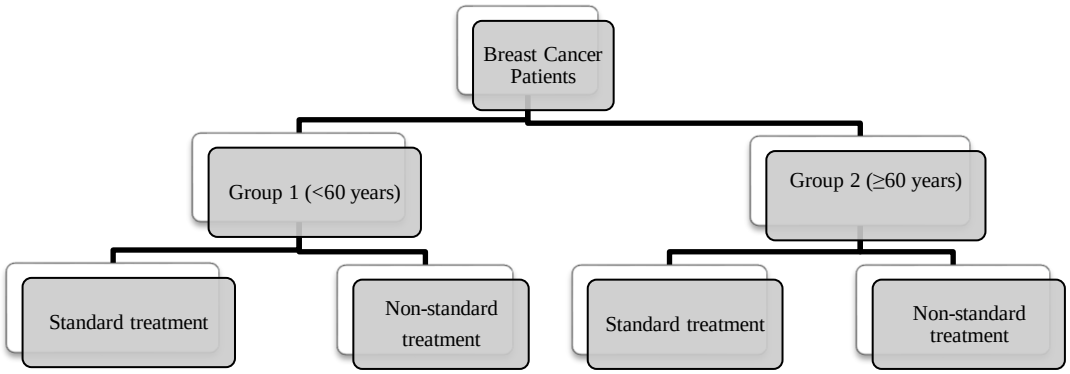

Figure 2.1 Patients' cohorts

Standard (intensive) and non-standard (less-intensive) treatment protocols for non-metastatic breast cancer cases are described in Figure 2.2. Standard palliative treatment for metastatic patients included first-line systemic chemotherapy, while non-standard treatment included either less-intensive systemic chemotherapy or targeted monotherapy (complete omission of systemic cytotoxic chemotherapy).

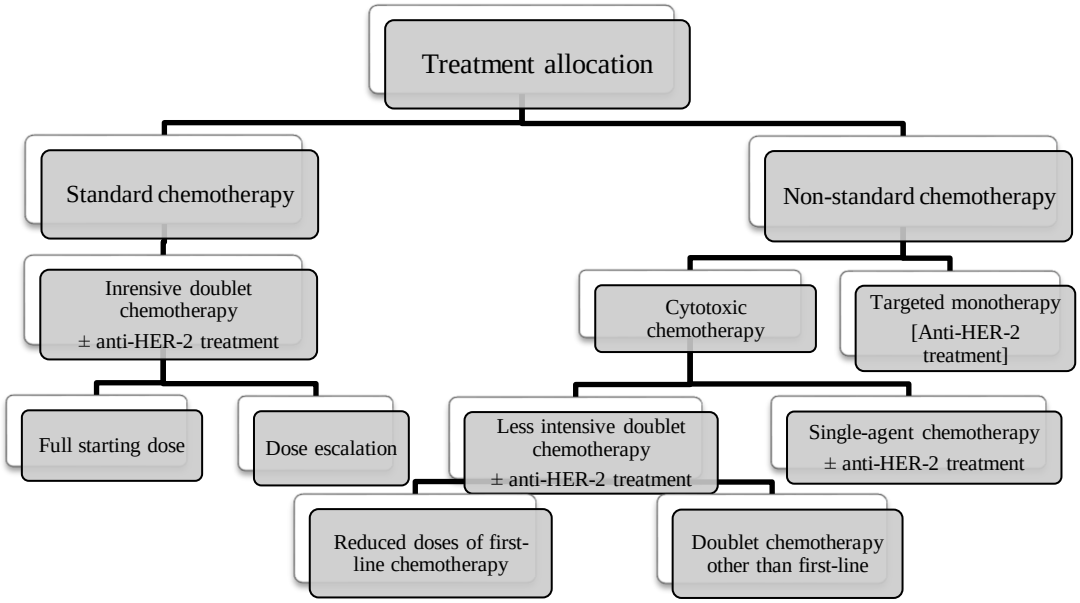

Figure 2.2 Describing treatment allocation patterns for non-metastatic breast cancer patients in our study

Patients allocated for treatment other than first-line protocol or reduced doses of the first-line protocol were included in the non-standard treatment allocation arm. This is

because landmark studies demonstrated that full doses of first-line treatment contributed to superior therapeutic and survival outcomes compared to less intensive doses or treatment protocols other than first-line, as discussed in section 1.4.4.3.1. Beyond treatment allocation, treatment modification or deviation from the initial allocated intensive protocol were not considered less intensive treatment allocation, as patients started their treatment as candidates for intensive treatment protocols. The requirement for treatment modification (dose reduction, dose delay, or both) or treatment deviation were described separately as a part of treatment tolerance rather than treatment allocation.

The prospective cohort study is an appropriate design of observational studies and a powerful source of clinical data used to follow and compare two patients' cohorts to determine the incidence rate of particular outcomes and establish correlations. As this research aimed to investigate the baseline factors contributing to less intensive treatment allocation among breast cancer patients and detect the differences by the age factor without interfering with the decision-making process, it was decided to conduct an observational prospective cohort study because it would fit the nature of data of interest and answer the research questions. Besides, the prospective design allowed following and monitoring the two age cohorts during systemic cancer treatment and documenting the subsequent treatment outcomes, modifications, and deviations.

A quantitative approach was used to describe the characteristics of the two age cohorts and measure the differences in multiple variables that could differ by age and affect the treatment allocation. Besides, the prevalence of patients' interference with the recommended treatment, manifested by rejecting or delaying chemotherapy, was quantified. A short semi-structured interview was conducted to explore the

contributing factors for interfering with the treatment plan by asking patients about the causes.

2.2 Study population

At the start of the PhD research, it was hoped to recruit patients with the most commonly occurring cancers in Kuwait and worldwide, including breast, colorectal, and lung cancers. The estimated number of patients to be included was around 600 patients based on previous incidence data from the Kuwait Cancer Registry. However, the patients' journey in KCCC was complicated and challenging for including different types of solid tumours. Section 2.2.1 briefly explains how cancer patients proceed through the cancer care delivery system in KCCC, which is referred to as "Process Mapping," and mentions the leading factors to focus on breast cancer patients while excluding patients with other tumours.[209]

2.2.1 Process mapping

A series of steps that are captured in a diagram to show the activities, tasks, connections, and individuals involved in a specific procedure is called a process map.[210, 211] This method is essential in healthcare systems to visualize patients' journey that includes diagnosis, treatment, and referrals to assess the time required to complete each procedure, bottlenecks in the system, and identify the source of errors or delays. Within Kuwait, the cancer care system is centralised and divided into five buildings: medical oncology, surgical oncology, radiology, nuclear medicine, and palliative care centre [Best Supportive Care Centre (BSCC)]. All buildings that provide cancer care services are connected to the main KCCC building, except for BSCC, which is located

in a separate building and provides palliative healthcare services for end-stage cancer patients who are not receiving any active cancer treatment.

2.2.1.1 New case clinic and patients' recruitment

Cancer patients are usually diagnosed with tumours or suspicious lesions in general hospitals, where they undergo multiple laboratory tests, radiological investigations, and biopsy if possible. Then, they are referred to the outpatient medical oncology department in KCCC. Patients attend first with referral notes to book appointments in the new case clinics, which are divided into six main units based on the primary tumour type: breast cancers, gastro-intestinal cancers, thoracic cancers, gynaecological cancers, haematological cancers, and lymphomas. Besides, a separate unit called "other tumours" includes less common and rare cancers, such as melanomas, head and neck cancers, neuroendocrine cancers, CNS cancers, and cancers of unknown origin. This clinic is carried out occasionally if there is a new case; otherwise, it is not scheduled. Patients usually meet an oncologist after two to three days of booking their appointment in the OPD.

The new case clinics from all oncology units are carried out concomitantly twice a week by different oncologists. This created the main barrier that led to missing a large number of patients as I could attend only one clinic at a time. Besides, the expected number of patients to be seen by the oncologist in each new case clinic was four to six patients; however, not all the new cases met the inclusion criteria discussed previously in section 2.1 for research purposes. Initial attendance at the various new case clinics indicated low numbers of patients in gastrointestinal and thoracic clinics. In contrast, large numbers of patients were observed in the breast cancer clinic, with many

matching the inclusion criteria. Therefore, I decided to focus on a single cancer type and recruit patients from the new case breast cancer clinic only.

The first meeting with individual patients in the new case clinic took 40-45 minutes to perform a complete case assessment, clinical examination, and history (medical, social, and occupational) documentation. Also, it included general counseling about the nature of the disease and treatment options. The exact treatment regimen and potential side effects were not discussed until the case was presented and discussed in the multi-disciplinary team (MDT), usually after one to two days of the new case clinic (Figure 2.3).

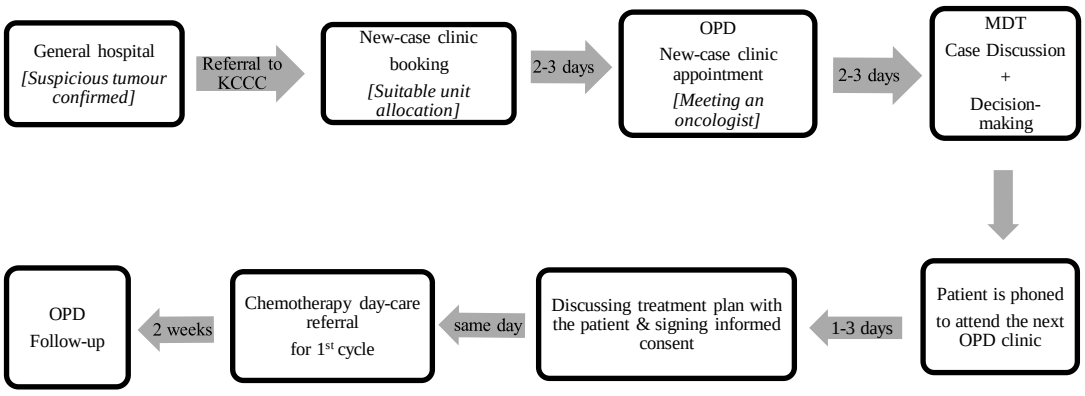

Figure 2.3 Journey map of patients undergoing chemotherapy in KCCC

2.2.1.2 MDT case discussion and chemotherapy day-care referral

After initial assessments, new cases were discussed during the MDT meeting, which was carried out once weekly in the thoracic unit, and twice weekly in the breast and gastrointestinal units. The MDT was led by a senior oncologist and involved a group of healthcare professionals, including oncologists from the same cancer unit, a

radiologist, and a pathologist. A specialist surgeon attended the MDT case discussion if patients were candidates for tumour resection and expected to receive chemotherapy. During the MDT meeting, all investigations and reports were presented and reviewed. The radiologist presented the available x-rays, CT scans, PET scans, and/or MRIs. The pathologist presented and discussed tissue samples biopsied from the tumour site. Then the treating oncologist suggested a suitable individualized treatment protocol based on the comprehensive discussion, and the senior oncologist approved it. After that, patients were phoned to be informed about the unit decision, and the first chemotherapy dose was booked accordingly with the next OPD appointment by a nurse. Within two days, patients attended the regular OPD clinic to discuss their treatment regimen with more details about the dose, duration, and common side effects. Afterward, they signed informed consent forms indicating their awareness about potential treatment therapeutic outcomes and side effects. In case patients agreed to the offered treatment plan, they were usually referred to the chemotherapy day-care ward to receive the first dose within one to two hours, depending on beds' availability.

2.2.1.3 Follow up

Patients' follow-up was based on their scheduled OPD and chemotherapy appointments. Before each chemotherapy dose administration, the complete blood count was checked and approved by a clinician. Then a chemotherapy regimen request was sent to the pharmacy for preparation. Patients usually receive their treatment after one to two hours. In case more laboratory tests were required (for example, renal function test), patients might wait for three hours to have their blood report released and signed, and treatment prepared.

During patients' follow up in the chemotherapy day-care, the new case clinics were carried out concomitantly, which created a challenge in collecting all required data. Retrieving patients' data was achieved using specified patient code, hospital file number, or civil ID number and permitted during the data collection period. Unfortunately, many patients discontinued their treatment in KCCC and transferred to receive treatment abroad. The Ministry of Health of Kuwait offers this option for citizens to receive medical care in the United Kingdom, the United States, or France. As a result, the number of recruited patients continued to decline during data collection. Besides, the Ministry of Health policy changed from 2016 with regard to the healthcare expenses for services provided to non-Kuwaiti residents. Previously, all services in the hospitals were free at the point of delivery and not subject to monetary charges. However, after the amendment of policies, healthcare services (lab tests, scans, and surgical interventions) became chargeable. As a result, many non-Kuwaiti patients returned to their countries to receive cancer treatment. Consequently, many patients were lost at follow-up, dramatically reducing anticipated patient recruitment.

2.2.2 Focusing on breast cancer

Due to the discussed challenges in the cancer care system in KCCC, I decided to focus on breast cancer while excluding data collected from other types of tumours. Recruiting patients from the breast cancer unit afforded the largest number of patients who matched the inclusion criteria and allowed regularly attending the scheduled new case clinics and MDT meetings. As a result, the data collection process became more organised and time-efficient. The decline in the total number of non-citizen patients in the breast cancer unit was relatively less than what was recorded in the lung and

colorectal unit. Probably this was because patients were females who lived with their families in Kuwait and had sufficient social and financial support. In contrast, most non-citizen male patients lived alone and traveled back to their countries after being diagnosed with cancer.

2.3 Ethical approval

Within Kuwait, cancer chemotherapy is centralised and delivered through one hospital, which provides the opportunity to approach most breast cancer patients. The research proposal, including a copy of the informed consent sheet and data collection sheets, was submitted to the research committee in the Ministry of Health (MOH) of Kuwait and discussed during the committee regular meeting to authorize data collection and provide access to relevant computerized and non-computerized reports. Research approval (No. 303/2015) was obtained from the research committee on the 26th of October, 2015 (Appendix 2). Accordingly, a professional ID was issued to authorize accessing all KCCC buildings, including the filing room. Besides, the medical oncology department issued a letter allowing OPD clinics attendance for data collection. Before each clinic, I took the oncologist's permission to join the discussion and offer research participation (with signing informed consent) for patients matching the inclusion criteria. Also, I took permission to ask questions for the patients and relatives/caregivers when required.

2.4 Data collection

After research approval and oncologists' permission were granted, data was collected prospectively from the breast cancer clinics and documented manually in individualized data collection forms using individual patients' case notes between April 2016 and April 2019 (Appendix 3). Quantitative data included patient demographics, family history of tumours, histopathology, radiology, biochemistry, and haematology lab reports. In addition, data collection included baseline assessments, treatment allocation, toxicity profiles, requirements for treatment modification or deviation, and treatment outcome. In addition, oncologists' causes of offering less intensive treatment were explored and documented through a short semi-structured interview during the clinic. Similarly, patients' causes for requesting less intensive treatment were documented.

2.4.1 Baseline assessment and treatment allocation

Factors affecting the process of individual patient treatment allocation (baseline patients and tumour characteristics) were observed and documented. The subsequent allocated treatment plans were also documented without interfering with the treating oncologists' decisions. Besides, patients' causes for interfering with the recommended treatment by their oncologists and requesting less intensive treatment were explored and documented through a short semi-structured interview during the clinic.

In addition, individual patient comorbidity burden, age-related (geriatric) conditions, performance status, and anaemia, were documented during baseline assessments from patients' discussion and medical notes (Table 2.1).

Table 2.1 Patients' assessment tools applied in the present study.[68, 71, 160, 214]

Assessment	Method
Performance status	The Eastern Cooperative Oncology Group (ECOG)
Geriatric conditions	American Society of Clinical Oncology (ASCO) guidelines
Cardiotoxicity	ESMO Guidelines and recommendations
The 10-year risk of heart disease or stroke estimator	The athero-sclerotic cardiovascular disease (ASCVD) risk estimator.
Anaemia classification	NCI grading system

Baseline comorbidities were identified and documented based on individual patient medical history using patients' medical case notes. Common age-related conditions (geriatric conditions) were identified according to the ASCO Geriatric Oncology Expert Panel guidelines and scored as absent or present (pre-cancer diagnosis) based on individual patient medical history and not assessed by the oncologist at baseline.[68] This included cognition status (depression, dementia, and delirium), osteoporosis, hearing impairment, vision impairment, falls, nutrition, sleep disorders, incontinence, and chronic pain.[68] The aim of extracting these data was to assess the general health condition of older patients and predict their eligibility for cytotoxic treatment.

Besides comorbidities and geriatric conditions, poly pharmacy was investigated during the new-case clinic. Oncologists ask the patients about the chronic medications they consume and their compliance, which was documented in the research data collection sheets accordingly. In addition, drug-Related Problems (DRP) and Potentially Inappropriate Medication (PIM) among breast cancer patients were identified based on the Medication Appropriateness Index (MAI) and START/STOP criteria before starting systemic treatment (Table 2.2). Inappropriate medication use among older patients was considered a domain of drug-related problems.

Table 2.2 Baseline medication assessment [55, 206, 215]

Drug-related problems domains	Categories	Assessment Criteria
Indication	Unnecessary drug Needs additional drug (undiagnosed condition)	Medication Appropriateness Index (MAI)
Effectiveness	Ineffective drug/ dose (uncontrolled condition)	
Safety	Adverse drug reaction High dose Drug-drug interaction	
Compliance	Non-compliance	
Potentially Inappropriate Medication	Efficacy and safety	STOP/ START Criteria

Besides patient characteristics assessments, tumour characteristics were assessed based on individual histopathological and molecular reports (Table 2.3).

Table 2.3 Baseline tumour characteristics assessment

Tumour characteristic	Category
Stage	TNM score
*HER-2 and HR overexpression	HR +ve/ HER-2 +ve HR -ve/ HER-2 +ve HR +ve/ HER-2 –ve HR -ve/ HER-2 –ve
Ki67% Proliferative Index	≥ 14% ≥ 30%

*HR: Hormonal overexpression
HER-2: Human Epidermal Growth factor overexpression

2.4.2 Treatment-induced toxicity

Patients had regular appointments with their treating oncologists every three weeks to assess treatment toxicity and monitor Renal Function Test (RFT) and Liver Function Test (LFT). The Complete Blood Count (CBC) was monitored before each chemotherapy dose. Treatment-induced toxicity was documented accordingly based on individual medical notes and included non-haematological toxicities, haematological toxicities, and hypersensitivity reactions (Table 2.4).

Table 2.4 Treatment-induced toxicities assessed in the present study

Toxicities Profiles	
Non-haematological	Fatigue Nausea Vomiting Bowel movement changes Loss of appetite Weight loss Mucositis Skin and nail changes Neurotoxicity Cardiotoxicity Depression
Haematological	Neutropenia Thrombocytopenia Anaemia

Data collection started from the first meeting in the new case clinic and continued until the last dose of systemic treatment. Chemotherapy was delivered within three to six months after a non-metastatic breast cancer diagnosis and continued with different protocols for metastatic patients for life; trastuzumab was the only treatment delivered during 12-months for metastatic and non-metastatic patients. Therefore, data were identified and collected during 12 months for all patients and not affected by deaths incidence, as the first death occurred after 15 months of a breast cancer diagnosis. According to the clinical practice guidelines, non-metastatic patients were followed post-remission in the OPD every three or six months for routine lab reports and annual mammograms for the first two years. No related data were collected during follow up unless disease recurrence was detected (relapse incidence). On the other hand, data of interest (baseline characteristics and toxicity outcomes) for metastatic patients were documented based on the initially allocated treatment protocol within three-12 months and not combined with treatment outcomes data after deviating to different treatment protocols, as metastatic patients receive subsequent single-agent chemotherapy protocols until disease progression or intolerable toxicity for life.

Identifying patients with treatment-induced depression was challenging as assessment tools, such as the Mini-Mental State Exam (MMSE), could not be applied due to restrictions in the policy and resources. Therefore, I relied on individual medical notes to identify patients considered to have depression by their treating oncologists and referred to a specialized clinic called the "hope clinic" to manage the collateral mental and emotional side effects of the disease and treatment. Cognitive dysfunction, psychiatric disorders, and chronic pain were further assessed and managed in a different department. Occasionally, patients were transferred to the Palliative Care Centre (PCC) for better specialized healthcare services. Unfortunately, their psychiatric medical notes (assessment/ treatment) could not be accessed.

The risk of treatment-induced cardiotoxicity among HER-2 positive patients who were candidates for trastuzumab treatment was estimated at baseline as a part of this research but not routinely assessed in clinical practice of oncology. The athero-sclerotic cardiovascular disease (ASCVD) risk estimator published by the American College of Cardiology (ACC) and the American Heart Association (AHA) was applied at baseline (before starting chemotherapy) to predict the 10-year risk (mild/ moderate/ high) of heart disease or stroke as it was widely used in clinical practice in Kuwait.[214] In accordance with the ESMO guidelines, an event of cardiotoxicity was defined as ≥10% decline in the LVEF from the baseline or reaching a value below the accepted normal limit (<50%).[160] The baseline left ventricular ejection fraction (LVEF) was documented before starting potential cardiotoxic chemotherapies (anthracyclines and/or trastuzumab) and monitored every three months (for 12 months) during trastuzumab therapy but not routinely performed after anthracycline therapy.[160] Occasionally, LVEF assessment was urgently requested for patients exhibiting signs

or symptoms of congestive heart failure (CHF). The number of breast cancer patients who developed cardiotoxicity during trastuzumab treatment was quantified and compared between the two age cohorts to investigate the correlation between advanced age and cancer treatment-induced cardiotoxicity incidence. Besides advanced age, the impact of comorbidity burden, history of hypertension/ diabetes, previous exposure to anthracyclines, and low baseline LVEF on treatment-induced cardiotoxicity was investigated.

2.4.3 Treatment modification and deviation

Treatment modification in the initial treatment was classified as dose delay, dose reduction, or both. On the other hand, the requirement for discontinuing the initial allocated treatment, whether intensive or less intensive protocol, and starting an alternative protocol was referred to as "treatment deviation". Treatment modifications and deviation data were collected from the medical case notes because occasionally, modifications are requested during casualty or the day care ward (even during holidays) by phoning the treating oncologists. Treatment modifications and deviations were quantified to be compared between the two age cohorts.

2.4.4 Disease control

Disease control (therapeutic success) in non-metastatic patients was considered achieving complete remission, while disease relapse post-remission was quantified and presented separately as incidence of relapse. On the other hand, disease control in metastatic patients was considered either achieving tumour regression or stable disease. Disease progression was considered therapeutic failure in both metastatic and non-metastatic patients. The death incidence (all cause mortality) was also quantified. Time to death was calculated as time (months) to an event from diagnosis and

presented as a median time for metastatic and non-metastatic patients. Disease control data were collected from patients' medical records based on the oncologists' notes, which were written based on physical examination or radiology reports.

Data collection was anonymised and excluded identifiable patient information. Data collection sheets were numbered sequentially, and patients' names were recorded with a corresponding code on a separate document (coding sheet) to allow identifying patients for follow up (Appendix 4). Hard data was stored in a filing cabinet in a locked room on hospital premises to ensure confidentially while collecting and retrieving data. The collected data was computerized on a weekly basis and stored on a secure laptop with password protection.

2.5 Research outcomes

This research provided a representation of baseline patients and tumours' characteristics of breast cancer patients aged 60 years and above and younger patients in Kuwait and identified and compared the factors contributing to less intensive treatment allocation between both age cohorts. It was hypothesized that older patients were most likely to receive less intensive breast cancer treatment compared to younger patients despite having acceptable baseline characteristics, which contributed to poor therapeutic outcomes in this population. Also, the research clarified whether similar essential baseline characteristics (performance status and comorbidity burden scores) contributed to different treatment allocations between older and younger.

The secondary outcome of this research was to quantify and compare the consequent toxicity profiles, requirements for treatment modification/ deviation, and disease control between the two age cohorts based on the initial treatment allocation. Also, to

conduct a subgroup analysis within the older age cohort to assess the impact of receiving intensive versus less-intensive chemotherapy protocols on treatment tolerance and outcomes.

2.6 Data analysis

In clinical and scientific studies, descriptive analysis is essential to elaborate on the information and expand the topic by converting data into statistics to generalize the findings to represent the population. Descriptive analysis was performed using Microsoft Excel™ 2016 and Stata version 16. Categorical descriptive variables were expressed as percentages, while continuous variables were expressed using the median because it is less sensitive to extreme values. In addition, the range and interquartile range (mid-spread) were calculated to show statistical dispersion. Chi-square Test was applied to detect statistically significant differences in the categorical variables between two independent age cohorts, while the T-test was used for continuous variables.

Multivariate logistic regression analyses were performed to investigate the association between independent variables (baseline patient and tumour characteristics) and binary treatment allocation (intensive versus less intensive protocols). A subgroup logistic regression analyses were conducted to compare the correlation between specific baseline performance status and comorbidity burden scores between older and younger patients. This approach was conducted to clarify whether patients from the two age cohorts having similar scores were allocated similarly or differently. This predictive method was selected because it could better represent the data and answer the research questions by estimating the correlation between an outcome and one or more

exposures. In addition, the Akaike Information Criteria (AIC) was used for the best statistical model selection and best fit for the data describing baseline factors contributing to treatment-induced cardiotoxicity as recommended by an expert statistician. As evidence on this topic was still emerging, factors contributing to cardiotoxicity were not well described in the literature and could vary between different populations. For clinical significance, multiple variables (baseline factors) were selected (Table 3.19), and the suitability of testing the combination of the variables was statistically confirmed by the AIC method.

A p-value <0.05 was considered statistically significant because it is a widely used and generally accepted threshold in clinical and scientific studies as, unlike clinical trials, researchers do not have control over the data. The power was computed using Stata (two-sided test) based on the study sample size and a significance level of 0.05 and was 0.99.

RESULTS

3. RESULTS

Among all newly diagnosed breast cancer patients in the Kuwait Cancer Control Centre (KCCC), 241 patients from the two new-case clinics matched the inclusion criteria and were recruited during the first 12 months of the study between April 2016 and April 2017. However, only 180 patients were followed until the end of the study period in April 2019 (61 patients were excluded, Figure 3.1).

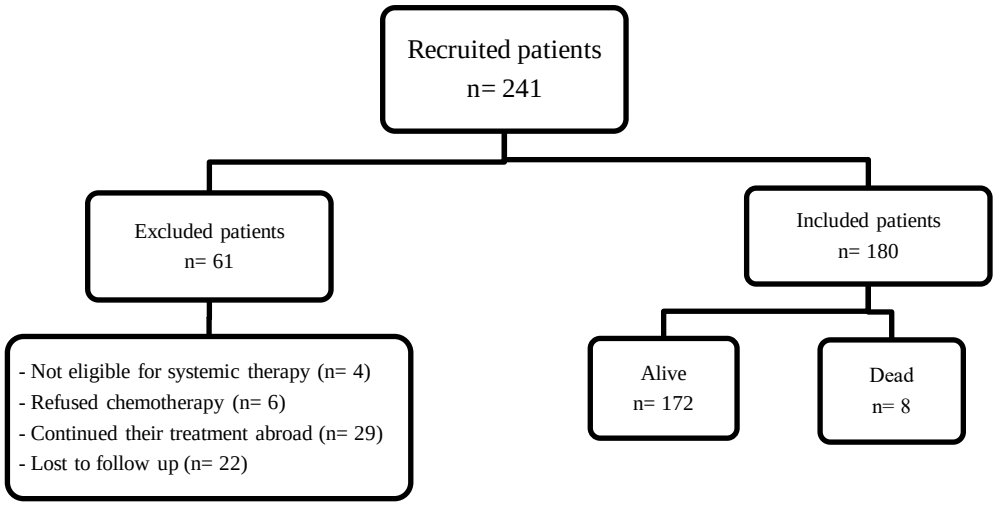

Figure 3.1 The number of patients included/ excluded in this study

Patients were divided into two age cohorts based on their age (Table 3.1). Of the total number of patients, 60 patients were classified as older adults with a median age of 64 years (range 60-83 years), and 120 patients were classified as younger adults with a median age of 45 years (range 22-59 years). Patients were followed up for data collection from diagnosis until the last dose of chemotherapy or death. After completing chemotherapy, patients were followed to report disease relapse incidence only. The median duration of patients' follow-up from diagnosis was 23 months (IQR= 19-27).

Table 3.1. Descriptive statistics of baseline patients and tumours' characteristics in older and younger patients

Patients		Group 1 <60 yrs n= 120	Group 2 ≥60 yrs n= 60	P-Value
Patient Characteristics	Age (years)			
	Median	45	64	
	*IQR	38-51.5	62-68	
	Range	22- 59	60- 83	-
	Nationality: Non-national	36:84	32:28	0.003
	Kuwaiti %	30%	53.3%	
	BMI (kg/m$^{2)}$			
	Median	28.5	28.5	0.22
	IQR	25-32	26-35	
	BMI category n (%)			
	<18.5 [underweight]	1 (0.8%)	0	
	18.5- 24.9 [normal weight]	33 (27.5%)	11 (18.3%)	
	25- 29.9 [overweight]	34 (28.3%)	21 (35%)	-
	≥30 [obese]	52 (43.3%)	28 (46.7%)	
	Family history of malignancy n (%)	40 (33.3%)	19 (30.6%)	0.82
Medical History and Baseline Assessment	Patients with organ dysfunction n (%)	4/120 (3.3%)	7/60 (11.7%)	<0.001
	**Renal	2 (1.6%)	5 (8.1%)	
	Hepatic	1 (0.8%)	1 (1.6%)	-
	Cardiac	1 (0.8%)	1 (1.6%)	
	Lung	0	0	
	Baseline haemoglobin level (g/dL)			
	Median	12	12	
	IQR	11.5- 12.3	11.4- 12.5	0.5
	Range	7.8- 14.6	10- 13.8	
	Patients having at least one comorbidity n (%)	46 (38.3%)	49 (81.7%)	<0.001
	Number of comorbidities			
	Median	1	2	-
	Range	0- 3	0- 5	
	Patients taking at least one medication n (%)	41/120 (34.2%)	46/60 (76.7%)	<0.001
	Number of medications			
	Median	0	2.5	
	Range	0- 4	0- 13	
	Patients with at least one drug-related problem n (%)	15/120 (12.5%)	23/60 (38.3%)	<0.001
	Number of drug-related problems			
	Median	0	0	
	Range	0- 4	0- 5	

Tumour Characteristics	Performance status (PS) n (%)			
	0	116 (95.1%)	45 (72.6%)	
	I	2 (1.6%)	12 (19.4%)	<0.001
	II	2 (1.6%)	2 (3.2%)	
	III	0	1 (1.6%)	
	IV	0	0	
	Metastatic cases n (%)	18 (12.5%)	4 (6.7%)	0.11
	Non-metastatic cases n (%)	102 (85%)	56 (93.3%)	
	TNM stage n (%)			
	I	0	0	
	II	34 (28.3%)	27 (43.5%)	0.046
	III	68 (55.7%)	29 (46.8%)	0.4
	IV	18 (14.8%)	4 (6.5%)	0.12
	Intrinsic subtypes n (%)			
	***HR +ve/ HER-2 +ve	53/120(44.2%)	25/60 (41.7%)	0.75
	HR -ve/ HER-2 +ve	10/120 (8.3%)	5/60 (8.3%)	-
	HR +ve/ HER-2 –ve	39/120 (32.5%)	19/60 (31.7%)	0.9
	HR -ve/ HER-2 –ve	18/120 (15%)	11/60 (18.3%)	0.77
	Histology ****IDC	112 (93.3%)	58 (96.7%)	0.4
	****IMC	8 (6.7%)	2 (3.3%)	
	Others	0	0	
	Ki67 % n (%)			
	≥ 14%	114/120 (95%)	53/60 (88.3%)	0.11
	≥ 30%	83/120 (69.2%)	43/60 (71.7%)	0.73

* IQR: Interquartile Range
** Renal dysfunction, defined as an estimated Glomerular Filtration Rate (eGFR) <60 ml/min/1.73m^2
*** HR: Hormonal HER-2: Human Epidermal Growth Factor Receptor-2
**** IDC: Invasive Ductal Carcinoma
***** IMC: Invasive Mammary Carcinoma

Sections 3.1 and 3.2 will compare the main baseline patients and tumour characteristics in Table 3.1 between the two age cohorts of the study. Understanding the differences in the baseline characteristics and assessments between older and younger patients will demystify the potential factors that could significantly impact the decision-making process of treating breast cancer patients in clinical practice.

3.1 Descriptive comparison of tumour characteristics between younger and older patients

For descriptive analysis, Chi-square Test was applied to detect statistically significant differences in the categorical variables between two independent age cohorts, while the T-test was used for continuous variables.

3.1.1 Tumour stage

On diagnosis, no statistical differences were detected in tumour metastases status between the two age cohorts. The majority of cases were non-metastatic and accounted for 93.3% and 85% of older and younger patients, respectively (p-value 0.11). However, based on the TNM scoring system, a higher prevalence of early-stage breast cancer (stage II) was detected in the older age cohort compared to the younger age cohort (46.5% and 28.3%, respectively; p value= 0.046). Patients with stage I breast cancer were not included in the present study as they were not considered candidates for chemotherapy.

3.1.2 Histological and molecular characteristics

When the intrinsic subtypes (histopathological and molecular characteristics) of breast tumours were compared, no statistical differences were detected between the two age cohorts, with Invasive Ductal Carcinoma (IDC) the most predominant type (93.3% and 96.7% in older and younger patients, respectively; p-value= 0.4). The most common subtype of breast tumours was associated with both hormonal and HER-2 receptor over-expression, and the least common was associated with only HER-2 receptor over-expression (Figure 3.2).

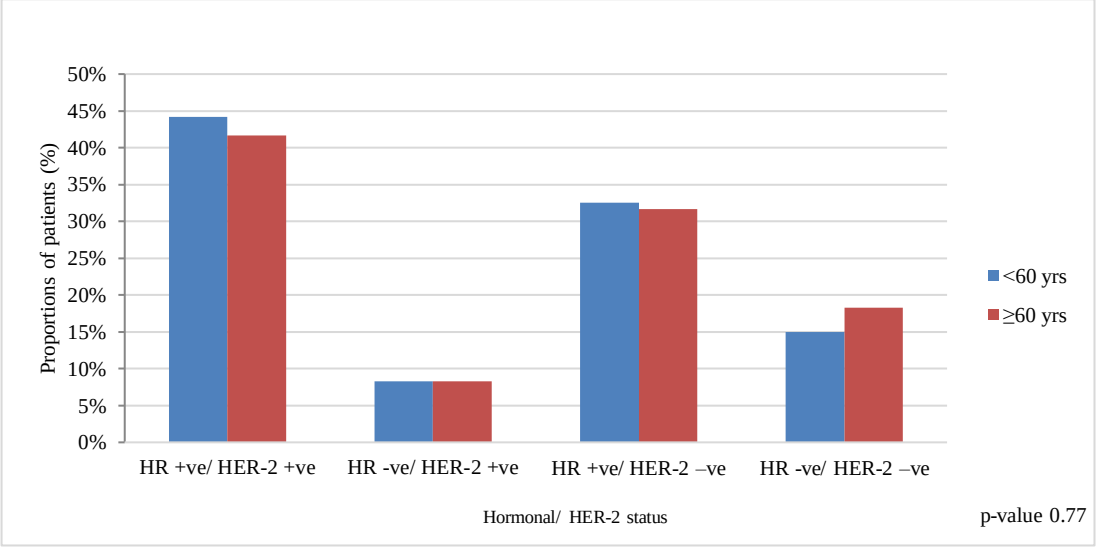

Figure 3.2 Comparing the proportions of hormone and HER-2 receptors expression status between patients from the two age cohorts

The Ki67 proliferation status as ≥14% expression did not differ by age cohort and was detected in 88.3% and 95% of older and younger patients, respectively (p value= 0.11). Similarly, the Ki67 ≥30% expression status did not differ by age cohort (p value= 0.73).

In the present study, histopathological and molecular characteristics of breast tumours did not significantly differ by age cohort. The only significant difference detected was the disease stage at diagnosis, with more advanced tumours detected in younger patients.

3.2 Descriptive comparison of patient characteristics between younger and older patients

Data showed that patients from the two age cohorts had relatively similar Body Mass Index (BMI) (p-value 0.22). When overweight and obesity parameters were combined, a prevalence of 81% in older and 71.3% in younger patients was documented. Similarly, no significant differences were noticed in the patients'

nutritional status (malnutrition/ underweight) between the two age cohorts. Besides the BMI, a positive family history of malignancy did not differ by age cohort at diagnosis.

Regarding nationality, only 37.8% of overall patients recruited into the study from both age cohorts were Kuwait nationals. A significant difference was detected in nationality distribution between the two age cohorts, where 53.3% versus 30% of older and younger patients, respectively, were nationals (p value= 0.003).

3.2.1 Performance status

The majority of patients (n= 161; 89.4%) from both age cohorts had a performance status (PS) of 0, indicating that they were clinically eligible for intensive systemic chemotherapy based on clinical practice guidelines. Older patients had a higher prevalence of poorer performance status (PS ≥1) compared to younger patients (p-value <0.001), which could be attributed to a higher comorbidity burden and organ dysfunction. A very limited number of patients recruited had performance status ≥2 (n=4; two younger metastatic patients and two older non-metastatic patients).

3.2.2 Prevalence of comorbidities and organ dysfunction

The prevalence of breast cancer patients having at least one comorbidity was significantly higher in older patients than younger patients (81.7% and 39.1%, respectively; p-value <0.001). The median baseline comorbidity burden score was two (range 0-5) in older patients and one (range 0-3) in younger patients (Table 3.2). None of the younger age cohort patients had a comorbidity burden score of more than three conditions. In comparison, 13.3% of older patients had a comorbidity burden score of more than three comorbidities.

Table 3.2 Comparing baseline comorbidity burden score between younger and older patients before starting breast cancer treatment

Number of comorbidities	Group 1 (<60 years) n (%)	Group 2 (≥60 years) n (%)
0	73 (60.8%)	11 (18.3%)
1	29 (24.2%)	16 (26.7%)
2	14 (11.7%)	10 (16.7%)
3	4 (3.3%)	15 (25%)
4	0	5 (8.3%)
5	0	3 (5%)
Chi-square test P-value <0.001		

The most commonly documented comorbidities among the two age cohorts were hypertension, diabetes mellitus, and thyroid dysfunction (Figure 3.3). The prevalence of asthma was relatively similar between the two age cohorts. Dyslipidaemia and ischemic heart disease (IHD) were uncommon in the younger age cohort. Other comorbidities, such as rheumatoid arthritis and chronic obstructive pulmonary disease (COPD), were not detected in the present study.

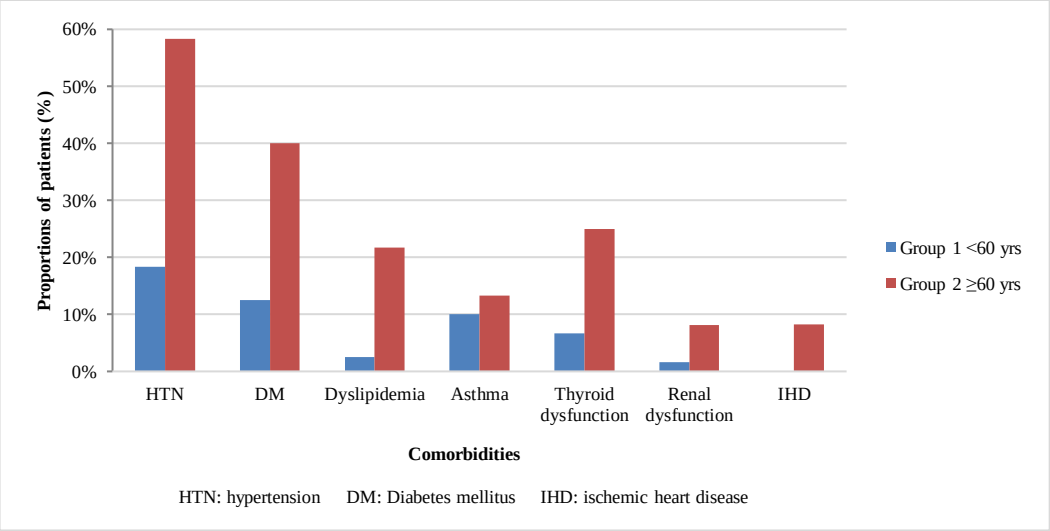

Figure 3.3 Incidence of chronic comorbidities within older and younger patient cohorts before starting breast cancer treatment

The coexistence of diabetes and hypertension at baseline was documented among 17.2% (n=31/180) of patients, accounting for 33.3% (n=20/60) of older patients and 9.2% (n=11/120) of younger patients. Besides comorbidities, older age was associated

with a higher prevalence of organ dysfunction (11.7% and 3.3% in older and younger patients, respectively). Renal dysfunction, defined as an estimated Glomerular Filtration Rate (eGFR) <60 ml/min/1.73m^2, was the most common organ dysfunction documented amongst both age cohorts and occurred in 8.1% and 1.6% of older and younger patients, respectively.

3.2.3 Geriatric conditions among older patients

Age-related health conditions (geriatric conditions) were identified according to the ASCO Geriatric Oncology Expert Panel guidelines and scored as absent or present (pre-cancer diagnosis) based on individual patient case notes and not assessed by the oncologist at baseline (section 2.4).[112] Results showed that the majority of older patients (n= 43; 71.7%) had good general health and normal functional reserve (no limitations) that was considered comparable to their younger counterparts. However, around 18.3% of older patients had some degree of age-related functional/physical limitations (Figure 3.4).

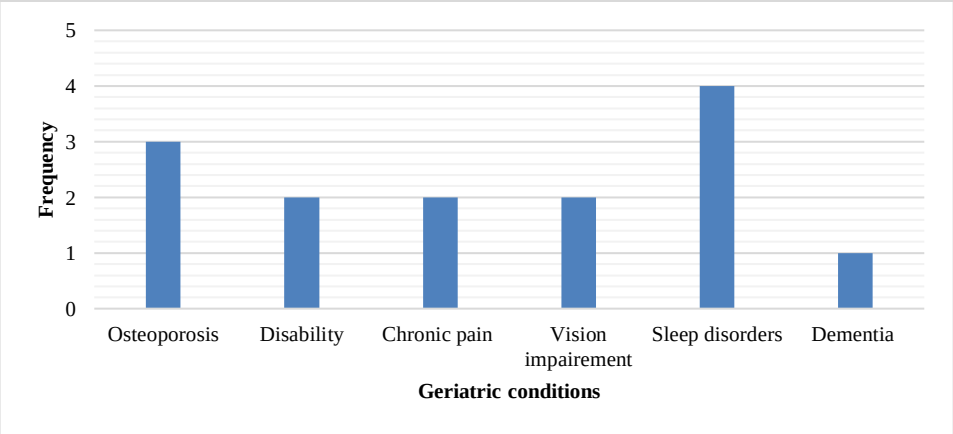

Figure 3.4 Incidence of geriatric conditions documented among older patients before starting breast cancer treatment

The most commonly documented geriatric conditions among older patients were sleep disorders and osteoporosis. Vision impairment, chronic pain, physical disability, and dementia were also documented.

3.2.4 Prevalence of polypharmacy and drug-related problems

The number of patients consuming at least one medication (before starting breast cancer treatment) represented 76.7% and 37.5% of older and younger patients, respectively (p-value <0.001). Polypharmacy, defined as taking ≥5 medications, was reported in only 20% (n= 12) of older patients. In comparison, none of the younger patients took five medications or more.

It was expected to have a pattern of medication burden in the two age cohorts parallel to the pattern of comorbidity burden. The proportions of patients taking between one to three medications did not differ by age cohort (p-value= 0.3). However, a higher proportion of patients taking more than three medications was observed in the older age cohort compared to the younger age cohort (Figure 3.5).

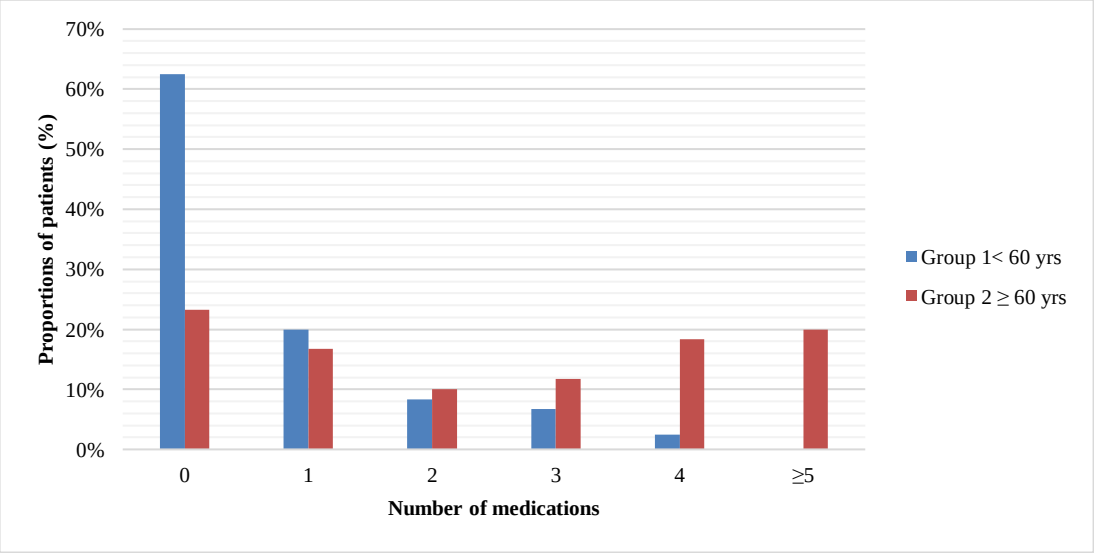

Figure 3.5 Comparing the proportions of younger and older patients based on the number of chronic medications consumed before starting breast cancer treatment

Drug-Related Problems (DRP) and Potentially Inappropriate Medication (PIM) among breast cancer patients in the present study were identified based on the Medication Appropriateness Index (MAI) and START/STOP criteria (Table 2.2). Inappropriate

medication use among older patients was considered a domain of drug-related problems. The total number of patients with at least one drug-related problem (before starting breast cancer treatment) represented 21.1% of all recruited patients. A significantly higher prevalence of medication consumption in older patients contributed to a higher prevalence of drug-related problems when compared to younger patients (38.3% versus 12.5%, respectively; OR 5.48, p-value <0.001).

The most common drug-related problems in both age cohorts were uncontrolled conditions (categorised as effectiveness drug-related problems), undiagnosed conditions (categorised as indication drug-related problems), and non-compliance (Figure 3.6). Adverse drug reactions (categorised as safety drug-related problems) were the least common.

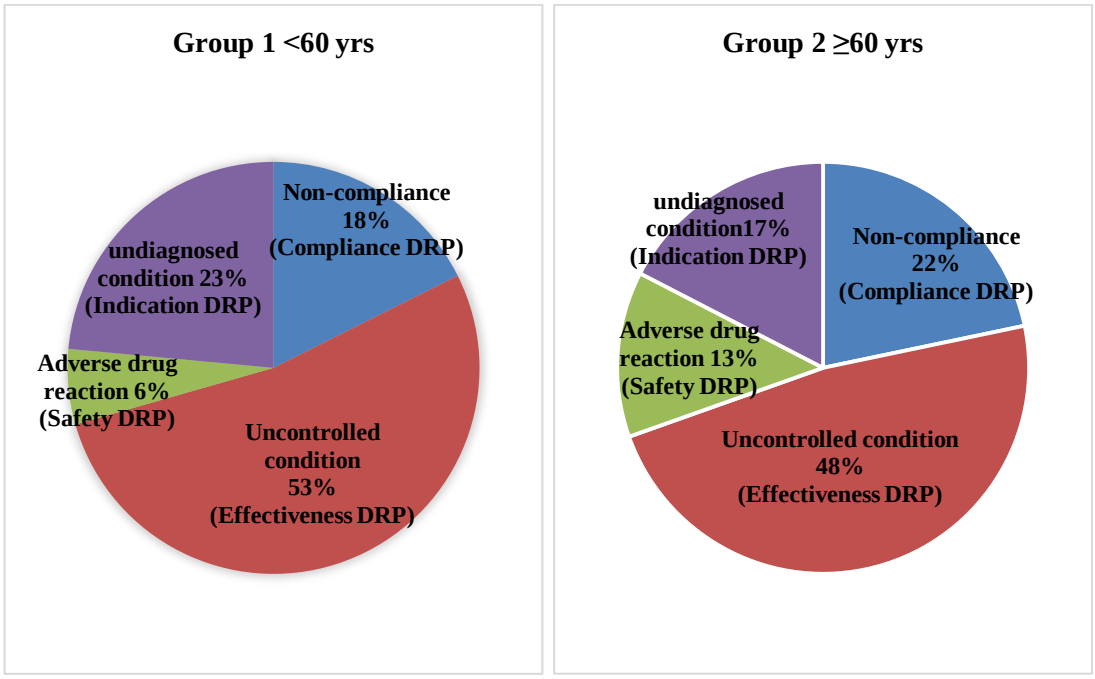

Figure 3.6 Comparing the most commonly documented drug-related problems (DRP) between younger and older breast cancer patients before starting breast cancer treatment

Uncontrolled diabetes (HbA1c ≥6%) was the most documented effectiveness drug-related problem among both age cohorts, followed by uncontrolled hypertension

(blood pressure ≥140/90 mmHg). Diabetes was documented among 40% (n=24/60) of older patients and 37.6% (n=9/24) were considered uncontrolled. In comparison, diabetes was documented among 12.5% (n=15/120) of younger patients, and 40% (n=6/15) were considered uncontrolled. On the other hand, hypertension was documented among 60% (n=36/60) of older patients and 16.7% (n=6/36) were considered uncontrolled. In comparison, hypertension was documented among 18.3% (n=22/120) of younger patients, and 9.1% (n=2/22) were considered uncontrolled.

Besides, relatively higher prevalence of drug-adverse events (safety drug-related problems) was reported in older patients when compared to younger patients before starting breast cancer treatment (13% and 6%, respectively). The most documented drug-related adverse events among both age cohorts were NSAID-induced gastric pain and ACE inhibitors-induced cough.

Overall, baseline assessments demonstrated that older age was associated with significantly worse performance status, higher prevalence of comorbidities, medication consumption, and drug-related problems compared to younger patients.

3.3 Treatment allocation

Data showed that patients aged 60 years and above had a significantly higher percentage of recipients receiving less intensive chemotherapy when compared to younger patients (Table 3.3).

Table 3.3 Comparing the proportions of patients allocated for intensive and less intensive treatment between the two age cohorts

Treatment	Group 1 <60 yrs	Group 2 ≥60 yrs
Intensive treatment n (%)		
Total	114/120 (95.1%)	35/60 (58.3%)
Reduced Starting dose	5/114 (4.4%)	2/35 (5.7%)
Less intensive treatment n (%)		
Total	6/120 (4.9%)	25/60 (41.2%)
Reduced Starting dose	0	0
P-value <0.001		

The most commonly documented standard intensive chemotherapy protocol in managing metastatic patients was a full dose of taxane monotherapy. Only two metastatic patients received intensive doublet anthracycline-based chemotherapy for potentially curable stage IV breast cancer. On the other hand, doublet anthracycline-based chemotherapy (mainly doxorubicin) was the intensive standard of care in managing non-metastatic patients. While younger patients received anthracyclines in a dose-dense (bi-weekly) interval schedule, older patients received it in a standard dose (every 3 weeks) interval schedule. PEGylated doxorubicin-based chemotherapy was indicated for recurrent or metastatic breast cancer management but not detected in the present study. Instead, epirubicin was prescribed for two patients relatively decreasing the cardiotoxicity risk.

A limited number of patients (n=7) from both age cohorts received a reduced starting dose (80% of the anticipated full dose) of standard intensive chemotherapy before the dose was subsequently escalated. The dose-escalating strategy was offered based on a previous agreement between the treating oncologists and selected patients who were considered eligible for intensive treatment but exhibited toxicity concerns. This strategy assisted in evaluating patient tolerance and encouraging patients to receive standard intensive chemotherapy if their initial preference was to receive less intensive

chemotherapy. Dose escalation was not detected among patients allocated for less intensive chemotherapy in the present study.

3.3.1 Patterns of less intensive treatment allocation

The non-standard treatment allocation arm included less intensive doublet chemotherapy (taxane-cyclophosphamide or epirubicin-cyclophosphamide combinations), single-agent chemotherapy (taxane monotherapy) ± targeted treatment, or a complete omission of cytotoxic chemotherapy (section 2.1, Figure 2.2).

Data showed that less intensive treatment was detected in chemotherapy allocation but not targeted treatment allocation. Among older patients allocated for less intensive treatment, no significant differences were detected in the proportions of patients allocated for less intensive doublet chemotherapy and single-agent chemotherapy (17% and 20%, respectively). Among older patients allocated for single-agent chemotherapy, two patients delayed initiating chemotherapy. On the other hand, the number of patients allocated for less intensive treatment from the younger age cohort was too small (n=6) to be stratified by treatment patterns and analysed. However, the treatment allocation pattern was comparative to older patients and equally distributed between less intensive doublet and single-agent chemotherapy (Figure 3.7). In comparison, none of the younger patients delayed initiating chemotherapy.

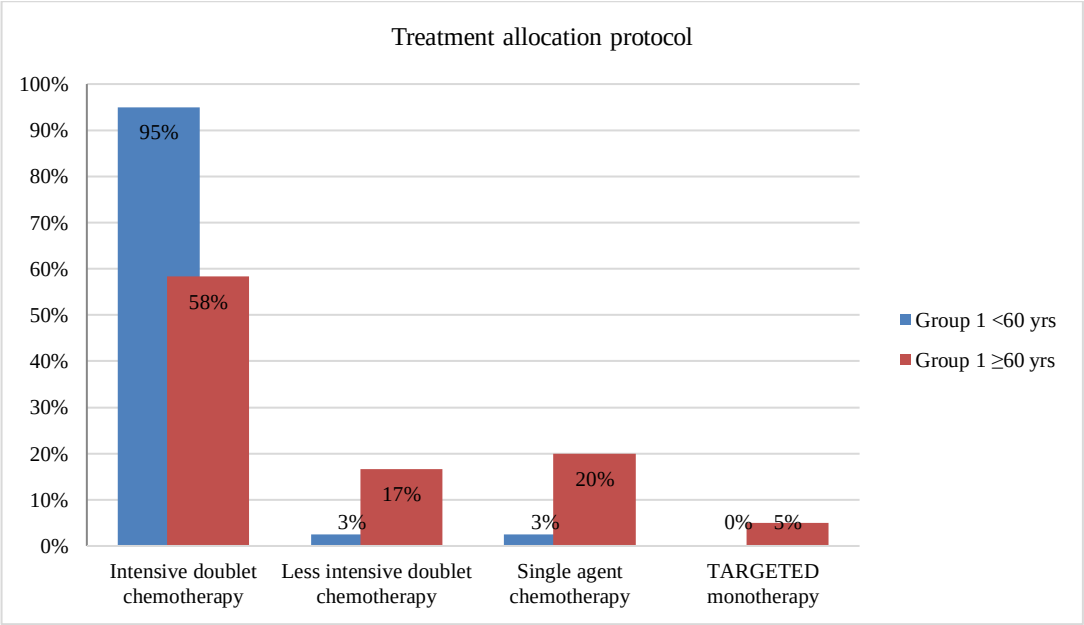

Figure 3.7 Comparing the proportions of intensive and less intensive treatment allocation patterns between younger and older breast cancer patients

Only two selected older patients were considered ineligible for cytotoxic chemotherapy and allocated to receive anti-HER-2 targeted monotherapy. Frail patients who were ineligible for either cytotoxic chemotherapy or targeted therapy (negative for receptor expression) were not included in the present study as they did not receive active treatment for managing breast cancer and were transferred to the Palliative Care Centre (PCC).

3.3.2 Investigating the factors correlated with less intensive treatment allocation

In multivariate regression analysis, chronological age, performance status score and number of comorbidities were significantly associated with less intensive treatment allocation (Table 3.4). In contrast, BMI, TNM stage at diagnosis, and the status of tumour metastasis were not correlated with treatment allocation.

Table 3.4 The correlation between baseline assessment factors and intensive treatment allocation

Characteristics	Odd Ratio	95% CI	p-value
Age (≥60 years)	0.16	0.52-0.049	0.001
Performance status (PS ≥1)	0.24	0.091-0.65	0.005
Number of comorbidities	0.64	0.42-0.99	0.042
BMI	1.02	0.93-1.11	0.7
TNM stage	0.58	0.92-1.11	0.21

Reference group: Intensive treatment allocation

Baseline factors significantly associated with less intensive treatment allocation will be discussed independently.

3.3.2.1 Performance Status

Multivariate logistic regression analysis detected a significant association between baseline performance status (PS) ≥1 and less intensive treatment allocation among patients from both age cohorts after adjusting for disease stage and number of comorbidities (p-value 0.005). Among the older age cohort, all patients with a PS ≥1 (n=15) were allocated for less intensive treatment (Table 3.5). According to their medical history, all patients had at least one comorbidity (median= 3, range 1-5). The under treatment was clearly justified in five patients with organ dysfunction (three had renal dysfunction, one had renal and hepatic dysfunction, and one patient had cardiac dysfunction). Seven patients were considered at risk of cardiotoxicity. Among this subgroup of patients, one death occurred during the study period, and five cases had treatment failure (not achieving disease control).

The number of younger patients with a PS ≥1 was too small (n=4) to be stratified by treatment allocation and analysed, making an informative statistical comparison between the two age cohorts impossible. However, three of the four younger patients with a PS ≥1 were allocated for less intensive treatment.

Table 3.5 Treatment allocation distribution among older patients based on baseline performance status score

Performance status	Frequency n (%)	Intensive vs Less intensive Treatment n (%)
PS= 0	45 (75%)	36/45 (80%) vs 9/45 (20%)
PS= 1	12 (20%)	0 vs 12/12 (100%)
PS≥ 2	3 (5%)	0 vs 3/3 (100%)

Also, this study investigated whether older patients with PS=0 were more likely to be allocated for intensive treatment to a similar extent to younger patients (Figure 3.8). In contrast to younger patients, older patients were 83% less likely to be allocated for intensive treatment despite having PS=0 (OR 0.17, p-value= 0.001). Among the nine elderly patients with PS=0, two patients had a history of embolism and were considered ineligible for intensive doublet-anthracycline-based chemotherapy due to increased cardiotoxicity risk. Besides, two patients refused the offered treatment by their oncologists against their recommendations and requested less intensive treatment. The remaining five patients were considered at risk of treatment-induced cardiotoxicity.

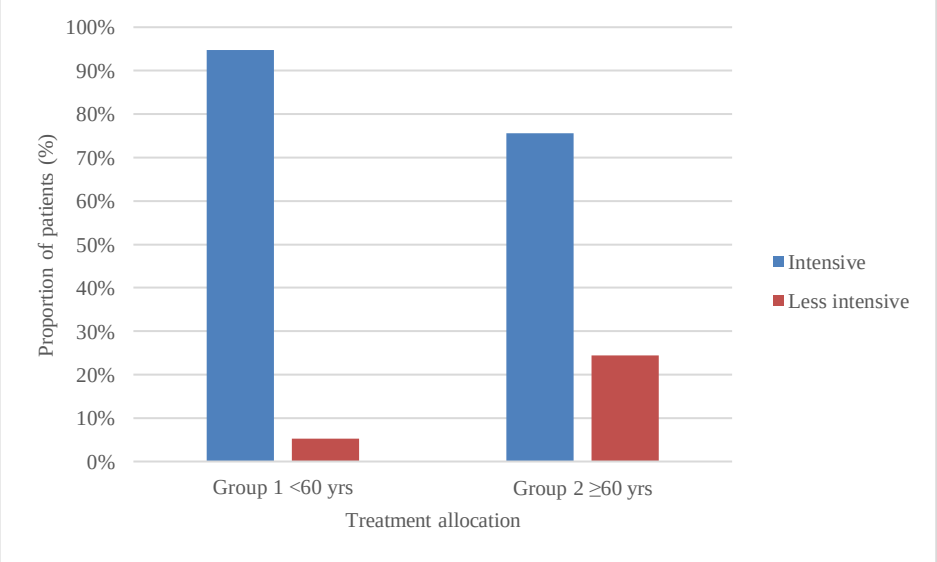

Figure 3.8 Comparing the proportions of intensive and less intensive treatment allocation between younger and older patients who had PS=0

Data from table 3.5 showed that age was a major factor negatively affecting the correlation between clinically eligible baseline performance status (PS=0) and intensive treatment allocation. Occasionally, this was attributed to older patients being considered at a higher risk of intensive-treatment-induced cardiotoxicity. Other factors, such as comorbidities and age-related conditions, contributed to allocating older patients for less intensive treatment and will be discussed separately.

3.3.2.2 Comorbidities

Chi-square test was used to compare the prevalence of comorbidities between patients allocated for intensive and less intensive treatment. A significantly higher proportion of patients with at least one comorbidity was reported among the less intensive treatment group than the intensive treatment combining both age cohorts (OR 0.59, p-value 0.04). In clinical practice, single comorbidity usually does not affect the decision-making of cancer treatment allocation unless it contributes to significant organ dysfunction. In other words, correlating baseline comorbidity score ≥1 with treatment allocation does not make sense in clinical practice, especially for younger patients who are expected to have normal organ function reserve.

A subgroup multivariate logistic regression analysis of the older age cohort showed a statistically significant correlation between advanced baseline number of comorbidities and less intensive treatment allocation after adjusting for disease stage and PS score [OR=20, CI (9-46), P-value<0.000] (Figure 3.9).

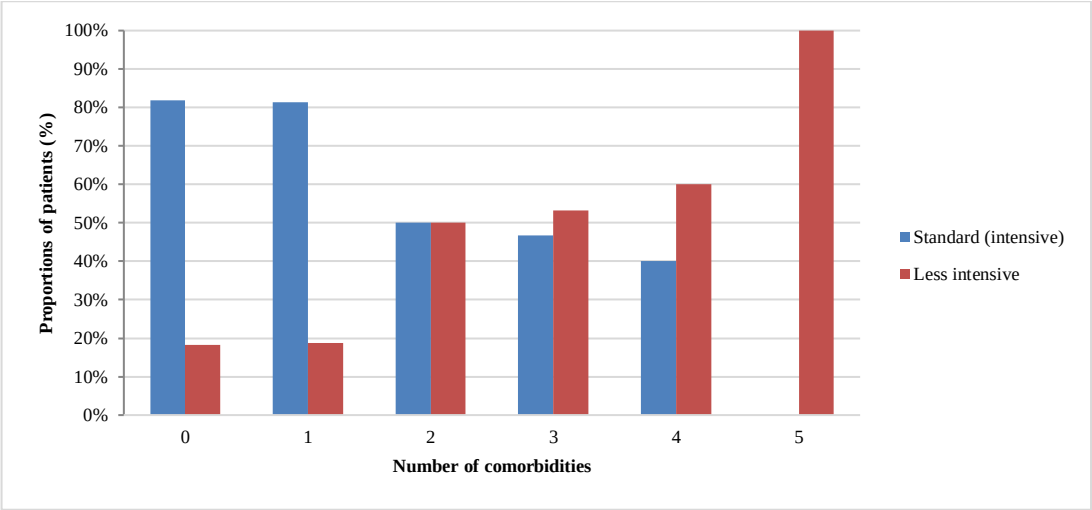

Figure 3.9 Comparing the proportions of older patients allocated to receive intensive versus less intensive treatment based on the baseline comorbidity burden score

Older patients with one comorbidity were more likely to be allocated for intensive chemotherapy to a similar extent compared to patients with no baseline comorbidities. On the other hand, older patients with two to three comorbidities at baseline were approximately 50% less likely to be allocated for intensive treatment. However, more than three comorbidities score was associated with more than 60% less likelihood of intensive treatment allocation.

The association between having ≥3 chronic comorbidities (rather than ≥1 comorbidities) at baseline and less intensive treatment allocation was investigated and compared for clinical significance between the two age cohorts. The prevalence of ≥3 comorbidities was reported in 15% of patients recruited from both age cohorts representing 38.3% and 3.3% of older and younger patients, respectively. After adjusting for age, a comorbidities score ≥3 was significantly associated with less intensive treatment allocation [OR 0.32, CI (0.11-0.93), p-value= 0.037]. These statistics showed that patients having ≥3 comorbidities at baseline were 68% less likely to be allocated for intensive treatment. This correlation was tested after stratifying the

data by age, and the results demonstrated patients having ≥3 comorbidities at baseline were 86% less likely to be allocated for intensive treatment [OR 0.14, CI (0.01-0.16)]. In multivariate logistic regression analysis, none of the documented comorbidities in Figure 3.3 was correlated with less intensive treatment as an independent factor; ischemic heart disease was excluded from this analysis because all patients (n=5) were allocated for less intensive treatment based on the guidelines. Hypertension and diabetes were the most commonly documented comorbidities among patients included in this study and coexisted in 33.3% (n=20/60) of older patients and 9.2% (n=11/120) of younger patients. Among those, 65% (n=13/20) of older and 18% (n=2/11) of younger patients were allocated for less intensive treatment. The impact of hypertension and diabetes co-existence at baseline and intensive treatment allocation was investigated using univariate logistic regression analysis stratified by age cohort. Results showed that, unlike younger patients, older patients having hypertension and diabetes at baseline were 89% less likely to be allocated for intensive treatment [OR 0.11, CI (0.04-0.31), p-value <0.001].

Baseline comorbidities scores were significantly associated with less intensive treatment allocation among breast cancer patients in KCCC. The correlation between a comorbidity score <3 and intensive treatment allocation was negatively affected by age. However, older and younger breast cancer patients with at least three comorbidities were similarly more likely to receive less intensive treatment. Co-existence of hypertension and diabetes at baseline negatively impacted intensive treatment allocation.

3.3.2.3 Geriatric conditions

Among older patients, 18.3% (n=11) had at least one geriatric condition (range 1-3). Ten of the eleven patients were allocated for less intensive treatment. Among those, the general health condition manifested by individual physical status was considered eligible for cytotoxic treatment in 15% (n=9/11) of older patients, while 3.3% (n=2/11) were considered ineligible for cytotoxic treatment. All eleven patients had at least two comorbidities (range 2-5), three had organ dysfunction, and seven had at least one drug-related problem. The distribution of the performance status among older patients with at least one geriatric condition is presented in Table 3.6.

Table 3.6 Distribution of performance status among older patients having at least one geriatric condition before starting breast cancer treatment

Performance status (PS)	Number of patients (n)
0	2
1	7
≥2	2

The majority of patients (n= 9/11) with at least one geriatric condition had a performance status score ≥1, and they were all allocated for less intensive treatment allocation. Only one patient (n= 1/2) with PS=0 was allocated for intensive treatment, while the other patient received less intensive treatment because of a previous pulmonary embolism.

Geriatric conditions among older breast cancer patients were associated with clinical concerns about treatment tolerability contributing to less intensive treatment allocation.

3.3.2.4 Polypharmacy and drug-related problems

In a multivariate logistic regression analysis, the correlation between consuming ≥1 medication and less intensive treatment allocation was tested after adjusting for disease stage, comorbidities, and performance status scores; the results were not statistically significant (OR 2.1, p-value= 0.3). Among the older age cohort, 20% (n= 12) of patients consumed at least five medications and were allocated for less intensive treatment protocols. Unlike older patients, the maximum number of medications consumed by younger patients at baseline was three.

Section 1.3.2 raised some concerns regarding drug-related problems rather than the absolute number of medications that might negatively impact cancer treatment management. Data from the present study showed that the drug-related problems and treatment allocation were not correlated (Table 3.7).

Table 3.7 Comparing the distribution of intensive and less intensive treatment allocation between older and younger patients having at least one drug-related problem before starting breast cancer treatment

	Group 1 <60 yrs **n=15**	**Group 2** ≥60 yrs **n=23**
Intensive treatment n (%)	12/15 (80%)	11 (47.8%)
Less intensive treatment n (%)	3/15 (20%)	12 (52.2%)

Table 3.7 showed that younger patients with drug-related problems were more likely to be allocated for intensive treatment allocation. In comparison, older patients with drug-related problems were almost equally distributed between intensive and less intensive treatment groups. This could be attributed to acceptable baseline performance status and general health conditions rather than drug-related problems. Besides, drug-related problems were assessed for research purposes and not investigated otherwise in the medical oncology department.

Beyond drug-related problems assessment, it was noticed that patients receiving cardioprotective drugs (warfarin/ digoxin) were allocated for less intensive treatment (n=2). This is because patients at risk of a primary or secondary cardiovascular event and receiving cardioprotective drugs were considered at a high risk of chemotherapy-related cardiotoxicity.

The previously discussed findings from the present study suggest that some older patients exhibit acceptable baseline characteristics with no clear contraindication for intensive treatment allocation. However, they were allocated for less intensive treatment due to the increased age-related cardiotoxicity risk. This concept was detected in 48% (n=12/25) of older patients who were allocated for less intensive treatment.

3.3.3 Patient involvement in the decision-making process of breast cancer treatment

Among all patients included in the present study, 4.2% of patients (n=5: four older and one younger patient) rejected the treatment offered by their treating oncologist during the decision-making process and requested less intensive treatment. Even though not all those patients were allocated for intensive treatment as 2/4 older patients were allocated for single-agent chemotherapy but refused to receive cytotoxic chemotherapy in any case. Besides, two cases were documented where older patients delayed initiating chemotherapy despite being allocated for less intensive treatment. Beyond the decision-making process of treatment allocation, three (5%) older patients accepted the initial treatment and received a limited number of chemotherapy cycles but refused to continue with the same protocol. As a result, one patient received a

single agent instead of a doublet chemotherapy protocol, while two patients continued with targeted monotherapy.

Overall, the total number of patients who interfered with the initial treatment plan was six older and one younger patients (representing 10% and 0.8% of older and younger patients, respectively; p-value <0.001). Patients who interfered with the recommended treatment plan were interviewed to explore the cause of their intervention. This was conducted through a simple semi-structured interview while following patients during chemotherapy delivery in the breast cancer clinics. It was noticed that being familiar with the availability of targeted and hormonal therapies as newly developed treatment options directed this subgroup of patients to delay or reject cytotoxic chemotherapy. Patients believed that targeted anti-cancer agents would replace classic chemotherapy protocols, and they were not always being prescribed because they were expensive compared to cytotoxic chemotherapy rather than they target specific tumor subtypes. Also, two patients did not believe that international standardized guidelines for cancer management were applied in Kuwait. Only one patient from the younger age cohort rejected the offered treatment plan because of toxicity concerns (mainly hair loss). On the other hand, patients who agreed to the recommended treatment plan but refused to continue expressed toxicity intolerance and concerns. Table 3.8 summarizes the causes of rejecting/ delaying treatment among patients against the oncologists' recommendations.

Table 3.8 Patients' attitudes and causes of rejecting the offered treatment plan reported in a semi-structured interview

No	Age category	Offered treatment	Attitude	Cause
1	Young (<60 yrs)	Intensive	Rejected the treatment and requested less intensive protocol.	Toxicity concerns
2	Elderly (60-69 yrs)	Less intensive doublet cytotoxic chemotherapy		Not satisfied with the local guidelines
3	Elderly (60-69 yrs)	Less intensive doublet cytotoxic chemotherapy		
4	Elderly (≥70 yrs)	Single-agent chemotherapy		Prefers targeted monotherapy
5	Elderly (≥70 yrs)	Single-agent chemotherapy		
6	Elderly (≥70 yrs)	Single-agent chemotherapy	Delayed initiating treatment	Prefers targeted monotherapy
7	Elderly (≥70 yrs)	Single-agent chemotherapy		
8	Elderly (<60-69 yrs)	Less intensive doublet cytotoxic chemotherapy	Received <3 cycles and refused to continue.	Toxicity concerns/ intolerance
9	Elderly (≥70 yrs)	Single-agent chemotherapy		
10	Elderly (≥70 yrs)	Single-agent chemotherapy		

Generally, the majority of breast cancer patients from both age cohorts accepted the offered plan by their treating oncologists. Occasionally, patients rejected (or refused to continue) the initial allocated treatment and requested less intensive treatment. This was documented in 15% (n=9) of older patients, among those 10% (n=6) aged 70 years and above), and 0.3% (n=1) of younger patients.

3.4 Treatment modification

Treatment modification was classified either as a dose delay, dose reduction, or both in initial chemotherapy schedules. Discontinuing the initial treatment and starting different treatment protocols is referred to as 'treatment deviation' and discussed separately in section 3.5.

Data showed that overall, 36.7% of patients amongst both age cohorts required at least one dose modification in their initial allocated treatment schedule, indicating that most patients tolerated the allocated treatment (Table 3.9). Multivariate logistic regression

analysis was used to detect differences in the requirement for at least one treatment modification between older and younger patients. In general, older patients had a significantly higher requirement for at least one treatment modification when compared to younger patients combining both treatment allocations (50% and 30%, respectively; OR 2.33, p-value= 0.01). After adjusting for treatment allocation, disease stage, and performance status, advanced age was significantly associated with higher requirements for treatment modifications (OR 1.6, p-value= 0.048).

Table 3.9 Comparing the requirement for breast cancer treatment modification between the two age cohorts combining both treatment allocations

	Group 1 <60 yrs n=120 (%)	**Group 2** ≥60 yrs n=60 (%)
Treatment modification (%)		
No modifications	70%	50%
Dose reduction	19.2%	30%
Dose delay	7.5%	13.3%
Both dose reduction and delay	4%	6.7%
P-value= 0.01		

It was hypothesized that stratifying data by treatment allocation would significantly contribute to higher requirements for treatment modifications in the intensive treatment group. Unexpectedly, less intensive treatment was associated with a marginally higher requirement for at least one treatment modification than intensive treatment; however, this did not reach statistical significance (p-value= 0.06).

Based on these findings, advanced age was considered a major contributor to higher requirements for treatment modifications regardless of allocated treatment. According to individual patients' medical notes, the most commonly documented causes for treatment modifications were uncontrolled nausea or neutropenia during anthracycline treatment and treatment-induced asthenia (general weakness), diarrhoea, or neurotoxicity during taxane treatment. In addition, it was noticed that patients (n=2)

receiving cardioprotective drugs (warfarin/ digoxin) had at least one requirement for dose delay.

The Chi-square test was used to compare treatment modification patterns between the two age cohorts stratified by treatment allocation. Results showed that intensive treatment allocation contributed to comparable requirements for treatment modifications between the two age cohorts (Table 3.10). Delaying treatment dose was similar in both age cohorts, while a relatively higher requirement for dose reduction was reported in older patients than in younger patients receiving intensive treatment.

Table 3.10 Comparing the proportions of breast cancer treatment modification patterns between the two age cohorts stratified by treatment allocation protocol

	Group 1 <60 yrs n (%)	**Group 2** ≥60 yrs n (%)	**p-value**
Intensive treatment n (%)			
Reduce dose	9/114 (7.9%)	7/35 (20%)	
Delay cycle	23/114 (20.2%)	7/35 (20%)	
Reduce dose and delay cycle	3/114 (2.6%)	1/35 (2.9%)	
Total	35/114 (30.7%)	15/35 (42.9%)	0.44
Less intensive treatment n (%)			
Reduce dose	1/6 (16.7%)	2/25 (8%)	
Delay cycle	0	10/25 (40%)	
Reduce dose and delay	1/6 (16.7%)	2/25 (8%)	
Total	2/6 (33.3%)	14/25 (56%)	0.048

Chi-square test

Treatment modification patterns in patients receiving less intensive treatment protocols showed a higher requirement for dose delay among older patients. In contrast, none of the younger patients allocated to receive less intensive treatment protocols required dose delay.

3.5 Treatment deviation

The requirement for discontinuing the initial allocated treatment, whether intensive or less intensive, and starting an alternative treatment was referred to as

"treatment deviation". This situation was indicated in clinical practice in treatment intolerance (toxicity or hypersensitivity) or unsatisfactory therapeutic response. The causes of treatment deviation were identified and quantified.

The Chi-square test was used to compare the requirement for treatment deviation patterns between the two age cohorts stratified by treatment allocation. Data showed that 5% (n=3) and 11.7% (n=14) of older and younger patients required treatment deviation combining both treatment allocations. Surprisingly, advanced age was not associated with higher requirements for treatment deviation (OR 0.21, P-value= 14). Stratifying data by treatment allocation showed that all patients from the younger age cohort who required treatment deviation were allocated for intensive treatment protocols (Table 3.11).

Table 3.11 Comparing the requirement for deviation from the allocated breast cancer treatment protocol between the two age groups

	Group 1 <60 yrs	**Group 2** ≥60 yrs
Deviated from standard intensive protocol (n)	14/114 (12.3%)	1/35 (2.9%)
Deviated from non-standard less intensive protocol (n)	0	2/25 (8%)
Chi-square test		

The number of older patients who deviated from the initial protocol was too small to be stratified and compared by treatment allocation, making statistical analysis meaningless. Generally, intensive treatment protocols were not associated with higher requirements for treatment deviation among older breast cancer patients when compared to less intensive treatment.

Treatment intolerance was not the only cause of treatment deviation in the present study. Figure 3.10 shows the causes contributing to treatment deviation in both age

cohorts, excluding patients transferred to the palliative care centre for best supportive care (BSC) as they were not receiving active anti-cancer treatment.

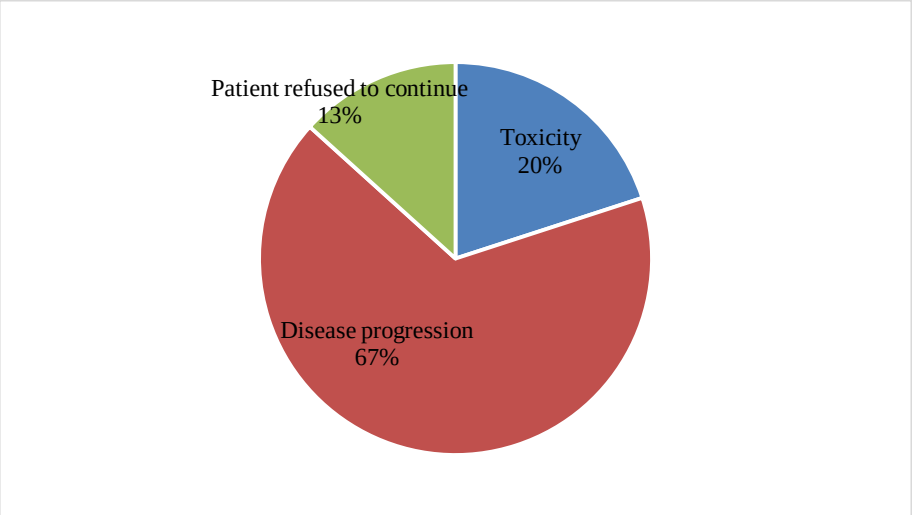

Figure 3.10 The reasons for deviating from the initial treatment allocation combining both age cohorts

Among older patients receiving intensive protocols, only one patient deviated from the initial treatment due to intolerable toxicity (neutropenia). Also, two older patients were allocated for less intensive treatment and deviated from the initial treatment (discontinued cytotoxic chemotherapy) because they requested targeted monotherapy despite their treating oncologists' recommendation. On the other hand, ten younger patients deviated from the initially allocated chemotherapy due to disease progression (eight metastatic cases versus two non-metastatic patients).

3.6 Treatment discontinuation and best supportive care referral

During the study period, only three patients from the younger age cohort discontinued their active anti-cancer treatment and transferred to receive palliative treatment in the Best Supportive Care Centre (BSCC). These patients were metastatic cases and received different chemotherapeutic protocols that eventually became ineffective (multi-drug resistance). In comparison, four non-metastatic patients from

the older age cohort received less intensive treatment protocols that resulted in suboptimal tumour control and therapeutic failure. As a result, they were transferred to BSCC for palliative care.

3.7 Treatment toxicity

This section quantified and compared the side effects between the two age cohorts when undergoing systemic treatment. Additionally, it focused on two specific treatment-induced toxicities commonly encountered in clinical practice: cardiotoxicity and anaemia. Besides, chemotherapy-induced allergic reactions were quantified and compared as undesirable effects that might contribute to chemotherapy deviation or discontinuation. Chi-Square test was conducted to investigate the differences in general toxicity profiles incidence (haematological and non-haematological) between younger and older patients.

3.7.1 General toxicity profile

The general side effects profiles were comparable between the two age cohorts combining both treatment allocations. The only significant differences were detected in the prevalence of nausea and neurotoxicity (Table 3.12).

Table 3.12 Comparing the prevalence of side effects between younger and older breast cancer patients undergoing different chemotherapy protocols

Toxicity profile	**Group 1: <60 yrs n=120**	**Group 2: ≥60 yrs n=60**	**P-value**
Fatigue	74 (61.7%)	39 (65%)	0.66
Nausea	68 (56.7%)	23 (38.3%)	0.02
Vomiting	19 (15.8%)	4 (6.7%)	0.082
Change in bowel movement	43 (35.8%)	25 (41.7%)	0.45
Loss of appetite	32 (26.7%)	15 (25%)	0.81
Weight loss	18 (15%)	13 (21.7%)	0.26
Depression	17 (14.2%)	9 (15%)	0.88
Skin and nail changes	33 (27.5%)	18 (30%)	0.73
Mucositis	30 (25%)	11 (18.3%)	0.31
Neutropenia	26 (21.7%)	10 (16.7%)	0.43
Fever	22 (18.3%)	9 (15%)	0.58
Thrombocytopenia	8 (6.7%)	2 (3.3%)	0.36
Neurotoxicity	23 (19.2%)	20 (33.3%)	0.036

Among patients allocated for intensive treatment, a wide range of variation was observed in the side effects rates between the two age cohorts, but none of these were significantly different (Table 3.13).

Table 3.13 Comparing the prevalence of side effects between younger and older breast cancer patients undergoing INTENSIVE chemotherapy protocols

Toxicity profile	**Group 1: <60 yrs n=114**	**Group 2: ≥60 yrs n=35**	**P-value**
Fatigue	72 (63.2%)	24 (68.6%)	0.56
Nausea	64 (56.1%)	20 (57.1%)	0.92
Vomiting	17 (14.9%)	4 (11.4%)	0.6
Change in bowel movement	41 (36%)	14 (40%)	0.67
Loss of appetite	31 (27.2%)	8 (22.9%)	0.61
Weight loss	17 (14.9%)	6 (17.1%)	0.75
Depression	16 (14%)	2 (5.7%)	0.19
Skin and nail changes	32 (28.1%)	9 (25.7%)	0.78
Mucositis	29 (25.4%)	9 (25.7%)	0.97
Neutropenia	24 (21.1%)	7 (20%)	0.89
Fever	21 (18.4%)	6 (17.1%)	0.86
Thrombocytopenia	7 (6.1%)	1 (2.9%)	0.45
Neurotoxicity	23 (20.2%)	11 (31.4%)	0.17

A subgroup analysis was conducted amongst older patients to compare the toxicity profiles between patients allocated for intensive versus less intensive treatment protocols. Statistical analysis revealed that intensive treatment was significantly associated with a higher prevalence of nausea (Table 3.14). On the other hand, less intensive treatment resulted in a higher prevalence of depression (p-value <0.02). The prevalence of other side effects was comparable between the two treatment allocation arms.

Table 3.14 Comparing the prevalence of side effects profile among older breast cancer patients stratified by initial treatment allocation protocols

Toxicity profile	Group 1: ≥60 yrs		
	Intensive treatment n (%) n=35	Less intensive treatment n (%) n=25	P-value
Fatigue	24 (69%)	15 (60%)	0.49
Nausea	20 (57%)	3 (12%)	<0.001
Vomiting	4 (11%)	0 (0%)	0.08
Change in bowel movement	14 (40%)	11 (44%)	0.76
Loss of appetite	8 (23%)	7 (28%)	0.65
Weight loss	6 (17%)	7 (28%)	0.31
Depression	2 (6%)	7 (28%)	0.017
Skin and nail changes	9 (26%)	9 (36%)	0.39
Mucositis	9 (26%)	2 (8%)	0.08
Neutropenia	7 (20%)	3 (12%)	0.41
Fever	6 (17%)	3 (12)	0.58
Thrombocytopenia	1 (3%)	1 (4%)	0.58
Neurotoxicity	11 (31%)	9 (36%)	0.81

The number of patients who developed depression during breast cancer treatment was too small (n=9) to be analysed and investigate the contributing factors. The baseline characteristics for older patients receiving less intensive treatment and developed depression (n=7) were reviewed, and data showed that they had a relatively higher prevalence of comorbidities (Range 2-5 versus 0-3) and number of medications consumed (Range 4-13 versus 0-3) than patients who did not develop depression. Besides, five of those patients had advanced poor performance status, and four patients had at least one drug-related problem.

Unlike older patients, the number of younger patients allocated for less intensive treatment was too small (n=6) to be analysed, making an informative statistical comparison of the toxicity outcomes with younger patients allocated for intensive

treatment or older patients allocated for less intensive treatment impossible. Overall, older breast cancer patients could tolerate intensive treatment to an extent similar to their younger counterparts. Among the older age cohort, a variation was seen in the toxicity profiles prevalence by treatment allocation. While intensive treatment was associated with a higher prevalence of nausea, vomiting, and mucositis, less intensive treatment was associated with a higher prevalence of depression. Haematological toxicities (neutropenia and thrombocytopenia) did not differ by treatment allocation. Treatment-induced anaemia is discussed independently.

3.7.2 Treatment-induced anaemia and blood transfusion

The baseline haemoglobin level was documented before initiating systemic treatment and regularly monitored to assess and compare the severity of chemotherapy-induced anaemia between the two age cohorts. T-test was used to detect differences in the haemoglobin levels between the two age cohorts, and the results showed that they were not statistically significant (P-value= 0.8). Table 3.15 compares the median baseline and post-treatment (the lowest levels detected during chemotherapy) haemoglobin level between the two age cohorts.

Table 3.15 Comparing the median baseline and post-treatment haemoglobin level between the two age cohorts.

	Group 1 <60 yrs n=120	**Group 2** ≥60 yrs n=60
Baseline haemoglobin (g/dL)		
Median	12	12
*IQR	11.5-12.3	11.4-12.5
Post-treatment haemoglobin (g/dL)		
Median	10	10
*IQR	9-11	8.7-11

*IQR: Interquartile range

Approximately 61.7% of younger breast cancer patients started their chemotherapy with a normal haemoglobin level, and 36.7% had mild anaemia based on the National

Cancer Institute (NCI) grading system for anaemia (Table 3.16). In comparison, 58.3% of older patients started their chemotherapy with normal haemoglobin levels, and 41.7% had mild anaemia. The frequency of baseline moderate-severe anaemia was insignificant in both age cohorts.

Table 3.16 Comparing the severity of anaemia between younger and older breast cancer patients pre and post breast cancer treatment

Anaemia grade	Group 1: <60 yrs n (%)	Group 2: ≥60 yrs n (%)
Baseline haemoglobin (g/dL)		
Normal ≥ 12	74/120 (61.7%)	35/60 (58.3%)
Mild 10 – 11.9	44/120 (36.7%)	25/60 (41.7%)
Moderate 8- 9.9	1/120 (0.8%)	0
Severe 6-7.9	1/120 (0.8%)	0
Life-threatening <6	0	0
T-Test (p-value= 0.58)		
Post-treatment haemoglobin level (g/dL)		
Normal ≥ 12	8/120 (6.7%)	5/60 (8.3%)
Mild 10 – 11.9	64/120 (53.3%)	26/60 (43.3%)
Moderate 8- 9.9	31/120 (25.4%)	23/60 (36.3%)
Severe 6.5-7.9	14/120 (11.5%)	6/60 (10%)
Life-threatening <6.5	3/120 (2.5%)	0
T-test (p-value= 0.5)		

By the end of chemotherapy, only 8.3% and 6.7% of older and younger patients, respectively, maintained normal haemoglobin levels, while 93.3% of younger patients and 91.7% of older patients developed some degree of anaemia ranging from mild to life-threatening anaemia. The two age cohorts maintained a similar pattern of anaemia severity prevalence. Mild anaemia was the most common degree of treatment-induced anaemia, followed by moderate, severe, and life-threatening anaemia was least common. In subgroup comparison of anaemia categories between younger and older patients allocated for intensive treatment, the severity pattern remained similar between the two age cohorts (p-value 0.3).

Blood transfusion was clinically indicated during chemotherapy when the haemoglobin level was less than 7.5 g/dL. However, blood transfusion was considered if the haemoglobin level ranged between 7.5-7.9 g/dL and was accompanied by clinical

signs and symptoms such as fatigue, shortness of breath, headache, and dizziness as they negatively cancer patients' quality of life.

The Chi-square test was used to detect statistical differences in the requirement for blood transfusion during chemotherapy between the two age cohorts. The proportion of patients who required blood transfusion was 13.3% combining both age cohorts and accounting for 10% of older and 15% of younger patients (p-value 0.3). Stratifying data by age cohort and treatment allocation revealed significantly higher blood transfusion requirements among younger patients allocated for intensive treatment compared to less intensive treatment (Table 3.17). In contrast, higher blood transfusion requirements were reported among older patients allocated for less intensive treatment compared to intensive treatment.

Table 3.17 Comparing the proportions of patients who required at least one blood transfusions between the two age cohorts stratified by initial treatment allocation

Treatment allocation	**Group 1: <60 yrs n=18**	**Group 2: ≥60 yrs n=6**
Intensive treatment	17/18 (94.4%)	1/6 (16.7%)
Less-intensive treatment	1/18 (5.6%)	5/6 (83.3%)

3.7.3 Treatment-induced cardiotoxicity

The total number of patients allocated to receive trastuzumab therapy for 12 months and monitored for treatment-related cardiotoxicity was 93 (63 younger and 30 older patients). T-test was used to detect differences in the LVEF levels at baseline and post treatment (the lowest LVEF value documented) between the two age cohorts. Data showed that baseline LVEF values did not differ by age cohort (median= 65%, IQR= 60-68% and 59-66% for older and younger patients, respectively; p-value= 0.59). Whilst post-treatment LVEF levels were slightly lower among older patients (median=

51%, IQR= 49-56%) compared to younger patients (median= 55%, IQR= 50-58%), but this was not (p-value = 0.22) (Figure 3.11).

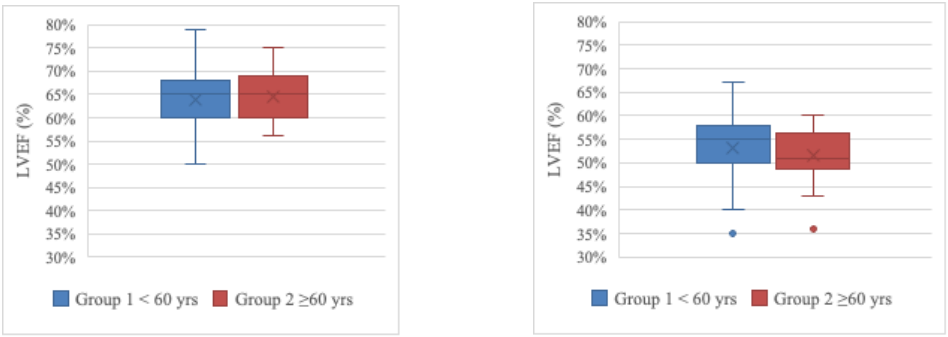

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Figure 3.11 Comparing the LVEF documented between the two age cohorts at baseline (pre- breast cancer treatment) and post-exposure to cardiotoxic treatment

During trastuzumab treatment, the individual decline in LVEF from the baseline value was calculated, and the outcome values were categorized as either <10% or ≥10% decline (Table 3.18). The consequent intervention of either with-holding treatment (temporary discontinuation and re-challenge) or permanent discontinuing treatment was documented to compare treatment tolerance between the two age cohorts.

Table 3.18 Comparing the proportions of LVEF decline (<10% or ≥10%) from the baseline value during trastuzumab treatment (within 12 months) and the clinical intervention between two age cohorts

	Group 1: <60 yrs n=63	**Group 2: ≥60 yrs n=30**
Decline in the LVEF n (%)		
<10%	28/63 (44.4%)	4/30 (13.3%)
≥10%	35/63 (55.6%)	26/30 (86.7%)
No intervention n (%)	48/63 (76.2%)	17/30 (56.7%)
Intervention n (%)	15/63 (23.8)	13/30 (43.3%)
With-hold Trastuzumab	9/15 (60%)	8/13 (61.6%)
Discontinue Trastuzumab	6/15 (40%)	5/13 (38.4%)

During trastuzumab treatment, 34.4% of patients from both age cohorts had a clinically insignificant (<10%) decline in their LVEF from the baseline value indicating good tolerance to treatment. The Chi-square test showed that younger patients showed better tolerance to trastuzumab than older patients (44.4% and 13.3%, respectively; p-value <0.001), even though they had higher overall exposure to anthracycline prior to trastuzumab therapy (81% and 60% of younger and older patients, respectively; p-value <0.001). On the other hand, a clinically significant decline (≥10%) in the LVEF was documented in 65.6% of patients receiving trastuzumab combining both age cohorts. Statistical analysis showed that older patients had a significantly higher LVEF decline compared to younger patients (86.7% and 55.6%, respectively; p-value <0.001). As a result, the subsequent requirement for treatment intervention of with-holding or discontinuing trastuzumab treatment was relatively higher among the older age cohort.

The intervention was dependent on individual LVEF values and/or clinical signs and symptoms of congestive heart failure rather than the percentage decline in the LVEF from the baseline value. Among patients who had ≥10% decline, 73.1% (n=19) and 71.4% (n=25) of older and younger patients, respectively, maintained acceptable LVEF (≥50%) and completed their treatment (Figure 3.12). Among those patients, 11.8% (n=11: six older and five younger patients) had LVEF values equal to 50% during the first six months of treatment. Therefore, they discontinued trastuzumab for 1-2 months and received a cardioprotective drug such as an Angiotensin Converting Enzyme Inhibitor (ACE-I) or Beta Blocker (BB). Trastuzumab treatment was re-started (re-challenged) after restoring clinically accepted LVEF levels (≥55%). Among those, none of the patients developed clinical symptoms of CHF.

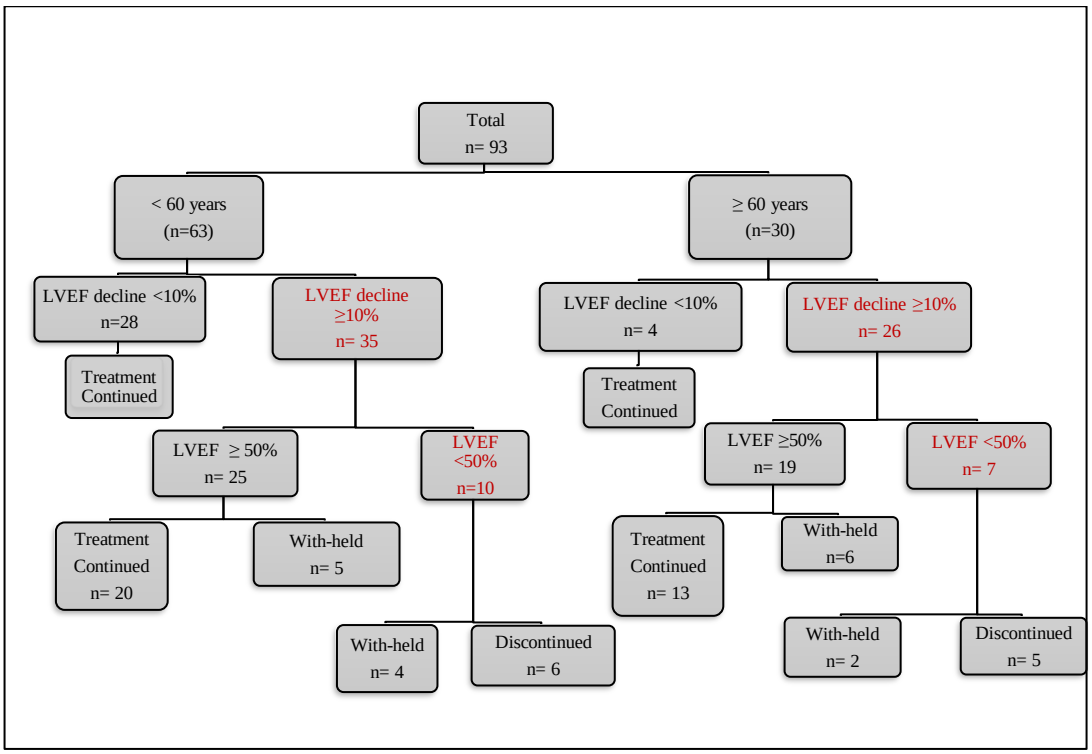

Figure 3.12 Comparing the incidence of LVEF decline (<10% or ≥10%) from the baseline value between younger and older breast cancer patients undergoing trastuzumab treatment and the clinical intervention of with-holding or discontinuing treatment

Patients who developed ≥10% decline from the baseline and reached a value below accepted LVEF limits <50% represented only 18.3% (n=17) of patients combining both age cohorts. Statistical analyses of this subgroup of patients showed that the distribution was not significantly different by age cohort (23.3% and 15.9% in older and younger patients, respectively, p-value= 0.2; Figure 3.13). Permanent trastuzumab treatment discontinuation occurred in 11.8% (n=11) of patients combining both age cohorts, representing 16.7% (n=5) of older and 9.5% (n=6) of younger patients. Those patients were considered not eligible for treatment re-challenge following cardioprotective therapy. Otherwise, treatment was re-initiated and completed. Only one patient from the younger age cohort had clinical symptoms of CHF, while all other patients were asymptomatic.

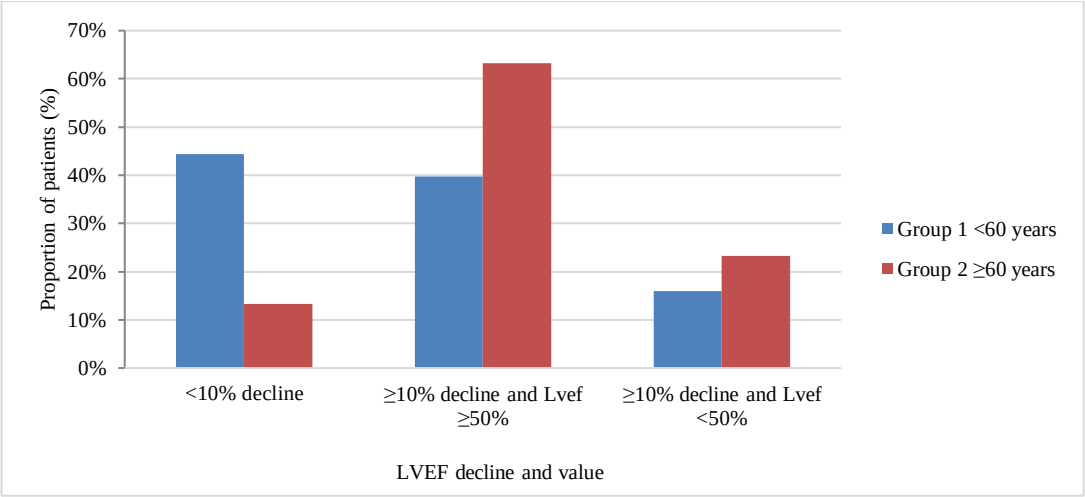

Figure 3.13 Comparing the decline in the LVEF from the baseline value (<10% or ≥10%) and the LVEF value (<50% or ≥50%) during trastuzumab therapy between the two age cohorts

Chi-square test was used for subgroup analyses of patients who maintained clinically accepted LVEF values (≥50%) despite the percentage decline (whether ≥10% or <10%) from baseline and showed no statistical differences in patients' distribution between the two age cohorts (82.5% and 76.7% in younger and older patients, respectively, p-value= 0.4; Figure 3.14).

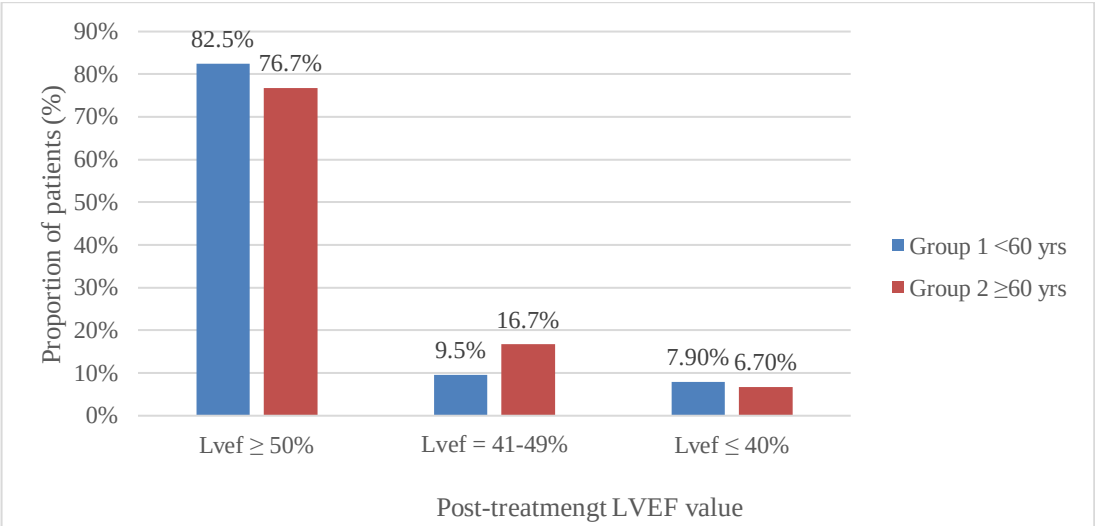

Figure 3.14 Comparing post-treatment LVEF value documented for patients undergoing trastuzumab treatment between the two age cohorts

On the other hand, among patients who developed ≥10% decline in their LVEF from baseline, the proportion of patients who reached LVEF values below normal ranges

(<50%) was statistically comparable between the two age cohorts (27% and 29% in older and younger patients, respectively, p-value= 0.88). Overall, age was not correlated with developing LVEF below normal ranges among patients who developed ≥10% decline during trastuzumab treatment.

3.7.3.1 Investigating the risk factors correlated with treatment-induced cardiotoxicity

In a simple descriptive comparison of baseline characteristics of older and younger patients who developed ≥10% decline in their LVEF from baseline values, the median baseline LVEF was 65% in both age cohorts with comparable interquartile ranges (IQR= 60-69%% and 60-68%% in older and younger patients, respectively). The median body mass index (BMI) difference was statistically insignificant between the two age cohorts. The prevalence of baseline comorbidities was significantly higher among older patients than younger patients (84.6% and 51%, respectively; p-value <0.001). Hypertension was reported in 65.4% and 20% of older and younger patients, respectively (p-value <0.001). Similarly, diabetes was reported in 48% and 17.1% of older and younger patients, respectively (p-value <0.001). None of the patients from the two age cohorts had a history of ischemic heart disease. Only two patients from the older age cohort had a history of pulmonary embolism.

Besides, all patients from both age cohorts received paclitaxel concomitantly with trastuzumab except for two patients from the older age cohort who received targeted monotherapy. Younger patients had significantly higher exposure to anthracycline treatment prior to trastuzumab treatment (81% and 60% of younger and older patients, respectively; p-value <0.001).

A multivariate logistic regression analysis was conducted to detect baseline factors associated with increased risk of trastuzumab-induced cardiotoxicity, defined as developing a clinically significant decline (≥10%) in the LVEF from the baseline value. The analysis included age, BMI, comorbidities, and previous exposure to anthracycline treatment (Table 3.19).

Table 3.19 Investigating the factors that are correlated with ≥10% decline from the baseline LVEF among breast cancer patients undergoing trastuzumab treatment

Factors	Odds Ratio	CI (95%)	p-value
Age ≥60 years	4	1.35-11.86	0.012
BMI	0.98	0.91-1.05	0.57
Comorbidities score ≥3	3.1	0.63-15.22	0.16
History of hypertension	1.54	0.61-3.93	0.36
History of diabetes	1.93	0.68-5.5	0.22
Anthracycline treatment	0.44	0.16-1.26	0.13

Data analysis showed that advanced age (≥60 years) was the only significant independent factor associated with increased treatment-induced cardiotoxicity. Statistically, older patients were at a 4-fold higher risk of developing ≥10% decline in their LVEF from the baseline value than younger patients. Unexpectedly, previous exposure to anthracycline treatment, having multiple comorbidities at baseline, and history of hypertension or diabetes were not associated with increased risk of cardiotoxicity in the present study.

3.7.3.2 Impact of baseline LVEF

The impact of baseline LVEF values was investigated separately to be correlated with treatment-induced cardiotoxicity and reaching LVEF values below normal ranges for clinical significance. The LVEF values were standardized by calculating the percentage change from the mean LVEF (60%), which is considered the midpoint of the normal LVEF range (50-70%) for better statistical outcomes as data included

uncommon normal LVEF values, such as 80% and 72%.[216] After that, data were categorized into two groups (≥60% or <60%) for clinical significance. A univariate logistic regression analysis was conducted to investigate the correlation between a baseline LVEF value <60% and developing ≥10% decline from the baseline value. Also, the correlation between a baseline LVEF value <60% and maintaining LVEF values within normal ranges (≥50%) was investigated.

Results showed that patients with baseline LVEF values <60% were at a 2.1-fold risk of developing ≥10% decline during trastuzumab treatment, but that did not reach statistical significance [OR 2.1, CI (0.73-7.99), p-value 0.15]. On the other hand, patients with baseline LVEF values less than 60% were significantly 86% less likely to maintain LVEF within normal ranges (≥50%) during treatment [OR 0.14, CI (0.04-0.49), p-value 0.002].

Based on this data analysis, age was an independent risk factor for developing ≥10% decline in the LVEF during trastuzumab treatment. Also, a baseline LVEF value below 60% has shown to be significantly correlated with reaching LVEF value below normal ranges (<50%). The risk of treatment-induced cardiotoxicity among breast cancer patients receiving trastuzumab was significantly increased with age and a baseline LVEF value below 60%.

3.7.3.3 Baseline cardiovascular diseases risk estimation

The risk of cardiotoxicity was calculated during baseline assessments based on the traditional Athero-Sclerotic Cardiovascular Disease (ASCVD) risk estimator to be correlated with treatment-induced cardiotoxicity defined as developing ≥10% decline from the baseline value or reaching values below normal ranges <50%.[214] The findings suggested that the majority of patients eligible for trastuzumab treatment were

considered at low risk of cardiovascular diseases. Only 26.9% (n=25/93) of patients were considered at a borderline or intermediate-high risk and represented 76.7% (n=23/30) of older and 3.2% (n=2/63) of younger patients (Figure 3.15). However, the proportion of patients who developed ≥10% decline in their LVEF from the baseline value was 65.6% (n=61/93) and represented 86.7% (n=26/30) and 55.6% (n=35/63) of older and younger patients, respectively.

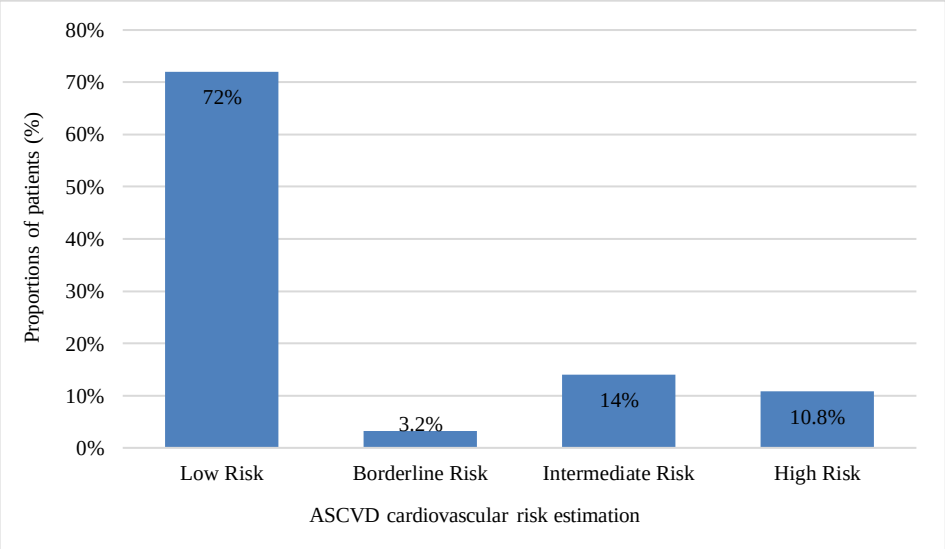

Figure 3.15 Comparing the proportions of breast cancer patients allocated for potential cardiotoxic treatment based on the calculated 10-year ASCVD cardiovascular risk estimator regardless of age

The Chi-square test was used to compare the proportions of patients who developed ≥10% decline in their LVEF and who developed <10% among patients considered at borderline, intermediate, and high risks of cardiotoxicity at baseline based on the ASCVD risk estimator. Results showed that the ASCVD risk was significantly higher among patients who developed ≥10% decline in their LVEF compared to patients who developed <10% decline (p-value 0.001) (Figure 3.16).

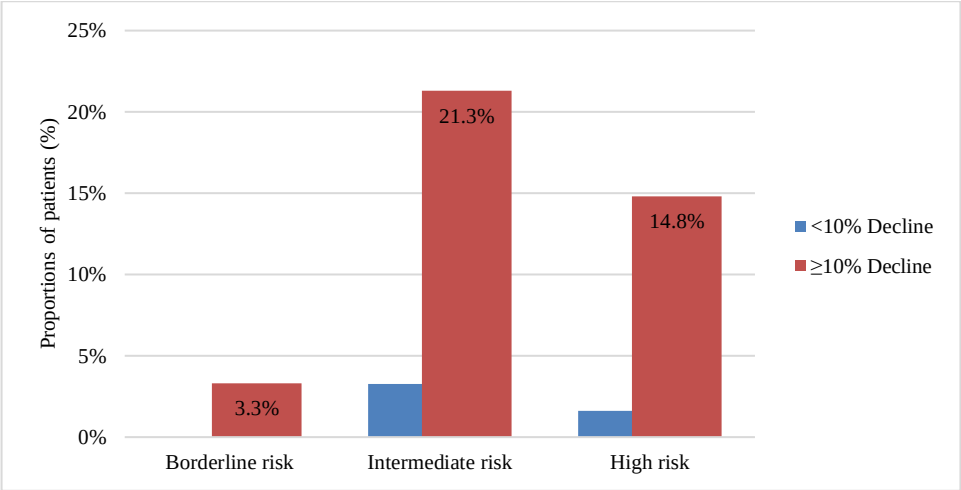

Figure 3.16 Comparing the baseline cardiovascular risk between patients who developed ≥10% decline versus <10% in their LVEF from the baseline value.

Among younger patients considered at a moderate-high ASCVD risk, no statistical differences were detected between younger patients who developed ≥10% decline in their LVEF compared to patients who developed <10% decline (p-value 0.48). In contrast, a marginal (did not reach statistical significance) increase in the estimated cardiovascular risk was detected among older patients who developed ≥10% decline in their LVEF compared to patients who developed <10% decline (p-value 0.058). According to these findings, the traditional ASCVD cardiovascular risk estimator underestimated the risk of trastuzumab-induced cardiotoxicity among breast cancer patients, especially those aged less than 60 years.

3.7.4 Hypersensitivity reaction

Hypersensitivity reaction to breast cancer systemic (all delivered intavenously) treatment occurred in 15.6% (n=28: 23 younger and five older patients) of patients combining the two age cohorts. A higher prevalence of hypersensitivity was reported among younger patients compared to older patients (p value= 0.06). The most common therapeutic agent responsible for inducing hypersensitivity reaction was trastuzumab

and accounted for 85.7% of the cases. On the other hand, taxanes infusion accounted for 14.3% of the hypersensitivity incidence cases.

Overall, hypersensitivity reactions were mild-moderate and immediately managed in the chemotherapy day-care ward. Treatment was temporarily discontinued to avoid patient distress and allow sufficient recovery before being re-started on the next scheduled dose (re-challenge). Severe trastuzumab-induced anaphylactic shock occurred in only one patient from the younger age cohort leading to permanent treatment discontinuation. The patient was admitted to the Intensive Care Unit (ICU) for 36 hours of observation before being discharged without complications.

3.8 Disease control

The median duration of patients' follow-up from diagnosis was 23 months (IQR= 19-27). Results showed that among non-metastatic patients, 99% of younger versus 87.5% of older patients achieved complete remission (therapeutic success) during this period (Table 3.20).

Table 3.20 Comparing disease control during a median 23-month follow-up period between younger and older breast cancer patients stratified by status of metastasis

Response	Group 1: <60 yrs n=120	Group 2: ≥60 yrs n=60
Non-metastatic cases n (%)		
Total	102/120 (85%)	56/60 (93.3%)
Complete remission	101/102 (99%)	48/56 (85.7%)
Complete remission was NOT achieved	1/102 (1%)	6/56 (14.3%)
Metastatic cases n (%)		
Total	18/120 (15%)	4/60 (6.7%)
Complete remission	0	0
Regression	3/18 (16.7%)	1/4 (25%)
Progression	10/18 (55.6%)	2/4 (50%)
Stable disease	5/18 (27.8%)	1/4 (25%)

Among non-metastatic patients, the tumour metastasized (therapeutic failure) in 12.5% (n=6) of older patients and 0.98% (n=1) of younger patients (Chi-square test, p-value <0.001) and all of those did not receive standard intensive treatment. Among older patients, two patients were allocated for targeted monotherapy because they were considered ineligible for cytotoxic chemotherapy. Five patients were allocated for single-agent chemotherapy protocol; two of those delayed their treatment, and three received ≤3 cycles and refused to continue with cytotoxic treatment resulting in poor disease control and therapeutic failure.

Among metastatic patients from the younger age cohort, more than 50% of patients had tumour progression (therapeutic failure) despite receiving intensive treatment, 16.7% of patients achieved and maintained disease regression, and 27.8% maintained stable disease. In comparison, the number of metastatic cases among the older age cohort was too small (n=4) to state definite conclusions about disease control outcomes; however, it varied between disease progression, regression, and stable disease.

3.8.1 Relapse incidence

The incidence of disease relapse (detection of tumour recurrence post disease remission) among non-metastatic breast cancer patients who achieved complete remission occurred in 5.4% of patients (n=8: one older patient and seven younger patients) during a period between 19 and 29 months after diagnosis. The number of relapsed patients was insufficient to conduct logistic analysis or make definitive conclusions about factors contributing to disease relapse. However, data showed that those patients had aggressive invasive ductal carcinomas with a proliferative index

Ki67 ≥30% (range 30%-80%), median BMI of 29 and received standard intensive treatment protocols. Among those, six patients had triple negative breast tumours.

3.9 Death incidence

The death incidence of breast cancer patients included in the present study accounted for 4.4% (n= 8/180) of patients during a median follow-up period of 23 months (IQR 19-27), and the distribution did not differ by age cohort (Table 3.21).

Table 3.21 Comparing deaths incidence between younger and older breast cancer patients during a 23-months follow-up period stratified by status of disease metastasis at diagnosis

Death incidence	Group 1: <60 yrs	Group 2: ≥60 yrs	Total
Non-metastatic cases n (%)			
Total	102/120 (85%)	56/60 (93.3%)	
Deaths n	1/102	2/56	3/158 (1.9%)
Time to death (months)	31	(20, 21)	
Metastatic cases n (%)			
Total	18/120 (15%)	4/60 (6.7%)	
Deaths n	4/18	1/4	5/22 (22.7%)
Time to death (months)			
Range	21-27	15	
Total number of deaths	5/120 (4.2%)	3/60 (5%)	8/180 (4.4%)

The death incidence in the present study was insufficient to conduct logistic analysis or make definitive conclusions about the contributing factors and investigate death incidence in each treatment allocation arm. However, the death incidence be correlated with breast tumour subtypes and disease stage at diagnosis. Data showed a significantly higher death incidence among patients with metastatic disease compared to non-metastatic disease (22.7% versus 1.9%, respectively), which was expected. Among older metastatic patients, a shorter duration of survival could be attributed to different causes, including cancer-related and non-cancer-related factors such as comorbidities/ organ dysfunction. Also, less intensive treatment, toxicity intolerance,

poor quality of life, and earlier cytotoxic treatment discontinuation lead to therapeutic failure and shorter survival duration. On the other hand, younger patients with metastatic breast tumours were allocated for standard intensive treatment protocols; however, tumours developed resistance to chemotherapy and contributed to therapeutic failure. Among younger non-metastatic patients, only a single death occurred in a triple negative case who relapsed after 20 months of diagnosis.

Disease progression and survival were expected to be highly correlated with individual tumour characteristics manifested by the histological and molecular subtype and the extent of metastases. Table 3.22 presents tumour characteristics for patients who died during the study period stratified by age cohort and status of metastasis. All patients with poor survival had a Ki67% (proliferative index) of more than 30% (range 40%-60%).

Table 3.22 Comparing the number of deaths during a 23-months follow-up period between the two age cohorts stratified by tumour characteristics and status of metastases at diagnosis

	Group 1: <60 yrs n=5	**Group 2: ≥60 yrs n=3**
Non-metastatic cases n (%)		
Total number of deaths n	1	2
Triple Negative Tumour	1	1
Triple Positive Tumour	0	1
*HER-2 Positive & HR Negative	0	0
Metastatic cases n (%)		
	4	1
Total number of deaths n		
	0	0
Triple Negative Tumour	3	1
Triple Positive Tumour	1	0
HER-2 Positive & HR Negative		

* HR: Hormonal positive tumour

Among non-metastatic patients combining the two age cohorts, triple negative breast tumours contributed to two deaths, while triple positive breast tumours contributed to one death that occurred in an older patient who was considered ineligible for cytotoxic treatment.

CHAPTER 4

DISCUSSION

4. DISCUSSION

Lack of pharmaco-epidemiological and clinical trials outcomes with commonly used chemotherapeutic agents in older patients contributed to a lack of effective treatment protocols adopted in breast cancer management guidelines. Treatment guidelines rely on traditional performance status scores to allocate patients to cytotoxic chemotherapy rather than integrate standardized baseline assessment tools to evaluate individual patient eligibility. Also, the guidelines do not provide guidance on allocating breast cancer patients with multiple comorbidities or advanced age, which are considered unfavorable baseline factors. Consequently, baseline assessments and treatment allocation of those patients depend primarily on individual oncologist decisions. Previous epidemiological studies show that older breast cancer patients are undertreated. In clinical practice, factors affecting the decision-making process of breast cancer management may overlap and be negatively affected by advanced age due to concerns about age-related physiological changes in body organ functions and regulatory systems.

There is a lack of data on treatment allocation patterns among breast cancer patients in Kuwait, and factors contributing to less intensive treatment among older and younger patients are still unclear. The present observational study compared the differences in baseline characteristics, treatment allocation, tolerance, and outcomes between older and younger patients with breast cancer in the Kuwait Cancer Control Centre. It was hypothesized that older breast cancer patients were most likely to receive less intensive chemotherapy compared to younger patients despite having acceptable baseline characteristics. Through this study, the differences in the baseline characteristics (patient and tumour) between older and younger breast cancer patients were

investigated and correlated with treatment allocation. This approach demystified the factors that govern the clinical decision-making process of treating breast cancer patients in clinical practice and led oncologists to deviate from prescribing standard intensive treatment. Besides, subgroup analyses of allocating older and younger patients with similar performance status or comorbidity burden scores were conducted to demystify whether baseline characteristics were weighed differently and negatively affected by age.

The impact of baseline characteristics and treatment allocation on breast cancer survival was not investigated in the present study as the study period was relatively short and longitudinal data was incomplete. Figure 4.1 exhibits the main sections discussed in this chapter.

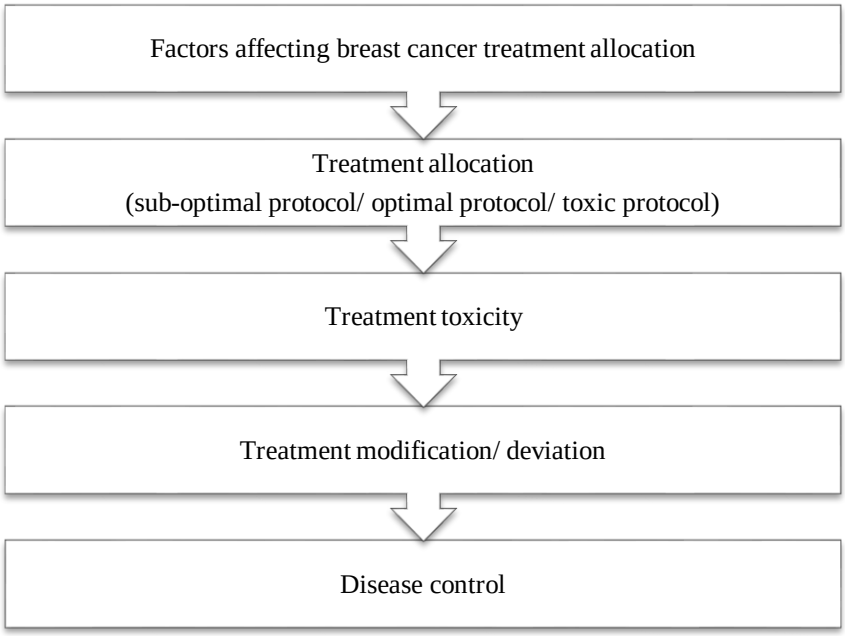

Figure 4.1 The main discussion sections

Chapter 4 will discuss the requirement for baseline assessments for breast cancer patients to enhance effective individualized breast cancer management and improve healthcare in the clinical practice of oncology.

4.1 Factors that govern the clinical decision-making process of treating patients with breast cancer

According to results from the present study, the factors that influence the management plan of treating older and younger breast cancer patients can be divided into baseline characteristics assessment and patient involvement in the decision-making process (patient interference), which will be discussed throughout this chapter (Figure 4.2).

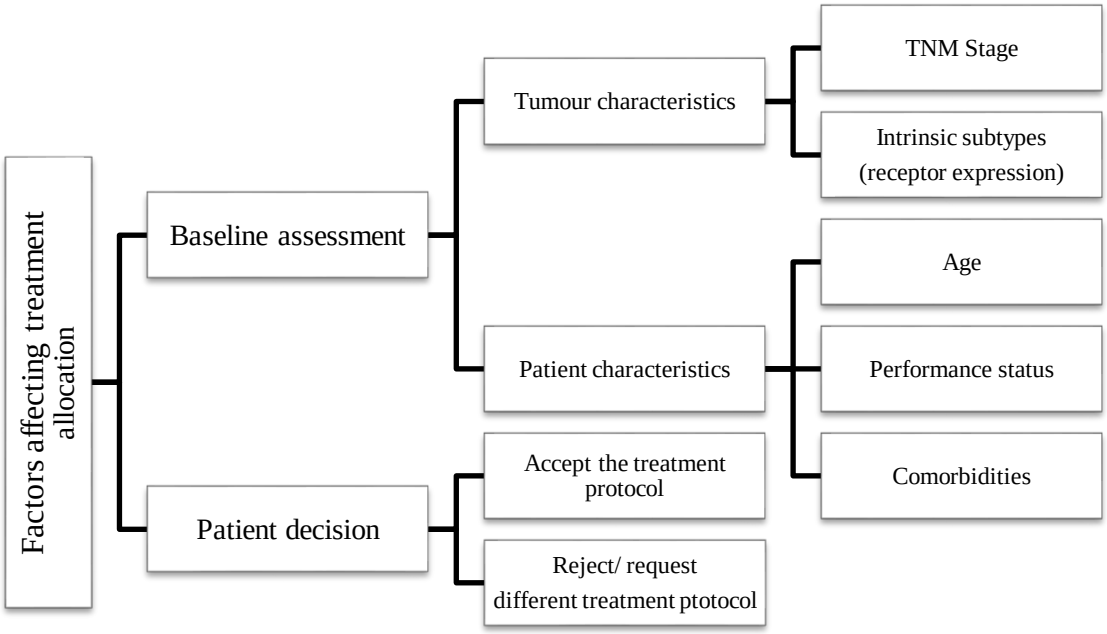

Figure 4.2 Factors affecting treatment allocation of breast cancer management in KCCC

4.1.1 The impact of baseline characteristics assessment on treatment allocation

The baseline assessment included individual tumour characteristics and patient characteristics. Overall, no statistical differences were detected in BMI, family history of malignant tumours, and baseline haemoglobin levels between the two age cohorts (Table 3.1). Also, the intrinsic subtypes of breast tumours were similar between

younger and older patients with regard to tumour histology, HER-2/ HR expressions, Ki67% proliferation, and status of metastasis. The only significant difference detected in tumour characteristics was the TNM stage at diagnosis, where older age was associated with less advanced breast tumours when compared to younger patients. Besides, baseline assessments demonstrated that older age was associated with a higher prevalence of comorbidities, medication use, drug-related problems, and advanced performance status. In regression analysis, advanced age, comorbidities, and advanced performance status were the only factors associated with less intensive treatment allocation for breast cancer management in Kuwait (Table 3.4).

4.1.1.1 Age

The majority of previous studies in the literature were conducted retrospectively and focused on the prevalence and patterns of less intensive treatment protocols and outcomes rather than investigating the actual causes of deviating from allocating older patients for intensive treatment protocols (section 1.4.4.2). It was crucial to clarify whether older patients received less intensive treatment due to age bias in treatment allocation or a clear clinical requirement for this decision.

After adjusting for comorbidities, performance status, and disease stage, the present study's findings showed that age (≥60 years) was an independent factor that negatively affected treatment allocation among breast cancer patients and contributed to 42% of less intensive treatment allocation in Kuwait (Table 3.4). Theoretically and practically, advanced age is associated with an increased comorbidity burden, polypharmacy, organ dysfunction, and poor PS (section 1.3). These factors often overlap, necessitating complicated and comprehensive clinical assessments (Figure 4.3).

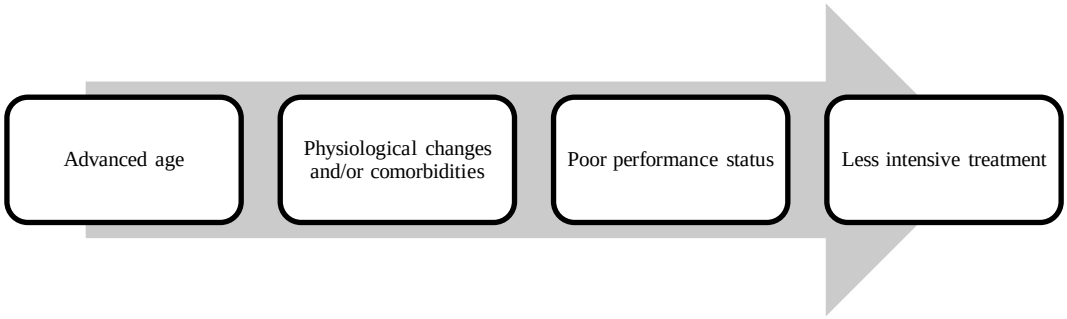

Figure 4.3 Conceptional association between age and less intensive treatment allocation for breast cancer

In clinical practice, any of these factors are more likely to be weighted differently in an older patient compared to a younger patient with similar scores because the ideology of physiological changes may lead to an overestimation of age-related limitations and cancer treatment intolerance. For example, this study demonstrated that older patients with <3 comorbidities were at a higher risk of less intensive treatment allocation compared to younger patients with similar comorbidities scores after adjusting for disease stage and performance status score. Besides, a baseline PS=0 was strongly associated with intensive treatment allocation among younger patients (after adjusting for disease stage and comorbidities) but not older patients, as 20% were allocated for less intensive treatment (OR 0.17, p-value= 0.001). These findings suggest that older and younger breast cancer patients with similar comorbidities and performance status scores were not always allocated for similar treatment protocols. Standard intensive cytotoxic treatment was highly dependent on the treating oncologist's opinion.

Chronological age is a poor indicator of an individual patient's functional status and evaluating breast cancer treatment risks and benefits. A high heterogeneity is seen in the older population; while some older patients may be frail and cannot tolerate cytotoxic treatment, other patients may have an organ reserve comparative to younger patients and can tolerate intensive chemotherapy. The lack of individualized baseline

assessments may lead to biased conclusions regarding older patient eligibility and standard treatment tolerability.

4.1.1.2 Physical and functional status assessment

In clinical practice, traditional methods are applied to assess a patient's baseline general health condition and their eligibility for standard cytotoxic protocols. The most commonly used method is the performance status (PS) scale, which is applicable for all adult cancer patients regardless of age and recommended by the treatment guidelines. Geriatric assessment (GA) tools, which are specified for identifying vulnerabilities among older cancer patients, are also available but not commonly used.[68, 69]

Breast cancer patients are expected to have better PS at diagnosis compared to patients with other solid tumours that precipitate a wide range of intolerable symptoms. For example, it is common to see young patients with lung cancer having poor PS and a wide range of limitations in their daily activities.[217] Kelly *et al.* (2018) demonstrated that cough and dyspnea (shortness of breath) are the most common presenting symptoms among lung cancer patients, negatively affecting individual performance status and quality of life.[218] In comparison, young patients with breast cancer are usually active and can perform their daily tasks without (or with minimal) limitations. Koo *et al.* (2017) analysed data of 2361 breast cancer patients collected from the English National Audit of Cancer Diagnosis in Primary Care to investigate the most common presenting symptoms of breast cancer patients at diagnosis.[219] This study demonstrated that 83% of patients presented with painless breast lump(s). Besides, only 6% presented with breast pain, 1% presented with back pain, and only 0.3% presented with weight loss. [219] This can be attributed to the nature of the disease not

being destructive to normal organ function unless the patients' disease is advanced/metastatic and invades other organs. Otherwise, poor performance status in non-metastatic breast cancer patients is attributed to uncontrolled comorbidities or frailty syndrome.[220, 221]

In consistence with published data, the present study demonstrated that advanced age was associated with poor PS.[220, 221] However, in my opinion, it is not always clear whether the functional limitations in older cancer patients are due to physical disability, multiple comorbidities, or significant organ dysfunction. The PS score does not actually provide a comprehensive assessment of an individual patient's functional status and can underestimate or overestimate an individual cancer patient's eligibility for standard cytotoxic treatment.[220, 221] For example, a bedridden cancer patient (with a physical disability) is supposed to have a poor PS score (PS= 3-4) because, by definition, she is not able to perform her daily activities independently. As a result, this patient may be allocated for less intensive chemotherapy leading to suboptimal therapeutic outcomes. While in fact, this patient may have normal body organ function and can tolerate cytotoxic chemotherapy to the same extent as for a patient with PS=0. Consistent with published data, this study showed that advanced performance status (PS ≥1) was considered an independent factor of less intensive treatment allocation in older patients.[73, 74] This deviation from standard protocols allocation is supported by the clinical practice of oncology guidelines recommendations as previous studies demonstrated that advanced PS is a prognostic factor contributing to increased chemotherapy toxicity and poor therapeutic outcomes.[222] Less intensive treatment allocation among older patients with PS ≥1 (represented 20%, n=12) was definite as they were all allocated for less intensive treatment. Five of those patients had an organ

dysfunction, and seven were considered at risk of treatment-induced cardiotoxicity. Among this subgroup of patients, one death occurred during the study period, and five cases had a therapeutic failure. Causes of therapeutic failure among those patients could be attributed to overlapped factors, including comorbidities/ organ dysfunction, and under treatment, rather than the age or advanced PS alone.

Unexpectedly, a baseline PS=0 was not always associated with intensive cytotoxic treatment allocation among older patients recruited in KCCC as 20% (n=9) of patients received less intensive protocols. This subgroup of older patients had a comparative general health condition and a limited number of comorbidities (range 0-3) to their younger counterparts. Besides, none of those patients had an organ dysfunction at baseline. This deviation in breast cancer management plan among older patients could be misinterpreted as "age-bias" in the decision-making. However, the prospective nature of the present study allowed investigating and reporting the actual causes that led the treating oncologist to allocate patients for treatment protocols other than intensive standard protocols. Among those nine patients, two patients were ineligible for standard anthracycline-based protocol due to a history of embolism, two patients refused the initial treatment protocol recommended by their treating oncologists, and five patients were considered at risk of treatment-induced cardiotoxicity.

These findings demonstrated that age was a major factor that negatively affected the correlation between clinically eligible baseline performance status (PS=0) and intensive treatment allocation. This was attributed to older patients being considered at a higher risk of intensive-treatment-induced cardiotoxicity. The performance status is a subjective score and does not actually provide a comprehensive assessment of an individual patient's general condition. For example, an oncologist may consider an

elderly patient fit (PS=0) and can tolerate standard treatment, and another oncologist may speculate that being elderly precipitates limitations in the performance status and treatment intolerance. This may introduce bias in assessing patients with advanced age. In my opinion, neither PS nor chronological age is sufficient to crucially explain whether patients were clinically ineligible for intensive treatment or were undertreated. Geriatric assessment tools have been developed to provide a better evaluation of the general health condition of older patients.[193] Applying comprehensive assessment tools in oncology clinics is quite challenging because of time constraints and the effort required to produce a final comprehensive evaluation of an older patient's status.[71] In KCCC, treatment allocation was dependent on the PS rather than geriatric assessment tools. In parallel, age-related limitations and vulnerabilities among the older age cohort were identified based on the American Society of Clinical Oncology (ASCO) guidelines for the research purposes.[71] Data showed that only 18.3% (n=11) of older patients had some degree of age-related limitations. The incidence of geriatric conditions in the present study was consistent with the William GR and CALGB 369901 (Alliance) studies.[223, 224]

Besides, older patients with geriatric conditions had different performance status scores (range 0-2) rather than absolute advanced scores in the present study. The documented conditions were sleep disorders, physical disability, osteoporosis, and chronic pain (Figure 3.4). Other studies reported higher incidence of dementia among older patients with cancer, which negatively impacted a patient's quality of life and therapeutic outcomes.[225-227] Dementia could be under-represented amongst older patients in KCCC because cognitive disorders were documented as medical history rather than formally screened during baseline assessment. Unfortunately, the majority

of older patients did not undergo a cognitive function assessment prior to cancer diagnosis, so there is a possibility of undiagnosed dementia cases.

In the literature, many studies correlated frailty and age-related conditions with poor quality of life in older patients, and that concept also contributed to less intensive treatment allocation in older patients.[69, 228, 229] In my opinion, detecting geriatric conditions among older patients does not always indicate frailty syndrome or poor performance status. Some conditions may be associated with minimal accepted limitations as they are not associated with physiological organ function changes, and the pharmacokinetic and pharmacodynamics of chemotherapeutic agents are not affected. For example, physical limitations due to disability, vision impairment, sleep disorders, or chronic pain are not barriers to allocating cancer patients for intensive treatment. These conditions are manageable with appropriate assessment and intervention if indicated instead of relying on simple assessment scales that may lead to excluding patients from being allocated for intensive treatment. In such cases, maximizing therapeutic outcomes and maintaining a good quality of life is a major challenge in clinical practice.

4.1.1.3 Baseline comorbidities

The literature has extensively studied measuring comorbidity burden in older cancer patients since management guidelines do not contain definite statements concerning patients' eligibility for standard intensive cytotoxic treatment.[224] Retrospective studies focused on investigating the impact of comorbidity burden on treatment toxicity, quality of life, and survival rates rather than treatment allocation patterns.[230-234] This section discusses the prevalence of comorbidities among cancer patients, correlations between baseline comorbidities and cancer management. Besides, this

section emphasizes the requirement for effective assessments of older patients' vulnerabilities in clinical practice to enhance cancer treatment allocation and outcomes.

Before addressing the complexity in assessing older cancer patients with comorbidities, it is crucial to understand whether comorbidity burden and cancer are correlated. Comorbidities are associated with physiological abnormalities, which raises a crucial debate whether chronic comorbidities are associated with increased risk of cancer incidence or aggressiveness, or cancers are associated with increased risk of chronic comorbidities among older patients? According to the U.S Medicare population, the prevalence of comorbidities in females aged 65 years and above is similar between breast cancer patients and cancer-free cohorts (equals 32%), indicating that comorbidity burden and breast cancer risk (or vice versa) are not correlated.[235] In comparison, lung and colorectal cancers are associated with a higher prevalence of comorbidities (53% and 41%, respectively) compared to breast cancer. For example, a higher incidence of congestive heart failure (CHF) is reported in patients with lung and colorectal cancers (12.4% and 11.6%, respectively) compared to cancer-free cohorts (6.9%). Besides CHF, COPD is reported in 33.6% of lung cancer patients. On the other hand, diabetes is reported in 17.2% of colorectal cancer patients.[235] These statistics suggest that the comorbidity burden among cancer patients varies depending on the characteristics of the primary tumour, organs involved, and risk factors. The risk of both colorectal cancer and diabetes significantly increases with advanced body weight and metabolic syndrome, while the risk of both cardiovascular diseases and lung cancer significantly increases with smoking.

When the most commonly diagnosed solid tumours among adults were combined (breast, lung, colorectal, and prostate cancers), the most common documented comorbidities were diabetes (16%), COPD (15.5%), CHF (9.7%), and cerebrovascular disease (6%).[235] Among breast cancer patients specifically, high frequencies of hypertension (21.8%), COPD (19.9%), rheumatoid arthritis (18.6%), and diabetes (17.6%) were reported.[236] Higher incidence of diabetes and cardiovascular diseases were documented among older patients compared to younger patients.

Unlike data presented from previous studies, a higher incidence of asthma was reported in the present study. Family history of asthma, passive smoking, and allergic rhinitis were considered the most common predisposing factors among the middle east population.[237] Also, compared with data presented from previous studies, rheumatoid arthritis and COPD were not detected in the present study. This could be attributed to the absence of the major risk factor (smoking) among females in Kuwait due to social barriers and traditional restrictions. Also, patients had a relatively higher incidence of hypertension, diabetes, and thyroid dysfunction compared to other studies. This could be attributed to the population lifestyle manifested by lack of exercise, advanced body weight, and high intake of unhealthy meals, which increases the risk of metabolic syndrome in general.[238] A lower incidence of CHF was noticed in the present study compared to data from different populations and could also be attributed to the fact that smoking has a crucial role in inducing CHF. It is essential to mention that the number of older patients included in the present study is relatively low to detect higher CHF incidence. Recruiting a larger number of patients and longer follow up is expected to result in a higher incidence of IHD and CHF due to the existence of risk factors (diabetes, hypertension, and advanced BMI) among recruited patients.

Besides comorbidities prevalence, questions were raised regarding the association between comorbidities and stage or aggressiveness of tumours. Søgaard *et al.* (2013) stated that comorbidities were not associated with aggressive types of tumours. The present study's findings were consistent with Søgaard *et al.* (2013), where older patients had dramatically higher prevalence of baseline comorbidities, their tumour characteristics were comparable to younger patients.[239] In fact, older patients recruited in the present study had a higher incidence of early-stage (stage II) breast tumour at diagnosis when compared to younger patients (p-value= 0.046). Yasmeen *et al.* (2011) demonstrated that increased comorbidity burden contributes to higher mammography and early detection of the disease due to constant exposure to healthcare professionals.[240] More details about the disease stage at diagnosis among older patients will be discussed under tumour characteristics (section 4.1.1.5).

4.1.1.3.1 Comorbidities and cancer management

The impact of comorbidity burden on managing breast cancer patients in Kuwait was not investigated before this study. In the literature, investigators focused on correlating the comorbidity burden scores with treatment allocation and outcomes (toxicity and mortality) among cancer patients, as discussed earlier. A limited number of studies correlated comorbidities severity with cancer treatment allocation and outcomes. Houterman *et al.* (2004) investigated the impact of age and serious comorbidities on treatment allocation (surgical therapy, radiotherapy, and chemotherapy protocols) and outcomes in newly diagnosed breast cancer patients who were aged 40 years and above in the southern part of the Netherlands and registered in the Eindhoven Cancer Registry.[241] According to an adapted version of the severity model 'Life Threat' developed by Yanick *et al.* (1998), the investigators classified comorbidities based on

their severity.[242] Results showed that patients aged 80 years and above had a significantly higher prevalence of severe comorbidities than those aged 40-49 years (80% and 6%, respectively). [241] However, all patients aged 40 years and above were treated similarly despite the differences in comorbidities severity. Poor prognosis was reported among patients aged 70 years and above with low/moderately severe comorbidities after adjusting for nodal status and treatment allocation. [241] Based on the Houterman *et al.* study, concluding that comorbidities severity was not correlated with treatment allocation is not attributed to the fact that the severity did not affect treatment allocation, but that comorbidities severity was not assessed at baseline in the first place. The investigators retrieved the data and categorized baseline comorbidities severity retrospectively and found that advanced age was associated with higher prevalence of comorbidities severity that negatively impacted diseases prognosis.

Wallwiener *et al*. (2016) included 634 post-menopausal patients with non-metastatic breast cancer retrospectively from the German University Hospital and divided them into two age cohorts (55-64 years and ≥65 years) to investigate the association between age and number of comorbidities with less intensive chemotherapy.[243] After adjusting for disease stage, grade, and number of comorbidities, data showed that the older age cohort received fewer chemotherapy cycles (<3 cycles) than the younger age cohort (56% and 18%, respectively; p-value <0.001) despite having similar tumour characteristics. A comorbidity score of ≥3 conditions was correlated with offering less intensive chemotherapy among older patients, negatively impacting disease-free survival (HR, 0.598; 95 % CI, 0.358–0.963; p-value 0.048).[243]

In comparison, the present study demonstrated that age was the main contributor to less intensive treatment allocation among patients with a limited number (≤2) of

chronic comorbidities. Because, unlike older patients, the co-existence of two comorbidities or less at baseline did not contribute to less intensive treatment among younger patients after adjusting for disease stage and performance status. However, patients with ≥3 comorbidities were 68% less likely to be allocated for intensive treatment than patients with ≤2 comorbidities after adjusting for age [OR 0.32, CI (0.11-0.93), p-value= 0.037]. Stratifying the analysis by age cohort showed that older and younger patients with a baseline comorbidity score of ≥3 were less likely to be allocated for intensive treatment to similar extents. The interpretation may not be definite as the number of this subgroup of patients was too small and insufficiently powered after stratification. Larger sample sizes in subsequent studies may conclusively determine whether age was a contributor to this correlation or whether three comorbidities and more contribute to less intensive treatment despite age.

The impact of baseline diabetes and hypertension on treatment allocation was investigated in the present study because they were the most commonly documented comorbidities in both age cohorts and co-existed in 33.3% and 9.2% of older and younger patients, respectively. Unlike younger patients, older patients with diabetes and hypertension were 89% less likely to be allocated for intensive treatment. This could illustrate the previously discussed results, which showed that having a baseline comorbidity score of two negatively affected intensive treatment allocation among older patients, but not younger patients. Diabetes was the most studied comorbidity among breast cancer patients in the literature. Jarvandi *et al.* (2016) demonstrated that diabetic patients aged 65 years and above enrolled in the prospective Women Health Initiative (WHI) cohort study had poorer treatment tolerance and quality of life than non-diabetic patients. [244-246] This was attributed to exacerbating diabetes-related

microvascular complications, which increase the risk of renal dysfunction, cerebrovascular events, and cardiac events.[190] Besides Jarvandi, a recent retrospective study investigated the association between diabetes severity (based on the Adult Evaluation-27 Index) and adjuvant chemotherapy allocation in 6912 breast cancer patients stratified by age (<70 and ≥70 years).[190] Data showed that the older age cohort was associated with a higher diabetes severity than the younger cohort. In regression analysis, diabetes severity was associated with non-standard chemotherapy allocation (p-value= 0.001). Besides, diabetic patients were less likely to receive standard adjuvant chemotherapy compared to non-diabetic patients, even among the younger age cohort. The previously discussed studies raised concerns regarding the negative impact of diabetes complications on breast cancer management.

Unlike diabetes, hypertension was not correlated with breast cancer management or outcomes in the literature.[190] However, the clinical practice of oncology guidelines recommended caution while offering intensive chemotherapy for patients with uncontrolled hypertension.[156] The correlation between diabetes and hypertension coexistence with less intensive treatment allocation among older patients could be attributed to the associated cardiotoxicity risk, which increases with age.[166] Individual patient characteristics were considered risk factors for cardiotoxicity, such as advanced age, comorbidities, especially hypertension and coronary artery disease, and previous cumulative exposure to cardiotoxic treatments (radiation).[247] The impact of cardiotoxicity risk on breast cancer treatment allocation and the requirement for effective cardiotoxicity risk assessment will be discussed throughout this chapter.

In addition to the previously discussed comorbidities, heart failure was extensively studied among breast cancer patients and correlated with poor therapeutic

outcomes.[248, 249] Pre-existing cardiac dysfunction was associated with early treatment discontinuation and poor disease control, and hence higher mortality rate compared to patients with normal cardiac function.[192] Other comorbidities documented in the present study, such as thyroid dysfunction and osteoporosis, failed to be correlated with cancer treatment intolerance or therapeutic failure.[192]

Beyond treatment allocation, many concerns were raised regarding the impact of increased comorbidity burden on cancer treatment outcomes, including toxicity profiles, patients' quality of life and survival.[192, 231, 250] Wu *et al.* (2019) suggested that increased comorbidity burden was significantly associated with poorer quality of life, including greater pain and poorer sleep quality, among breast cancer patients undergoing chemotherapy despite age. [251] Also, increased comorbidity burden contributed to worse treatment-related fatigue, nausea, vomiting, dyspnea, and loss of appetite. In the present study, older and younger patients undergoing intensive treatment protocols had similar treatment-related toxicity regardless of baseline comorbidities score because they had a good performance status and were considered eligible for intensive treatment. However, higher requirements for dose modifications were documented among older patients compared to younger patients, whether adjusted or stratified by treatment allocation. Data illustrated that age was the main factor correlated with requirements for treatment modifications rather than intensive treatment allocation.

Similarly, the Cancer and Leukaemia Group B (CALGB 49907 and CALGB 361004) trial (briefly discussed in section 1.4.4.3) found that comorbidities were not associated with increased treatment-related toxicity among early-stage breast cancer patients aged 65 years and above (median= 70; range 65-89 years) with selected performance status

(0-2).[192] However, patients with ≥2 comorbidities were more likely to require treatment modifications than those with <2 conditions (59% and 46% respectively; p-value= 0.03).[182] Dose modification was not correlated with the incidence of toxicity (p-value= 0.21). In exploratory analyses, this trial demonstrated that patients with ≥2 comorbid conditions were at a 15% risk of early treatment discontinuation when compared with patients with <2 comorbid conditions.[182] In the present study, treatment discontinuation occurred in a limited number of patients (n=7, three younger and four older patients) and was attributed disease progression and therapeutic failure rather than comorbidity burden. The CALGB 49907 and CALGB 361004 trial and other studies reported crucial evidence regarding the impact of negative impact of baseline comorbidities on breast cancer treatment management and outcomes.[252]

Baseline comorbidity burden was associated with an increased risk of less intensive treatment allocation among older patients compared to younger patients with breast cancer in Kuwait. This could be attributed to the coexistence of diabetes and hypertension, the most commonly reported in the present study, which have been shown to increase the risk of microvascular complications and hence treatment induced cardiotoxicity. Beyond treatment allocation, comorbidities may contribute to increased the requirement for treatment modification and occasionally discontinuation. In the Kuwait Cancer Control Centre, comorbidities other than cancer were not assessed at baseline, medication appropriateness was not evaluated, and drug-related problems were not investigated in clinical practice. There is an increased requirement for effective baseline assessment to detect drug-related problems at baseline and control chronic comorbidities to prevent complications and enhance treatment tolerance during cancer treatment.

4.1.1.3.2 The requirement for effective assessment of older patients' comorbidities and vulnerabilities in clinical practice of oncolog

The European Society of Breast Cancer Specialists (EUSOMA) and the International Society of Geriatric Oncology (SIOG) multidisciplinary task force stated that the decision-making process of older breast cancer patient management should consider different aspects, including physiological age and life expectancy rather than chronological age.[253] The ASCO guidelines for Geriatric Oncology encourage clinicians to apply their validated life expectancy estimators for selected older patients to enhance cytotoxic treatment allocation and avoid over or under treatment.[71]. Unfortunately, both advanced age and comorbidities were correlated with less intensive treatment allocation in the present study despite the fact that comprehensive baseline assessments were not applied by the oncologists and comorbidities were quantified and scored rather than assessed. In my opinion, the comorbidity burden score does not provide a comprehensive assessment of an individual patient's health status, which may lead to an overestimation or underestimation of patients' eligibility for cytotoxic treatment tolerance. According to the literature, not all comorbidities were correlated with poor therapeutic outcomes among breast cancer patients and necessitated nonstandard chemotherapy allocation. For example, according to Ewert *et al.* (2018), asthma, thyroid dysfunction, and dyslipidemia (reported in the present study) were not correlated with poor therapeutic outcomes among breast cancer patients.[252] On the other hand, cardiovascular diseases and diabetes were correlated with poor quality of life and therapeutic outcomes among breast cancer patients, as will be demonstrated throughout this section.

Hypertension and diabetes were the most commonly documented comorbidities among patients in the present study and were correlated with less intensive treatment when they co-existed at baseline. As reported, diabetes and hypertension were associated with increased effectiveness drug-related problems (uncontrolled condition) and effectiveness drug-related problems (undiagnosed condition). Uncontrolled diabetes is concerning in managing cancer patients even when it exists as single comorbidity. This is due to diabetes-related microvascular complications, such as neuropathy and nephropathy, which can be augmented by standard cytotoxic treatment. These complications worsen patients' quality of life and contribute to cancer treatment discontinuation, hence therapeutic failure. Diabetes related microvascular complications are not investigated prior to chemotherapy among breast cancer patients in the literature nor in the clinical practice of oncology. They may vary among patients depending on the blood glucose control and anti-diabetic medication compliance. Accordingly, it is not simple to decide whether allocating patients with diabetes for less intensive treatment is justified or not.

There is a growing recognition of the importance of diabetes management among cancer patients in the literature. Flory J *et al.* (2016) discussed diabetes management in cancer patients receiving chemotherapy to prevent acute and subacute complications rather than long-term outcomes, such as dehydration from polyuria, infection, catabolic weight loss, hyperosmolar nonketotic states (HNK), and diabetic ketoacidosis.[254] On the other hand, Shahid *et al.* (2021) discussed the challenges and risks in managing cancer patients with diabetes.[255] Their article included a discussion about the negative impact of diabetes on cancer patients' eligibility for treatment allocation in clinical practice. Among breast cancer patients, diabetes increases the risk

of cardiotoxicity among patients receiving chemotherapy, targeted treatment, or hormonal treatment.[255] In addition, diabetes is significantly associated with neuropathy exacerbation contributing to dose modifications.[255] Shahid *et al.* (2021) suggested initiating diabetes screening at baseline and hyperglycemia management by integrating a multi-disciplinary team (including a pharmacist) in managing cancer patients with pre-existing diabetes.[255] This can be achieved by investigating the blood glucose level (HbA1c) and assessing baseline diabetes-related complications. Besides, assessing diabetes medication appropriateness and considering dose adjustments to achieve glucose level control.[255] In addition, ensuring patient compliance to the prescribed medications and regularly monitoring blood glucose in parallel with cancer management.

Besides diabetes, the Kuwait clinical practice guidelines of oncology considered significant hypertension unfavorable baseline factor that necessitates caution when prescribing anthracycline treatment due to cardiotoxicity concerns.[156] However, the definition of significant hypertension (blood pressure threshold) was not stated in the guidelines. Besides, hypertension was documented in the patient history section of the medical case notes but not assessed or evaluated even though uncontrolled hypertension as a drug-related problem was detected in older and younger patients. The co-existence of hypertension and diabetes at baseline negatively impacted intensive treatment allocation because both were considered cardiotoxicity risk factors. Besides diabetes and hypertension, cardiovascular diseases are correlated with an increased risk of treatment discontinuation and mortality rates among breast cancer patients. Therefore, patients with a history of ischemic heart diseases or at risk of

cardiovascular events require a comprehensive baseline assessment to predict cardiotoxic treatment tolerance (section 4.1.2.1).

In recognition of the valuable requirement for baseline comorbidities assessment, the present research recommends changing the baseline assessment from documenting history of comorbidities evaluating comorbidities (Figure 4.4). Also, to assess baseline drug-related problems and predict subclinical complications pre-cancer treatment.

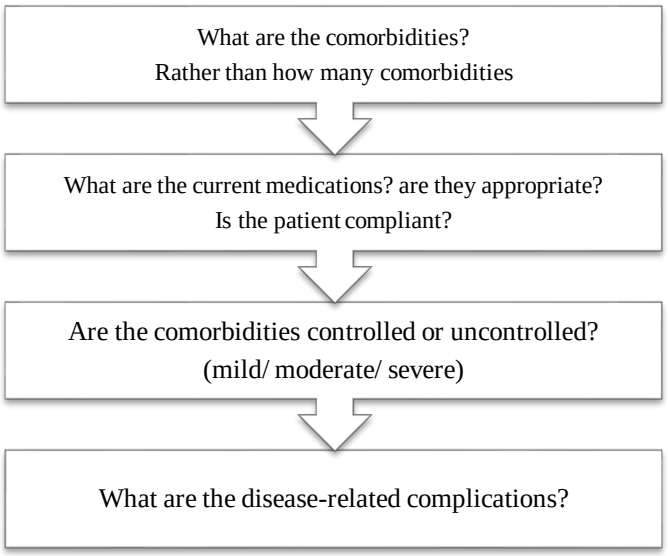

Figure 4.4 Considerations in assessing baseline comorbidities in clinical practice

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Polypharmacy and potential/actual drug-related problems are not usually assessed during cancer patients' baseline assessment in clinical practice. As the arena of geriatric medicine is growing, many studies are being published to emphasize the importance of enhancing medication use among older patients to maximize therapeutic outcomes while minimizing undesirable side effects. In the present study, patients allocated for less intensive treatment had a higher prevalence of polypharmacy when compared to patients allocated for intensive treatment. The less intensive treatment allocation could be attributed to age and comorbidity burden rather than medication burden. This is because the assessment of drug-related problems was carried out for

research purposes and not integrated into baseline assessment otherwise. However, the detection of drug-related problems raises concerns about comorbidities severity and control during cancer treatment. It is hoped to integrate drug-related problems assessment among newly diagnosed cancer patients with history of comorbidities as a routine in the Kuwait Cancer Control Centre to decrease the requirement of treatment modifications as documented in the present study and other studies (discussed in section 4.1.1.3.1).

The only drug-related problem that has been shown to impact treatment allocation was drug-drug interaction among patients taking cardioprotective drugs (warfarin or digoxin). Even though from the oncologist's point of view, patients receiving cardioprotective drugs are not eligible for intensive treatment due to cardiotoxicity risks rather than potential chemotherapy-drug interaction risks. Those patients had at least one requirement for treatment modification (dose delay). According to Lund (2018), the anticoagulant effect of warfarin increases if co-administered with cyclophosphamide or paclitaxel, which is reported in 9% and 11% of patients, respectively.[256] On the other hand, digoxin efficacy decreases if co-administered with cyclophosphamide and doxorubicin, which is reported in 9% and 2% of patients, respectively. In addition, co-administering hydrochlorothiazide with cyclophosphamide increases cyclophosphamide-related myelosuppression, which is reported in 31% of breast cancer patients in the same study.[255] Besides Lund, Christine et al. (2020) found that 27% of patients aged 66 years and above and allocated for cyclophosphamide-based chemotherapy received hydrochlorothiazide.[257] Among those, 11% of patients were hospitalized due to treatment-related neutropenia, and 21% had their breast cancer treatment discontinued.

Christine *et al.* (2020) demonstrated that drug-drug interactions in older breast cancer patients undergoing chemotherapy might lead to serious toxicity and hence treatment discontinuation negatively impacting the therapeutic outcomes.

Evaluating cancer patients with multiple comorbidities is complicated and requires longer time and effort than is usually scheduled for medical oncology clinics. Also, these healthcare services could be beyond the role of the medical oncologists who are responsible for assessing and managing tumours. In order to provide a better baseline assessment for older patients or patients with chronic comorbidities despite age, Balducci *et al.* (2013) and Shahid *et al.* (2021) suggested including pharmacists in the multidisciplinary team and integrating their services into centralised cancer patient care.[255, 258] As a clinical pharmacist, I have managed to evaluate medication appropriateness among breast cancer patients and detect drug-related approblems during this observational study, which is expected to lay foundation of expanding the pharmacist role in the Kuwait Cancer Centre and enhance patients' management. Clinical pharmacy services include different patient care aspects, such as reviewing medication appropriateness, predicting potential drug-related problems, and identifying older cancer patients' vulnerabilities. Besides, clinical pharmacists can recommend appropriate interventions and monitoring plans for better comorbidities control among cancer patients. In addition, they can apply a screening strategy to identify older patients who may benefit from comprehensive assessment tools to assess to predict treatment-related toxicities and enhance treatment allocation.

Compared to the simple performance status (PS) scoring tool applied in the clinical practice of oncology, the Comprehensive Geriatric Assessments (CGA) and chemotherapy toxicity assessment tools require prolonged time and effort to complete.

Therefore, the EUSOMA and SIOG recommend initiating screening assessment among older patients to identify patients that may benefit from the extended assessment tools. Accordingly, clinical pharmacists can identify age-related limitations and discuss the findings with the treating oncologists efficiently.

In general, cancer management is complicated, especially if patients have multiple comorbidities. Effective baseline assessment can be carried out with the assistance of clinical pharmacists in the multidisciplinary team to ensure medication appropriateness and comorbidities control before and during cancer treatment. This eventually will reduce the risk of allocating eligible patients for less intensive treatment and enhance their therapeutic outcomes. Besides, optimizing medication utilization and controlling chronic comorbidities improves the healthcare system's services and decreases disease complications management costs.

4.1.1.4 Other patient characteristics

The Body Mass Index (BMI) and positive family history of breast cancer are other patient characteristics discussed in the literature investigating their impact on cancer management in terms of offering more intensive doses for obese patients and patients with positive family history and subsequent therapeutic outcomes.[240, 259-263] These characteristics will be briefly discussed and compared by age cohorts in this section.

4.1.1.4.1 Body Mass Index (BMI)

In the present study, more than 40% of patients overall were obese, with no significant weight differences detected between the two age cohorts (p-value= 0.22). On regression analysis, BMI and treatment allocation were not correlated. In the literature, obesity was correlated with poor therapeutic outcomes in breast cancer patients receiving chemotherapy. [240, 259, 260, 262] Different studies found an association between

increased weight and advanced tumour stage at diagnosis and high recurrence rate in non-metastatic cases, resulting in decreased survival.[240, 259, 260, 262] In accordance with these findings, obesity/overweight could be one of the factors contributing to more advanced tumour stages at diagnosis among younger breast cancer patients compared to older patients in the present study. In comparison, less advanced tumour stage among older patients could be attributed to higher prevalence of comorbidities and hospital visits, leading to early tumour detection (section 4.1.1.5.1).

The impact of increased BMI on disease response to systemic chemotherapy is controversial. The correlation between the BMI and pathological complete response (pCR) to neoadjuvant chemotherapy was investigated in 295 patients with similar baseline clinical and pathological characteristics (similar breast tumour subtypes) in Hacettep University Cancer Institute, Turkey.[264] Their results showed that increased weight was associated with decreased pathological response. Obese patients had a significantly lower median Recurrence-Free Survival (RFS) compared to patients with normal or lower weight (76 versus 150 months respectively, p-value= 0.03).[264] In contrast to the Turkish study, Thalia *et al.* (2016) found that involvement of lymph vascular invasion, grading 3 tumors, and HER-2 status are independent factors associated with poor pCR but not BMI categories among 324 non-metastatic patients from the Medical Centre- University of Freiburg, Germany and.[265] Compared to the published literature, an advanced BMI (≥25) was detected in patients who relapsed during post-treatment follow-up in the present study; however, the interpretation is not definite as the number of this subgroup of patients was too small to detect significance and was insufficiently powered. A larger number of patients and longer follow up duration will demystify the impact of advanced baseline BMI on disease control.

There is still a lack of evidence about the requirement for offering higher chemotherapy doses for cancer patients with advanced body weight, but this is not compromising their management. On the other hand, decreased body weight is considered an unfavorable sign of malnutrition among cancer patients, which is believed to decrease survival rates. According to the Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR), maintaining a healthy body weight may improve breast cancer survival.[266] Also, it decreases the risk of other comorbidities, such as diabetes, hypertension, and dyslipidemia; consequently, the risk of non-cancer-related mortality decreases.

4.1.1.4.2 Family history

Since the late 1980s, a positive correlation was established between positive family history of breast cancer and increased incidence rates. Brewe *et al.* (2017) found that females with a positive family history of breast cancer in the UK were at a 3.5-fold higher risk of developing breast cancer than the general population.[267] Also, Lynch *et al*. (1988) found a significant association between having a positive family history and breast cancer diagnosis at young ages.[268] In the present study, older and younger patients had a similar prevalence of family history (30.6% and 33.3% respectively, p-value= 0.8) and was comparative to Brewer and Lynch. Accordingly, a higher incidence of breast cancer incidence at younger age among patients with family history was not detected in the present study.

The correlation between positive family history and poor survival outcomes is controversial. It was suggested that positive family history of breast cancer was associated with poor survival. Surprisingly, some studies correlated positive family history with favourable survival outcomes.[269-271] Based on the previous debate,

offering more intensive treatment for breast cancer patients with positive family history was not supported.

4.1.1.5 Individual tumour characteristics assessments

Besides individual patient characteristics, tumour characteristics assessment is a crucial element in the treatment decision-making process. Breast tumour subtypes guide designing individualized management plans and defining therapeutic targets. Theoretically, aggressive tumour subtypes require intensive treatment to achieve disease control and therapeutic success. Before addressing the correlation between tumour characteristics and treatment allocation, the debate raised about the correlation between tumour aggressiveness and age at diagnosis and whether older age is associated with more aggressive breast tumour subtypes is worth mentioning.

In the literature, various studies presented different conclusions on the impact of age on breast tumour characteristics. The majority of these studies suggested that advanced age was associated with more favourable histopathological tumour characteristics but advanced stages at diagnosis. [264, 272-276] This was attributed to many factors, such as lack of awareness of the disease signs and symptoms, living in deprived areas, less access to healthcare facilities or other social/economic factors.[264, 272-276] Sections 4.1.1.5.1 and 4.1.1.5.2 will compare the findings from the present study.

4.1.1.5.1 Tumour stage

In the present study, no statistical differences were detected in the status of disease metastasis between the two age cohorts (p-value= 0.11). However, younger age was associated with more advanced (stage III) breast tumours among non-metastatic cases based on the TNM scoring system (Table 3.1). In contrast to the established knowledge in the literature, older age was associated with less advanced (stage II) breast tumour

stage at diagnosis in Kuwait. It was believed that a high prevalence of comorbidities among the older age cohort was correlated with increased hospital visits and direct referrals to the "Fast Breast Cancer Diagnostic Clinic". This clinic is responsible for screening suspicious cases and directing the confirmed cases to the oncology department with the necessary paperwork completed in a short timeframe. In Kuwait, this clinic is part of the governmental health services and not subjected to monetary charges. A similar screening approach is also applied in other cancer hospitas, such as the Cromwell Hospital and Mayo Clinic, and referred to as 'one-stop clinic' but they are private healthcare services.

In addition, the Kuwait Cancer Control Centre implemented the "National Program for Early Diagnosis of Breast Cancer", which is responsible for organizing an annual breast cancer awareness campaign. [277] The program provides various activities and events for the public, such as marathons, lectures, TV programs, and interviews with breast cancer survivors to promote a healthy lifestyle and raise awareness about breast cancer prevalence, signs, symptoms, treatment, and survival rates nationally and globally. [277] This national program assisted in familiarizing females (mainly aged 40 years and above) about the Breast Self-Exam (BSE) and the importance of early detection in improving breast cancer treatment outcomes and survival rates. [277] Also, this program assisted in familiarizing the population with the healthcare centres providing mammograms across the country.[277]

Unlike older patients, decreased comorbidity burden among younger patients contributed to less hospital visits before breast cancer diagnosis. The lack of direct contact with healthcare professionals in healthy patients may delay early breast tumour detection. Besides, as discussed in section 4.1.1.4.1, the present study could be the case

for the correlation between advanced BMI and being diagnosed with advanced tumour stage.

4.1.1.5.2 Histological and molecular subtypes

Different population-based studies demonstrated a significant correlation between HER-2 and hormonal receptors overexpression with breast tumour prognosis.[278-281] HER-2 overexpression was considered a strong prognostic factor associated with poor disease control and survival rates. Multiple studies detected significant correlations between HER-2 positive status and increased tumour size, grade, and stage. [278-281] Histology reports consistently demonstrated that HER-2 overexpression was more common in invasive ductal carcinomas (IDC) than in invasive lobular carcinoma (ILC) and invasive mammary carcinoma (IMC).[282] This may explain the high prevalence of HER-2 overexpression (51.7%) among younger and older patients to similar extents in the present study as they had similar tumour histology with IDC more predominant.[283, 284]

Also, previous studies detected higher hormonal receptor expression in post-menopausal patients than younger patients. [285-287] Sami *et al*. (2000) investigated the impact of age on tumour characteristics in 307,115 patients aged 55 years and above registered in the San Antonio breast cancer database and the Surveillance, Epidemiology and End Result program (SEER) registry. They found that advanced age was significantly associated with more favourable tumour biology and hormonal expression (p-value< 0.001).[288] In this study, the proportions of oestrogen receptor overexpression were 68% and 84% in breast cancer patients aged between 55-64 years and 85 years and above, respectively. [288] In comparison, results from the present study suggested that the hormonal receptor expression was similar between younger and

older patients in Kuwait. The medical literature discussed multiple hormonal-related risk factors associated with hormonal breast tumours due to increased oestrogen exposure. The risk factors include early age of first menstruation, late age of first childbirth, and late-onset of menopause. [289, 290] Besides those factors, obesity could contribute to increased prevalence of hormonal breast tumours among females aged less than 50 years, which was noticed in our study.[289, 291]

4.1.2 The impact of treatment-induced cardiotoxicity risk on treatment allocation

Findings from the present study demonstrated that, unlike younger patients, the association between a limited number of comorbidities (<3 conditions) and a baseline PS=0 with standard intensive treatment allocation was negatively affected by advanced age. This treatment allocation in eligible older patients could be wrongfully attributed to age bias because patients did not exhibit a clear contraindication for anthracycline treatment. However, according to the oncologists' notes, those patients were considered at high risk of chemotherapy-induced cardiotoxicity that may augment patients' health condition and lead to treatment discontinuation. In comparison, eligible patients from the younger age cohort were allocated for intensive cardiotoxic treatment unless they exhibited a clear contraindication, such as cardiac dysfunction, history of IHD, embolisms, or myocarditis.

The breast cancer management guidelines recommend against allocating patients at risk of cardiotoxicity for intensive doublet anthracycline-based chemotherapy but do not provide methods or validated tools to assess individual patient risk. Occasionally, oncologists apply traditional cardiovascular risk estimators to assess selected cancer patients' eligibility for intensive treatment. All traditional cardiovascular risk scores

consider age as a main risk factor for cardiac diseases. This includes the classic Framingham Risk Score, the Athero-Sclerotic Cardiovascular Disease (ASCVD) risk estimator published by the American College of Cardiology (ACC) and the American Heart Association (AHA), the UK QRISK score, the ASSIGN score from the Scottish Heart Health Extended Cohort (SHHEC) and recommended by the Scottish Intercollegiate Guidelines Network (SIGN), and New Zealand cardiovascular disease risk assessment charts.[292-296] Besides age, being overweight, race (black populations), smoking status, and specific comorbidities (hypertension, diabetes, and dyslipidemia) were included in the risk estimators' criteria. Family history of cardiac diseases and deprivation were also considered predisposing risk factors in the ASSIGN score. The impact of smoking as a risk of cardiotoxicity was not considered in the present study because of cultural and traditional barrier among females in Arabian Gulf countries. Smoking is not common among females in Kuwait, and even if patients were smokers, they would feel uncomfortable being asked about it, and they would never admit it

According to Law *et al.* (2017), the classic Framingham risk score underestimated the cardiotoxicity risk among breast cancer patients with HER-2 receptor overexpression and received anthracyclines, or HER-2 targeted treatment, or both.[297] Consistent with Law *et al.*, the ASCVD risk estimator underestimated the cardiotoxicity risk among patients recruited in the present study. The underestimation was still significant even after stratifying the correlation by age cohort. Applying risk assessment tools was not effective in the clinical practice of oncology because they do not account for the risk of administering cardiotoxic drugs, which is considered an additional crucial risk criterion, especially among younger patients.

Standardized validated risk estimators that effectively assess chemotherapy-related cardiotoxicity among cancer patients have not been established yet. Relying on the baseline LVEF value is insufficient to predict patients at high risk of cardiotoxicity unless the LVEF value is below 60%, as demonstrated in the present study. As a result, the treatment allocation of older patients with or without potential cardiotoxicity risk factors depends primarily on individual oncologists' decisions. In contrast to older patients, the main cause of treatment-induced cardiotoxicity among younger patients is still unknown but usually attributed to previous exposure to anthracycline treatment.[298-300] Unfortunately, the cardiotoxicity risk can not be predicted among younger patients because they still develop cardiac dysfunction even in the absence of the potential risk factors. This created a major challenge in the clinical practice of oncology not only in KCCC but also worldwide.

4.1.2.1 The requirement for effective cardiotoxicity risk assessment

Florescu and Nistor (2019) described treatment-induced cardiotoxicity in breast cancer patients as "a well-known yet unresolved problem".[301] Both breast cancer and cardiovascular diseases are considered major healthcare issues associated with increased morbidity and mortality that significantly contribute to increased healthcare costs worldwide. In recognition of this, multiple articles were recently published providing different approaches to improve baseline cardiotoxicity risk assessment in cancer patients but have not been integrated into standardized guidelines yet.

Ezaz *et al.* (2014) developed a 7-risk scoring tool to predict the 3-year trastuzumab-induced cardiotoxicity risk among patients aged 65 and above (mean 73.6 years, SD 5.3) and operated for non-metastatic breast cancer.[171] The predisposing factors

correlated with the event of cardiotoxicity were advanced age (80-94 years), coronary artery disease, hypertension, diabetes, atrial fibrillation or flutter, renal failure, and previous exposure to chemotherapy.[171] The risk scores were calculated by adding a point for each predisposing factor and then classified into low (0-3), medium (4-5), and high (≥6) risk strata. Overall, the 3-year cardiotoxicity rate was 19%. The low, medium, and high risk of cardiotoxicity among older patients receiving trastuzumab treatment was 16%, 26%, and 39%, respectively. In this article, exposure to anthracycline-based chemotherapy and non-anthracycline-based chemotherapy was associated with a 1.93-fold and 1.64-fold higher risk of cardiotoxicity. This risk assessment score demonstrated the impact of baseline characteristics as predisposing factors for trastuzumab-induced cardiotoxicity. However, it can not be generalized or applied to all breast cancer populations because the data were extracted retrospectively from 1664 patients with a mean age of 73.6 (SD 5.3), limiting the risk assessment model utilization in clinical practice. Further prospective studies with larger sample sizes and different age cohorts are expected to develop an applicable cardiovascular risk assessment score.

Besides Ezaz, Lyon *et al.* (2020) suggested general principles and evidence-based recommendations for baseline cardiotoxicity risk stratification in all cancer patients, including patients with haematological tumours, who are considered candidates for cardiotoxic treatment.[302] They published a position statement from the Cardio-Oncology Study Group of the Heart Failure Association of the European Society of Cardiology in collaboration with the International Cardio-Oncology Society (HFA-ICOS). This multidisciplinary cardio-oncology approach stratified the cardiotoxicity risk as low, medium, high, and very high risk based on assessing the previously

discussed cardiovascular medical and lifestyle risk factors in parallel with other baseline factors, including cardiac biomarkers (troponin and brain natriuretic peptide), electrocardiogram (ECG), HbA1c, glycated haemoglobin, NT-proBNP, N-terminal pro-brain natriuretic peptide. This is the only approach accounting for the cardiotoxicity risk associated with all individual chemotherapeutic agents, targeted therapies, and hormonal therapies and stratifying the severity risk based on the predisposing factors.[302] Also, this approach encourages the multidisciplinary cardio-oncology team to discuss the clinical decision of treatment allocation and balance the efficacy and toxicity risks before excluding cardiotoxic treatment among patients identified with high risks.

The validation of the HFA-ICOS score was recently tested by Battisti *et al.* (2021) among 931 breast cancer patients with a median age of 54 years (range 24-83 years).[303] Their study concluded that trastuzumab-related cardiotoxicity severity increased significantly with the HFA-ICOS score, which contributed to identifying high risk patients. In my opinion, the HFA-ICOS score provides valuable evidence-based guidance for assessing baseline cancer treatment-induced cardiotoxicity. However, it does not provide risk stratifications for combined predisposing factors, such as multiple cardiotoxic agents co-administration.

The previously discussed evidence illustrated that applying effective approaches for cardiotoxicity risk assessment and early detection among cancer patients requires establishing a cardio-oncology multi-disciplinary team, which is an emerging specialty focused on providing cardiac care for cancer patients.[304] Through this team, oncologists and cardiologists can collaborate to assess the predisposing baseline

factors and predict individual cardiotoxicity risk.[301] Also, this team is expected to enhance intensive treatment allocation and minimize the risk of undertreating eligible patients. Additionally, cardiologists can monitor cardiac function and biomarkers to detect sub-clinical cardiac dysfunction for high-risk patients and prescribe cardio-protective drugs, such as an Angiotensin Converting Enzyme Inhibitor (ACE-I) or Beta Blocker (BB), for selected patients when indicated. The cardio-oncology multi-disciplinary patient care will minimize cardiac morbidity and mortality in cancer patients.

Beyond clinical practice, it is hoped that through this specialised field, more research will be conducted to fully understand cancer treatment-induced cardiotoxicity mechanisms and risks to provide better preventing, monitoring, and predicting strategies among breast cancer patients.

4.1.3 Patient involvement in the decision-making process of breast cancer management

Undertreatment among older breast cancer patients is not always attributed to age bias in treatment allocation or patient ineligibility for intensive standard treatment.[305] Cancer management is complicated and involves patients and their relatives in an extended discussion to explain treatment options, complications, and life expectancy. Cancer treatment delivery requires two sides of agreement on the treatment plan: first, the treating oncologist suggests the recommended treatment based on standardized guidelines and individual patient assessment. Second, patients' agreement to the recommended treatment. Occasionally, patients reject the allocated treatment plan or request modifications due to multiple factors, such as personal concerns or beliefs,

social or economic barriers.[121, 123] The oncologists respect individual patient opinions while emphasizing the potential risks and consequences of such a choice.

Cancer management plans are not confirmed unless patients sign an informed consent form indicating their agreement and awareness about treatment-relevant information, such as treatment protocol, dose, duration, side effects, and expected therapeutic outcomes. Aligning allocated treatment to patients' desires is a critical element in the ongoing decision-making process of cancer management that extends from the time of diagnosis before starting any treatment until the end of the last intervention (Figure 4.5).

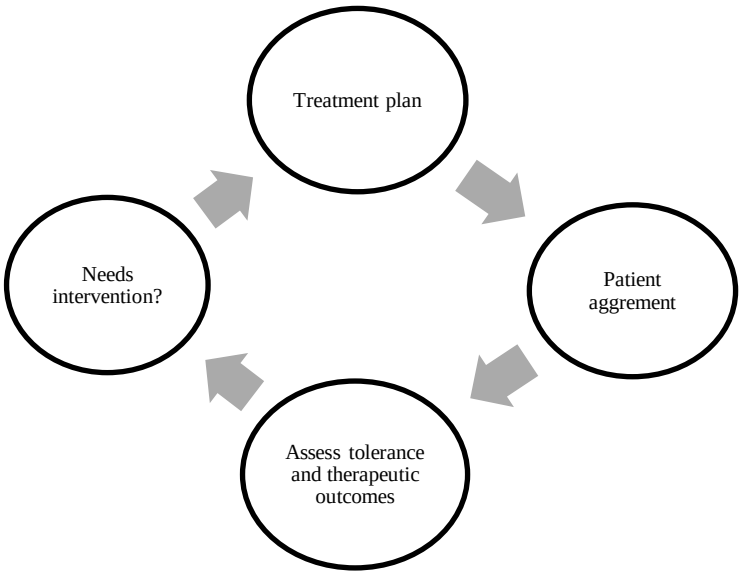

Figure 4.5 The ongoing relationship between cancer patients and their treating oncologists during cancer management

In the present study, the majority of patients accepted the offered treatment plan. Only 3.8% of patients rejected the initial treatment plan, representing 10% and 0.8% of older and younger patients, respectively. Among patients who accepted the initial treatment plan, 5% of older patients received ≤ 3 chemotherapy cycles but refused to continue with the same protocol. Overall, 15% of older patients interfered with the treatment

plan compared to 0.83% of younger patients. This deviation in treatment allocation was more common in older patients aged 70 years and above than in younger patients due to toxicity concerns or intolerance (Table 3.8).

According to the data collected from MD Anderson Cancer Center between Sept/1989 and Sept/2004, 2.2% of patients aged 80 years and above refused to receive any treatment against their treating oncologist recommendations.[305] Also, in a retrospective Taiwanian population-based study of 35,059 newly diagnosed breast cancer patients, investigators found that age, cancer stage, and increased comorbidities burden were significantly associated with refusing or delaying the allocated treatment by the patients (OR = 1.30–19.69; p-value <0.05). [305] This resulted in a significant decrease in the 5-year survival of this group of patients compared to patients who received their allocated treatment as recommended (45% and 84%, respectively; p-value <0.05). This indicated that patients' interference against their oncologists' recommendation negatively impacted the therapeutic outcomes and survival.

Hershman *et al.* (2006) investigated the timelines of initiating adjuvant chemotherapy among non-metastatic patients aged 65 years and above and reported that 47% and 37% of patients initiated their chemotherapy within one month and two months of diagnosis, respectively. [306] Beyond that, 6% of patients initiated their chemotherapy between 2-3 months, and 10% of patients delayed it for more than three months. On regression analysis, Hershman found that being diagnosed with early-stage tumours and hormonal receptor positivity were associated with delaying adjuvant chemotherapy delivery.[306] This was attributed to patients being satisfied with the hormonal treatment or at lower risk for early disease relapse from the patient's point of view. In contrast to patients' expectations, this study demonstrated that delaying

chemotherapy delivery for more than three months was associated with increased disease-specific mortality and overall mortality because of increased tumour burden and drug-resistance risks and hence therapeutic failure.[306]

At the start of the research, it was thought that the reputation of chemotherapy side effects and how they were being presented in the media might have directed the patients to request less intensive chemotherapy regimens to minimize the suffering and maintain an acceptable quality of life during cancer treatment. Surprisingly, that was not the case in the present study population. Being familiar with the availability of targeted and hormonal therapies as newly developed treatment options was the main factor directing patients to delay or reject systemic cytotoxic chemotherapy. There was an overall lack of awareness about targeted therapies indication and utilization among cancer patients and their relatives. Patients' statements were documented during the decision-making process to understand the reasons behind rejecting the recommended treatment plan. Some patients thought they were not being offered targeted therapies because they were expensive compared to traditional cytotoxic chemotherapy and not because they would not benefit from them. Other patients did not believe that there were international standardized guidelines for cancer management applied in Kuwait. More than 29 patients either refused to start or discontinued their treatment and traveled to the UK, USA, or France, believing that superior guidelines were being followed and more treatment options (newer targeted therapies) would be offered. External treatment is an available option provided by the Ministry of Health (MOH) to Kuwaiti nationals with cancer, critical or incurable conditions, children, or candidates for complicated surgery. Patients not satisfied with the local healthcare services can request a case report and apply for an interview with a specialized

committee that reviews and assess patients' eligibility for external treatment. Accordingly, eligible patients are referred to the Higher Medical Committee to arrange suitable external funded treatment and start the travel procedures.

In contrast to older patients, few factors played a critical role in the decision-making process of breast cancer management among younger patients, such as being diagnosed with more advanced disease, longer life expectancy, and individual patients' desire for a cure.[307] These concerns supported the requirement for intensive treatment allocation among younger patients despite other risks if they existed, such as comorbidity burden or clinical ineligibility, as long as there was an agreement between patients and oncologists to consider the challenges.

4.2 Treatment allocation patterns in older breast cancer patients

The concept of cancer patients management should aim to improve patients' quality of life rather than quantity of life alone. Traditionally, intensive cytotoxic chemotherapy protocols were the treatment of choice for cancer patients because they were associated with improved therapeutic and survival outcomes compared to less intensive protocols. However, intensive chemotherapy protocols are not always associated with treatment completion and therapeutic success among older patients, making treating older patients challenging. Treatment tolerance and outcomes depend highly on the individual patient and tumour characteristics, necessitating a comprehensive baseline assessment and individualized treatment allocation. In the literature, less intensive treatment was referred to as "undertreatment" and "suboptimal treatment" even though it could be more appropriate than intensive treatment, which might precipitate a wide range of toxicity for selected patients. In clinical practice,

treatment guidelines were not always adhered to when allocating older patients for treatment protocols due to toxicity and treatment discontinuation risks. There has been an ongoing debate about the chemotherapy protocols associated with maximum therapeutic benefits and minimum toxicity profiles among patients with advanced age or multiple chronic comorbidities. Unfortunately, there is no specific or simple answer to this question due to the vast heterogeneity in older patients' characteristics. The following section will address evidence-based rational selection of chemotherapy protocols in older patients with breast cancer to enhance the individualized patient management concept. This will be compared to the findings from the present study.

4.2.1 The rational of less intensive chemotherapy allocation

Before introducing anti-HER-2 targeted treatment to the marketplace, anthracyclines were considered the most effective chemotherapeutic agents in managing high-risk breast cancer patients despite breast tumour subtypes. The Early Breast Cancer Trialists' Collaborative Group (EBCTG) meta-analysis of 10-year outcomes of different chemotherapeutic protocols among 100,000 patients from 123 randomized trials concluded that an anthracycline-based chemotherapy protocol followed by taxane treatment showed superior therapeutic outcomes when compared to non-anthracycline chemotherapy in high-risk patients despite breast tumour characteristics, such as nodal status, hormonal status, tumour size, and tumour differentiation. [308] In this meta-analysis, dose-dense (bi-weekly) anthracycline chemotherapy had superior outcomes than standard dosing intervals (every 3 weeks). Non-anthracycline based chemotherapy protocols were considered inferior less intensive protocols.

Doxorubicin is the most commonly prescribed anthracycline drug for breast cancer management; however, it is associated with a higher risk of cardiotoxicity than other

anthracyclines such as epirubicin (Table 1.9). Ibrahim *et al.* (2000) compared the clinical outcomes of adjuvant doxorubicin-based chemotherapy between two age cohorts (patients aged between 50-64 years and patients aged 65 years and above) with non-metastatic breast cancer in the M.D Anderson Anderson Cancer Center.[309] The two age cohorts had similar baseline patient and tumour characteristics, including performance status, hormonal receptor status, tumour size, and nodal status. No statistical differences were detected in the treatment-related outcomes, including haematologic toxicities, non-haematologic toxicities, disease recurrence, disease-free survival, and overall survival between the two age cohorts. This study illustrated that older patients with good performance status and cardiac ejection fraction have similar tolerance and therapeutic outcomes to doxorubicin-based chemotherapy to their younger counterparts. [309]

In the present study, doxorubicin-based chemotherapy followed by taxane was considered the standard anthracycline-based protocol. Epirubicin-based chemotherapy was prescribed for two patients (without taxane) to decrease the cardiotoxicity risk. Ryberg *et al.* (2008) reported that epirubicin is also associated with a high risk of cardiotoxicity that reaches 11.4% if co-existed with multiple factors, including patients' age, increased cumulative doses, history of cardiac disease, history of mediastinal irradiation, and hormonal treatment.[310] It is crucial to mention that while cumulative doses of epirubicin are associated with a relatively reduced cardiotoxicity risk than doxorubicin, they are also associated with reduced efficacy and increased tumour burden.[311] The literature demonstrated that doxorubicin is considered superior to epirubicin among eligible patients in terms of therapeutic outcomes. Epirubicin is

not always considered a safe anthracycline alternative for older patients with multiple baseline cardiotoxicity risk factors.

Anthracycline cardiotoxicity is dose-related; however, reduced anthracyclince dodses are not recommended because they were associated with compromised anti-tumour activity and increased mortality in all breast tumour subtypes and not recommended in managing patients with anticipated high toxicity risks. The literature demonstrated that doxorubicin is considered superior to epirubicin among eligible patients in terms of therapeutic outcomes. Epirubicin is not always considered a safe anthracycline alternative for older patients with multiple baseline cardiotoxicity risk factors. Also, reduced anthracycline doses are not recommended. Patients considered candidates for cytotoxic chemotherapy but ineligible for anthracyclines were allocated for non-anthracycline basedanthracycline-based protocols, such as taxane and cyclophosphamide (TC) combination or cyclophosphamide, methotrexate, and fluorouracil (CMF) combination. Also, doublet chemotherapy protocols allow dose modifications when required without compromising the anti-tumour activity.[164] Therefore, patients considered candidates for cytotoxic chemotherapy but ineligible for anthracyclines were allocated for non-anthracycline-based protocols, such as taxane and cyclophosphamide (TC) combination or cyclophosphamide, methotrexate, and fluorouracil (CMF) combination. In the present study, patients from the older age cohort considered unsuitable for anthracycline-based chemotherapy were allocated for single-agent chemotherapy (taxane monotherapy) ± trastuzumab treatment despite having accepted performance status (PS= 0 or 1). None of the older patients were allocated for the classic cyclophosphamide, methotrexate, and fluorouracil (CMF) combination and only one patient received docetaxel and cyclophosphamide (TC)

combination. Based on the ELDA randomized phase III trial findings, taxane (docetaxel) monotherapy did not improve survival among patients aged between 65-79 years and operated for breast cancer compared to CMF combination.[169] Taxane monotherapy was associated with a higher prevalence of fatigue, hair loss, dysgeusia, diarrhoea, abdominal pain, and neuropathy that significantly worsened individual patients' quality of life compared to the CMF combination. Besides these side effects, taxane monotherapy precipitated more cardiac and skin toxicities compared to the CMF combination. On the other hand, the CMF combination precipitated higher incidence of haematological toxicity, nausea, and mucositis. Unlike less intensive taxane monotherapy allocation reported in the present study, the ELDA trial supported treating older breast cancer patients with classic CMF combination.

The introduction of trastuzumab as a targeted treatment changed the prescribing patterns in clinical practice as it played a crucial role in controlling HER-2 positive breast tumours when combined with classic cytotoxic chemotherapy protocols. After approving trastuzumab treatment in the adjuvant management of early breast cancer in 2006, Giordano *et al*. (2012) detected a significant decline in anthracycline-based protocols utilization in 4458 patients aged 65 years and above and registered in the Medicare database to minimize the cardiotoxicity risk among older patients. [312] This change in the treatment allocation pattern in older patients was accompanied by increased taxane-based protocols utilization. According to Giordano, 51% and 32% of older patients received taxane-based and anthracyclines-based protocols by 2008 despite HER-2 receptor status since the guidelines recommended not omitting cytotoxic treatment and offering less cardiotoxic chemotherapy for eligible patients.[312] In addition to the Medicare database cohort, the marketscan cohort

showed that docetaxel utilization increased from 34.4% to 61.7% between 2005 and 2008 among HER-2 positive patients. [312] At that point, non-anthracycline chemotherapy was considered a nonstandard less intensive treatment.

Essential efficacy and toxicity-related questions were raised while integrating trastuzumab in a rational prescribing frame among breast cancer patients, which are:

1. Does anthracycline-based protocol (dose-dense or standard interval) have superior therapeutic outcomes compared to non-anthracycline-based protocol when combined with trastuzumab treatment in managing HER-2 breast tumours?

2. Does trastuzumab targeted monotherapy (omitting cytotoxic chemotherapy) have comparable therapeutic outcomes to trastuzumab-cytotoxic chemotherapy combination protocols in managing HER-2 breast tumours?

Answering the previously addressed questions would clarify the rational of less intensive chemotherapy protocols in patients receiving trastuzumab. Salmon *et al.* (2011) investigated the impact of administering adjuvant trastuzumab with cytotoxic chemotherapy in 3222 patients allocated randomly to receive either anthracycline-based protocol (doxorubicin/cyclophosphamide followed by docetaxel± trastuzumab) or non-anthracycline-based protocol (docetaxel and carboplatin± trastuzumab). This study confirmed that administering trastuzumab with systemic cytotoxic chemotherapy was associated with a significant improvement in the 5-year disease-free survival (p-value <0.001); however, that did not differ between anthracycline-based versus non-anthracycline-based protocols.[313] Statistical analysis showed that the estimated 5-year overall survival among patients who received anthracycline-based chemotherapy and non-anthracycline-based chemotherapy was 92% and 91%, respectively. These findings indicated that anthracycline-based chemotherapy was not

superior to taxane-based chemotherapy among patients receiving trastuzumab treatment while emphasizing the role of trastuzumab in improving both disease-free and overall survival rates in patients with HER-2 receptor overexpression.[313] Anthracyclines were administered in standard dosing intervals (every 3 weeks) to enhance treatment tolerance among elderly patients. The impact of dose-dense anthracycline treatment on the therapeutic outcomes of HER-2 positive patients receiving trastuzumab was not established in this study.[313]

Lambertini *et al*. (2020), on the other hand, were the first to compare the outcomes of dose-dense anthracycline-based chemotherapy versus standard dosing interval among patients receiving trastuzumab treatment from the Gruppo Italiano Mammella (GIM) 2 trial.[314] Their study included 2003 patients stratified by the HER-2 receptor status and trastuzumab treatment allocation (whether received or omitted) and investigated the 7-year disease-free survival and overall survival.[314] Statistical analysis demonstrated that dose-dense anthracycline-based protocols had a significantly superior disease-free survival and overall survival among patients with HER-2 negative (or unknown receptor status) breast tumours compared to standard dosing interval.[314] Among patients with HER-2 positive breast tumours and receiving trastuzumab, the Lambertini *et al*. findings did not support dose-dense anthracycline chemotherapy.[308] While among patients with HER-2 breast tumours and not receiving trastuzumab, Lambertini *et al*.'s findings were consistent with the Early Breast Cancer Trialists' Collaborative Group (EBCTG) meta-analysis. Otherwise, combining trastuzumab treatment with dose-dense anthracycline-based chemotherapy was not supported.

The previously discussed studies illustrated that cytotoxic treatment prescribing patterns changed throughout the years, and the use of standard first-line treatment in the guidelines declined because of the increasing evidence on targeted treatment efficacy in managing breast cancer patients. Although anthracyclines were considered the standard of care in managing high risk breast cancer patients, non-anthracyclines in combination with targeted treatment achieved therapeutic success in eligible patients. In parallel with the previously discussed evidence in this section, the present study reported a lower anthracycline-based treatment allocation among older patients compared to younger patients. Taxane monotherapy was a commonly reported less intensive treatment allocation, even though no evidence supported single-agent chemotherapy allocation and previous studies reported inferior quality of life and therapeutic outcomes. Accordingly, this could be a nonstandard and potentially suboptimal treatment allocation. On the other hand, less intensive doublet chemotherapy treatment (docetaxel and cyclophosphamide combination) reported in the present study was considered feasible. Doublet chemotherapy protocols are superior to single-agent protocols because they provide different mechanisms of action and less/delayed drug resistance and hence better therapeutic response. Also, doublet chemotherapy protocols allow dose modifications when required without compromising the anti-tumour activity.

The change in cytotoxic treatment prescribing patterns throughout the years demonstrated that the use of intensive treatment was declined because of the increased evidence on targeted treatment efficacy in managing breast cancer patients. Less intensive cytotoxic treatment was still associated with complete therapeutic response when combined with targeted treatment in eligible patients.

4.2.2 Targeted monotherapy protocols

Park *et al.* (2017) studied treatment allocation patterns in 161 patients with HER-2 receptor overexpression from South Korea and found that advanced age was significantly associated with cytotoxic chemotherapy undertreatment but not anti-HER-2 undertreatment.[315] This trend in chemotherapy undertreatment was significant among patients aged 75 years and above. Findings from the present study showed that less intensive treatment was reported in chemotherapy allocation but not targeted treatment, which was parallel with Park *et al.* Findings from the present study were paralle with Park *et al*. This is reasonable because anti-HER-2 treatment is associated with fewer systemic side effects than cytotoxic chemotherapy and better tolerance among older patients.[316] The significant beneficial outcomes of trastuzumab treatment created an opportunity to allocate older breast cancer patients considered ineligible for cytotoxic chemotherapy combinations to receive targeted treatment instead of only palliative treatment. Survival benefits were reported among patients receiving trastuzumab in adjuvant and palliative settings even after cytotoxic treatment failure.[317, 318]

Many questions were raised in the literature repeatedly about the differences in the therapeutic outcomes between trastuzumab-cytotoxic chemotherapy combination and trastuzumab monotherapy among older patients considered ineligible for standard chemotherapy protocols. Dall et al. (2018) reported a significant improvement in the 3-year relapse-free survival and overall survival in patients from different age cohorts who received adjuvant trastuzumab-cytotoxic chemotherapy combination when compared to patients who received trastuzumab monotherapy (p-value= 0.022).**[319]** In

addition, trastuzumab-cytotoxic chemotherapy combination contributed to a marginal improvement in the 5-year survival outcomes in this study (p-value= 0.052).

On the other hand, the RESPECT trial recruited 275 elderly patients with HER-2 positive breast tumours (median age 73.5 years, range 70-80 years) and randomly allocated them to receive either trastuzumab monotherapy or trastuzumab-docetaxel/ cyclophosphamide (TDC) combination protocol. The aim was to evaluate the beneficial 3-year outcomes of adding or omitting systemic cytotoxic chemotherapy to trastuzumab treatment.[320] Results of the RESPECT trial revealed that combining cytotoxic chemotherapy with trastuzumab treatment did not significantly improve disease-free survival or relapse-free survival. The trastuzumab-cytotoxic chemotherapy combination resulted in a significantly higher toxicities, including anorexia, alopecia, and grade 3-4 non-haematological toxicities, and poorer quality of life compared to trastuzumab monotherapy.[320] The RESPECT trial recruited patients aged 70 years and above and patients and allocated for a cyclophosphamide and taxane combination. According to the literature, those patients were expected to experience higher rates and grades of haematological and non haematological toxicities compared to younger patients.[321, 322] The poor therapeutic outcomes of cytotoxic treatment could be attributed to multiple overlapping factors, including patients' characteristics (advanced age, performance status and comorbidities) and physiological changes rather than cytotoxic treatment being unbeneficial. The chemotherapy related toxicities led to poor tolerance and deteriorated quality of life among older patients.[321] The RESPECT trial suggested targeted treatment monotherapy and omitting cytotoxic treatment among selected patients with advanced age to maintain accepted tolerance and quality of life. In comparison, Dall *et al.* recruited patients from different age

cohorts and received different chemotherapy protocols, resulting in accepted tolerance and superior therapeutic outcomes with trastuzumab-cytotoxic treatment combination compared to trastuzumab monotherapy. Their results supported allocating eligible patients who were expected to show accepted tolerance for trastuzumab-cytotoxic treatment combination.

In the present study, a limited number of older patients received targeted monotherapy (n=6). Two patients aged >70 years old were considered ineligible for cytotoxic chemotherapy, two patients were allocated to receive single-agent chemotherapy and targeted therapy but refused cytotoxic chemotherapy against their doctor's recommendations, and two patients received limited doses (≤3 cycles) of cytotoxic chemotherapy and refused to continue their cytotoxic regimen. Among those, therapeutic failure occurred in five cases. Patients with metastatic tumours progressed and were subsequently referred to the best supportive care unit (BSC). Besides, three patients with non-metastatic tumours also progressed, resulting in distant metastases. Poor therapeutic outcomes among this subgroup of patients could be attributed to multiple overlapping factors, including advanced age, poor performance status, deteriorated quality of life, and of course, undertreating breast cancer by omitting cytotoxic chemotherapy.

Trastuzumab treatment significantly improved therapeutic outcomes and survival in both metastatic and non-metastatic patients. Cytotoxic chemotherapy is still indicated in high risk patients who were expected to tolerate treatment-related toxicities. Among patients considered ineligible for cytotoxic treatment, trastuzumab monotherapy is still expected to show therapeutic benefits, especially when combined with hormonal treatment in eligible patients. Besides HER-2 targeted treatment, the same concept is

applied to targeted hormonal treatment. The TAILORx trial emerging results demonstrated that hormonal monotherapy has comparative 9-year outcomes to hormonal-cytotoxic therapy combination in low-risk and intermediate-risk patients with HER-2 negative breast cancer and tested for 21-gene expression assay.[323] This trial supported the concept of individualized breast cancer management and provided evidence on targeted hormonal monotherapy and omitting cytotoxic treatment. This emerging evidence is expected to change the breast cancer management guidelines in the future and minimize the utilization of intensive treatment protocols.

This section illustrated that although anthracycline-based chemotherapy is still standard of care for managing high-risk patients, evolving evidence demonstrated that combining trastuzumab with anthracycline-based or non-anthracycline-based treatment has comparable outcomes. Accordingly, allocating selected patients for non-anthracycline and targeted treatment combination is considered an effective and less cardiotoxic treatment rather than suboptimal treatment as long as therapeutic outcomes can be achieved and cardiotoxicity is avoided. Offering less intensive chemotherapy for selected patients receiving targeted treatment and considered at high risk of cytotoxic treatment-related toxicity is considered reasonable individualized allocation. Avoiding cancer treatment toxicity minimizes the risk of treatment discontinuation and decreases the healthcare expense of complications management. More studies and trials are required to assess the therapeutic outcomes of targeted treatment among older cancer patients combined with different cytotoxic chemotherapy regimens. This is expected to introduce many changes to cancer treatment guidelines and provide suitable protocols for managing patients with advanced age or multiple comorbidities.

4.3 Treatment outcomes in older breast cancer patients

The discussion of breast cancer treatment outcomes is divided into two main sections: treatment-induced toxicity and disease control (Figure 4.6).

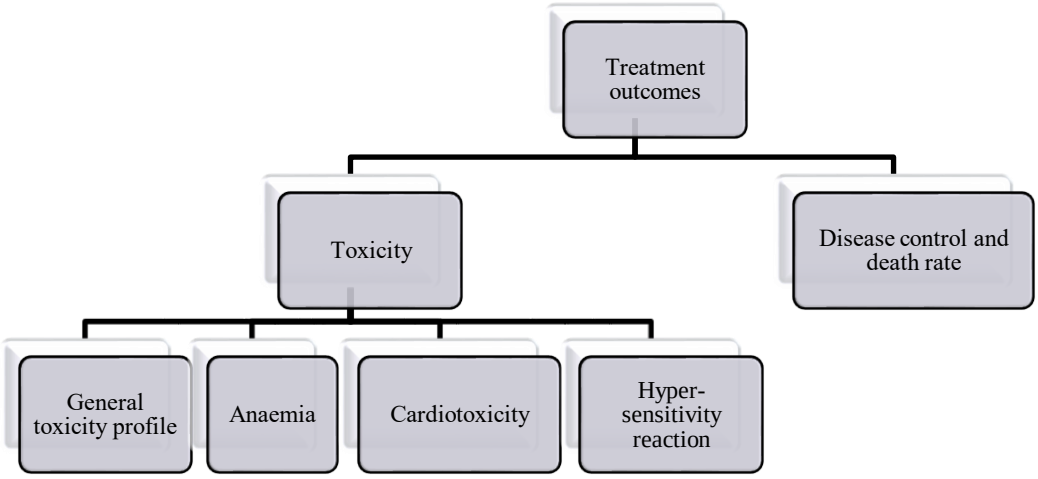

Figure 4.6 Treatment outcomes discussion outline

In the present study, the earliest death occurred after 15 months of diagnosis. Data of interest, such as baseline characteristics and toxicity outcomes, were documented for all patients and were not affected by the death incidence as chemotherapy was delivered within three to six months after a breast cancer diagnosis. As mentioned earlier, trastuzumab was the only treatment delivered during 12-months (LVEF was monitored every three months). During this period, data were identified, documented, and analysed. After that, patients were followed in the OPD for routine lab reports every three or six months and annual mammograms for the first two years. No related data were collected during follow up unless disease recurrence (relapse) was detected. The number of relapsed patients was insufficient to conduct analysis or make definitive conclusions. As a result, longitudinal data analysis was considered out of the scope of the thesis (more details were included in the limitations). All analyses were conducted in a non-time-dependent manner. This is because treatment related outcomes were

documented in patients' case notes in a non-time-dependent manner (accurate time to event was not available).

4.3.1 Treatment-induced toxicity

Toxicity among older breast cancer patients has been extensively studied in the literature to enhance cancer treatment tolerance.[321, 322] So far, identifying older patients at risk of chemotherapy-induced toxicity is quite challenging in clinical practice. The Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH) was the first risk assessment scale developed (published in 2012) to systematically integrate assessing chemotherapy toxicity and advanced age risks in cancer patients.[324] Besides the CRASH risk scale, the Cancer and Aging Research Group developed a risk assessment tool to predict chemotherapy toxicity stratified by severity among older cancer patients.[325] These traditional risk assessment tools are not applied in clinical practice in Kuwait and worldwide due to limited resources and time scheduled for individual patients. Also, because they are not included in the baseline assessment of the standardized clinical practice guidelines. In addition, the ideology of older populations' heterogeneity drives healthcare professionals to prescribe a planned chemotherapy dose-escalation strategy instead of depending on risk assessment tools in managing older patients whose tolerance is questionable. Chemotherapy dose-escalation allows administering a reduced first cycle dose and monitors patient tolerance before administering full chemotherapy doses. According to Gajra *et al*. (2016), advanced age (65 years and above) and comorbidity burden were independent risk factors of first chemotherapy cycle dose reduction in managing patients with solid tumours.[326] Unlike age and comorbidities, the performance status score and first chemotherapy cycle dose reduction were not correlated in their study.

In a subgroup analysis of chemotherapy intent, a higher incidence of first chemotherapy cycle dose reduction was reported in older patients allocated for palliative chemotherapy protocols than curative chemotherapy protocols (25% and 15% respectively; p-value= 0.005). [326] The dose-escalation delivery strategy is feasible in clinical practice because it allows oncologists to assess individual older patients' tolerance to cytotoxic treatment-related toxicities before offering full doses of intensive treatment.

4.3.1.1 General toxicity profile

In the literature, age was associated with an increased rate/grade of chemotherapy toxicity.[287] However, Hurria *et al*. (2005) suggested that high-grade toxicities were significantly correlated with the chemotherapeutic protocols rather than chronological age or number of comorbidities.[327] For example, adjuvant anthracycline-based chemotherapy protocols were associated with higher rates of grade 3 toxicities compared to taxane-based chemotherapy protocols in older patients with breast cancer (28% versus 10%, respectively).[328]

At the beginning of this study, it was speculated that older patients would have higher incidence of treatment-induced toxicity, significantly increasing among patients allocated for intensive treatment protocols. However, data showed that neurotoxicity was the only toxicity reported at a significantly higher incidence among older patients compared to younger patients combining both treatment allocations (Table 3.12). In comparison, significantly higher incidence of nausea and relatively higher (but did not reach statistical significance) incidence of vomiting were reported among younger patients compared to older patients. This could be attributed to the higher exposure to anthracycline-based chemotherapy protocols among younger patients.[329, 330]

Otherwise, the incidence of both haematological and non-haematological toxicities was similar between younger and older patients.

Surprisingly, a subgroup analysis of younger and older patients allocated for intensive treatment showed that intensive treatment did not significantly increase toxicity among older patients compared to younger patients. Neurotoxicity occurred at a relatively higher incidence among older patients but did not reach statistical significance, while the incidence of haematological and non-haematological toxicity was similar between younger and older patients. In contrast to what was published, neutropenia occurrence was not correlated with either advanced age or intensive treatment allocation in the present study.[331]

In the literature, the safety of adjuvant standard anthracycline-based chemotherapy was compared between younger and older breast cancer patients, and results showed that advanced age was associated with a higher rate and grade of toxicities.[290] Karavasilis *et al.* (2009) retrieved data of 2640 patients from 3 randomized controlled trials and compared anthracyclines tolerability by age cohort.[332] Patients aged >65 years had significantly higher rates of grade 3 and 4 anthracycline-induced toxicity compared to younger patients (32% and 21% respectively; p-value <0.0001).[332] In contrast to findings from the present study, Karavasilis *et al.* found that neutropenia, fatigue, diarrhoea, and mucositis were significantly higher among older patients, but this did not result in a higher treatment discontinuation rate.

In the present study, younger patients received anthracycline-based chemotherapy in a dose-dense interval (2-weekly) schedule, while older patients received it in a standard interval (3-weekly) schedule to enhance treatment tolerance. Based on Karavasilis' findings, allocating older patients for dose-dense anthracycline treatment

as their younger counterparts is expected to precipitate higher toxicity rates, including gastrointestinal toxicities and neutropenia, among older patients. In the present study, older patients considered eligible for intensive treatment had comparable baseline characteristics to younger patients, including performance status and comorbidities scores. Consequently, their tolerance to anthracyclines chemotherapy was not compromised by the chronological age factor.

Based on findings from previous studies, taxane-containing chemotherapy protocols (monotherapy or combination) increase the risk of treatment-induced neurotoxicity. Jones *et al.* (2005) reported that docetaxel and paclitaxel were associated with 64.4% and 59% of neurotoxicity incidence among metastatic breast cancer patients; among those, 7.4% and 4.1%, respectively, were considered severe neuropathy.[333] Other studies reported taxane-induced neurotoxicity ranging between 57%-83% and 11%-64% among patients receiving paclitaxel and docetaxel, respectively.[334-337] All previous studies confirmed that cancer treatment-induced neurotoxicity increases with age, which explains the high rate reported among older patients compared to younger patients in the present study. [334-337]

As well as neurotoxicity, depression is considered one of the undesirable effects significantly worsening cancer patients' quality of life. Among older patients, unexpectedly, less intensive treatment contributed to significantly higher incidence of depression compared to intensive treatment in the present study. Generally, breast cancer diagnosis, undergoing chemotherapy, and breast surgery increase the risk of depression. A Danish nationwide population-based study investigated the factors associated with depression incidence among 44,494 patients with breast cancer and found that older age, comorbidity burden, living alone, and limited education increased

depression incidence after a breast cancer diagnosis.[338] Besides the Danish study, data from the Korean Health Insurance Review and Assessment Service (HIRA) showed that patients who underwent mastectomy had significantly higher depression incidence than patients who did not during the first two years post the surgery.[339] Also, Christensen *et al*. (2009) identified other pre-cancer factors associated with increased risk of depression among breast cancer patients, including poor physical function, smoking, alcohol use, social status, and BMI.[340] In addition to the previously mentioned factors, Jim *et al.* (2012) detected a correlation between chemotherapy-induced fatigue and depression among cancer patients. [341] They found that fatigue incidence increased post chemotherapy infusion, decreasing daytime activity and sleeps regularity (p-value= 0.005). This also contributed to depression among cancer patients undergoing cytotoxic chemotherapy.[341]

It was speculated that intensive treatment allocation would contribute to higher incidence of depression among patients from both age cohorts due to the higher toxicity burden precipitated compared to less intensive treatment allocation. Besides, the association between intensive treatment allocation and depression would be affected by age because age was considered a risk factor of depression in the general population.[342, 343] Previous studies demonstrated that older age was associated with a progressive decline in cognitive functions that could be attributed to normal physiological changes or as a consequence of chronic comorbidities or medications.[344] This decline in cognitive functions has been shown to worsen the individual quality of life and induce depression.[302] Among cancer patients, the elderly were considered more vulnerable to cancer treatment-induced toxicities, which worsen

patients' quality of life and hence contribute to a higher incidence of depression compared to younger patients.[19,297,299]

According to the results from the present study, neither advanced age nor intensive treatment allocation was associated with increased depression incidence. In subgroup analysis, older patients allocated for less intensive treatment had a higher incidence of depression incidence than older patients receiving intensive treatment. Baseline characteristics showed that this subgroup of patients had a relatively higher prevalence of comorbidities and medication use compared to patients who did not develop depression after a breast cancer diagnosis. Besides, most patients had advanced performance status and at least one drug-related problem. These factors were considered indicators for poor health conditions and potential causes for less intensive treatment allocation. Accordingly, depression incidence in this subgroup of patients could be attributed to patients' vulnerabilities rather than less intensive treatment allocation. Besides these potential factors, a correlation between taxane-based chemotherapy and worse emotional distress and mental quality of life was documented in the literature.[345]

The number of older patients who developed depression during less intensive cancer treatment was insufficient to make definitive conclusions about the factors contributing to depression. Also, depression incidence could be underestimated in this study because depression was not routinely assessed in the clinical practice in KCCC, but patients with major symptoms of depression were referred to a specialist for further evaluation and management. Overall, depression incidence among older patients was attributed to high prevalence of comorbidities, medication use, drug-related problems,

and poor performance status rather than disease stage or treatment allocation. This reflected the poor quality of life among patients who developed depression.

4.3.1.1.1 Treatment modification

The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis demonstrated that standard chemotherapy delivery (dose/ duration) was associated with a 40% reduction in the 10-year overall survival among patients with early-stage breast cancer.[346] However, dose modification is sometimes indicated in clinical practice because some patients experience intolerable toxicities that prevent completing chemotherapy protocols as scheduled initially. A nationwide study of 1243 community practices reviewed data of 20,799 patients with early-stage breast cancer and found that ≥15% dose reduction of different chemotherapy protocols occurred in 36.5% of patients, and ≥7 days dose delay occurred in 24.9% of patients.[345] Dose modifications occurred due to different factors, including older age, being overweight, and receiving three-drug combinations. Besides, Rashid *et al.* (2015) found that multiple comorbidities and medication burden and prolonged hospitalization due to treatment-related toxicities were significantly associated with chemotherapy dose modification among metastatic breast cancer patients.[347]

In the present study, the requirement for chemotherapy dose modification was correlated with advanced age rather than intensive treatment allocation (Table 3.10). Intensive treatment contributed to similar treatment modifications between older and younger patients. Surprisingly, older patients allocated for less intensive treatment had a relatively higher requirement for treatment modifications than older patients who received intensive treatment and younger patients who received either intensive or less intensive treatment. It is believed that this was not attributed to treatment being more

toxic but to the ideology that older patients allocated for less intensive treatment had multiple baseline factors that could compromise chemotherapy tolerance, such as poor performance status, age-related conditions, high comorbidity burden scores, and polypharmacy, as demonstrated by Rashid *et al.*

Besides Rashid, Raza *et al.* (2009) retrieved the data of 275 patients with early-stage breast cancer who received different adjuvant anthracycline-based chemotherapy combinations at the London Regional Cancer Program in Ontario, Canada, and found that 14.4% of patients received a chemotherapy dose intensity less than 85%.[348] Among those, patients aged 65 years and above were more likely to receive modified doses than younger patients (35% and 6.6%, respectively). The standard chemotherapy AC-T (Doxorubicin/ cyclophosphamide followed by paclitaxel) combination contributed to 37% of the reported dose modifications (25% dose delays and 18% dose reductions). However, 96% of patients who received AC-T combination maintained a dose intensity above 85%.[348] This indicates that dose modifications contribute to better tolerance and treatment completion in case of intolerable related toxicities. According to Raza, it is crucial to maintain more than 85% of chemotherapy doses intensity in managing early-stage breast cancer to achieve and maintain disease-free survival and overall survival in both pre and postmenopausal patients.

According to individual patient medical notes in the present study, anthracyclines-related neutropenia or nausea and taxane-related neurotoxicity or diarrhoea were the most common causes of treatment modifications among breast cancer patients in Kuwait. In agreement with those findings, Sigita *et al.* (2018) reported that neutropenia was the most common cause of anthracyclines dose modification (reduction or delay) among non-metastatic patients.[349] Other reported causes of anthracyclines dose

modifications included thrombocytopenia, anaemia, fatigue, and infection. Occasionally, anthracyclines dose reduction or delay occurred without an objective medical cause. [293]

Besides anthracyclines, Bhatnagar *et al.* (2014) reported a 40% dose reduction of taxane-based chemotherapy protocols among patients with early-stage breast cancer (median age of 53 years, range 32-78 years) at the University of Maryland Greenebaum Cancer Center.[336] Among those, 17% of dose reductions were attributed to chemotherapy-induced peripheral neuropathy (CIPN) and were highly correlated with pre-existing diabetes (p-value= 0.01). Data showed that 65% and 35% of diabetic and non-diabetic patients respectively required dose reduction (p-value= 0.02).[336] Other common causes of taxane-based chemotherapy dose reduction were diarrhoea, infection, myelosuppression, hypersensitivity reaction, and rash.[336]

According to the previously discussed studies, modified chemotherapy doses are usually well-tolerated and contribute to treatment completion rather than discontinuation.[350] It is recommended to maintain a chemotherapy dose intensity above 85% to avoid compromising disease control. In cases of treatment intolerance despite modifications, treatment deviation is indicated.

4.3.1.1.2 Treatment deviation

Breast cancer is associated with a high rate of standard treatment completion despite age.[351] It was hypothesized that older patients would have higher treatment deviation than younger patients due to toxicity intolerance. In contrast, data from the present study showed higher treatment deviation among younger patients than older patients regardless of treatment allocation (11.7% versus 5%, respectively) (Table 3.11). This was not always attributable to intensive treatment intolerance since approximately

50% of those younger patients had metastatic diseases and failed on first-line treatment. According to the guidelines, metastatic patients receive first-line treatment until disease progression or treatment intolerance for life.[156] Accordingly, treatment deviation was a common practice among metastatic patients. On the other hand, toxicity intolerance contributed to only 3.9% of treatment deviation combining the two age cohorts. Usually, the treating oncologist modifies the initial treatment doses before discontinuing initial treatment protocols. Occasionally, severe side effects lead to discontinuing treatment without re-challenge, such as prophylactic shock or seizures.

Contrary to the initial expectations, only 1.7% of older patients deviated from initial treatment due to treatment intolerance, and 3.3% deviated because they refused to continue receiving cytotoxic treatment because of toxicity concerns despite being allocated to receive less intensive cytotoxic treatment and exhibiting accepted tolerance. Early discontinuation of initial chemotherapy protocols among cancer patients was attributed to treatment-related anxiety and distress in the literature.[352] Neugut *et al.* (2016) stated that the psychological side effects of chemotherapy were considered the main barrier to treatment completion.[351] In the present study, the treating oncologists managed the subgroup of patients who refused to continue their initial without being offered a psychologist consultation. Psychological side effects could be under-assessed as only patients with major behavioural or mental changes or patients with end-stage diseases were referred to a psychologist for further assessments and management. Unfortunately, it was not possible to access the psychological evaluation or intervention notes.

Findings from the present study suggest that treatment-induced toxicity among older patients receiving cytotoxic chemotherapy can be managed by dose modification.

Treatment deviation due to toxicity intolerance does not widely occur in clinical practice in Kuwait, and it is statistically similar between younger and older patients with breast cancer. These results were consistent with Karavasilis *et al.* (discussed in section 4.3.1.1).[296]

4.3.1.2 Hypersensitivity reaction

Chemotherapy infusion is associated with hypersensitivity reaction risks that usually precipitate mild symptoms, such as chills, fever, headache, and skin rash.[353, 354] The likelihood of a patient experiencing a hypersensitivity reaction can not be predicted. In clinical practice, it has been most commonly reported in cancer patients receiving taxanes, targeted drugs, or platinum agents.[355] There is a lack of evidence-based information about the incidence of infusion-related hypersensitivity reactions among breast cancer patients in general. Based on reports from a single cancer institute experience in Turkey, breast cancer treatment was associated with the highest incidence of infusion-related hypersensitivity, followed by lung, colorectal and ovarian cancer (39.2%, 17.8%, 10%, and 8.5%, respectively).[356] Overall, docetaxel accounted for 48.5% of the hypersensitivity reactions. The hypersensitivity reaction incidence was similar between patients receiving paclitaxel and trastuzumab and accounted for 10.1% of all cases.[356] Besides, Parinyanitikul *et al.* (2018) reported that paclitaxel infusion-related hypersensitivity reaction occurred in 6.25% of patients with early-stage breast cancer leading to temporary discontinuation of the infusion.[357]

In the present study, taxane infusion-related hypersensitivity reaction was within the incidence range previously reported in the literature. In contrast, trastuzumab infusion-related hypersensitivity reaction was dramatically higher than what was reported. The majority of patients who experienced trastuzumab-related hypersensitivity were from

the younger age cohort. Thompson *et al.* (2014) demonstrated that advanced BMI, consuming chronic medications, and metastatic breast cancer are associated with an increased risk of trastuzumab-related hypersensitivity among breast cancer patients, which could explain the higher incidence detected in the present study.[358]

4.3.1.3 Treatment-induced anaemia

Breast cancer patients are at a high risk of developing anaemia either due to the nature of their disease (such as haematological tumours or bone marrow infiltration) or as a consequence of administering myelosuppressive chemotherapeutic agents. [359] Previous studies reported that anaemia in cancer patients increases to approximately 90% after chemotherapy administration, negatively impacting treatment completion and therapeutic response.[360] Besides, radiotherapy and surgical interventions induce gastro-intestinal toxicity leading to poor appetite and compromised nutritional status. As a result, cancer patients suffer from anaemia-related symptoms, including fatigue, general weakness, and shortness of breath, which reduce their quality of life and lead to poor performance status.[361] According to the National Cancer Institute (NCI), anaemia is classified into four grades [mild (>10 g/dL), moderate (8-10 g/dL), severe (6.5-7.9 g/dL), and life-threatening (<6.5 g/dL) anaemia] based on the haemoglobin level. A previous study reported that the standard adjuvant anthracycline-based chemotherapy contributed to 88.3% of anaemia incidence among stage II-III breast cancer patients with normal baseline hemoglobin levels.[362] Among those, only 27.7% were moderate to severe anaemia cases. In comparison, 31.3% of patients had mild baseline anaemia; among those, 61.9% developed moderate to severe anaemia during chemotherapy.[362] A similar pattern of treatment-induced anaemia severity was reported in the present study.

In cancer patients, insufficient haemoglobin levels may lead to tumour hypoxia, which induces angiogenesis and promotes further tumour growth.[360] Consequently, tumours become resistant to radiotherapy. Anaemia is also associated with poor disease control and overall survival when studied and compared as an independent prognostic factor in anaemic versus non-anaemic patients.[363] Chaumard *et al.* (2012) suggested that the incidence of chemotherapy-induced anaemia among early-stage breast cancer patients increases with advanced age, high anthracycline dose, exposure to taxanes, low baseline haemoglobin levels, and decreased BMI ($\leq$25 kg/m^2).[364] Advanced age has been extensively studied as a risk factor of chemotherapy-induced haematological toxicity among cancer patients in general. It has been suggested that the aging process is an intrinsic factor of anaemia development because the organs' ability to maintain their normal physiological state declines with age.[365] Besides, biological interaction between aging and Interleukin-6 (IL-6) has been shown to contribute to higher incidence and severity of anaemia among older populations.[366] In contrast to Chaumard *et al.*, obesity was also considered a risk factor for anaemia.[27] The main cause of high anaemia prevalence among obese patients is still unknown. It was hypothesized that obesity precipitates anaemia of chronic disease as a consequence of chronic, low-grade inflammatory conditions.[366]

The present study showed that advanced age was not correlated with a higher incidence or severity of chemotherapy-induced anaemia compared to younger patients (Table 3.16). Consequently, patients from both age cohorts had similar requirements for blood transfusion. Among patients who developed severe-life threatening anaemia during cancer treatment, 44.4% of younger patients versus 16.7% of older patients were metastatic cases. This may indicate that, unlike older patients, relatively higher

incidence of tumour metastases among younger patients relatively increased blood transfusion requirement. Also, blood loss through menstruations was expected to increase the severity anaemia and hence the requirement for blood transfusion in younger patients.

Consistent with published data, intensive treatment contributed to higher requirements for blood transfusion among younger patients than less intensive treatment.[362] In contrast, less intensive treatment contributed to higher requirements for blood transfusions among older patients than intensive treatment. This could be attributed to higher prevalence of comorbidities, organ dysfunction, and poor performance status, rather than less intensive treatment protocols being more haematological toxic.

The comparable severity pattern of treatment-induced anaemia between younger and older patients was not attributed to comparable treatment tolerance but the significantly higher proportion of intensive treatment allocation among younger patients compared to older patients. On the other hand, older patients had a higher comorbidity burden, which was expected to augment the risk of anaemia due to chronic diseases.

4.3.1.4 Treatment-induced cardiotoxicity

In the present study, cardiotoxicity was assessed in patients receiving trastuzumab with or without prior exposure to anthracycline treatment. Event of cardiotoxicity was defined as developing ≥10% decline in the LVEF from the baseline value or reaching a value below the accepted normal limit (<50%) as described in the ESMO guidelines and different population-based studies in the UK, Canada, France, and Spain, and the international multicenter HERA trial.[367-370]

Data showed that ≥10% decline in the LVEF from the baseline value occurred in 65.6% of patients combining the two age cohorts, representing 55.6% and 86.7% of younger and older patients, respectively. However, only 18.3% of patients reached a value below accepted LVEF limits (<50%), with no statistical difference in patients' distribution by age cohorts. Baseline characteristics, including age, BMI, comorbidity score of ≥3, history of hypertension or diabetes, baseline LVEF value, and previous exposure to anthracycline treatment, were investigated as potential predisposing factors of cardiotoxicity. Age was associated with a 4-fold higher risk of developing ≥10% decline in the LVEF from the baseline during trastuzumab treatment. Also, a baseline LVEF value <60% was significantly associated with reaching LVEF value below normal ranges (<50%). Statistically, patients who started chemotherapy with a baseline LVEF value below 60% were 81% less likely to maintain LVEF within normal ranges. Other factors failed to be correlated with treatment-induced cardiotoxicity.

Doaa *et al.* (2021) reported relatively comparable results in a retrospective population-based study conducted in Oman, which also lies in the same gulf region near Kuwait.[371] Their data showed that 24% of patients developed ≥10% decline in the LVEF from the baseline and reached a value below <50%. Also, a relatively comparable incidence was reported in a prospective descriptive observational study among 1065 Uruguayan breast cancer patients.[372] Among those, 75% experienced ≥10% decline in the LVEF from the baseline; however, only 9.7% reached a value below <50%. These findings were within the range of reported international data but higher than what was initially reported in controlled clinical trials.[165, 373] Unlike clinical practice, patients recruited in clinical trials were highly selected, excluding

patients with advanced age, multiple comorbidities, or receiving cardioprotective drugs. As a result, the potential cardiotoxicity risk decreases among selected patients. Although advanced age was associated with a higher proportion of patients developing ≥10% decline in their LVEF from the baseline value, this did not contribute to high proportions of patients reaching LVEF values below normal ranges (LVEF <50%) compared to younger patients. Older patients had a relatively higher temporary trastuzumab discontinuation; however, a cardio-protective drug such as an Angiotensin Converting Enzyme Inhibitor (ACE-I) or Beta Blocker (BB) was prescribed, and trastuzumab treatment re-initiated (re-challenged) after restoring clinically accepted LVEF levels (≥55%). Consequently, the proportion of patients who had permanent trastuzumab treatment discontinuation was not statistically different between the two age cohorts.

Besides advanced age, chronic comorbidities were considered as predisposing factors for cancer treatment-related cardiotoxicity in the literature. Onitilo *et al*. (2014) suggested that diabetes-related chronic oxidative stress reaction pathways contribute to the trastuzumab-induced cardiotoxicity.[374] Also, hypertension and renal dysfunction were considered risk factors for cardiovascular diseases and treatment-induced cardiotoxicity. In addition to the previously discussed risk factors, a few studies correlated obesity with increased cardiotoxicity risks.[375, 376] In contrast to what has been published, data from the present study showed that the event of cardiotoxicity was not correlated with multiple baseline comorbidities, history of hypertension or diabetes, or BMI.[371] Besides, none of the patients who developed cardiotoxicity had a history of ischemic heart disease (IHD). Surprisingly, the only two patients who had a history of IHD maintained acceptable LVEF value during trastuzumab treatment

indicating good tolerance. These findings were consistent with the Omani population-based study.

In contrast to what has been reported in all previous studies, exposure to anthracycline treatment was not correlated with cardiotoxicity in the present study. Some articles suggested that genetic predisposition increases the sensitivity of anthracycline-related cardiotoxicity in some patients.[377, 378] Lack of genetic predisposition could be the case in the present study population, but this could not be confirmed. More studies are required to validate applying genetic testing in clinical practice as it will dramatically enhance the prescribing pattern in managing breast cancer patients despite age. Also, probably the number of patients receiving anthracycline treatment was insufficient to detect the impact of anthracycline exposure on treatment-related cardiotoxicity. It is anticipated that including a larger number may alter the results.

Treatment-induced cardiotoxicity contributed to an 11.8% incidence of trastuzumab treatment permanent discontinuation in Kuwait, which was relatively higher than what was reported in the literature. According to the Swiss Cardiovascular Centre experience, trastuzumab discontinuation occurred in only 4.3% of patients.[379] The international multicentre HERA trial reported an 3.6% incidence of trastuzumab treatment discontinuation.[380] Besides, the Uruguayan population-based study reported an 7.4% incidence of trastuzumab treatment discontinuation. The relatively higher incidence of trastuzumab discontinuation reported in the present study was not always attributed to a failure in achieving accepted LVEF level during cardioprotective treatment, but because 4.3% of patients had rapidly progressive disease, indicating that the tumour developed resistance to the treatment, and very poor quality of life. As a result, patients were considered ineligible for treatment re-challenge and being

exposed to additional cardiac complications. Among those, 2.2% had their active cancer treatment discontinued without re-challenge and transferred to receive palliative treatment in the Best Supportive Care Centre (BSCC).

Overall, breast cancer patients aged 60 years and above in Kuwait were at a 4-fold higher risk of developing ≥10% decline in their LVEF from the baseline value than younger patients during trastuzumab treatment. Previous exposure to cardiotoxic treatment and comorbidities may be potential but were not significant risk factors of treatment-induced cardiotoxicity in the present study. Trastuzumab treatment was not associated with a significantly higher risk of treatment discontinuation among older breast cancer patients when compared to younger patients as they showed acceptable tolerance under regular LVEF monitoring and appropriate cardioprotective interventions when indicated.

4.3.2 Disease control and death incidence

During the last decade, a dramatic improvement in the survival rate of breast cancer patients was observed across all breast tumour subtypes.[381, 382] The continuous progress of cancer treatment development and modification of individualized treatment protocols improved the survival rates even among metastatic breast cancer patients as illustrated in section 1.4.2. The literature suggested superior survival rates among younger patients compared to older patients with breast cancer.[383] Unfortunately, the survival data of the present study is incomplete due to the short data collection period (details were included in the limitations, section 5.2.2).

Understanding breast tumour characteristics is crucial in predicting disease prognosis and mortality. It is well established that patients with early-stage breast cancer have significantly better disease prognosis and survival than patients with advanced or

metastatic breast cancer. Also, poor disease control is highly correlated with breast tumour aggressiveness and disease stage rather than chronological age (section 1.4.2.2). In the present study, no differences were detected in the prevalence of breast tumour histopathological and molecular subtypes between the two age cohorts. The death incidence accounted for 4.4% of patients during a median duration of 23 months (IQR 19-27) and was almost equally distributed between the two age cohorts. As established, the death incidence was negatively affected by the metastasis status. Among metastatic patients, older patients had a therapeutic failure and a shorter survival duration than younger patients because of poor tolerance to cytotoxic treatment, deteriorated quality of life, and earlier treatment discontinuation.

Among non-metastatic patients, on the other hand, complete remission (therapeutic success) was achieved in 99% and 85.7% of younger and older patients, respectively. However, disease relapse occurred in 5.4% of patients between 19 and 29 months after diagnosis despite receiving standard intensive chemotherapy. Disease relapse could be attributed to aggressive breast tumour characteristics manifested by elevated Ki67 (range 30%-80%) and triple negative tumour subtypes rather than age, less intensive treatment allocation, or comorbidities. It was noticed that triple negative tumours were associated with higher relapse incidence among younger patients than older patients, even though all patients received standard treatment despite age. It was suggested that triple negative tumours exhibit more aggressive features, such as elevated Ki67% and advanced pathological grade, when diagnosed at a young age. Ovcaricek *et al*. (2011) reported a higher relapse incidence of triple negative breast tumours among older patients than younger patients, but this was attributed to the differences in treatment allocation patterns rather than tumour aggressiveness.[384] Factors affecting relapse

incidence by age cohort could not be investigated in the present study because the number of patients with triple negative tumours was insufficient to provide definitive conclusions. However, baseline characteristics exhibited elevated Ki67% and advanced BMI among relapsed patients (discussed in section 4.1.1.4.1).

Triple negative breast tumours were reported at higher incidence among younger patients than older patients in the literature.[385] They were associated with more advanced stages at diagnosis, a larger tumour size, higher grade, and relapse incidence during the first two years after diagnosis compared to other breast tumour subtypes, and peaked at approximately three years.[386-388] Steward *et al.* (2014) found that patients with triple negative breast cancer were at a 25% risk of relapse (loco-regional or distant recurrence) during a mean time of 18.8 months.[389] Among those, the risk of breast cancer-specific mortality was greater than 75%. Factors correlated with increased risk of disease relapse included increased tumour size, nodal involvement, and disease stage at diagnosis.[389] In the present study, data regarding tumour size and pathological grade were not compared because those tumour characteristics were investigated in clinical practice to identify the disease stage. The younger patients exhibited a higher prevalence of advanced TNM stage at diagnosis compared to older patients (Table 3.1).

Failure to achieve disease remission occurred in 12.5% and 0.98% of younger and older non-metastatic patients, respectively. In those cases, disease progression was attributed to multiple overlapping factors including, less intensive treatment allocation, advanced performance status, multiple comorbidities, polypharmacy, and patient interference with the treatment allocation against their oncologists' recommendations.

4.4 Improving healthcare for older patients with cancer

The requirement for effective clinical governance of treating older patients with breast cancer is becoming of increasing clinical significance due to increased life expectancy and breast cancer incidence among older populations.[20] Optimal healthcare of older patients with cancer requires healthcare providers from different specialties integrated into a Multidisciplinary Team (MDT).[255, 258] The teamwork approach can be effective with individual collaboration, good communication, and coordination between healthcare providers to save time and effort.[390] Identifying individual patient vulnerabilities at baseline allows healthcare professionals to request further assessments or measurements and apply suitable intervention if indicated before breast cancer treatment allocation. As noticed, clinical pharmacists were not involved in cancer patient management in Kuwait, even though this research detected baseline comorbidities with drug-related problems in older and younger patients. Integrating clinical pharmacy services in the healthcare of older cancer patients enhances medication use and minimizes potential drug-related problems among high risk patients. [255, 258]

As the Comprehensive Geriatric Assessments (CGA) require prolonged time and effort to complete compared to the simple performance status (PS) scoring tool, EUSOMA and SIOG recommend initiating screening assessment among older patients to patients that may benefit from the extended CGA tools, which can be successfully conducted by the collaboration of the MDT. Identifying age-related conditions during baseline assessments assists in providing suitable interventions that dramatically decrease morbidity and mortality among cancer patients.[391] In addition, comorbidities baseline assessment should change from identifying and documenting the

comorbidities to evaluating comorbidities severity and ensuring their control with the prescribed medications, as discussed previously in this study. If chronic comorbidities were uncontrolled, dose adjustments or referral to a specialist is considered. Non-compliance to the prescribed medication was reported while investigating baseline drug-related problems. Therefore, it is important to encourage patients to comply with the prescribed medication and not consider cancer management a priority because controlling chronic comorbidities and regulating body systems are crucial in tolerating cytotoxic treatment side effects and decreasing the requirements for treatment modification and discontinuation. Clinical pharmacists are expected to collaborate with medical oncologists to assess and monitor patients during cancer management in a time-efficient manner. In addition, clinical pharmacists can discuss the treatment side effects with the patients and ensure their understanding of side effects management. These patient-centered care services can be introduced as part of baseline assessments and considered fundamental requirements for individualized treatment allocation for older patients' management. [255, 258]

As illustrated in this study, the lack of standardized cardiotoxicity risk assessment is a barrier to allocating older patients for standard breast cancer treatment. This leads the oncologists to allocate selected older patients for less intensive (less cardiotoxic) chemotherapy protocols for age-related safety concerns. Beyond treatment allocation, treatment-induced cardiotoxicity increases the risk of treatment discontinuation among all breast cancer patients despite age. Traditional cardiovascular risk estimators are not adequate in predicting cancer treatment-related cardiotoxicity, especially in assessing patients aged less than 60 years. Comprehensive cardiotoxicity risk scores suggested by the HFA-ICOS are expected to provide a better assessment in selected patients to

weigh the risks and benefits of standard cardiotoxic treatment (section 4.1.2.1). This can be achieved by integrating cardiology care in the MDT to enhance treatment allocation, monitoring, and completion.[392]

5. STRENGTHS AND LIMITATIONS

5.1 Strengths

The present study is considered the first to extract clinical and pharmacoepidemiological data from breast cancer patients and compare age cohorts in Kuwait. Previous studies among the Arabian Gulf populations were focused mainly on disease epidemiology rather than illustrating treatment patterns of breast cancer management. Cancer outcomes data are usually collected retrospectively from population-based registries to study disease incidence, prevalence, and the influence of various factors on therapeutic outcomes, while registries usually do not provide comprehensive clinical data. Instead, this study was conducted prospectively because this approach is more powerful in observing factors influencing the clinical decision-making process of breast cancer treatment allocation in real life and capturing barriers to intensive treatment allocation. Also, prospective studies allow collecting all relevant data, monitoring different parameters throughout the study period, and identifying the correlation between the exposures and outcomes.

The study design aimed to provide solid evidence on differences in breast cancer patients' baseline characteristics, assessments, treatment allocation, and outcomes by age. A sufficient sample size provides powered findings and facts, which could be generalized to represent the population. The power of the present study was computed based on the sample size and was 0.9.

5.2 Limitations

5.2.1 Patient assessment and data collection

Like other studies, this study has multiple limitations due to the nature and complexity of the clinical practice of oncology in Kuwait. Unfortunately, patients' medical notes and reports were non-electronic, making it time-consuming to collect and retrieve individual patient medical notes throughout their cancer treatment journey, especially without a research assistant. At baseline assessments, few restrictions and obstacles were faced while collecting the data. As a researcher, I was not able to apply any assessment tools other than what was approved by the Ministry of Health (MOH) and hospital administration. Consequently, the comprehensive geriatric assessment tools provided by the ASCO Geriatric Oncology Expert Panel were not applied because of the hospital policy and timeframe restrictions. As a result, identifying the geriatric conditions were documented as absent or present based on the oncologists' pre-cancer medical notes. Unlike tumour characterisation, assessing baseline geriatric oncology was not considered a priority for patients and oncologists. Therefore, the prevalence of geriatric conditions in the present study could be under-recognised at baseline assessment. Applying comprehensive assessment tools in further studies may identify a relatively higher prevalence of geriatric conditions among older patients in Kuwait and necessitate integrating appropriate interventions into the management plan. Besides geriatric conditions, cancer treatment-related cognitive dysfunction and psychological side effects could also be under-assessed because the screening was not considered, and patients were not further evaluated unless they exhibited significant behavioural signs and symptoms. Those patients were referred to a specialist, and their assessment and management notes could not be accessed.

In addition, the study design was observational because the research committee in the MOH does not legalize interventions to be conducted by students. It is hoped that identifying baseline drug-related problems in the present study and considering applying interventions in further studies would emphasize the clinical pharmacist's contribution to centralised patient care.

5.2.2 Incomplete survival data

In the present study, death incidence was quantified and presented rather than analysed based on treatment allocation. The correlation between treatment allocation and survival outcomes of breast cancer management was not considered an outcome of the present study because survival conclusions can not be made based on systemic treatment allocation alone. Breast cancer management includes different treatment modalities, including surgical interventions, radiation, and hormonal treatment, which significantly affect survival outcomes. The complexity of recruiting and following patients was a barrier to not considering the collection of other treatment modalities' data. Besides, as a clinical pharmacist, I was interested in researching cancer drugs allocation and outcomes rather than cancer surgery and radiation outcomes in order to implement clinical pharmacy services in the clinical practice of oncology. In addition, hormonal treatment allocation and outcomes were not included because project data collection was limited to 36 months, while hormonal treatment was offered post-completing chemotherapy for eligible patients with hormonal positive tumours only, and outcomes require a treatment duration of five to ten years to appreciate their value. This has been highlighted in the ATLAS and aTTom landmark trials.[98, 99]

In the literature, breast cancers have higher survival rates than other tumours, and published articles present the 10-year and 15-year survival outcomes of specific

treatments or specific intrinsic subtypes. Therefore, correlating the 2-year survival rates among breast cancer patients with different breast tumour subtypes and receiving different chemotherapy protocols will not make an identifiable contribution to knowledge. Also, the current study's sample size is too small to analyse the survival outcomes after stratifying patients based on different breast tumour stages, intrinsic subtypes, and treatment allocations.

According to the previously discussed issues, the survival data were considered incomplete. A longer follow up and including hormonal treatment outcomes would provide valuable data to make conclusions about the correlation between both chemotherapy and hormonal treatment allocation and long-term survival outcomes among older and younger breast cancer patients in Kuwait. Also, this would allow conducting time-dependent analyses in future studies to investigate the impact of baseline assessments on disease and overall survival.

5.2.3 Interpretation of subgroup data analyses

In addition to the mentioned limitations, investigating correlations in subgroups of patients with specific characteristics, resulted in small sample sizes, such as the number of comorbidities and less intensive treatment allocation among younger patients, factors contributing to disease relapse or treatment-induced depression. In such cases, the interpretation of statistical analysis results could not be definite.

5.2.4 Triangulation

Triangulation is a commonly used strategy in research to verify the findings by applying two methods (one quantitative and one qualitative method or different types of either qualitative or quantitative methods), considering two or more independent

investigators collecting the same data, or considering two different independent data sources. In this research, an external expert statistician recommended providing a questionnaire to collect data from patients and doctors to understand their attitudes toward the treatment allocation. This would necessitate requesting a research assistant from the hospital administration to make data collection time efficient and avoid exceeding the period allowed for the research. Unfortunately, the request was rejected. The statistician suggested that looking at the nature of the data and the hospital restrictions, it would be difficult to apply other methods. Accordingly, triangulation was not added to the thesis.

6. CONCLUSION

In conclusion, treating older breast cancer patients is challenging due to the wide range of toxicity risks associated with intensive management protocols. Standard cytotoxic treatment has comparable tolerance and therapeutic outcomes between younger patients and selected older patients with similar baseline characteristics and is not associated with increased requirements for treatment modification or discontinuation compared to less intensive cytotoxic treatment in the Kuwait Cancer Control Centre (KCCC)

Patients aged 60 years and above are at a higher risk of less intensive treatment allocation than younger patients. Besides, advanced performance status ≥1 and comorbidities ≥3 contributed to less intensive treatment allocation in both age cohorts. However, unlike younger patients, the correlation between performance status= 0 and a limited number of baseline comorbidities (0-2) and intensive treatment allocation

was negatively affected by age. The co-existence of diabetes and hypertension has been a contributing factor to less intensive treatment allocation among eligible older patients. This was attributed to the associated risk of treatment-related cardiotoxicity, even though comorbidities severity was not evaluated at baseline, and drug-related problems were not assessed to predict patinets' eligibility and tolerance. Besides baseline factors, patients occasionally request less intensive treatment against their oncologists' recommendations to avoid chemotherapy toxicities and maintain a good quality of life, which was more common among older patients.

Overall, there was a lack of effective baseline assessments, which could be due to the lack of validated standardized risk assessment tools integrated into the clinical practice guidelines. Patients with comorbidities and advanced age require comorbidities and polypharmacy assessments prior to treatment allocation to evaluate tolerance and identify patients who benefit from standard treatment. Also, optimizing comorbidities control and medication use is expected to minimize the requirement for treatment modifications or deviations. Integrating clinical pharmacy services in cancer patient-centered care multi-disciplinary team can assist in multiple aspects of baseline assessments and monitoring. The team collaboration will enhance treatment allocation, compliance, and outcomes among older and younger patients with breast cancer.

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APPENDIX

Appendix 1

Informed Consent (21 years old and above)

Research: Age Differences in The Factors Affecting Baseline Assessment and Systemic Treatment Allocation for Breast Cancer Females in Kuwait.

Section 1: Information sheet

I am pharmacist Afrah Aladwani, working for the Ministry of Health (MOH) of Kuwait and a PhD student at the University of Strathclyde. I am doing research on breast cancer, which is very common worldwide and in this country. I am going to give you information and invite you to be part of this research.

- This consent form may contain words that you do not understand. Please ask me to stop as we go through the information, and I will take time to explain.
- The aim of this research is to learn about the differences in treating older and younger patients with breast cancer and investigate the impact of comorbidities on treatment decision and outcomes. This knowledge about local health practices might help us to learn how to better control breast cancer in this community.
- You are being invited to take part in this research because I feel that your experience can contribute much to our understanding and knowledge of breast cancer management in the Kuwait Cancer Control Centre.
- This research is not a medical experiment and does not include giving drugs or taking samples or intervention in the treatment plan.
- Your participation in this research is entirely voluntary. It is your choice whether to participate or not. If you choose not to participate all the services you receive at this Centre will continue and nothing will change.
- The information that I collect from this research project will be kept private. Any information about you will have a number on it instead of your name. Documents including your information will be locked up with a lock and key in a secured office and will not be shared. Electronic data will be kept on a secured laptop with a password.

- You may stop participating in the research at any time that you wish without your treatment being affected.
- If you have any questions, you can ask them now or later. If you wish to ask questions later, you may send an email: ph.aladwani@hotmail.com

Section 2: Certificate of consent

I have read the research information, or it has been read to me. I have had the opportunity to ask questions about it and any questions I asked, have been answered to my satisfaction. I consent voluntarily to be a participant in this study

A. THE PARTICIPANT CONSENT

Name of Participant_____

Signature of Participant _____

Date _____

Day/month/year

B. THE RESEARCHER CONSENT

I confirm that the participant was given an opportunity to ask questions about the study, and all the questions asked by the participant have been answered correctly and to the best of my ability. I confirm that the individual has not been coerced into giving consent, and the consent has been given freely and voluntarily.

Name of Researcher _____

Signature of Researcher _____

Date _____

Day/month/year

Appendix 2
Research Approval Letter

State of Kuwait
Ministry of Health
Asst. Undersecretary for Assistance Medical
Services Affairs

Date: 01/11/2015
Number: 435

Respectable Mr. / Doctor Undersecretary

Kind regards,

Subject/ Facilitate the task of the researcher / AFRAH S M N DH ALADWANI
(Search Number / 303/2015) under the title:
Enhancing Clinical Pharmacy Services for Cancer Patients
Using Patient – Derived Pharmacoepidemiology Data

Please kindly informing that Standing Committee for the Coordination of medical and health research that was formed under the Ministerial Decree No. 207 for year 2012 that recommended in its meeting number twenty one (7/2015) that was held on Tuesday 27/10/2015 approved to make the research submitted by the researcher/ Afrah Salem Aloudwani on 26/10/2015 under the title:

Enhancing Clinical Pharmacy Services for Cancer Patients
Using Patient – Derived Pharmacoepidemiology Data

After the Committee, based on the Ministerial Decree No. 207 for year 2012 and the circulation issued from Mr. / Undersecretary No. 156 for year 2012, poll of the concerned authorities to the subject of the research as Mr. / Representative of the Legal Affairs sector has approved to conduct the research, also poll of Mr. / director of the pharmaceutical services department in the letter number 425 dated on 27/10/2015 and approved to conduct the research.

Appendix 3

Confidential Patient File

Code

Code: ……..……. Date: / /

Age: y File no:

Sex: M / F Unit:

Weight: Kg Nationality: K / NK

Ht: cm

Past Medical History (PMH):

- ☐ Diabetes
- ☐ Hypertension
- ☐ IHD
- ☐ Thyroid dysfunction
- ☐ Asthma/ COPD
- ☐ Arthritis
- ☐ CKD

……
……
……
……

Others

- ☐ Non-smoker
- ☐ Smoker
- ☐ Ex- smoker

Related Family History:

……
……
……

Known Drug Allergies:

- **PS:**
- **TNM:**

Current Diagnosis **Stage:**

Medication Reconciliation

Medication	Direction	Indication	Notes

Additional Notes:

……

……

……

……

Drug-related Care issues

Patient compliance

- ☐ Yes
- ☐ No

Care issue	Recommendation	Intervention

Counseling points:

Elderly Patient Assessment (or Not Applicable)

- ☐ Depression
- ☐ Dementia
- ☐ Delirium
- ☐ Falls
- ☐ Osteoporosis
- ☐ Vision impairment
- ☐ Hearing impairment
- ☐ Incontinence
- ☐ Sleep disorder
- ☐ Chronic pain
- ☐ Disability
- ☐ Poor nutrition status/ lack of appetite

Additional notes:

☐ Liver function:	☐ Renal function:
☐ Cardiac function: baseline LVEF:	

Treatment Plan

- ☐ Chemotherapy
- ☐ Surgery
- ☐ Radiation therapy
- ☐ Hormonal therapy
- ☐ Palliative therapy (Best Supportive Care)

Systemic Treatment Protocol:

- ☐ Standard (intensive)
- ☐ Non-standard (less intensive)

  Reason (based on the oncologist opinion)
  - Not eligible for standard treatment
  - Toxicity risk ……
  - Patient rejection against the doctor's recommendation ……..
  - Others ……
    ……..

Patient decision:

- ☐ Accepted the offered treatment plan
- ☐ Rejected the offered treatment plan

  Reason (based on the patient opinion)
  - Toxicity concerns
  - Lack of awareness (the patient thinks that targeted therapies replaced traditional systemic chemotherapy)
  - Patient beliefs ……
  - Others ……
    ……

Treatment regimen:

……

……

……

……

……

……

Follow Up

Cycle/ Date	Regimen	Notes

Follow Up

Cycle	Regimen	Notes

Tolerance/ toxicity

- ☐ Hair loss
- ☐ Nausea
- ☐ Vomiting
- ☐ Fatigue
- ☐ Ototoxicity
- ☐ Loss of appetite
    - o Need of nasogastric tube
    - o No intervention
- ☐ Bowel movement problems (constipation/ diarrhea)
- ☐ Cognitive impairment
    - o Mood swings
    - o Memory problems
    - o Reduced concentration/ attention
    - o Judgment and skills problems
- ☐ Depression
- ☐ Weight loss
- ☐ Anti-diuresis
- ☐ Anemia
    - o Need of erythropoietin
    - o Blood transfusion
    - o No intervention
- ☐ Mucositis
- ☐ Neutropenia
- ☐ Thrombocytopenia
- ☐ Skin and nails changes

Other complications (chemotherapy-related/ non-chemotherapy-related):

Cardiotoxicity

LVEF Monitoring for Patients Receiving Trastuzumab Treatment

Date: / /

Baseline LVEF:

The athero-sclerotic cardiovascular disease (ASCVD) risk estimation

- Low risk
- Moderate risk
- Severe risk

The patient developed a hypersensitivity reaction to trastuzumab treatment

- Yes
- No

LVEF Monitoring						
Date						
LVEF (%)						

The lowest LVEF documented

- > 50%
- = 50% Intervention: ……..
- < 50% Intervention: ……..

Trastuzumab treatment

- Completed Re-challenge: with/ without
- Discontinued

Symptoms of heart failure

- No
- Yes: ……

Notes:

……

……

……

……

Complications and Interventions

Appendix 4

Coding Sheet

No	File no.	Patient Name	Civil ID	Code

Appendix 5
Publication

European Review for Medical and Pharmacological Sciences

5-Year Impact Factor 3.111
2020 Impact Factor: 3.507

Editor in Chief: Camillo Ricordi, Md, Fnai
Co-Editor in Chief: David Della Morte Canosci, MD, PhD

Rome, October 27, 2021

ARTICLE: "Comparing trastuzumab-related cardiotoxicity between elderly and younger patients with breast cancer: a prospective cohort study".

AUTHOR: A. Aladwani, A. Mullen, M. Alrashidi, O. Alfarisi, F. Alterkait, A. Aladwani, A. Kumar, M. Boyd, M.E. Eldosouky

The article "Comparing trastuzumab-related cardiotoxicity between elderly and younger patients with breast cancer: a prospective cohort study" has been accepted for publication on European Review for Medical and Pharmacological Sciences.

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Appendix 6

Poster Presentations

ABSTRACT 1

Comparing Trastuzumab-Related Cardiotoxicity Between Elderly and Younger Patients with Breast Cancer: A Prospective Cohort Study.

Conference detail:

- **10th World Heart Congress. August 23-24, 2021, Prague, Czech Republic.**
- **The Clinical Pharmacy Congress. September 24-25, London, United Kingdom.**
- **Excellence in Oncology Care Congress (EIOC 2021). October 21-23, 2021, Dubai, United Arab Emirates.**
- **2nd International Conference on Cancer Science and Therapy. December 07-08, 2021, Dubai, United Arab Emirates.**

Introduction: Trastuzumab is an HER-2 targeted humanized monoclonal antibody that significantly improves metastatic and non-metastatic breast cancer therapeutic outcomes. However, it is associated with an increased cardiotoxicity risk that ranges from a mild decline in the cardiac ejection fraction to permanent cardiomyopathy. Concerns have been raised in treating eligible older patients. This study compares trastuzumab outcomes between two age cohorts in the Kuwait Cancer Control Centre (KCCC).

Methods: In a prospective comparative observational study, 93 HER-2 positive breast cancer patients undergoing different chemotherapy protocols + trastuzumab between April 2016 and April 2019 were included and divided into two cohorts based on their age (<60 and ≥60 years old). The baseline left ventricular ejection fraction (LVEF) was assessed and monitored every three months. The event of cardiotoxicity was defined as ≥10% decline in the LVEF from the baseline value. The lower accepted standard limit of the LVEF was 50%. The individual decline in the LVEF from the baseline was calculated and compared between the two age cohorts. Logistic regression analysis was applied to investigate the association between age, comorbidities, BMI, anthracycline treatment, and baseline LVEF value, and trastuzumab-induced cardiotoxicity after adjustments made for the disease stage.

Results: The median baseline LVEF was 65% in both age cohorts (IQR 8% and 9% for older and younger patients, respectively). Whereas the median LVEF post-trastuzumab treatment was 51% and 55% in older and younger patients, respectively (IQR 8%; p-value = 0.22), even though older patients had significantly lower exposure to anthracyclines compared to younger patients (60% and 84.1%, respectively; p-value <0.001). 86.7% and 55.6% of older and younger patients, respectively, developed ≥10% decline in their LVEF from the baseline. Among those, only 29% of older and 27% of younger patients reached a LVEF value below 50% (p-value = 0.88). Statistically, age was the only factor that significantly correlated with developing ≥10% decline in the LVEF (OR 4; p-value <0.012), but it did not increase the permanent discontinuation requirement of trastuzumab. A baseline LVEF value below 60% contributed to developing a post-treatment value below normal ranges (<50%).

Conclusion: Breast cancer patients aged 60 years and above in Kuwait were at a 4-fold higher risk of developing ≥10% decline in their LVEF from the baseline value compared to younger patients during trastuzumab treatment. Previous exposure to anthracyclines and comorbidities were not associated with a significantly increased cardiotoxicity risk in this study.

ABSTRACT 2

Comparing Histopathological and Molecular Subtypes of Breast Tumours Between Elderly and Younger Patients: A Population-Based Study.

Conference detail:

- **11th World Congress on Breast Cancer. October 06-07, 2021, Barcelona, Spain.**

Introduction: Breast cancer is a heterogeneous disease that exhibits different biological characteristics, and hence different responses to therapeutic agents. Understanding histological and molecular characteristics has led to introducing more classifications and subtypes of breast tumours in the treatment guidelines and changing aspects of treating patients from applying standardized treatment protocols to tailoring individualized treatment protocols. Questions were raised regarding the impact of advanced age on biological changes of tumour cells. The current study compares the intrinsic subtypes of breast tumours between younger and older patients in the Kuwait Cancer Control Centre (KCCC).

Methods: In a comparative population-based cross-sectional study, a total of 180 patients with breast cancer were randomly selected and subdivided into two age categories (<60 yrs or ≥60 yrs). Principle characteristics were: newly diagnosed female patients aged 21 years and above and referred to the Medical Oncology Department in the Kuwait Cancer Control Centre (KCCC) to receive systemic treatment between April 2016 and April 2018. Individual baseline tumour characteristics, including histopathology, TNM staging, Ki67% proliferative index status, hormonal (HR) and Human Epidermal Growth Factor (HER-2) receptor status, were assessed and compared between the two age cohorts using the Chi-Square Test.

Results: On diagnosis, non-metastatic breast cancer occurred in 93.3% and 85% of older and younger patients, respectively (p-value 0.11). Invasive Ductal Carcinoma (IDC) was the most predominant histopathological subtype in both age cohorts (93.3% and 96.7% in older and younger patients, respectively). Based on the TNM staging system, a statistically significant higher rate of stage II breast cancer was detected in older patients compared to younger patients (46.5% and 28.3% respectively; p value= 0.046). The Ki67% status did not differ by age cohort, whether considering ≥14% or ≥30% over-expression. Intrinsic molecular subtypes did not differ by age with HR and HER-2 positive tumours being the most common (p-value= 0.77).

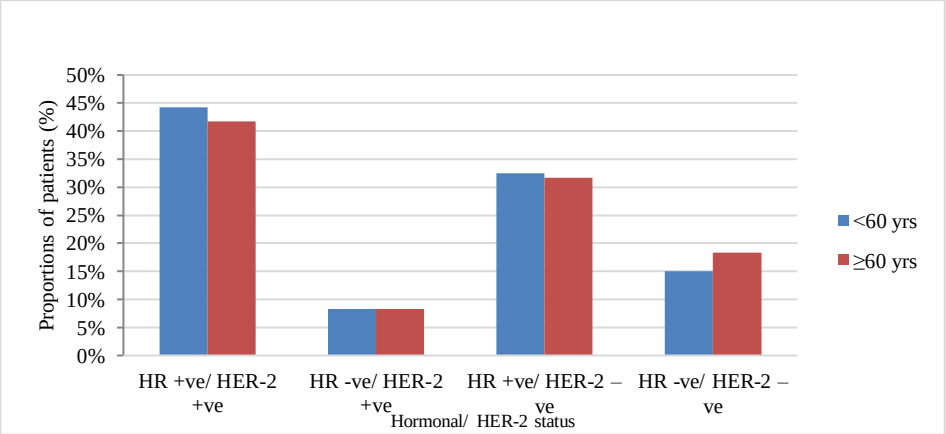

Figure 1. Comparing the proportions of HR and HER-2 receptors expression status between patients from the two age

Conclusion:

Breast cancer patients aged 60 years and above exhibited histopathological and molecular characteristics similar to younger patients in Kuwait. Also, the status of disease metastasis and proliferation did not differ by age. The only significant difference detected was the disease stage at diagnosis with more advanced non-metastatic tumours detected in younger patients.

ABSTRACT 3

Chemotherapy-Induced Anaemia: Comparing Prevalence and Severity Pattern Between Elderly and Younger Patients with Breast Cancer In Kuwait.

Conference detail:

- **Excellence In Oncology Care (EIOC). October 21-23, 2021, Dubai, United Arab Emirates.**

Introduction: Cancer patients are at a high risk of developing anaemia as a consequence of administering myelo-suppressive chemotherapy. Previous studies correlated anaemia with poor quality of life and unfavourable therapeutic outcomes. Older patients are expected to develop higher grades of anaemia than younger patients due to poor tolerance to chemotherapy and/or comorbidities. The current study compares the prevalence and severity of chemotherapy-induced anaemia between two age cohorts in the Kuwait Cancer Control Centre (KCCC).

Methods: In a prospective comparative observational study, 180 breast cancer patients undergoing different chemotherapy protocols between April 2016 and April 2019 were included and divided into two cohorts based on their age (<60 and ≥60 years old). The baseline haemoglobin level was documented and monitored throughout the study. The severity of post-treatment haemoglobin level was classified based on the NCI anaemia grading system. The consequent requirement for blood transfusion was quantified. The outcomes were analysed and compared between the two age cohorts using a T-test for continuous variables and a Chi-Square test for categorical variables.

Results: Patients from both age cohorts had similar median baseline and post-chemotherapy haemoglobin levels (12 g/dL and 10 g/dL respectively; p-value= 0.8). Only 8.3% and 6.7% of older and younger patients, respectively, maintained normal haemoglobin levels, while 93.3% of younger patients and 91.7% of older patients developed some grade of anaemia. The two age cohorts maintained a similar pattern of chemotherapy-induced anaemia prevalence and severity (p-value= 0.5). Mild anaemia was the most common grade and life-threatening anaemia was the least common (Figure 1). The requirement for blood transfusion was similar between the two age cohorts and accounted for 10% and 15% of older and younger patients (p-value= 0.3).

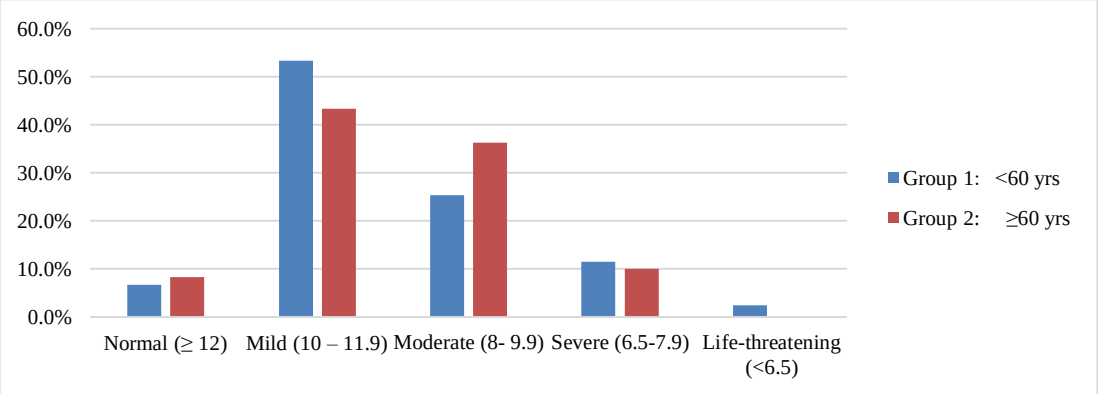

Figure 1. Comparing the prevalence and severity of treatment-induced anaemia between younger and older patients based on the haemoglobin levels (g/dL).

Conclusion: Breast cancer patients aged 60 years and above were not at a higher risk of developing higher rates or grades of chemotherapy-induced anaemia compared to younger patients in Kuwait. Mild anaemia was the most common grade, while life-threating anaemia was the least common. Comorbidity burden did not increase the requirement for blood transfusion among older patients.