TURKISH REPUBLIC OF NORTH CYPRUS

NEAR EAST UNIVERSITY

INSTITUTE OF GRADUATE STUDIES

EVALUATION OF HEMATOLOGICAL TOXICITY IN BREAST CANCER PATIENTS RECEIVING PACLITAXEL

By:

SHAD ADIL NOORI NOORI

MASTERS

A THESIS SUBMITTED TO THE INSTITUTE OF GRADUATE STUDIES

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CLINICAL PHARMACY

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2022-NICOSIA

APPROVAL PAGE

We declare that we have read **Shad Adil Noori Noori** thesis, **"Evaluation of Hematological Toxicity in Breast Cancer Patients Receiving Paclitaxel"** and that in our combined opinion it is fully adequate, in scope and in quality, as a thesis for the degree of Master of science in Clinical Pharmacy.

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DECLARATION

I, **Shad Adil Noori Noori**, declare that the thesis hereby submitted to the Near East University for the degree of Master of Clinical Pharmacy, in the School of Pharmacy, has not previously been submitted to this or any other university; that it is my work in design and execution; and that all material contained herein has been duly acknowledged.

Shad Adil Noori Noori

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“Evaluation of Hematological Toxicity in Breast Cancer Patients Receiving Paclitaxel’’

Shad Adil Noori Noori

MA, Department of Clinical Pharmacy

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Abstract

Introduction: Breast cancer is considered the most prevalent malignant tumor in women worldwide. Noting that, in her lifetime, one in eight women will acquire breast cancer. On the other hand, one of the most well-known and effective chemotherapeutic drugs for the treatment of numerous kinds of cancer, including breast cancer, is paclitaxel. Yet, paclitaxel treatment is frequently associated with numerous side effect including bone marrow suppression that is considered one the most detrimental hematological toxicities resulting in a delay to receive chemotherapy and a subsequent decline in rates of success and survival.

Methodology: The study was conducted retrospectively at Hiwa Hospital, Iraq, where data of female patients diagnosed with breast Cancer was collected from January 2021 till May 2022. The aim of the study was to assess and compare the hematological toxicities of breast cancer patients receiving paclitaxel during four cycles.

Result: Out of the 141 included patient, 74 patients with breast cancer didn't receive Filgrastim before the baseline whereas 67 patients received Filgrastim before the baseline. There were found to be statistically significant differences in the White Blood Cells in cancer patients receiving Paclitaxel (received Filgrastim before) between the baseline-the second cycle. Also, there was found to be a statistically significant difference ($p=0.001$) in the Platelets parameter in cancer patients receiving Paclitaxel (received Filgrastim before) between the baseline-the second cycle. There were found to be statistically significant differences in the White Blood Cells in cancer patients receiving Paclitaxel (did not received Filgrastim before) between the second-the third cycle. Also, there was found to be a statistically significant difference in the Platelets

parameter in cancer patients receiving Paclitaxel (did not received Filgrastim before) between both the baseline-the second cycle and baseline-the third cycle.

Conclusion: Our study findings has shown that anemia is the most prevalent chemotherapy associated hematological toxicity followed with neutropenia in breast cancer patients receiving paclitaxel.

Keywords*: Breast Cancer, Paclitaxel, Hematological Toxicities, Neutropenia, Anemia.*

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ABBREVIATIONS

Abbreviations	Explanation
BC	Before Christ
AC	Doxorubicin Plus Cyclophosphamide
AD	Advanced Disease
WHO	World Health Organization
MRI	Magnetic Resonance Imaging
AT	Paclitaxel Plus Doxorubicin
BC	Breast Carcinoma/Breast Cancer
SERMs	Selective Estrogen Receptor Modulators
IL-6	Interleukin 6
CDC	Center for Disease Control and Prevention
AIs	Aromatase Inhibitors
TNF-a	Tumor Necrosis Factor Alpha
ECTO	European Cooperative Trial In Operable Breast Cancer
ER	Estrogen Receptor/Endoplasmic Reticulum
FDA	Food And Drug Administration
G-CSF	Granulocyte Colony-Stimulating Factor
GM-CSF	Granulocyte-macrophage colony-stimulating factor
HER2	Human Epidermal Growth Factor Receptor 2
IVF	Intravenous Infusion
LABC	Locally Advanced Breast Cancer
LDH	Lactate Dehydrogenase
MBC	Metastatic Breast Cancer
ESBC	Early Stage Breast Cancer
MHC	Major Histocompatibility Complex
MoA	Mechanism Of Action
MTD	Maximum Tolerated Dose
MTOC	Microtubule Organizing Center

ASCO	American Society of Clinical Oncology
NCI	National Cancer Institute
NO	Nitric Oxide
ORR	Overall Response Rate
OS	Overall Survival
pCR	Pathologic Complete Response
PFS	Progression-Free Survival
PR	Partial Response
PR	Progesterone Receptor
PTP	Permeability Transition Pore
PTX	Paclitaxel
RBC	Red Blood Cell
mAb	monoclonal antibody
ROS	Reactive Oxygen Species
BCT	Breast-Conserving Therapy
SD	Stable Disease
IHC	Immuno Histo Chemistry
IDC	Invasive Ductal Carcinoma
ILC	Invasive Lobular Carcinoma
TNBC	Triple-Negative Breast Cancer
FISH	fluorescence in situ hybridization
TTP	Time to Progression
DMSO	Dimethyl Sulfoxide
CIA	Chemotherapy Induced Anemia
NCCN	National Comprehensive Cancer Network
HRT	Hormonal Replacement Therapy
BRCA	Breast Cancer Gene
ESMO	European Society for Medical Oncology
AML	Acute Myeloid Leukemia
SD	Standard Deviation

CHAPTER I

INTRODUCTION

Overview

Since the dawn of time, people have been plagued with cancer. However, in recent decades, its frequency has significantly grown in synchronized with the aging of the population, the rise in harmful health behavior in the general population during the past 50 years, as well as the increasing prevalence of cancer-causing substances in the consumer goods and the environment (Rothschild, M., et al., 2003). Moreover, according to Paulus Aegineta, early medical writing's father, cancer occurs in every part of the body but it is more common in women's breasts that has traditionally been a symbol of femininity, fertility, and beauty (Adams, F., 1844). Breast cancer has also been linked to ancient Egypt, with the first example being mentioned in the Edwin Smith Papyrus from 1600 BC (van Middendorp, J., et al., 2010). Breast cancer regularly caught the vision and imagination of our ancestors sufficiently for them to record it since it is fairly outwardly obvious swelled and cold to the touch in its most advanced condition that is rarely reached nowadays owing to modern medicine. Worldwide, the advent of mammography screening and an increase in lifespan can partially account for the growing prevalence of BC. However, breast cancer continues to be the number one killer of women between the ages of 40 and 59 years old, where 43,250 women and 530 men according to the American cancer society are anticipated to pass away from breast cancer in 2022 (Arzanova, E., & Mayrovitz, N., 2022). On the other hand, chemotherapy using cytotoxic medicines, which kill rapidly proliferating cells, has been the mainstay cancer treatment while an essential component of the therapy for breast cancer is paclitaxel (Davidson, G., 1996). These medications work well to treat cancer when administered systemically, but they frequently have negative side effects. The majority of these negative consequences are seen in normally healthy cells that also divide quickly, such as those in the blood, intestines, mouth, and hair (Patil, S., et al., 2022).

Bone marrow toxicity for example, is among the most seen side effects of chemotherapy, because the hematopoietic cells in the bone marrow produce and mature blood cells at a rapid rate, it is vulnerable to chemicals that target cells with a high potential for growth in addition these toxicities reduce the formation of platelets (thrombocytopenia), white blood cells (neutropenia or granulocytopenia), and red blood cells (anemia), which might be fatal to the patient (Testart-Paillet, D., et al., 2007). Therefore, in order to treat patients more successfully, it would be beneficial to avoid such undesirable action, since hematological side effects are a major factor in people stopping their anticancer treatments and subsequent decline in rates of success and survival (Daniel, D., & Crawford, J., 2006).

Breast cancer

Breast cancer is known as a malignant development of epithelial cells lining the breast ducts or lobules and is considered the most prevalent malignant tumor in women worldwide, for which 36% of oncological patients are breast cancer patients. Noting that, in her lifetime, one in eight women will acquire breast cancer (Nardin, S., et al., 2020). Although it is more prevalent in developed nations, the prevalence of this cancerous tumor is rising all around the world, where nations with advanced economies account for over half of the cases. The "Western lifestyle," which is characterized by a poorer quality diet, smoking, excessive stress, and insufficient exercise, is largely to blame for this tendency (Bellanger, M., et al., 2018).

In 2020, 685 000 people worldwide died and 2.3 million women were diagnosed with breast cancer with 7.8 million women alive, as of the end of 2020, who had received a diagnosis in the previous five years (WHO, 2020). Additionally, during the same period, 7 515 cases of breast cancer were detected in Iraq, accounting for 22.2% of all cancer in the country and representing 37.9% of cancer affecting women. Hence, making breast cancer also the most common cancer among Iraqis women (World Health Organization, 2020). On the other hand, from the 1930s until the 1970s, there were few changes in

breast cancer mortality. However, in nations with early detection programs and various modalities of therapy to remove invasive illness, survival rates started to rise in the 1980s. Moreover, between more than 90% in high-income nations and 66% in India and 40% in South Africa, the survival rate for breast cancer for at least 5 years following diagnosis varies widely (McCormack, V., et al., 2020). In addition, between the 1980s and 2020, age-standardized breast cancer mortality decreased by 40% in high-income nations. Countries that have been successful in lowering breast cancer mortality have been able to achieve a 2-4% reduction in yearly breast cancer mortality while 2.5 million breast cancer deaths would be prevented between 2020 and 2040 if there is a global 2.5% annual mortality decrease (Wild, C., et al., 2020).

Although breast cancer is typically thought of as a female-only disease, it is estimated that 2,650 males were diagnosed with the disease in the United States in 2021 (Siegel, L., et al., 2021). Moreover, at the time of diagnosis, men are more likely to have more advanced illness where men with breast cancer have worse unadjusted overall survival rates than women. This discrepancy is caused by a combination of factors, including late identification of the disease, older age upon diagnosis, and a generally lower life expectancy (Giordano, H., 2018).

a. Prevention of Breast Cancer

Currently, risk-reducing strategies, also known as risk factor identification and removal, are the focus of breast cancer preventive efforts. However, it should be highlighted that all screening methods have dangers, which should be made clear to patients so they may decide whether or not to undergo the investigation. False-negative and false-positive findings, overdiagnosis that represents an actual positives that won't become clinically significant, and radiation exposure are all hazards associated with screening mammography. With present technology, the rate of false-negative outcomes is around 20%. Moreover, annual mammography is the most debatable breast cancer screening strategy. The advantages and risks of a screening test that is less than ideal among

people of different ages who are at average risk of getting breast cancer that makes it controversial, despite the fact that screening mammography demonstrably lowers death from the cancer of breast. Women aged 60 till 69 had the greatest reduction in the number of invitations for screening necessary to avert one breast cancer mortality. However, despite the great sensitivity of mammography (90%) most abnormal tests yield false-positive findings, resulting in more biopsies and emotional discomfort. (National Cancer Institute, 2022). Investigations into further radiologic breast imaging techniques are also ongoing including digital mammography, the two-dimensional, digital breast tomosynthesis, also known as tomosynthesis or three-dimensional mammography, in addition to ultrasonography, and magnetic resonance imaging (MRI) (NIH, 2022).

Additionally, for people who are at high risk for developing breast or ovarian cancer, prophylactic bilateral mastectomies or bilateral salpingo-oophorectomy may be an option. This is certainly relevant if the breast tissue is difficult to assess by physical exam or mammography and if the patient has persistent, incapacitating fears of being diagnosed with cancer (Lostumbo, L., et al., 2010). On the other hand, the selective estrogen receptor modulators (SERMs), tamoxifen and raloxifene, and the aromatase inhibitors (AIs), Anastrozole and Exemestane, are only a few of the medications that can be used to pharmacologically reduce the risk of cancer where for example Tamoxifen lowers the incidence of invasive and noninvasive estrogen receptor (ER)-positive breast cancers by roughly 50% in those who have a high risk of developing the disease (NCCN, 2021).

The basis for early breast cancer identification is the correlation between the stage of the disease at diagnosis and the likelihood of recovery. Theoretically, more individuals may be cured of their condition if all cases of cancer in the breast could be identified at a primary period of the illness since tumors are basically small in size and lymph nodes are mostly not involved (NCCN, 2021).

b. Clinical Presentation

The breast is a complicated organ made up of skin, adipose tissue, subcutaneous tissue, and glandular and branching structures (Dipiro, J., et al., 2021).

A palpable mass can result from a number of illnesses that damage any of the breast structures. Additionally, regular breast alterations might result from the physiologic changes brought on by the menstrual cycle. Fibroadenoma, fibrocystic disease, cancer, and fat necrosis are common causes of breast lumps in young people. However, the first indication of breast cancer in the majority of women is a painless lump. Malignant masses often occur alone, unilaterally, as solid, hard, irregular, immobile masses. In a tiny percentage of instances, stabbing or aching pain is the initial sign. Nipple discharge, retraction, or dimpling are less frequent symptoms that may signal the beginning of the illness. In cases that are farther along, it's possible to see noticeable skin edema, as well as skin turning to red, warmth, and the underlying tissue becoming indurated (Dye, D., et al., 2012).

Furthermore, Breast cancer that is contained inside a small area of the breast is frequently described as early, primary, localized, or curable and even if it has reached regional or local lymph nodes the cancer is still regarded as early stage. Unfortunately, breast cancer cells frequently invade new areas by moving close together, through lymphatic systems, and through blood. On the other hand, advanced or metastatic breast cancer (MBC) is the term used to describe the condition when cancer cells of the breast may be found clinically or by radiology means in locations other than the breast. The lymph nodes that are located as not local-regional lymph nodes, lungs, bone, liver, skin, and mind are the organs most frequently affected by distant metastases. The clinical appearance of MBC may be accompanied by symptoms such as bone pain, respiratory problems, abdominal swelling, jaundice, and changes in mental state. Only a small

proportion of women who initially seek therapy have symptoms and evidence of distant metastases. However, almost all affected have an ignored breast bulge that has been there for months or even years. Additionally, 20 to 30 percent of all individuals who initially exhibit early breast cancer will later show symptoms of MBC (Claessens, K., et al., 2020).

c. Breast Cancer Subtyping

Cancer of the breast is a tremendously diversified sickness, with various clinical, morphological, and molecular characteristics (Rivenbark, G., et al., 2013). It is typically categorized largely by the tumor grade, architectural pattern, and histological appearance (Makki, J., 2015).

Malignancy develops in stages, and invasive breast cancer has a pre-invasive (also known as insitu) stage. During the carcinoma insitu phase, normal epithelia undergo genetic alterations that result in malignant transformation. Transformed epithelial cells multiply and accumulate in lobules or ducts, but they lack the genetic modifications needed to allow them to pass through the basement membrane. When malignant cellular transformation has taken place but the basement membrane is still intact, the condition is known as carcinoma in situ. On the other hand, a histologically diverse collection of lesions is known as invasive breast cancers. However, the majority of breast tumors are adenocarcinomas and based on how they appear under a microscope, breast carcinomas are often categorized into two basic categories: invasive ductal carcinoma and invasive lobular carcinoma. Moreover, mixed ductal and lobular carcinomas are tumors that occasionally exhibit both of these characteristics (American cancer society, 2022).

Although the prognoses of the various histologic subtypes of breast cancer vary, it is uncertain if these subtypes respond differently to therapy since histologic type is not routinely used to stratify patients in therapeutic studies. Overall, the chances of axillary node involvement, disease recurrence, and mortality are comparable between ILC and IDC, however the locations of metastases may vary (Anbari, B., et al., 2020).

1. Infiltrating/Invasive ductal carcinoma

Typically, the breast outside of the duct is affected and about 75% of all invasive breast cancers have the most prevalent histology, infiltrating or invasive ductal carcinoma (Brown K., 2022). In comparison to certain other histologic categories, these tumors frequently migrate to the axillary lymph nodes and have a worse prognosis. Bone, the liver, the lung, or the brain are the sites where IDC metastasizes most commonly (Borst, J., & Ingold, A., 1993).

2. Infiltrating/Invasive lobular carcinoma

Eight % of breast tumors are invasive or infiltrating lobular carcinoma (DeSantis, C., et al., 2019). They are distinguished by tiny cells that stealthily invade adipose tissue and the mammary stroma in a single-file routine under the microscope. (Pathology of breast cancer, 2022). However, it might also be more challenging to identify ILC with mammography and it has a propensity to spread to odd places such the leptomeninges, retroperitoneum, gastrointestinal system, peritoneal surfaces and reproductive organs (Inoue, M., et al., 2017).

3. Mixed ductal/lobular carcinoma

A mixed invasive carcinoma is described as having a mixed histologic appearance with elements of both ductal and lobular features. These account for 7% of invasive breast cancers (Metzger-Filho O., 2019).

Other histologic types of breast cancer include inflammatory that has a rapid onset while mistaken for infectious cellulitis, in addition to metaplastic, mucinous, tubular, medullary, and papillary carcinomas and together they account for less than 5 percent of invasive cancers (Makki J., 2015).

d. Diagnosis of Breast Cancer

A woman should visit a specialist if she observes any worrying breast cancer symptoms. Breast cancer warning signals include (CDC Breast Cancer, 2021):

- A new lump in the breast or underarm (armpit)
- Thickening or swelling of a portion of the breast
- Irritation or dimpling of breast skin
- Redness or flaky skin in the nipple area or breast
- Nipple pulling in or soreness in the nipple area

Moreover, a thorough history, a checkup of the mammary glands, a three-dimensional diagnostic mammogram, and perhaps further breast imaging procedures like ultrasound imaging or MRI should all be part of the initial workup for a woman who presents with a breast mass or symptoms that are suggestive of breast cancer. On a mammography, the majority of breast cancers can be seen as a lump, a collection of calcifications, or as a mix of these findings. Breast density, which can be influenced by age, menopausal state, and hormone replacement therapy use, is one of the main factors that influences mammography's capacity to detect cancer. For ladies with thick breasts or further particular categories of breast cancer patients, alternative breast imaging techniques such as ultrasound, MRI, digital mammography, and tomosynthesis are being researched (National Comprehensive Cancer Network. 2020). Reliability is also significantly influenced by the practical magnitude of the physical investigation and the radiology physician experience.

Therefore, diagnosis is done based on one of the following tests (CDC Breast Cancer, 2021):

- Ultrasound of the breast: A gadget that employs sound waves to create detailed images of locations inside the breast, known as sonograms (Johns Hopkins Medicine, 2022).
- Mammogram for diagnosis: If the patient has an issue with her breast, such as lumps, or if an area of the breast seems suspicious on a screening mammography, the doctor may recommend a diagnostic mammography. This is a more detailed breast X-ray (Mammogram Procedure, 2022).
- Magnetic resonance imaging (MRI): A type of body scan that employs the usage of a magnet connected to a computer. The MRI scan will produce comprehensive images of locations within the breast (MRI - Mayo Clinic, 2022).
- Biopsy: This is a test that removes tissue or fluid from the breast to be examined under a microscope and subjected to additional testing. There are various types of biopsies comprising fine-needle aspiration, core-needle biopsy, and excisional biopsy or open biopsy. The aberrant tissue is entirely removed during excisional biopsy. However, mutually core-needle biopsy that extract a mainstay of tissue, and fine-needle aspiration, and that detaches cells from the doubtful area, are types of percutaneously done needle biopsies. On the other hand, for mammographically identified non-palpable abnormalities, core-needle biopsy is the preferable biopsy technique. However, a more accurate histologic diagnosis is provided by core-needle biopsy, which also minimizes using inappropriate illustrations and can discriminate between aggressive and in situ cancer of the mammal gland, during which fine-needle biopsy cannot (Breast biopsy - Mayo Clinic, 2022).

In summary, a biopsy is the only definitive way to make a diagnosis of breast cancer (Breast cancer - Diagnosis and treatment, 2022).

e. Staging and Prognosis

Breast cancer phase is determined by the size and location of the main tumor, whether or not there are any lymph nodes involved, and whether or not there are any distant metastases as observed in Table 1 (Edition, S., et al., 2017). Patients' experiences with breast cancer's natural course vary, with some experiencing more aggressive illness that advances quickly and others experiencing a more indolent course. Moreover, when creating individualized treatment suggestions, the capacity to estimate prognosis is crucial where numerous pathologic prognostic and predictive variables have been discovered. In the lack of neoadjuvant or adjuvant systemic therapy, prognostic variables are traits or measures that are established at the time of diagnosis or surgery and are linked to the recurrence rate, mortality rate, or other clinical outcomes (Kaufmann, M., 1996), whereas predictive factors are indicators that are present at diagnosis and are connected to a patient's response to a particular therapy (Bundred, J., 2001). Furthermore, prognostic and predictive factors can be divided into the following broad classifications: (a) patient features that are unrelated to the ailment, for example age; (b) cancer traits, like tumor bulk or histologic type; (c) additional biomarkers that are quantifiable boundaries in tissues, cells, or fluids, for instance hormone-receptor standing; and (d) genetic factors. Therefore, prognostic and predictive characteristics can be used to customize treatment to the needs of the individual patient, improve the probability that it will have a positive clinical outcome, and lower the danger of unneeded toxicities (Croft, P., et al., 2015).

Nevertheless, prognosis can be impacted by ethnicity and age upon diagnosis. A poorer prognosis and more aggressive types of breast cancer are seen in certain younger individuals, especially those under the age of 35. Therefore, Younger individuals tend to exhibit poor prognostic signs in a higher chance, such as lymph nodes that have been damaged as well as tumors that are big and lack hormone receptors (Maggard, A., et al., 2003). Moreover, compared to white people, black people have a lower rate of survival

and numerous factors have been proposed as potential causes of this racial gap, comprising access to wellness program, financial position, cultural differences, a higher stage at diagnosis, and more hostile biologic characteristics (Fregene, A., & Newman, A., 2005). On the other hand, alcohol consumption, dietary habits, weight, and exercise are examples of potentially modifiable prognostic factors where physical exercise, weight management, and food are acknowledged by organizations like the American Cancer Society as possibly adjustable risk elements for lowering the risk of recurring breast cancer and associated comorbidities, like disease of the heart or diabetes (Demark-Wahnefried, W., et al., 2015). Additionally, breast cancer recurrence and future metastatic illness are influenced by two recognized independent variables: tumor size and the number of affected lymph nodes where the likelihood of a disease recurrence is closely correlated with the number of impacted lymph nodes (Beenken, W., et al., 2003). The breast cancer staging system considers the total number of positive nodes to be a prognostic indicator. However, it is complicated and not easy to categorize the association between tumor size and lymph node status. In addition, prognostic significance is associated with specific histologic subtypes and clinical breast cancer presentations. Treatment options may differ as, for instance, women having solely tubular or mucinous tumors had better findings than individuals with invasive carcinomas involving the duct, while IBC has a bad prognosis since it is a clinical categorization rather than a specific histologic subtype (NCCN, 2021).

Table 1: Cancer Staging (Edition, S., et al., 2017).

TX	Primary tumor cannot be assessed	
T0	No evidence of primary tumor	
Tis (DCIS)	Ductal carcinoma in situ	
Tis (Paget)	Paget's disease of the nipple NOT associated with invasive carcinoma or carcinoma in situ	
T1	Tumor ≤2 cm in greatest dimension	
	T1mi	<0.1 cm; microinvasion
	T1a	>0.1 cm ≤0.5 cm
	T1b	>0.5 cm ≤1 cm
	T1c	>1 cm ≤2 cm
T2	Tumor >2 cm ≤5 cm	
T3	Tumor >5 cm	
T4	Tumor of any size with direct extension to the chest wall and/or to the skin	
	T4a	Extension to the chest wall; invasion or adherence to pectoralis muscle in the absence of invasion of chest wall structures
	T4b	Ulceration and/or ipsilateral macroscopic satellite nodules and/or edema (including peau d'orange) of the skin that does not meet the criteria of inflammatory carcinoma
	T4c	Both T4a and T4b present
	T4d	Inflammatory carcinoma

Regional Lymph Nodes: Clinical (cN)		
cNX	Regional lymph nodes cannot be assessed	
cN0	No regional lymph node metastases	
cN1	Metastases to movable ipsilateral level 1, II axillary lymph node(s)	
	cN1mi	Micrometastases (approximately 200 cells, >0.02 cm <0.2 cm)
cN2	Metastases in ipsilateral level I, II axillary lymph nodes that are clinically fixed or matted; or in ipsilateral internal mammary nodes in the absence of axillary lymph node metastases	
	cN2a	Metastases in ipsilateral level I, II axillary lymph nodes fixed to one another (matted) or to other structures
	cN2b	Metastases only in ipsilateral internal mammary nodes in the absence of axillary lymph node metastases
cN3	Metastases in ipsilateral infraclavicular (level III axillary) lymph node(s) with or without level I, II axillary lymph node involvement; or in ipsilateral internal mammary lymph node(s) with level I, II axillary lymph node metastases; or metastases in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement	
	cN3a	Metastases in ipsilateral infraclavicular lymph node(s)
	cN3b	Metastases in ipsilateral internal mammary lymph node(s) and axillary lymph node(s)
	cN3c	Metastases in ipsilateral supraclavicular lymph node(s)

Regional Lymph Nodes: Pathologic (pN)		
pNX	Regional lymph nodes cannot be assessed	
pN0	No regional lymph node metastasis identified or ITCs only	
	pN0(i+)	ITCs only, no larger than 0.02 cm in regional lymph nodes
	pN0(mol+)	Positive molecular findings by reverse transcriptase polymerase chain reaction; no ITCs detected
pN1	Micrometastases; or metastases in 1-3 axillary lymph nodes; and/or clinically negative internal mammary nodes with micrometastases or macrometastases by sentinel lymph node biopsy	
	pN1mi	Micrometastases, (approximately 200 cells, >0.02 cm <0.2 cm)
	pN1a	Metastases in ipsilateral internal mammary sentinel nodes, excluding ITCs
	pN1c	pN1a and pN1b combined
pN2	Metastases in 4-9 axillary lymph nodes; or positive ipsilateral internal mammary lymph nodes by imaging in the absence of axillary lymph node metastases	
	pN2a	Metastases in 4-9 lymph nodes (at least one deposit >0.2 cm)
	pN2b	Metastases in clinically detected internal mammary lymph nodes with or without microscopic confirmation; with pathologically negative axillary nodes
pN3	Metastases ≥10 or more axillary lymph nodes; or in infraclavicular (level III axillary) lymph nodes; or positive ipsilateral internal mammary lymph nodes by imaging in the presence ≥1 positive level I, II axillary lymph nodes; or in >3 axillary lymph nodes and micrometastases or macrometastases by sentinel lymph node biopsy in clinically negative ipsilateral internal mammary lymph nodes; or in ipsilateral mammary lymph nodes	
	pN3a	Metastases in ≥10 axillary lymph nodes (at least one tumor deposit >0.2 cm) or metastatses to infraclavicular (level III axillary lymph) nodes
	pN3b	pN1a or pN2a in the presence of cN2b (positive internal mammary nodes by imaging) or pN2a in presence of pN1b
	pN3c	Metastases in ipsilateral supraclavicular lymph nodes
Distant Metastasis (M)		
M0	No clinical or radiographic evidence of distant metastases	
	cM0(i+)	No clinical or radiographic evidence of distant metastases in the presence of tumor cells or deposits <0.02 cm detected microscopically or by molecular techniques in circulating blood, bone marrow, or other nonregional nodal tissue in a patient without symptoms or signs of metastases
cM1	Distant metastases detected by clinical and radiographic means	
pM1	Any histologically proven metastases in distant organs; or if in nonregional nodes, metastases >0.02 cm	

Likewise, distinctive prognostic factors include tumor differentiation based on histologic heterogeneity and nuclear grade. Numerous histologic grading systems have been created, and the majority of them assign tumors a score from 1 to 3 according to their degree of differentiation: grade 1, highly differentiated; grade 2, moderately differentiated; and grade 3, poorly differentiated. However, as a component of the staging system, grading is included (Edition, S., et al., 2017). Noting that poorer survival and greater incidence of distant metastasis are linked to higher grade malignancies. Therefore, when choosing a course of therapy, this aspect is helpful, especially for sick people possessing minor tumors plus lymph nodes that are negative, making proliferation indices and lymphovascular invasion a potential additional variables (Mohammed, Z., et al., 2013).

On the other hand, once breast cancer is identified, hormone receptor status is determined since this information is critical for both prognostic and therapeutic purposes (Bonnie, J., 2021).

1. Breast cancer receptor testing:

Newly diagnosed breast cancers must be tested for:

a. Estrogen (ER) receptor expression
b. Progesterone (PR) receptor expression
c. Overexpression of human epidermal growth factor 2 (HER2) receptors (Bonnie, J., 2021)

2. ER and PR receptor expression

It is standard practice to determine the ER and PR status, and doing so is crucial for breast cancer care. Hormone receptor-positive tumors are seen in the majority of primary or MBC patients. Greater endocrine treatment response and longer disease-free lifespan are linked to hormone receptor positivity, which is more prevalent in postmenopausal people. In other words, it is helpful in choosing a course of treatment and serves as a

prognostic indicator for invasive breast cancer, especially in the first five years after diagnosis (ASCO, 2020). Moreover, these receptors enable cancer cells to grow by using estrogen and related substances like progesterone (Hormone Receptor Status, 2022). Breast cancer is referred to be ER-positive when estrogen receptors are expressed by the cancerous cells and it is referred to be PR-positive breast cancer if progesterone receptors are detected in the tumor cells. Whereas, the malignancy is referred to be ER/PR-negative if any of these two receptors are absent from the cells (Mayo Clinic, 2022). With the fact that approximately two-thirds of all breast malignancies are ER and/or PR positive (Davis, C., 2022). Immunohistochemistry, or IHC, is the most often used method for testing a tumor for estrogen and progesterone receptors where this method can detect estrogen and progesterone receptors in cancer cells derived from a tissue sample (American Cancer Society Breast Cancer, 2022). Based on this testing, patients who are ER and/or PR positive are candidates for endocrine therapy (Kinsella, D., et al., 2012).

3. HER2 receptor overexpression

Human epidermal growth factor receptor 2 (HER2) is a member of the epidermal growth factor receptor family having tyrosine kinase activity. When a receptor dimerizes, tyrosine residues in the cytoplasmic region of the receptor undergo autophosphorylation, which activates a number of signaling pathways that support cancer cell growth. (Iqbal, N., & Iqbal, N., 2014). However, about 15% to 20% of breast cancers have HER2 overexpression (Albagoush, A., & Limaiem, F., 2019), which is linked to more aggressive tumors, higher recurrence rates, and higher fatality rates (Loibl, S., & Gianni, L., 2017). Fluorescence in situ hybridization (FISH) and immunohistochemistry operate to detect the presence of HER2 overexpression, which is linked to a poor prognosis (IHC), and HER2 expression is regarded as positive in tumors that show an IHC of 3+ or FISH positive (NCCN, 2021). Moreover, response to HER2-targeted treatment is well predicted by HER2-positive status. Patients with HER2-positive MBC treated with trastuzumab, a monoclonal antibody (mAb) designed with a goal to affect the

extracellular domain of the HER2 receptor, exhibited higher survival rates than patients with HER2-negative MBC or patients with HER2-positive MBC who do not receive the mAb (Mastro, D., et al., 2012).

Additionally, the clinical outcomes of breast cancer are prognosticated and predicted using genetic profiling where studies that have questioned the idea that breast cancer is a single illness with differences in clinical behavior and histological characteristics have been made possible by the development of high-throughput technologies for gene expression research, such as microarrays. The studies also demonstrated that instead of morphological prognostic variables such as tumor size or nodal status, the response to therapy is decided by the intrinsic molecular properties of the tumors which may be examined using molecular techniques (Reis-Filho, S., & Pusztai, L. 2011).

f. Risk factors

To varied degrees, a number of endocrine, genetic, environmental, and lifestyle variables are linked to the development of breast cancer. While some aspects may be modified, others cannot. Depending on other confounding factors such age, family history, estrogen usage, and menopausal state, the influence of certain risk factors may differ (Patel, S., 2018).

Age and gender have the strongest correlations with the development of breast cancer. In terms of breast cancer, 62 years old is the median age of diagnosis (DeSantis, C., et al., 2019). Moreover, despite the fact that lung cancer kills more women than any other type of cancer, breast cancer is the principal killer responsible for the death of women between the ages of 20 and 59 years (Siegel, L., et al., 2021). However, with age, there is an increase in the likelihood of breast cancer. One in eight women will acquire breast cancer at some point in their lifetime, according to an often cited estimate for the disease. It should be underlined that this represents a lifetime cumulative risk of contracting the illness from womb to tomb. Yet, women frequently read the one-in-eight women statistic incorrectly, believing it to mean that one in eight women will be

diagnosed with breast cancer annually. The risk statistics can be presented more effectively using age intervals. For instance, a 20-year-old person has a 10-year likelihood of breast cancer diagnosis of 1 in 1479, whereas a 60-year-old person has a chance of 1 in 28 (Ravikumar, M., & Rachana, G., 2022). In addition, while it's a general knowledge that breast cancer primarily affects women, in the United States during the year of 2021, it was anticipated that 2,650 cases of the illness was detected in men with the female-to-male ratio being approximately 150:1 (Siegel, L., et al., 2021). However, no matter the patient's gender or sex, breast cancer is treated similarly.

Incidence rates of breast cancer differ significantly between racial and ethnic groupings. For instance, the average annual age-adjusted prevalence rate for non-Hispanic white women was 130.8 cases per 100,000 from 2012 to 2016, while the rates for non-Hispanic black women were 126.7 cases during the same period of time, American Indian/Alaska Native women were 94.7 cases, Hispanic women seem to be 93.7 cases, and Asian/Pacific Islander women were 93.2 cases. Consequently, white women have greater incidence rates than women from other racial and ethnic groups, which may be due to accessibility to and use of screening as well as variations in reproductive and lifestyle variables (Hirko, A., et al., 2022).

The risk of breast cancer has been linked to several endocrine variables and many of these are concerned with the overall length of menstruation. Menstruation starting before the age of 11 is typically referred to as early menarche, and it raises the overall lifespan danger of acquiring breast cancer. The chance of obtaining breast cancer is also increased through a late age for natural menopause such as 55 years or later (Zafar, T., et al., 2022). In contrast, having a bilateral ovary removed before the age of 45 years lowers the chance of getting breast cancer (East, M., & Edition, M., 2021). Moreover, the chance of acquiring breast cancer throughout the course of one's lifetime is said to rise with never giving birth and a late age at first birth, identified as having a child at the age of 30 years or more. Researchers hypothesize that a significant portion of the global variations in breast cancer incidence may be explained by differences in menarche age, menopause age, and childbearing (Gao, T., et al., 2000). Exogenous hormones and breast cancer development have been examined in several research. A series of clinical trials

known as the Women's Health Initiative (WHI) were conducted to examine the advantages and disadvantages of various treatment options that may have an impact on women's health conditions including breast cancer. In women receiving combined estrogen and progestin, the estrogen plus progestin study found a higher risk of breast cancer (Shapiro, S., et al., 2011). However, breast cancer incidence was lower in those receiving estrogen alone than in those receiving placebo in the estrogen alone study, which included postmenopausal women who had undergone hysterectomy before (Anderson, L., et al., 2012). There are still unanswered questions regarding the safety and efficacy of using shorter durations or lower dosages of estrogen or estrogen-progestin for menopausal symptoms since the risk of breast cancer increases with longer HRT courses and progestin usage concurrently. Additionally, depending on BMI and breast density, the effect of HRT usage on breast cancer risk varies. Therefore, in general, postmenopausal HRT is prohibited for ladies enduring a past of breast cancer. However, in people requiring HRT, the physician should carefully weigh the risks and advantages (Rossouw, E., et al., 2013). Similarly, the usage of female hormones exogenously also contributes to the occurrence of breast cancer. Yet, the use of oral contraceptives increases the risk of breast cancer by a minor amount (Marchbanks, A., et al., 2002).

Furthermore, a woman's chance of acquiring breast cancer is influenced by both her personal and family history where a higher chance of acquiring contralateral breast cancer is linked to a personal history of breast cancer. Also, 5-10% of breast cancer patients who receive a new diagnosis have a family history of the disease or ovarian cancer. Therefore, the chance of developing breast cancer is also enhanced by ovarian and uterine cancers (Bray, F., et al., 2018).

National comprehensive Cancer network suggests the following regarding breast cancer family history (Daly, B., et al., 2021):

- A woman is around 50% more likely to develop breast cancer if she has any first-degree relatives who have the disease. The risk rises as the number of first-degree relatives impacted expands.

- Age of the lady and age of the relative when they received a diagnosis both have an impact on risk. When a woman and her relative at the time of diagnosis are less than 50 years old, a greater risk is seen.
- It depends on other family history patterns how risky it is to have a second-degree relative who has breast malignancy. Generally speaking, the hazard is smaller than that of first-degree relatives.
- In assessing risk, it's crucial to take influenced family associates into account on both the maternal and paternal sides.

Even though those with a positive family history are more likely to get the disease, breast cancer is still not commonly detected in young people with positive ancestors' history. Hence, the elevated risk linked with a family member who has had breast cancer appears to be connected to multi-gene germline susceptibility and/or comparable exposure to environmental/lifestyle risk factors in most women (Lesueur, F., et al., 2021). The BRCA1 and BRCA2 genes are the most clinically important as these genes serve as tumor suppressors, preserving DNA repair and genomic stability. Women who inherit a mutant allele of this gene from either parent have a 60–80% lifetime risk of having breast cancer by the age of 80 years and a 33 percent lifetime risk of developing ovarian cancer (Kuchenbaecker, B., et al., 2017). On the other hand, the likelihood of bearing a BRCA gene alteration is influenced by family background and ethnicity. Compared to the rest of the US population, Ashkenazi or Eastern European Jewish descendants have an extremely high carrier frequency of germline alteration in BRCA1 and BRCA2 of about 2.5% (Struewing, P., et al., 1997). BRCA1 and BRCA2 mutation testing is now widely available, although it is often only advised in cases where there is a personal or family history of hereditary cancer, where the test findings can be properly read, and in cases when the data would aid in diagnosis and treatment. Multiple organizations have released guidelines on genetic susceptibility testing for those who fit the criteria for higher risk, however the choice to test a person for a genetic mutation related to breast cancer risk is complicated (Daly, B., et al., 2021).

The fact that breast cancer incidence rates vary greatly between nations shows that environmental and lifestyle variables are key contributors. For example, central obesity

is a risk factor for the development and recurrence of breast cancer, whereas moderate alcohol use raises the risk through an unknown mechanism. Table 2 represents some environmental and lifestyle Factors influencing the threat of breast illness (Dipiro, J., et al., 2021).

Table 2: Environmental and Lifestyle Factors (Dipiro, J., et al., 2021).

Factor	Comments
Elevated Risk	
Alcohol consumption	Some evidence that consumption before first pregnancy may affect risk; women who have 2-3 alcoholic drinks per day have a 20% higher risk compared to non-drinkers
Tobacco	Slight increase, notably in long-term, heavy smokers who started smoking before first pregnancy
Radiation exposure	Exposure particularly if before 10-30 years of age, eg, Hodgkin lymphoma
Reduced Risk	
Diet: Fruit and vegetable intake	Limited but increased evidence
Physical activity	Has protective effect independent of BMI
No Association	
Diet: Fat intake	No association based on recent meta-analysis
Mixed Results	
Diet: Soy	Reduced risk in Asian women but not the case with Western populations
Excess body weight/weight gain	Reduced risk in premenopausal women but elevated risk in postmenopausal women

g. Treatment Strategies

The management of breast cancer relies on a sum of variables, taking into consideration (Cancer.Net, type of treatment, 2021) (De Guzman G., et al., 2020):

- Histology, clinical and pathologic characteristics of the primary tumor
- Axillary node status
- Tumor hormone receptor content (estrogen/progesterone)
- Tumor HER2 status
- Presence or absence of detectable metastatic disease
- Patient comorbid conditions
- Patient age and menopausal status

Treatment usually includes one or more of the following: Systemic therapy (chemotherapy, biologic or targeted therapy, and endocrine therapy), radiotherapy, and surgery. Based on the assessment of each patient's condition individually and his disease stage (I-II-III-IV) the suitable treatment will be assigned. Chemotherapy could be adjuvant which is done after surgery in small tumors or neoadjuvant which is done before surgery in large tumors in order to determine response vivo (an important prognostic indicator). The choice of chemotherapy is usually chosen depending on tumor characteristics and patient characteristics (Dipiro, J., et al., 2021) such as hormone receptor positive and HER2 positive (National Comprehensive Cancer, 2022). In comparison to MBC, ESBC's desired therapeutic result is very different. With the intention of curing, various treatments such as surgery, radiation, neoadjuvant/adjuvant therapy (chemotherapy, biologic or targeted therapy, and endocrine therapy) are carried out and given. As a result of adjuvant therapy, the patient will be cured of breast cancer and all micrometastases will be removed. In order to allow for breast-conserving surgery, if the patient so chooses, neoadjuvant treatment is used to reduce the tumor's size prior to surgery. Additionally, neoadjuvant therapy enables evaluation of the sensitivity or responsiveness to chemotherapy and/or biologic/targeted treatments. Local

imaging techniques, including mammography or ultrasound, are used in the neoadjuvant context to evaluate the tumor response to chemotherapy, biologic or targeted treatment, or endocrine therapy. After initial therapy is finished, patients are advised to undergo a history and physical examination every three to six months for the first three years, every six months for the next two years, and then once a year after that. Except in cases when there is a suspicion of recurrence or metastatic illness, routine laboratory testing or imaging are not advised (Runowicz, D., et al., 2016). On the other hand, the goal of therapy for MBC treatment is palliation. The general treatment objectives of any therapy delivered in this situation are to maximize benefits and minimize harm where sequential single-agent chemotherapy is frequently preferred over combination regimens, however in some clinical circumstances combination chemotherapy may be necessary for faster results. In this case, it is crucial to carefully take into account quality of life. Changes in laboratory testing, diagnostic imaging, or physical indications or symptoms can all be used to determine how well a treatment plan is working to treat a tumor. Unless the patient is unable to tolerate the regimen or the cancer is developing at a rate that would result in, or is causing symptoms already, the patient often continues therapy. Therefore, for MBC patients, improving quality of life is a crucial therapeutic goal that finally calls for stopping aggressive cancer treatments and switching to supportive care with hospice care (Chung, T., & Carlson, W. 2003).

1. Surgery

Due to a better understanding of the biology of breast cancer and the outcomes of several well-executed clinical studies done during this time, the selection of operational techniques has significantly converted during the 50 years that passed (Litière, S., et al., 2012). BCT, a less invasive procedure than mastectomy, that correspond to the total removal of the breast, can be used to treat the majority of patients who have been diagnosed with breast cancer while still achieving acceptable aesthetic outcomes and low risks of local and distant recurrence and death (NCCN, 2021). Furthermore, a number of variables supposed also to though about, including young age, family history,

and genetic susceptibility while choosing patients for BCT. The NCCN guidelines advise mastectomy and other risk-reduction measures such as bilateral mastectomies for women who have known BRCA1 or BRCA2 mutations. Owing to the fact that, in individuals with BRCA1 or BRCA2 mutations, bilateral complete mastectomy and oophorectomy lower the risk of breast cancer recurrence (Heemskerk-Gerritsen, M., et al., 2013). On the other hand, mastectomy is indicated when there are several cancerous breast tumors and when the breast specimen from the mastectomy did not achieve negative pathologic margins (Czajka, L., & Pfeifer, C. 2021).

2. Radiation

In comparison to no radiation, radiotherapy following BCT lowers the chance of a first recurrence within 10 years by 16% and the risk of breast cancer mortality within 15 years by 4% (Bartelink, H., et al., 2007). The majority of radiation treatment breast complications are modest and involve breast tissue turning red with erythema as well as later total breast mass decrease that is more than expected based on the elimination of breast tissue. In addition, for patients with four or more positive axillary lymph nodes, post-mastectomy radiation is advised. It should also be taken into consideration if the tumor is less than five centimeters in diameter, has margins that are less than one millimeter wide, is more than five centimeters in diameter with negative lymph nodes, one to three lymph nodes are positive, or has positive margins (NCCN, 2021). Radiation therapy is also a crucial component of the management of symptomatic MBC where hurting bone metastases or extra restricted disease spots that are resistant to systemic help are the most frequent indications for treatment with radiation therapy. 90% of patients receiving radiation treatment for severe bone metastases report considerable pain alleviation (Tong, D., et al., 1982). The palliative management of brain lesions that are metastatic, lesions concerning the spinal cord, eye or orbit lesions, as well as other areas where considerable tumor cell accumulation takes place and which do not react well to systemic therapy, involves the use of radiation. Radiation treatment for palliation

may also be used to treat lymph node and skin metastases that are restricted to the trunk wall region (eg, open wounds or painful lesions) (Chang, L., & Lo, S. 2003).

3. Biologic or Targeted Therapy

Several drugs are aimed at targets that are differently generated in breast cancer cells and are essential for the growth and survival of those cells. For example, the HER2-receptor protein is the target of the mAb trastuzumab. Tumors that overexpress HER2, the clinical prognosis of such malignancies was historically dismal. However, with the introduction of trastuzumab and other targeted medicines, the clinical result of HER2 positive patients has significantly improved compared to 20 or more years ago (Hayes, F., et al., 2018). It is recommended for patients with early-stage, HER2-positive breast cancer in conjunction with or immediately following adjuvant chemotherapy. This treatment improves disease-free and overall survival rates by 48% when compared to chemotherapy alone (Gianni, L., et al., 2010).

4. Endocrine Therapy

Also known as hormonal therapy or hormone treatment, it slows or prevents the growth of hormone-sensitive (ER positive, HER2 negative) cancers by interfering with the effects of hormones on breast cancer cells or by limiting the body's ability to manufacture hormones. Yet, the individual's menopausal state affects the choice of agent(s). Hormone-insensitive tumors lack hormone receptors and do not react to hormone treatment. Tamoxifen has been employed in this context for many years and is traditionally regarded as the gold standard adjuvant endocrine treatment. In breast cancer cells, tamoxifen is antiestrogenic, while in other tissues and organs, it exhibits estrogenic effects. However, compared to women who do not get adjuvant tamoxifen medication, those who do had a lower risk of death and recurrence (Makubate, B., et al., 2013).

5. Chemotherapy

Breast tumors that are PgR negative and show indications of increased proliferative activity with expressing of HER2, but not to the extent that "HER2 amplified" tumors, have poor prognosis but they might be more vulnerable to chemotherapy. Neoadjuvant systemic therapy is the gold standard of care for individuals with IBC and locally advanced breast cancer, and it is a significant therapeutic option for ESBC patients. This course of treatment often comprises of chemotherapy, either alone or in combination with biologic or targeted therapy, but, under some conditions, endocrine therapy may also be used (eg, in inoperable patients with significant comorbidities or in tumors with high sensitivity to endocrine therapy). Preoperative systemic therapy benefits include a reduction in tumor growth to reduce the need for surgery, monitoring the effectiveness of hormone therapy or chemotherapy (a crucial prognostic indicator), and other potential benefits (eg, delivery of chemotherapy through an intact vascular system). Moreover, most MBC patients eventually require cytotoxic chemotherapy. Chemotherapy is necessary for hormone receptor-positive cancers that do not respond to first endocrine/targeted therapy regimens or grow resistant to endocrine therapy and is necessary as the primary treatment for metastases in ill persons with TNBC. On the other hand, chemotherapy is selected based on overall effectiveness, risk of toxicity, patient performance status and the presence of comorbidities, aggressiveness of disease (e.g., indolent vs. visceral crisis), and patient preferences regarding schedules, dosing route (oral vs. intravenous), and frequency of the chemotherapy (weekly vs. every three weeks) (Hassan, U., et al., 2010). While sequential use of single-agent treatments is also a successful tactic and may be preferable due to lower risks of adverse medication responses, response rates for combination chemotherapy remain high. When effectiveness in the palliative context is comparable, the least harmful strategy is favored. The majority of patients only have marginal responses to treatment.

Chemotherapy administration takes between 12 and 24 weeks, depending on the regimen utilized, even if the ideal time frame is uncertain. Ideally, chemotherapy should be started within 12 weeks following the main tumor's surgical excision (Chavez-

MacGregor, M., et al., 2016). Satisfactory performance position, a small count (one to two) of illness sets (or affected organ systems), and a sustained prior response to chemotherapy (long disease-free interval) or hormone treatment are all factors linked to an enhanced probability of responding to chemotherapy. A patient's probability of responding to further treatment is decreased if they experience increasing illness while receiving chemotherapy. However, a chemotherapy program is typically continued after it has begun unless the illness progresses or there are severe adverse medication effects. (Zhang, H., et al., 2022).

A large number of chemotherapy drugs have shown promise in the healing from breast cancer, counting in doxorubicin (both conventional and liposomal), epirubicin, paclitaxel (both conventional and albumin-bound), docetaxel, gemcitabine, fluorouracil, methotrexate, cyclophosphamide, vinblastine, capecitabine, vinorelbine, ixabepilone, eribulin, carbop. The most effective chemotherapy classes for MBC are anthracyclines and taxanes including paclitaxel, which have hits rates of up to 50% in patients who have never had chemotherapy before for metastatic illness (Edman Kessler, L., 2022). Moreover, for the adjuvant treatment of breast cancer, anthracyclines and taxanes (paclitaxel or docetaxel) have emerged as the mainstays of contemporary chemotherapy (Goble, S., & Bear, D., 2003).

Additionally paclitaxel, docetaxel, and albumin-bound paclitaxel are FDA-approved for the treatment of MBC and are all thought to be therapeutically similar but do not exhibit complete cross-resistance (Phillips, C., & Mousa, A., 2022).

Paclitaxel

Amongst the greatest well-known, effective chemotherapeutic drugs for the treatment of numerous kinds of malignancy, embracing breast cancer, is paclitaxel (PTX) (Cancer Research, 2019). As part of a National Cancer Institute-led plant screening initiative of the United States, it was initially found in the 1960s from the bark of the Pacific yew (Taxus brevifolia), which includes endophytic fungi that produce compound with antineoplastic activity known as paclitaxel. Scientists gave it the name Taxol subsequently, in 1971, and further elucidated its chemical composition (Wani, C., et al., 1971). Susan Horwitz identified PTX's mode of action as a microtubule stabilizer in 1979 (Schiff, B., et al., 1979). However, PTX initially entered clinical trials in 1984 after displaying moderately encouraging outcomes in in vivo mice tumor models in 1978 (Walsh, V., & Goodman, J. 2002). When PTX was introduced to the market by Bristol-Myers Squibb, it was given the brand name "Taxol"® in addition to the generic name "PTX" Taxol. Historically, Taxol has been highly lucrative chemotherapy medicine and the sole drug to be chosen from a plant screening program (Walsh, V., & Goodman, J. 1999). PTX was initially isolated from Taxus bark, but because 4 trees had to be wasted to produce 2 grams of the powerful component, the bush is now rare. The acylation of 10-deacetylbaccatin III allowed the medicinal chemist to finally create this complicated molecule in around 40 step processes (Griffon-Etienne, G., et al., 1999). Moreover, in 1994 and 1999, respectively, the FDA authorized Taxol® for the treatment of BC and non-small cell lung cancer (NSCLC) (Tuma, S., 2003). Today, the FDA has authorized PTX for the treatment of advanced ovarian cancer, Kaposi's sarcoma, as a second line, BC, including metastatic and non-metastatic, and microcytic lung malignant neoplasm (metastatic or non-metastatic). Furthermore, PTX is employed as adjuvant or neoadjuvant treatment for testicular cancer, bladder cancer, cancer of the esophagus, prostate cancer, cervical cancer, cancer of the head and neck, stomach cancer, endometrial cancer, and brain oligodendroglia (Fu, Y., et al., 2009). Tricyclic diterpenoid PTX, which has a taxane ring and a C-13 side sequence, is what gives the

substance its cytotoxic properties (Singla, K., et al., 2002). Yet, due to its high lipophilicity, it is nearly insoluble in water and has a poor rate of dissolution and a little oral bioavailability of fewer than 8% (Cagel, M., et al., 2017). It is a hydroxylase that is cytochrome P450-dependent, and because of the carbon at the 2' position, it may acquire functional groups or undergo polymer conjugation, which increases its action, like in the circumstance of Taxol® (Walker, K., et al., 2002).

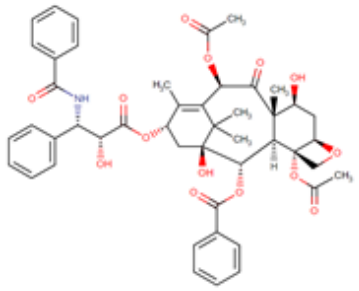
a. Mechanism of Action

The typical activity of microtubule growth in the cell is disrupted by paclitaxel (Mikuła-Pietrasik, J., et al., 2019). PTX works by binding the microtubule apparatus's beta-tubulin subunit's at the N-terminal 31 amino acids. Moreover, by boosting the function of tubulin dimers, making already-formed microtubules stable and preventing the disintegration step, disturbing the delayed G2 mitotic phase, and preventing cell duplication, paclitaxel increases microtubule assembly. To be more precise, the tubulin is considered as the construction unit of microtubules, and the attachment of paclitaxel freeze these building units in situ. Therefore, it is impossible for the resultant complex to disintegrate. Because microtubules must shorten and lengthen, a process known as dynamic instability, in order to serve as the cell's transportation system, this has a negative impact on how cells operate. For instance, during mitosis, chromosomes depend on this characteristic of microtubules. Consequently, the medication has the potential to damage chromosomes by distorting mitotic spindles. According to additional study, paclitaxel causes cancer cells to undergo programmed cell death, a process known as apoptosis by attaching to the apoptosis inhibitor protein Bcl-2 (B-cell leukemia 2) and inhibiting its activity causing morphologic alterations and DNA fragmentation. Additionally, paclitaxel may regulate immunological response and decrease cell growth (Drug Bank, 2022).

b. Properties of Paclitaxel

All the chemical and physical properties of the drug are summarized in Table 3 (Singla, A. K., et al., 2002) (National Center for Biotechnology Information, 2022).

Table 3: Physical and chemical properties of paclitaxel

Chemical structure	
Molecular formula	C47H51NO14
Color	White to off-white crystalline powder
Form	Fine white powder
Odor	Odorless
State	Solid
pKa	10.36
Melting temperature	216-217 °C
Log P	3

solubility	0.3 - 0.5 μg/ml
Molecular Sensitivity	degraded under acidic conditions

c. Pharmacodynamics/Kinetics

Paclitaxel is administered IV or intraperitoneally due its extremely low bioavailability. For a 24 hour infusion, the volume of distribution is around 227 to 688 L/m2. The distribution is affected by the dosage and time of infusion, since paclitaxel distribution is of two phase with a primary fast distribution to the peripheral compartment and a later phase of gradual efflux from the peripheral compartment (Pelletier-Dattu, E., 2015). However, since paclitaxel has a nonlinear disposition and a saturable distribution the rate of plasma clearance is influenced by tissue binding and distribution. If the schedule is maintained, it seems that the mean clearance of paclitaxel declines when the dosage is raised (Gelmon, K., 1994). For example, the clearance rate at a dosage of 135 mg/m2 is 14.7 L/hr. /m^2, whereas it is 8 L/hr. /m^2 for a dose of 250 mg/m^2. Because of this, dosage escalation causes an unbalanced rise in the intensity and duration of toxicity (Kearns, M., 1997). The vehicle of formulation for paclitaxel may be responsible for its nonlinear pharmacokinetics. In a mouse model, Sparreboom and colleagues showed that paclitaxel exhibited a nonlinear disposition when formed in a 50% polyoxyethylated castor oil derivative, but a linear disposition when formulated in 20/80. Although this offers an attractive hypothesis, it is challenging to apply these findings to the human species due to intrinsic variances in the metabolic pathways and those processes' rate-limiting characteristics (Sparreboom, A., et al., 1996). In addition 89% to 98% of Paclitaxel dose is tightly bound to plasma protein. Paclitaxel undergoes hydrolysis of its ester groups and then it is hepatically metabolized by the cytochrome P450 via CYP2C8 and 3A4, primarily forming 6α-hydroxypaclitaxel metabolite as well as other metabolites. Whereas, approximately 14% of the dosage is excreted in the urine. Moreover, the half-life of a 3 hours infusion ranges between 13 to 20 hours while for a 24-hour infusion it is approximately between 16 to 53 hours (Pelletier-Dattu, E., 2015).

d. Solubility

Paclitaxel is miscible in methanol forming a clear, colorless solution of 50 mg/ml, as well as in DMSO producing also a 50 mg/ml clear, colorless solution. Moreover, it is soluble in chloroform, and ethanol. For several months, DMSO solutions can be frozen and kept in aliquots at -20°C. It hydrolyzes in aqueous solutions and undergoes transesterification in methanol ((Singla, K., et al., 2002). However, these preparations are further diluted in NS or D5W to a concentration of 0.3-1.2 mg/mL (Medscape, 2022).

e. Indication and Dosing

Breast cancer: it is used for the treatment of metastatic breast cancer following the failure of combination chemotherapy or relapse within 6 months of adjuvant chemotherapy. However, prior therapy should have included an anthracycline. As well as adjuvant treatment for node-positive breast cancer (Wolters Kluwer Clinical Drug Information, 2022). Moreover the dose is 175 mg/m² IV administered over a period of 3 hours every 2-3 weeks (Medscape, 2022).

Lung cancer-non small cell: non-small cell lung cancer patients who are not candidates for radiation therapy and/or potentially curative surgery should receive paclitaxel in combination with cisplatin as their first-line treatment (Wolters Kluwer Clinical Drug Information, 2022). The dose is 135 mg/m² IV administered over a period of 24 hours every 3 weeks (Medscape, 2022).

AIDS-related Kaposi's sarcoma: PTX is considered as a second-line treatment of AIDS-related Kaposi sarcoma (Wolters Kluwer Clinical Drug Information, 2022). In this clinical setting the dose is either 135 mg/m² IV administered over 3 hours every 3 weeks, or administered IV over a period of 3 hours every 2 week at a dose of 100 mg/m² (Medscape, 2022).

Ovarian cancer: it is considered for treatment of advanced ovarian cancer as subsequent therapy as well as ovarian cancer first-line therapy when combined with cisplatin (Wolters Kluwer Clinical Drug Information, 2022). Moreover, it is recommended to pretreat using dexamethasone, diphenhydramine, or H2 blockers to prevent hypersensitivity reactions. For previously untreated patients the dose is 175 mg/m² administered through intravenous infusion over a duration of 3 hours every 3 weeks and alternatively, it can be administered IV over a period of 24 hours every 3 weeks at a dose of 135 mg/m² (Medscape, 2022).

Other uses includes (Fu, Y., et al., 2009):

- Pancreatic tumor.
- Cancer of the esophagus.
- Bladder cancer.
- Cancer of the cervix.
- Head and neck cancer.
- Endometrial cancer.

f. Administration

Paclitaxel should be delivered under the direction of a medical professional skilled in the use of cancer chemotherapy drugs since when sufficient diagnostic and therapeutic

services are easily accessible can problems be managed effectively. Patients with breast cancer have been treated with paclitaxel infusion regimens of 1 h, 3 h, 24 h, and 96 h (Mamounas, E., 1998). Yet, the most popular infusion right now is a 3-hour one due to how convenient it is in an outpatient setting and nowadays, 3-hour infusions with doses between 135-250 mg/m^2 are often used in clinical research every three weeks (Nabholtz, M., et al. 1996). The administration of paclitaxel in weekly cycles is a further topic of great interest. Higher cumulative dosages of paclitaxel can be administered on a weekly basis as opposed to every three weeks. Moreover, in comparison to dosing every three weeks, weekly administration of paclitaxel and albumin-bound paclitaxel leads in greater response rates, time to progression, and survival as well as a more favorable adverse drug reaction profile where delay in the onset of peripheral neuropathy and reduced myelosuppression were noticed, but somewhat higher fluid retention and alterations to the skin and nails, were observed in the toxicity profile of paclitaxel (NCCN, 2021). Additionally, the drug is irritant with vesicant-like properties. Therefore, it is recommended to avoid extravasation while ensuring suitable needle or catheter position preceding to its running. However, if extravasation arises, it should be treated as soon as possible by stopping the infusion and disconnecting the infusion while leaving the cannula or the needle in place. After that, it is recommended to gently aspirate the extravagated solution without flushing the line, then removing the needle/cannula is advised in addition to starting the antidote, which is hyaluronidase. Moreover, if necessary after removing the needle or cannula, elevating the affected extremity may be useful (Pérez Fidalgo, A., et al., 2012). Conflicting information exists on the usage of warm or cold compresses. Hyaluronidase could be employed in the treatment of paclitaxel expel, according to clinical experience. Nevertheless, there is a paucity of evidence (Stanford, L., & Hardwicke, F. 2003). Dexamethasone with a dose of 20 mg orally or IV at 12 and 6 hours before paclitaxel dose that is reduced to 10 mg with advanced HIV disease, diphenhydramine (50 mg IV 30 to 60 minutes before the dose), famotidine 20 mg, or cimetidine (300 mg oral or IV 30 to 60 minutes prior to paclitaxel) are all recommended premedications to reduce the risk of anaphylaxis (Lansinger, M., et al., 2021).

Furthermore, paclitaxel is administer through IV tubing equipped with a 0.22 micron in-line filter as well as non-PVC tubing that is polyethylene-lined needs to be utilized to reduce leaching. It's not advised to use undiluted solution on plasticized PVC equipment or devices and it should be distributed in either glass or Excel/PAB containers. On the other hand, the administration of taxane derivatives prior to the administration of platinum derivatives, such as cisplatin or carboplatin in consecutive infusions, can reduce myelosuppression and increase effectiveness (Medscape, 2022). Moreover, PTX can be administered intraperitoneally where warm saline is utilized to make the solution, and an implanted intraperitoneal catheter is used to administer it as quickly as feasible. However, this route is not FDA approved (Armstrong, K., et al., 2006).

g. Paclitaxel Protocols for Breast Cancer

Table 4 briefly reviews regimens including paclitaxel for breast cancer (UpToDate, 2022).

Table 4: regimens of breast cancer including paclitaxel	
adjuvant treatment + Anthracycline containing regimen	175 mg/m^2 lasting three hours every 3 weeks meant for 4 cycles
AC-T (dose dense):	175 mg/m2 every 2 weeks for 4 cycles (with growth factor support; following 4 cycles of dose-dense doxorubicin and cyclophosphamide [AC]).
AC -TH (HER-2 positive):	IV: 80 mg/m2 once weekly for 12 weeks or 175 mg/m2 every 3 weeks for 4 cycles (in combination with trastuzumab, following 4 cycles of AC) or 175 mg/m2 every 2 weeks for 4 cycles (with growth factor support; in

	combination with trastuzumab, following 4 cycles of dose-dense AC).
AC-THP (neoadjuvant therapy; HER-2 positive):	IV: 80 mg/m2 once weekly for 12 weeks (in combination with pertuzumab and trastuzumab; following 4 cycles of dose-dense AC).
TH (HER-2 positive):	IV: 80 mg/m2 once weekly for 12 weeks (in combination with trastuzumab).
Breast cancer, metastatic or relapsed using combination:	IV: 80 mg/m2 once weekly (in combination with trastuzumab and pertuzumab); or 90 mg/m2 on days 1, 8, and 15 of a 28-day cycle (with the addition of bevacizumab) until disease deterioration or unsupportable harmfulness, or 175 mg/m2 over 3 hours on day 1 every 3 weeks (in combination with gemcitabine) until the progression of the ailment or unsupportable toxicity.

h. Side effects associated with paclitaxel

Myelosuppression including neutropenia and thrombocytopenia are the most hazardous effect of paclitaxel in a dose-dependent manner where patients become more susceptible to bleeding, anemia, and/or infections as a result. According to pharmacology research conducted during paclitaxel clinical trials, the length of time plasma levels persist beyond 50-100 nmol/L is most closely related to the severity of neutropenia. The length of the paclitaxel infusion has an impact on how severe the neutropenia is. Therefore, the severity rises with longer infusions (Huizing, T., et al., 1993).

Peripheral nerve endings, which include the nerves to the hands, feet, and, in rare cases, other locations, are susceptible to injury from paclitaxel. This may cause tingling and numbness sensations, as well as occasionally excruciating burning sensations, this is known as peripheral neuropathy. When handling objects that are sharp, hot, or extremely cold, patients are advised to be caution when experiencing numbness. These symptoms often appear after few sessions, usually are not severe, and, once therapy is stopped, the symptoms will completely settle over a few months. However, only 5% of the time on average, these reactions may be intense, appear early, or last for some time. Therefore, patient are requested to notify the responsible physician if noticing any numbness or tingling (BC cancer, 2018).

After Paclitaxel has been injected, allergic reactions may happen. The symptoms of an allergic response might vary, however they could involve flushing, rash, itching, disorientation, swelling, breathing difficulties, as well as unexpected chest, back, or stomach discomfort (BC cancer, 2018).

Hair loss is common and within two to four weeks following the start of therapy, hair fall frequently starts. The scalp could feel sensitive and painful upon touching and patient might loss face and body hair. When the chemotherapy treatments are finished, and maybe even in between treatments, the hair will come back. However, it's possible that the new hair growth will have a different color and texture (BC cancer, 2018).

Cardiovascular toxicities can be seen including ECG abnormality such as cardiac arrhythmias, particularly asymptomatic bradycardias (Gelmon, K., 1994). A relative contraindication to paclitaxel includes having a pacemaker or having a history of cardiac conduction abnormalities. Moreover, the prevalence of congestive heart disease is raised by combinations with doxorubicin (Gianni, L., et al., 1995).

Mouth sores or stomatitis can develop during the cycle and can persist for many days or even weeks. Mouth sores can develop in the throat, on the tongue, gums, or on the mouth's sides (BC cancer, 2018).

Arthralgia and myalgia, joint or muscle pain for a few days such as 2 to 3 days, although with weekly treatments, this pain is often not severe. Following chemotherapy

completion, patient might experience worsened joint pain or stiffness as a result of the treatment's discontinuation (BC cancer, 2018).

Gastrointestinal side effect can occur, including diarrhea that can happen between treatments as well as nausea and vomiting (BC cancer, 2018). Although paclitaxel alone is a cytotoxic agent with a low emetic risk. Yet, when it is administered in combination with other agents' nausea vomiting might occur (ASCO, 2020).

Less frequent side effects of Taxol, occurring in 10-29%, include the following (Payne, A. et al., 2006) (Gilbar, P., et al., 2009) (Piccart, J., et al., 1995):

- Swelling of the feet or ankles (edema).
- Increases in blood tests measuring liver function. These return to normal once treatment is discontinued.
- Hypotension (occurring during the first 3 hours of infusion).
- Skin discoloration at injection site including darkening.
- Nail changes (discoloration of nail beds - rare).

i. Monitoring Parameters

Prior to every treatment cycle, a complete blood count (CBC) with differential and platelet count is performed as well as kidney and liver function tests.

Hypersensitivity responses and vital signs supervision, commonly during the first hour of infusion, in addition to ongoing heart monitoring specially in patient suffering from conduction abnormalities, are all essential parameters.

Personnel responsible for the administration of the regimen should keep an eye on the site of infusion in order to avoid extravasation as well as injection-site reactions.

Indications and symptoms for peripheral neuropathies should be monitored following the initiation of the therapy. In addition, patients should be routinely counselled concerning unusual symptoms and should be advised to reports any discomfort.

Before commencing or right before the commencement of systemic anticancer therapy, HBV scanning with hepatitis B surface antigen, hepatitis B main antibody, total Ig or IgG, and antibody to hepatitis B surface antigen is advised. However, treatment should not be postponed due to screening or while waiting for the results, according to the American Society of Clinical Oncology's provisional clinical opinion. Additionally, a risk assessment is necessary to identify the need for pretreatment with antiviral, supervision, and additional follow-up after the detection of chronic or previous HBV infection (Hwang, P., et al., 2020).

j. Suggested dose modifications for toxicity

- Myelotoxicity: Delaying subsequent cycles until the ANC is >1000/microL and the platelet count is >100,000/microL is advised. A 25% dose reduction is advised if the treatment is delayed for longer than three weeks (Citron, L., et al., 2003).

- Neurologic toxicity: For successive rounds of paclitaxel, the dose should be lowered by 20% for patients who experience severe neuropathy (grade 3 or 4) that lasts for a week or more and it should be held if severe toxicity continues following dose reduction (National Library of Medicine, 2021).

- Dose adjustment for liver or renal dysfunction: it is usually wise to use at least a 20 percent dose reduction for patients with grade 2 or worse hyperbilirubinemia. Both paclitaxel (Furuya, Y., et al., 2003) and docetaxel have been given to patients receiving chronic peritoneal dialysis or hemodialysis successfully at regular doses, while some recommendations call for a dose reduction for docetaxel in these patients (Mencoboni, M., et al., 2006).

- If there is a change in body weight of at least 10%, doses should be recalculated (Citron, M., et al., 2003).

k. Precautions

Patients with solid tumors who have baseline neutrophil counts of less than 1,500/mm3 or those with AIDS-related Kaposi sarcoma whose baseline neutrophil counts are less than 1,000/mm3 should not receive paclitaxel (Farrar, C., & Jacobs, F., 2019).

Paclitaxel should be used extremely cautiously in individuals with preexisting liver impairment, since the damage hinder the clearance of paclitaxel. Though, dosage reductions are advised due to the fact that myelotoxicity may aggravate in patients with total bilirubin more than 2 x the upper limit of normal (Joerger, M., et al., 2007).

The polyoxyl 35/polyoxyethylated castor oil included in conventional paclitaxel formulations is linked to hypersensitivity responses. Dehydrated alcohol, which is another ingredient in formulations, may have negative CNS effects. Therefore, patients with known allergies are contraindicated to receive paclitaxel (Singla, K., et al., 2002).

1. Special populations

Elderly: due to a higher change of harm, like severe neutropenia, neuropathy, and cardiovascular incidence it is advised to use the drug with caution while treating older patients.

Fertility: reduced fertility has been seen in animal experiments, with male testicles atrophying or degenerating, female pregnancy rates declining, and embryo loss rising. However, female patients with childbearing potential are advised to avoid pregnancy (Wang, R., et al., 2018).

Pregnancy and breast feeding: FDA Pregnancy Category D as paclitaxel traverses the placenta where in one instance, 7 days after the last maternal dosage, paclitaxel was found in cord blood (Berveiller, P., et al., 2019). Although there is evidence that using a drug while pregnant poses a danger to the fetus, there may be benefits to doing so. For example, if the medicine is required in a circumstance where life is at risk or for a critical illness where gentler alternatives are restricted for use or ineffective (Loibl, S., et al., 2015) (Korenaga, K., & Tewari, S., 2020). Animal investigations on paclitaxel have revealed it to be embryotoxic and toxic to the fetus where soft tissue and skeletal abnormalities were found. On the other hand, because of the probable release into breast milk, breastfeeding is not advised (ABM, 2020).

l. Drug Interactions of Paclitaxel

Paclitaxel interact with cisplatin causing an increase in the incidence of neutropenia, owing to the fact that paclitaxel clearance is reduced by 25-33%. Therefore, it is advised that when Cisplatin and paclitaxel are given as successive infusions, the best strategy is to deliver paclitaxel first (Baker, F., & Dorr, T., 2001). On the other hand, when paclitaxel is administered concomitantly with dexamethasone and diphenhydramine, paclitaxel binding to plasma protein is not disturbed. However, when administered simultaneously, paclitaxel may displace warfarin from plasma protein binding sites resulting in intensified warfarin's anticoagulant effects. For that reason, it is recommended to monitor INR and adjust warfarin dosage accordingly. The use of LMWH with chemotherapy is also a preferred alternative (Ussai, S., et al., 2015). Additionally, metronidazole and its derivatives are avoided while also taking paclitaxel, since metronidazole or its derivatives inhibit aldehyde dehydrogenase and eventually causing the formation of harmful ethanol metabolites that is a component of paclitaxel solution (Crommentuyn, L., et al., 1998). Similarly, disulfiram ingestion while patient is receiving paclitaxel results in the development of acute alcohol intolerance responses as aldehyde dehydrogenase enzyme responsible for the metabolism of ethanol presents in Paclitaxel solution is blocked by disulfiram (Fisher, S., et al., 2010). Lastly, cardiac toxicity from doxorubicin can be amplified when administered with paclitaxel

simultaneously, where serum concentration of doxorubicin is elevated due to decreased doxorubicin clearance. Hence, it is recommended to continuously monitor cardiac function and to administer doxorubicin prior to paclitaxel (Holmes, A., et al., 1996).

Hematological toxicities

Numerous cell types in the blood perform a wide variety of tasks, from carrying oxygen to producing antibodies. While some of these cells conduct their full job wholly within the circulatory system, others just use the vascular system as a method of transportation and carry out their functions somewhere else. However, the life histories of all blood cells have several characteristics. They all have short lives and are created during the person's lifetime. Most amazing of all, they are all eventually produced from a single stem cell found in the bone marrow. Due to its multipotency, this hemopoietic or blood-forming stem cell may give birth to all various types of terminally differentiated blood cells as well as certain other types of cells, such as osteoclasts in the bone (Alberts, B., et al., 2002). On the other hand, cytotoxic chemotherapy can destroy both malignant and healthy cells since it targets pathways present in all cells. The cell cycle is often involved in the mechanisms of action in order to benefit from the fast cell division of malignant cells (Hartwell, H., & Kastan, B., 1994). Additionally capable of fast division, bone marrow cells are a popular target for chemotherapy. In the bone marrow, these stem and progenitor cells undergo differentiation where extrinsic regulatory elements have the power to enhance or promote the division of blood cells into various lineages, to become circulating cells including platelets, neutrophils, RBC and lymphocytes. Therefore, numerous blood cell types are produced by the hematopoietic system, which is constantly reproducing. Hematopoietic cells may be divided into three major groups that can be arranged in ascending order and size. They are the mature or differentiated cells, progenitor cells, and stem cells (Metcalf, D., & Zon, L., 2001). Through successive phases of development, a tiny population of stem cells continuously replenishes the mature cells in the circulatory system. The clotting process, as well as innate and adaptive immunity, depend on these mature cells (DeNardo, G., & Coussens, M., 2007) (Josefsson, C., et al., 2014) (Shirai, Y., et al., 2015). Low cell numbers can impede these processes, which can lead to bleeding and infection. For example, following high dosage chemotherapy treatment, neutropenia, or a shortage of neutrophils, will frequently occur. For the patients' recovery and the success of their

treatment plan, the capacity to restore the reduced population is essential. Several strategies are employed to replenish the reduced population, including the administration of growth factors or bone marrow or stem cell transplants (Smith, L., et al., 1993). When a patient is extremely sensitive to a dose or does not have enough time to recover from the toxic side effects before the next dose, toxicities occur. Scheduled chemotherapy dosages may be interrupted or reduced due to toxins. Understanding why some patients can tolerate chemotherapy while others need lower, less frequent, or alternative therapies can be aided by modeling the hematological toxicities (Zandvliet, S., et al., 2008). This is why it's crucial for cancer treatment regimens to strike a balance between efficacy and toxicity of the drug. Even if more treatment slows tumor development when selecting an appropriate therapy, toxicity is the limiting factor (Kuhn, G., 2002).

On the other hand, all WBCs, with the exception of lymphocytes, derive from a single myeloid progenitor. According to how they look under a light microscope, white blood cells are often divided into three primary categories: granulocytes, monocytes, and lymphocytes. Numerous lysosomes and secretory vesicles (or granules) are present in granulocytes, which are categorized into three groups based on the morphology and staining characteristics of these organelles. Because of their multilobed nucleus, neutrophils, the most prevalent form of granulocyte, are also known as polymorphonuclear leucocytes. They phagocytose and kill microbes, particularly bacteria, and play a crucial role in innate immunity against bacterial infection. The blood also contains a significant amount of platelets, which are tiny, detached cell fragments or "minicells" generated from the cortical cytoplasm of big cells known as megakaryocytes rather than whole cells. Particularly, platelets stick to the endothelial cell lining of broken blood arteries, where they aid in blood clotting and assist in mending holes (Alberts, B., et al., 2002).

a. Lymphocytopenia

There are two major categories of lymphocytes, both of which participate in immunological reactions: T lymphocytes control the actions of other white blood cells

and destroy virus-infected cells, whereas B lymphocytes produce antibodies. Natural killer (NK) cells, which destroy some varieties of tumor cells and virus-infected cells, are furthermore lymphocyte-like cells. On the other hand, an absolute lymphocyte count (ALC) below a lower threshold that varies depending on age is referred to as Lymphocytopenia. There are several diseases that can lead to Lymphocytopenia. Examples include congenital immunodeficiency disorders like common variable immunodeficiency, as well as bacterial, mycobacterial, fungal, and parasitic infections, as well as viral infections like human immunodeficiency virus (HIV), influenza, coronaviruses (e.g., SARS, SARS-CoV-2), hepatitis, and measles. However, Lymphopenia is a typical side effect of chemotherapy and medications used to treat cancer, such as steroids (Castelino, J., et al., 1997). Moreover, patients with asymptomatic Lymphocytopenia who do not have a related disease are often not treated. Yet, reduced pretreatment lymphocyte counts and lower lymphocyte infiltration in pathologically resected specimens have been linked to lower disease-free survival (DFS) and overall survival (OS) rates in breast cancer. It seems reasonable to assume that circulating lymphocytes depletion may result in less than ideal treatment outcomes given that lymphocytes are the cells that eventually infiltrate tumors (Hong, J., et al., 2016).

b. Anemia

In 2017, the National Cancer Institute defined anemia as a situation presenting fewer red blood cells than usual. As a result, there is a drop in hemoglobin, which lowers the blood's ability to transport oxygen (Brown, G., 2010). Grade 4 anemia is classified as life-threatening or debilitating according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) and is an oncologic emergencies. However, Patients with cancer usually have anemia that is an anticipated side effect linked to cancer and its treatment, which is frequently not well managed. Poorer surgical outcomes and worse performance status are both related to anemia where it is also considered as a standalone predictor of a poor outcome in cancer patients. Consequently, before surgery, patients who have had cancer therapy or who run the risk of developing anemia as a result of

their malignancy should have a complete blood count with differential/platelets (Lee, H., et al., 2012). Anemia can result in poorer outcomes, such as a lower chance of survival, and patients with untreated anemia have lower quality of life. Therefore, in order to prevent and treat severe, incapacitating, or life-threatening anemia, it is crucial to identify each patient's risk (Birgegård, G., et al., 2006). Shading of the skin color and mucous membranes, shortness of breath, increase in heart beating, quiet systolic whispers, drowsiness, and exhaustion are all indications of anemia severity in all degrees (Basch, E., et al., 2014). The most frequent adverse impact of anemia, fatigue, can lower quality of life by reducing productivity and negatively affecting physical and mental health (Miceli, T., et al., 2008). If the anemia manifests acutely, the symptoms are likely to be severe. However, if anemia develops slowly, the body can make up for the blood's reduced ability to carry oxygen by enhancing cardiac output and coronary flow, changing blood viscosity, and regulating oxygen extraction and consumption. The patient may be less able to tolerate even moderate anemia due to previous cardiovascular, pulmonary, or cerebral vascular disease interfering with these compensatory processes, which might result in an emergency scenario. Correction of anemia in patients is associated with improved responses to chemotherapy, and failing to treat chemotherapy-induced anemia may lead to a suboptimal response to chemotherapy (Bryer, E., & Henry, D., 2018). Packed red blood cell transfusions, erythropoietin stimulating drugs (ESAs), and iron supplements are currently options indicated by the current guideline to treat CIA (Ludwig, H., et al., 2014). Maintaining or increasing the blood's ability to transport oxygen is the aim of red blood cell transfusions in order to speed up the delivery of oxygen to tissues (Rodgers, M., et al., 2012). However, red blood cell transfusions are recommended for cancer patients suffering from hypovolemic state and resistant to fluid replacement with crystalloid infusions, have persistent symptomatic anemia that is unresponsive to iron therapy, or who need an immediate correction of their hemoglobin levels (Koeller, M., 1998). There are presently no randomized controlled studies evaluating the use of red blood cell transfusions or the use of red blood cell transfusions with ESA in patients with cancer, despite the aforementioned indications for transfusion in patients with malignancy (Aapro, M., et al., 2018). On the other hand, although it is well established that hemoglobin has a

substantial impact on survival in chemotherapy patients, it is still debatable whether or not increasing hemoglobin by blood transfusions can enhance treatment response (Ye, X., et al., 2015). Lastly, prior to beginning myelosuppressive chemotherapy, the National Comprehensive Cancer Network recommendations advise evaluating and treating coagulopathies as well as checking for folate, B12, and iron deficits (Mesa, R., et al., 2016).

c. Thrombocytopenia

According to the National Cancer Institute, thrombocytopenia is the main reason for bleeding in people with all forms of cancer. It is characterized by an amount of platelets in the blood that is lower-than-normal. Moreover, adult individuals are classified as being thrombocytopenic when their platelet counts drop below normal levels and according to the severity of their thrombocytopenia, these patients can be further split into mild, moderate, and severe subgroups as specified by NCI Common Terminology Criteria for Adverse Events. On the other hand, despite the fact that the strongest predictor of the likelihood of bleeding is the platelet count, the correlation is erratic and depends on the underlying disease as well as other clinical parameters such as the use of medications that interfere with platelet activation, as well as issues like infection or fever or the existence of coagulation abnormalities. As a result, the number of functioning platelets rather than the absolute platelet count is crucial for the prevention of bleeding. In addition, it is regarded as a life-threatening oncological emergency when thrombocytopenia is severe. The risk of bleeding increases significantly as the patient's platelet count drops below 20,000 cell/l, despite the fact that spontaneous hemorrhage rarely happens when the patient's platelet count exceeds 50,000/l. however, intracranial bleeding is the thrombocytopenia complication that causes the most anxiety (Avvisati, G., et al., 2003). Ecchymosis and petechiae are mild indications and symptoms of bleeding brought on by thrombocytopenia. Other more obvious symptoms include hemoptysis, the presence of blood in the urine, epistaxis, vomiting of blood, dark stool, vaginal bleeding, and seeping from skin lesions or vascular access lines. An extreme loss

of blood, like a severe brain or gastrointestinal bleed, can also happen (Belansky, B., & Anna Schaal, N., 2009). Therefore, nurses should thoroughly interview patients to check for both apparent bleeding and hidden blood draining. While the grade of thrombocytopenia detected from a complete blood count is crucial to determine the chance of blood loss, it's also important to note the hemoglobin level because the rapid onset of anemia may be a sign of a potential hemorrhage. A vital component of contemporary supportive care in hematological oncology, particularly for patients with acute leukemia, is prophylactic platelet transfusion therapy. This procedure has significantly reduced bleeding incidents, increased survival rates, and enabled the intensification of therapy (Avvisati, G., et al., 2003).

d. Granulocytopenia

From stem cells, granulocytes are created in the bone marrow and subsequently discharged into the bloodstream. They are a component of the innate immune system, which responds quickly to infections. However, pathogens and damaged cells activate granulocytes (Cannistra, A., & Griffin, D., 1988). White blood cells called granulocytes have little sacs inside them that are known as granules. When there are infections, wounds, or allergic reactions, the contents of these granules are discharged into the blood. Reactive oxygen species, bacteria-digesting enzymes, and antibiotic proteins are among these components (Geering, B., et al., 2013). However, granulocytes can be classified as neutrophils, eosinophils, or basophils.

Granulocytopenia and cancer treatment have long been strongly linked. The tumor historically most frequently linked to granulocytopenia was acute leukemia (Pizzo, A., 1981). Recent results suggest that lymphoblasts may create an inhibitor of granulopoiesis that lowers normal bone marrow formation, although the straightforward explanation for this is that leukemia cells push out normal bone marrow precursors. Myelosuppression, however, is more frequently a side effect of chemotherapy or radiation therapy used to treat the underlying tumor (Broxmeyer, E., et al., 1981). Furthermore, an increasing proportion of cancer patients are becoming granulocytopenic

and at risk for serious infection as a result of the growing use of chemotherapy in patients with solid tumors. Treatment-related granulocytopenia might last for days or even weeks, depending on its severity and length. Granulocytopenia frequently determines the timetable of cancer treatment protocols and may cause chemotherapy to be delayed or modified. For instance, it is common practice to alter a chemotherapy course based on the anticipated myelosuppression rather than only the tumor cell kinetics. In addition, it is intriguing to note that, in contrast to the cancer cells that all too frequently develop resistance to chemotherapy, normal neutrophil progenitors consistently maintain their sensitivity to its cytotoxic effects. Therefore, the susceptibility of myeloid stem cells to chemotherapy is a drawback and obstacle to the treatment of cancer.

Bodey and colleagues first demonstrated the significance of granulocytopenia as a risk factor for developing major infectious problems in cancer patients, showing that a decline in the granulocyte count below 1000/mm3 resulted in an approximately 12% incidence of fever or infection. If the granulocyte count was fewer than 100/mm3, the likelihood of infection climbed to 28%, and if the granulocytopenia persisted for longer than 5 weeks, the likelihood of infection increased to almost 100%. The granulocyte count has been emphasized, sometimes singularly, as the main risk factor for significant infection in the cancer patient as a result of these and other investigations, and has served as a key guideline for therapeutic intervention and prophylaxis (Bodey, P., et al., 1966). On the other hand, it is challenging to distinguish between a patient with a life-threatening condition and a patient with a nonlethal cause of fever when the granulocytopenic patient becomes febrile due to reduced inflammatory reactivity. Several therapeutic strategies have been used to lower infection-related morbidity and mortality. When a patient with granulocytopenic cancer gets feverish, prompt early empiric antibiotic therapy should be started. This is the method that has been most successfully introduced into standard practice (Schimpff, S., et al., 1971).

e. Neutropenia

The blood contains a variety of granulocytes, although neutrophils are by far the most prevalent (Kruger, P., et al., 2015). This indicates that a patient neutrophil count frequently affects the granulocyte count (Pether, S., et al., 2017). Additionally, the body's immune cells that are most prevalent are neutrophils where they account for 50–70% of immune cells. They can only survive in the blood, where they ordinarily live, for 8 to 12 hours, and in tissues for 1 to 2 days like in case of an infection (Mayadas, N., et al., 2014). Neutrophils are among the first immune cells to reach an infection or wound site. Defensins, proteases, and reactive oxygen species (superoxide and hydrogen peroxide) are produced by them, which break down and eliminate microorganisms. These substances, however, may also harm nearby healthy tissue, which may delay recovery and result in excessive scarring. IL-6 and TNF-a, which neutrophils release as immunological messengers, attract additional immune cells (Wilgus, A., et al., 2013).

Contrariwise, The NCI defines neutropenia as a state in which there is a lower than normal concentration of neutrophils. Patients who already have functional immunoglobulin deficiency are in this case susceptible to all grades of neutropenia severity, which can result in oncological emergencies such sepsis, pneumonia, and neutropenic fever (Miceli, T., et al., 2008). Infections are a major cause of morbidity and mortality in patients with neutropenia and are substantially more likely to occur in them than in people with a normal neutrophil count. The most prevalent bacterial infections, in order of frequency, are pneumonia, septicemia, cellulitis, and pyelonephritis. Whereas the two most prevalent viral infections are herpes zoster and influenza (Blimark, C., et al., 2015). Traditional chemotherapy drugs like Melphalan or cyclophosphamide, which cause rapid, sustained neutropenia and destroy physical defense barriers like the mucosa, dramatically raise the risk of infection. Similar to other hematologic toxicities, Neutropenia is also categorized using NCI Common Terminology Criteria for Adverse Events standards. According to Bodey and his colleagues, having a pure neutrophil count lower than 0.5 $x10^9$ was the main risk factor for contracting an infection. In individuals who are extremely neutropenic, fever may be the first and only symptom of a bacterial infection because sufficient neutrophils are required to develop an inflammatory response in the location of live contamination (Bodey, P., et al., 1966).

One solitary oral temperature of 38.3°C (101°F) or more elevated, or two dispersed fever of 38°C (100.4°F) or greater, measured by a distance of an hour, are considered to be fevers (Hughes, T., et al., 2002). In addition, in the lack of pus-producing neutrophils and monocytes, local signs like Reddeness, fibrous elements, or pussy discharge could not be observed. In parallel, patients with neutropenia frequently do not have pulmonary infiltrates due to a decreased and delayed inflammatory response (Lewis, A., et al., 2011). Other signs of a local or systemic infection, aside from fever, may include chills, cough, rigidities, short breaths, nausea, diarrhea, disorientation, painful urination, exhaustion, and ache. Consequently, a complete system review is crucial when evaluating a patient with neutropenia. The oral mucosa, skin, and any venous access devices should also be carefully examined as part of a thorough physical examination that focuses on the painful areas. However, prior to beginning antibiotic treatment, paired blood cultures should be acquired. If clinical symptoms or signs are present, cultures of the nares, urine, or diarrheal stools may also be obtained and following the evaluation, patients must be started on early empirical antibiotic therapy within an hour to protect against both gram-positive and gram-negative bacteria. (Lustberg, B., 2012).

On the other hand, some recommendation to decrease the risk of infection during neutropenia state include maintaining appropriate hydration and diet that includes protein, vitamin B, and vitamin C helps to maintain skin integrity during therapy, shaving with an electronic razor rather than a razor, receiving the recommended vaccines, including the flu shot. However, a minimum of two weeks should pass after vaccination before starting chemotherapy or immune-suppressing medication and unless specifically directed by a doctor, patients receiving chemotherapy or radiation therapy shouldn't receive live attenuated vaccines. Prior to receiving dental care, the patient should explain any current medications to the dentist, and scheduling appointments should be limited to times when counts will be higher (within a couple of days of chemotherapy treatment). If the patient is extremely neutropenic, a consultation with a medical staff should be received to see if sexual activity should be postponed. Avoiding the handle with pet waste especially that found in fish tanks, bird cages, and cat litter boxes is highly recommended. Also, the patient should stay away from large groups and

people who appear to be sick (such as those who have chicken pox, measles, the flu, or shingles). In addition, all visitors should get training on fundamental infection control measures, such as proper hand hygiene practices and isolation techniques. All visitors who have a recent history of exposure to any communicable disease, an upper respiratory infection, a flu-like illness, a herpes zoster rash, or any other contagious condition should be restricted. If a guest develops a new rash, a cough, a fever, or diarrhea, it is important to inform them to reschedule their stay. Fresh or dried flowers and plants should be forbidden. It is also important to use soap and warm water or antiseptic hand sanitizer to wash the hands before handling foods, before and after eating, after using the restroom, or after coughing or sneezing in the hands. Bathing every day in warm water, and pat skin dry is likewise advised (Taplitz, A., et al., 2018).

Granulocyte colony stimulating factors

Colony-stimulating factor 3 (CSF3), commonly referred to as granulocyte colony-stimulating factor (G-CSF), is a glycoprotein that promotes granulopoiesis and causes neutrophil proliferation, maturation, and mobilization. Initially, it was thought that myeloid cells primarily expressed G-CSF and its receptor (G-CSFR), however there have been reports of expression in fibroblasts, endothelial cells, and bone marrow stromal cells as well (Demetri, D., & Griffin, D., 1991). Recent research has demonstrated that G-CSF is expressed in tissues other than the placenta, adult neural stem cells, B-cells, and cardiomyocytes (Shimoji, K., et al., 2010). G-CSFs, furthermore known as myeloid growth factors, have been studied for their potential prophylactic uses after the administration of chemotherapy when neutropenia is anticipated ("primary prophylaxis"), during retreatment after a previous cycle of chemotherapy that resulted in neutropenic fever ("secondary prophylaxis"), and to reduce the length of severe chemotherapy-induced neutropenia in patients who have neutropenia without fever ("afebrile neutropenia"). In patients with established fever and neutropenia, they are often not advised for usage on a regular basis (Freifeld, G., et al., 2011). G-CSF

promotes myeloid progenitors' proliferation, differentiation into neutrophils, and mobilization into the peripheral circulation in the hemopoietic system (Rutella, S., et al., 2005). G-CSF has also been found to regulate inflammation and present immunomodulatory effects via influencing innate and adaptive immune responses, in addition to regulating granulopoiesis by promoting hematopoietic mobilization of stem cells and the generation of neutrophils (Fleetwood, J., et al., 2005).

The main criteria determining whether prophylactic CSFs are necessary is the probability of developing neutropenic fever in individuals treated with a certain chemotherapy treatment. The degree of chemotherapy, the presence and severity of gastrointestinal mucosal damage, the possibility of underlying damage to the patient's hematopoietic stem cells, the use of radiation concurrently, and the patient's general clinical condition all affect the likelihood of neutropenic fever following treatment like age and comorbid conditions (Larson, R., 2022).

Initiating G-CSFs during the first cycle of myelosuppressive chemotherapy is known as primary prophylaxis, with the intention of preventing neutropenic problems across all of the chemotherapy cycles. To reduce the occurrence of neutropenic fever and the requirement for hospitalization, primary prophylaxis may be employed. Primary prophylaxis may also be used to keep up chemotherapy regimens that are dose-dense or dose-intense and have been shown to improve survival, or if decreases in chemotherapy dose-intensity or dose-density are known to be linked to a worse prognosis (Schenfeld, J., 2022).

a. Indications, benefits, and guidelines

The 2010 guidelines from the Infectious Diseases institute of America (IDSA) (Freifeld, G., et al., 2011), updated 2015 guidelines from the American Society of Clinical Oncology (ASCO) (Smith, J., et al., 2015), updated 2016 guidelines from the European Society for Medical Oncology (ESMO) (Klastersky, J., et al., 2016), and consensus-based recommendations from the National Comprehensive Cancer Network (NCCN) all advise primary prophylaxis when the anticipated incidence of neutropenic fever is

expected to be 20% or higher with a specific regimen (NCCN, 2021). A 40 percent cutoff has been suggested by earlier recommendations (Ozer, H., et al., 2000). Randomized studies demonstrating that primary prophylaxis was financially advantageous when the risk of neutropenic fever with a particular regimen surpassed 20% were the key motivators for the change in advice (Vogel, L., et al., 2005) (Timmer-Bonte, N., et al., 2006). Given the high cost of treating neutropenic fever, which often necessitates hospitalization, this criterion may change (Lathia, N., et al., 2010). Furthermore, at least some evidence points to observational cohorts having considerably greater rates of febrile neutropenia than randomized trials do. In one comprehensive analysis, a 13 percent rate of febrile neutropenia in randomized trial populations transformed into a 20 percent rate in observational studies after controlling for age, treatment purpose, and regimen (Truong, J., et al., 2016). Large population-built investigations are required to prove actual proportions of febrile neutropenia. In the meantime, it is fair to continue using the 20 percent threshold for primary prophylaxis usage and to tailor primary prophylaxis use in patients receiving regimens with a risk of between 10 and 20 percent based on additional risk factors for higher consequences from protracted neutropenia (Larson, R., 2022). Regardless of the tumor type or chemotherapy protocol, the incidence of febrile neutropenia seems to be highest during the first two cycles of chemotherapy (Vogel, L., et al., 2005) (Martin, M., et al., 2006). This has led some to doubt the efficacy of using G-CSF during later cycles. This problem was specifically addressed in a randomized experiment where 167 breast cancer patients receiving chemotherapy were randomly assigned to receive G-CSF for the first two cycles only, or for the entire course of treatment, with an estimated >20 percent risk for febrile neutropenia . When an interim analysis revealed a considerably greater rate of febrile neutropenia in the group only receiving the first two cycles of G-CSF, (36 versus 10 percent), the experiment was prematurely terminated. Therefore, it is advised to continue primary G-CSF prophylaxis during all treatment cycles (Aarts, J., et al., 2013). Patients receiving treatment for a disease with a curative aim (such as lymphoma, adjuvant therapy for breast cancer, or testicular cancer) may benefit from primary prophylaxis to lessen the risk of dose-limiting neutropenia (Rivera, E., et al., 2003) (Bennett, L., et al., 2013).

The systematic prescription of G-CSFs for primary prophylaxis in previously untreated adult patients receiving chemotherapy regimens with a low likelihood (10%) of inducing fever during expected neutropenia periods is particularly discouraged by guidelines, including those from the NCCN (NCCN, 2021). ASCO's revised 2015 recommendations urge primary CSF prophylaxis in certain circumstances (Smith, J., et al., 2015):

- Patients receiving curative chemotherapy for diffuse aggressive lymphoma who are 65 years or older, especially when there are concomitant conditions.
- Patients undergoing chemotherapy regimens with high doses and strong evidence of efficacy (eg, treatment following surgery for high-threat breast cancer; high-dose-intensity methotrexate, doxorubicin, and cisplatin for urothelial cancer).
- Other times, after a neutropenic consequence from a past chemotherapy round, they advise secondary rather than primary prevention.

If a patient has one or more risk factors for febrile neutropenia and is being treated with a less myelosuppressive regimen, prophylactic CSFs may also be beneficial (Weycker, D., et al., 2015). Age >65 years, preexisting neutropenia or extensive bone marrow involvement by tumor, more advanced cancer, poor performance and/or nutritional status, renal or hepatic dysfunction, or, in the case of epithelial ovarian cancer, extensive prechemotherapy surgery, especially if it involved a bowel resection are all factors that increase the risk of neutropenia (Dranitsaris, G., et al., 2008) (Lyman, H., et al., 2011).

b. Secondary prophylaxis

When neutropenic fever occurs during a chemotherapy cycle, secondary prophylaxis refers to the administration of a G-CSF in following cycles. With recurrences reported in 50–60% of individuals, fever during neutropenia is more likely to occur in subsequent cycles in patients who have previously had it (Haim, N., et al., 2005). This risk is reduced by roughly 50% with secondary CSF prophylaxis (Crawford, J., et al., 1991). The use of a G-CSF to hasten the recovery from neutropenia brought on by a previous cycle of chemotherapy is also included in the concept of secondary prophylaxis,

preventing a delay in the administration of a subsequent chemotherapy cycle. According to ASCO and ESMO recommendations, only patients who develop a neutropenic consequence (such as fever or a delay in treatment) following a previous cycle of chemotherapy should get secondary prophylaxis with granulocyte CSFs (for which primary prophylaxis was not received) if a lower dose intensity could harm the effectiveness of the treatment (Smith, J., et al., 2015), (Klastersky, J., et al., 2016).

c. Therapeutic use in patients with neutropenia

Neutropenia without fever: in afebrile patients who have already had severe neutropenia as a result of chemotherapy, there is no documented function for the use of CSFs, hence the recommendation states against use.

Neutropenic fever: in comparison to using antibiotics alone, the use of CSFs did not significantly reduce overall death or infection-related mortality. Individuals who received CSFs had significantly shorter durations of neutropenia, antibiotic use, and fever recovery. They were also significantly less likely to spend more than 10 days in the hospital. Use of CSFs was linked to a noticeably greater frequency of joint or bone pain as well as flu-like symptoms (Mhaskar, R., et al., 2014). Antibiotics always function more quickly since it takes many days for CSF to respond with an increase in circulating neutrophils. Patients who are still neutropenic and feverish and are not quickly responding to antibiotics may find CSFs to be a helpful adjuvant (Larson, R., 2022).

d. GM-CSF versus G-CSF and biosimilars

Both G-CSF and GM-CSF (sargramostim) are beneficial at lowering the incidence of neutropenic fever and infectious complications in cancer patients receiving chemotherapy, according to numerous placebo-controlled trials. G-CSF is commercially accessible as lenograstim and filgrastim in several areas (Granocyte, Neutrogin, and

Myelostim). Worldwide, filgrastim is offered in a number of biosimilar variations. According to updated ASCO recommendations, all of these G-CSF preparations, including biosimilars, can be used to avoid treatment-related febrile neutropenia, and the selection of medicine must be built on practicality, cost, and clinical circumstances (Smith, J., et al., 2015).

e. Dose and timing of G-CSF and GM-CSF

The dose of G-CSF (filgrastim) for primary and secondary prophylaxis is 5 mcg/kg per day, while the dose of GM-CSF (sargramostim) is 250 mcg/m2 per day. The dose is typically rounded to the closest vial size to save money. Usually, therapy starts 24 to 72 hours after chemotherapy ends. Until the post-nadir ANC returns to normal or almost normal levels by laboratory standards, NCCN guidelines advise daily treatment (Mo, L., et al., 2021). The administration of G-CSF is often done on a set schedule in dose-dense chemotherapy regimens. For instance, the dose-dense AC plus T chemotherapy for breast cancer adjuvant therapy recommends giving G-CSF for seven days straight. However, at least one randomized research indicates that daily G-CSF treatment for 5 days in the context of primary prophylaxis is at least as effective as daily administration for 7 or 10 days, less expensive, and linked to fewer side effects that necessitate schedule alterations for G-CSF (Clemons, M., et al., 2020).

f. Pegfilgrastim

Pegfilgrastim, a pegylated version of G-CSF, has an extended half-life that makes it possible to provide just one dose rather than daily. The recommended dose (6 mg) is administered 24 hours after chemotherapy [57] and at least 14 days must pass before the next scheduled chemotherapy dose. Patients using pegfilgrastim often don't get their blood counts checked on a regular basis (Lyman, H., et al., 2017).

g. Possible stimulation of malignancy

There has been concern that certain malignant cell lineages may respond to therapy with a granulocyte CSF, potentially worsening the underlying condition or causing malignancy to develop in a susceptible individual because myeloid growth factor receptors are expressed by a variety of hematopoietic and nonhematopoietic cell types. A case in point of this worry is the evidence that malignant myeloblasts express receptors for such growth factors, which has limited the use of G-CSFs in patients receiving induction therapy for acute myeloid leukemia (AML). In contrast to CSFs, prophylactic antibacterial and antifungal medicines are more frequently administered during chemotherapy for AML (Larson, R., 2022). Several observational studies have found a small but real increased risk of therapy-related hematologic neoplasms, such as AML, Myelodysplastic Syndrome (MDS), and possibly acute lymphoblastic leukemia/lymphocytic lymphoma, when CSFs are used during chemotherapy for other malignancies like breast and lung cancer (Lyman, H., et al., 2018). Therefore, even though utilizing myeloid growth factors during chemotherapy raises the risk of developing a therapy-related hematologic neoplasm, the absolute amount of the risk is low, and the advantages of using CSFs in this situation probably outweigh the risks (Larson, R., 2022).

h. Monitoring Parameters (Aras, E., et al., 2020)

- Earlier to chemotherapy and two times per week while receiving growth factor remedy, patients should have a complete blood count (CBC) with differential and platelets.
- Neutrophil numbers 4 days after starting filgrastim therapy.
- Before starting treatment, bone marrow and karyotype are checked, and marrow and cytogenetic are checked yearly after starting treatment.

– Capillary leak syndrome, inflammation of the aorta, cutaneous inflammation of the blood vessels, respiratory distress syndrome, and splenic break should all be kept an eye out for.

i. Adverse Reactions (D'Souza, A., et al., 2008)

Cardiovascular: Chest pain, Peripheral edema, hypertension.

Central nervous system: Fatigue, dizziness, pain and insomnia.

Dermatologic: Skin rash, Maculopapular rash, Alopecia

Gastrointestinal: Nausea, decreased appetite, constipation or diarrhea.

Hematologic & oncologic: Thrombocytopenia, decreased hemoglobin, splenomegaly, brutal long term neutropenia.

Hepatic: Augmented alkaline phosphatase level in the serum.

Neuromuscular & skeletal: Back pain, arthralgia, ostealgia, limb pain, muscle spasm.

Respiratory: Epistaxis, cough, dyspnea, Bronchitis.

Infection: Sepsis.

Immunologic: Antibody development.

Miscellaneous: Fever.

Impact of hematological toxicities in oncology department

The main dose-limiting toxicities of systemic cancer chemotherapy continue to be myelosuppression, neutropenia, and its consequences (Lyman, H., et al., 1998). An urgent hospitalization is usually required for examination and the administration of empiric broad-spectrum antibiotics in cases of febrile neutropenia, which is regarded as a medical emergency. Furthermore, FN typically results in treatment delays and chemotherapy dosage reductions, which may jeopardize long-term clinical outcomes in responsive and potentially curable cancers (Lyman, H., 2009). However, the risk for morbidity and death in oncological patient is increased by hematological toxicities including neutropenia, that can occur in up to 50% of patients (Kuderer, M., et al., 2006). Moreover, 40% to 50% of the entire cost of cancer care is attributed to hospital care where more than $96 billion has been calculated as the overall yearly cost of cancer treatment in the United States, including direct and indirect expenditures such as hospitalization due to chemotherapy adverse effects (Schuette, L., et al., 1995).

A study examining the clinical and demographic factors linked to death and extended hospital stays in order to provide information that might aid in the clinician's choice of cancer patients who are more likely to die from FN-related complications and who require more intensive supportive therapy and preventative measures revealed that after the inclusion of 41,779 adults aged 18 years suffering from cancer who were visiting the hospital with FN between 1995 and 2000 at the 115 institutions that made up the longitudinal University Health System Consortium (UHC) hospitalization database, in hospitals as a whole, mortality was 9.5%. Those without any significant comorbidities had a 2.6% death risk, but patients with one or more major comorbidities had a 10.3% and a 21.4% mortality risk, respectively. The average (median) duration of stay was 11.5 (6) days, and each episode of FN cost an average (median) of $19,110 ($8,376). 78% of all costs were incurred by patients who spent 10 days in the hospital (which represented 35% of all patients). Invasive fungal infections, Gram-negative sepsis, pneumonia and other lung diseases, cerebrovascular, renal, and liver illness were among the independent main risk factors for inpatient death. Leukemia, invasive fungal infections, various

forms of infections, and a number of concomitant diseases were the main predictors for length of stay 10 days. Therefore, despite better medical management, FN still has a high risk of morbidity, mortality, and expense, which has an impact not just on the patient as a person but also on the healthcare system as a whole and eventually emphasizing on the need to better target high-risk patients to provide preventative and supportive care interventions in an effort to further lower the risk of FN-related death and serious complications (Kuderer, M., et al., 2006).

Additionally, in a research conducted between October till the month of December 2017 in the hematology and oncology specialty of the Children's Hospital Lahore, Pakistan, data of patients treated for febrile neutropenia were evaluated in settings with low resources, such as a public sector hospital in Pakistan. The Children's Hospital, has a 60-bed oncology department that offers free care to more than 1300 new cases of pediatric cancer every single year and more than 200 admissions monthly with a bed habitation level of over 200%. Both Pakistan and Afghanistan send instances of pediatric cancer to the department. Therefore, treating cancer and infection concurrently in these settings is exceedingly difficult and places a greater load on public hospitals that offer free care as well as on medical staff who must manage patients with late stages and frequent infection episodes. 35% of patients had their chemotherapy in the week before FN hospitalization, whereas 53% received it in the last three days. They were getting either induction or intensive phase regimens in 84% of the cases. 48% of patients had an infection of the respiratory system, thenceforth by fever unaccompanied in 20%, and mucositis in 82%. More than 24 hours had passed in 52% of instances before seeking FN therapy. On admission, 60% of patients had an ANC (absolute neutrophil count) below 100 and 56% had platelets below 50,000. Only 44% of parents had appropriate knowledge on the care of FN, and 57% of cases were more than an hour's drive from the Children's hospital.

In addition, granulocyte-colony stimulating factor (G-CSF) was used in 30% of cases, blood products in 75% of cases, inotropes in 16% of cases, with a mean anticipated cost of 15,000 RS/patient (sum: 3.8 million RS), and 95% of cases residing for more than 48 hours. In conclusion, FN has been a significant burden on the treatment of pediatric

cancer in public hospitals in resource-constrained environments like Pakistan. In order to partake the burden of primary treatment wards and reduce morbidity and mortality, there is a great need for health education of nurses, physicians besides the relatives on typical management of febrile neutropenia as well as maintainable social backing and shared care oncology (Ahmad, A., 2018).

On the other hand, it makes sense that neutropenia would have a negative impact on patients' quality of life when it necessitates hospitalization. Hence, it has been shown in several research that chemotherapy may have a considerable negative influence on social, physical, and overall functioning (Broeckel, A., el al., 2000) (Macquart-Moulin, G., et al., 2000). A prospective investigation where patients with a range of malignancies had their quality of life assessed during the first cycle of myelosuppressive chemotherapy, demonstrated that neutropenia was associated with worse outcomes for pain, anxiety, and social interactions. When patients had neutropenia, their physical pain was greater than it was at baseline. Moreover, most patients when assessing their anxiety using HAD scale, they showed generalized distress. Therefore, the study revealed that the onset of neutropenia may be accompanied by a drop in superiority of life and that the reduction is quantifiable up to a week following the neutropenia occurrence (Fortner, V., et al., 2005).

Furthermore, following neutropenia development, chemotherapy rounds may require dosage reductions because of FN's long-term effects, which can drastically lower survival rates. However, avoiding lower chemotherapy dosages in order to get the most benefits is highly critical especially in the current evolution of breast cancer treatment were uninterrupted chemotherapy resulted in considerably higher rates of overall survival and relapse-free survival (Bonadonna, G., et al., 1995).

In general, following chemotherapy, hematological toxicities including neutropenia, anemia, thrombocytopenia and leukopenia worsen quality of life by raising complications, morbidity, and mortality risks as well as reducing dosage delivery. In addition cancer diagnosis can drastically alter the patient life. It might be challenging to process news at first, and it can occasionally become much more challenging to decide

how to move forward. Therefore, adverse effects may impose psychological impacts that add additional burden to the oncology patient. On the other hand, hospitalizations due to complications from neutropenia are associated with high medical expenses. Therefore, hospitalizations and related expenditures may be reduced if measures are taken to avoid and mitigate chemotherapy related myelosuppression among cancer patients. Moreover, quality of life in cancer patient may be also improved by avoiding preventable stress and anxiety.

Role of clinical pharmacist in oncology department

The position of the pharmacist has changed during the past century. At the turn of the century, a pharmacist's job mostly consisted of mechanical tasks including compounding, packaging, and delivering prescriptions while also offering advice on over-the-counter medications. This employment has declined as the pharmaceutical industry took over the preparation of drugs, and the role of the pharmacist has changed. Particularly as the population ages, the role of pharmacists in providing direct patient care is expanding. Moreover, collaborative practice, often known as team-based care, is an approach that has gained popularity all around the world that involves pharmacists and doctors working together to manage chronic illnesses including cancer (Carter, L., et al., 2015).

By offering thorough management to patients and medical professionals, both in the community and the hospital, clinical pharmacy (or clinical pharmacy services) attempts to support safe drug usage. These services in oncology include thorough medication reviews integrating chemotherapy, supportive care, and ambulatory treatment for co-morbidities, medication information for medical professionals and patients, therapeutic drug monitoring (anticancer, anti-infective, and immunosuppressive drugs in recipients of allogeneic stem cell transplantation), and supportive care counseling (nutrition support, pain management, chemotherapy side-effects prophylaxis, and elaboration of

therapeutic guidelines, as well as optimal use of economic resources (Liekweg, A., et al., 2004).

Most cancer patients are over 65 and frequently also suffer from other illnesses. In hospitals, a phase known as reconciliation may come before the review. This phase, which is typically carried out by pharmacists, aims to find and correct medication discrepancies during transition care, such as at admission, like to ensure that all of the medications the patient takes at home have been recorded by the oncologist. In 152 patients receiving chemotherapy in a clinic, a research conducted in the United States revealed that 24% of the prescription medications were missing from their medical records (Hanigan, H., et al., 2011).

Additionally, oncology pharmacists, also known as hematology/oncology pharmacists, are crucial to the treatment of cancer patients. Oncology pharmacists are a crucial member of the cancer care team and reflect a wide spectrum of knowledge, degrees of practice, abilities, and duties. They are involved in the care of cancer patients throughout all stages of their treatment, from evaluation and diagnosis through treatment choices, medication management, symptom management, and supportive care, and finally with survivorship programs after their treatment is complete. They collaborate with other healthcare professionals to maintain a current and accurate prescription list, choose the best course of treatment, keep an eye on the effectiveness of the drugs supplied, and control the side effects that frequently come with cancer treatment. The oncology pharmacist is heavily relied upon to support the clinical team in an effort to improve overall cancer care and patient quality of life as the care of cancer patients continues to be hampered by high cost therapies, medication shortages, regulatory requirements, and dwindling reimbursement (Holle, M., & Boehnke Michaud, L., 2014).

On a typical day, preparation of chemotherapy prescriptions and drugs takes place along with patient assessments for dose modifications due to toxicities or organ malfunction. In addition oncology pharmacists collaborate with the medical staff to make sure the patient is receiving thorough treatments for controlling or minimizing any bad side effects from the therapy or adverse drug reactions including infection prophylaxis,

venous thromboembolism prophylaxis, anti-emetic agents, and prevention of skeletal-related events.

Before each patient begins a new chemotherapy treatment, a member of the pharmacy team visits them to discuss their drug needs. Furthermore, while patients are receiving treatment, they frequently check in during clinic visits or hospital stays for inpatient chemotherapy, to address any fresh concerns about medications or offer suggestions for symptom management. Therefore, pharmacists who specialize in cancer offer continuity of treatment to patients moving between inpatient and outpatient settings. Thus, they frequently serve as the primary points of contact for both patients and caregivers (Schlafer, D., et al., 2017).

A study assessing the treatment of febrile neutropenia brought on by cancer treatment in outpatient settings revealed that although the development of febrile neutropenia in cancer chemotherapy patients typically resulted in hospitalization due to the risk of life-threatening consequences, pharmacists through participation in risk assessment to identify patients who should receive oral antimicrobial cure in a setting outside the hospital, preference of the most fitting pharmacological therapy, drug therapy monitoring, and creation of institutional guidelines or pathways, can play a significant role in the management of chemotherapy-associated febrile neutropenia (Pherwani, N., et al., 2015).

Another study evaluating the role of pharmacist in the interdisciplinary approach to the prevention and treatment of drug-related issues in cancer chemotherapy demonstrated that a total of 211 interventions (100%) were accepted and deemed therapeutically meaningful. Prescriber were only informed when the most prevalent methods of intervention were at the prescriber level. However, around 90% of the identified drug-related issues were resolved, indicating that clinical pharmacy services may improve therapeutic efficacy, avoid side effects, and resolve unclear/compliant issues. The pharmacist interventions were highly regarded by oncologists and patients, representing the presence of a high level of convenience and the necessity to deploy Clinical pharmacy services at alternative hospitals (Boşnak, A.et al., 2019).

In an observational research, patients were divided into two groups at random: an intervention group that got pre-chemotherapy counseling from a pharmacist and a control group that did not. In comparison to the control group, there was a significant improvement in the intervention group's comprehension of the chemotherapy regimen and its adverse effects. Additionally, compared to the control group, patients who received pharmacy counseling were able to recollect the information even after the sixth cycle of the chemotherapy treatment. The majority of breast cancer patients believed that pre-chemotherapy counseling led by a pharmacist was useful. Therefore, pre-chemotherapy counseling provided by a pharmacist helps patients better comprehend the chemotherapy treatment they will be receiving and eventually improving the quality of life by reducing chemotherapy related stress induced by medication concerns (Dang, C., et al., 2017).

In conclusion, an oncology pharmacist's expertise and abilities assist a wide range of tasks in all areas of patient care, from the bedside to introducing policies into practice, from primary research to influencing other doctors in the choice and administration of anticancer medicines. This in-depth understanding gives the medical staff a distinct perspective on illness treatment that takes into account not just the needs of individual patients but also the institution as a whole and the healthcare system. One of the few team members who thoroughly comprehends the safety, effectiveness, pharmacologic, and economical aspects of patient care for those with cancer is frequently the oncology pharmacist. The necessity for an oncology pharmacist to be a part of the oncology health care team will be highlighted by the changing nature of health care and the expanding approach to cancer care, such as oral medicines, targeted therapy, and customized medicine (Hudson-Disalle, S., et al., 2021).

CHAPTER II

METHODOLOGY

Study Setting

A retrospective observational study was carried out at Hiwa Hospital located in Sulaymaniyah Governorate of the Northern Kurdistan Region, Iraq, where Data has been collected from Oncology department starting January 2021 till May 2022. Electronic files of female patients diagnosed with breast Cancer admitted to the oncology department of the hospital were checked from the system. Based on the most recent patient file update in the oncology department archives, we examined and assessed patient data. The goal of the study was to assess and compare the hematological toxicities of breast cancer patients receiving paclitaxel during four cycles.

Inclusion Criteria

- Breast cancer patient receiving paclitaxel chemotherapy regimen.
- Patient 18 years of age and older.
- BC patients with medical files present at the archive of the hospital.

Exclusion Criteria

- BC patients who received less than four cycles of chemotherapy.
- Patients receiving Paclitaxel in combination with biological therapy or other chemotherapy.
- BC patients whom laboratory test was not carried out in the facility.
- Pregnant or lactating woman.

Dosage

Filgrastim, a recombinant human G-CSF, given at a dose of 5 mg/kg per day subcutaneously rounded to 300 mcg or 480 mcg on days 3 through 10, or pegfilgrastim 6 milligrams subcutaneously on day 2 or 3 is scheduled at least after 24-h following PTX chemotherapy. 80 mg/m^2, 175 mg /m^2 or 175 mg /m^2 dose of PTX constituting a four cycle's course was administered to patients either every 7 days, or every 14 days, or every 21 days respectively.

Data Collection and Analysis

Data sheets of Hemoglobin (HGB), Platelet (PLT), White blood cell (WBC), Red blood cell (RBC), Lymphocytes (LYMPH) and Granulocytes (GRAN) of BC patients receiving PTX were all gathered and then hematological toxicities were classified based on the grading criteria as seen in table 5 (National Cancer Institute CTCAE, 2017).

Table 5: Grading Criteria For Hematologic Toxicity Adverse Events

Adverse Event	Unit of Measure	Grade 1	Grade 2	Grade 3	Grade 4
Anemia	Hemoglobin (g/dl)	Less than LLN to 10	8–10	Less than 8	Life threatening; urgent intervention indicated
Neutropenia	Absolute neutrophil count (x 10^3)	<LLN to 1,500/mm^3	1,000–1,500/mm^3	500–1,000/mm^3	<500/mm^3
Thrombocytopenia	Platelet count (x 10^3)	<LLN to 75,000/mm^3	50,000–75,000/mm^3	25,000–50,000/mm^3	<25,000/mm^3
Lymphocytopenia	lymphocyte count K/mm^3	<LLN to 800/mm^3	500–800/mm^3	200–500/mm^3	<200/mm^3

LLN, lower limit of normal

Statically Analysis

After data collection and assessment, the assembled data was analysed using Microsoft Excel 2016 and statistical package for the Social Sciences (SPSS), software version 25. We used descriptive statistic to analyse continuous data. The continuous data was presented by Mean (± SD). While absolute information will be presented as frequency and percentage such as age, and various grades of Haematological Toxicity. All patients were assessed for four different side effects associated with PTX treatment including Neutropenia, Thrombocytopenia, Lymphocytopenia and Anemia. The Paired t-test test was used to assess the differences in hemogram parameters between the baseline and the first cycle or baseline and the second cycle or the first cycle and the second cycle in Table 8 and Table 9. Treatment phase consists of four cycles containing Baseline, 1^{st}, 2^{nd} and 3^{rd} cycle. The Mc Nemar test was used to determine the significant difference between the pairs in Table 10-14. All tests and conclusions were done at a 95% level of confidence. A P-value of less than 0.05 ($P<0.05$) was considered statistically significant.

Ethical Consideration

The study was approved by the General directorate of Sulaymaniyah.

CHAPTER III

RESULT

Patients Demographics

Following file scanning, out of 387 patients who were having breast cancer, 141 patients were included in the study while 246 didn't meet the criteria. In addition, out of the 141 included patient, 74 patients with breast cancer didn't receive Filgrastim before the baseline whereas 67 patients received Filgrastim before the baseline (figure 1). Demographics characteristics of the breast cancer patients included in the study are shown in table 6. All participants were female with a mean age (± SD) of 49.52 years (± 8.83). Moreover, the mean body surface area (BSA) was 1.75 m^2 (± 0.19) and the mean weight of the patient's was 72.57 kg (± 14.20), while the mean height was 153.56 cm (± 14.35). However, the mean BMI of the patients was found to be 31.32 (± 5.88), suggesting that most patients were obese. On the other hand, there was no additional information regarding the past medical history of the patients including comorbidities such as hypertension, coronary artery disease, diabetes or thyroid disease that might affect drug clearance and subsequent toxicities. In addition, social history such as smoking, alcohol intake as well as medication or food allergies were not available. On the other hand, table 7 shows the distribution of the patient among age categories where 48 patients (34 %) were having age between 30 and 45 years old, 15 patients (10.6 %) were having age between 62 and 75 years, whereas more than half of the patient, 78 patients (55.3 %) were belonging to the age category ranging from 46 to 61 years of age.

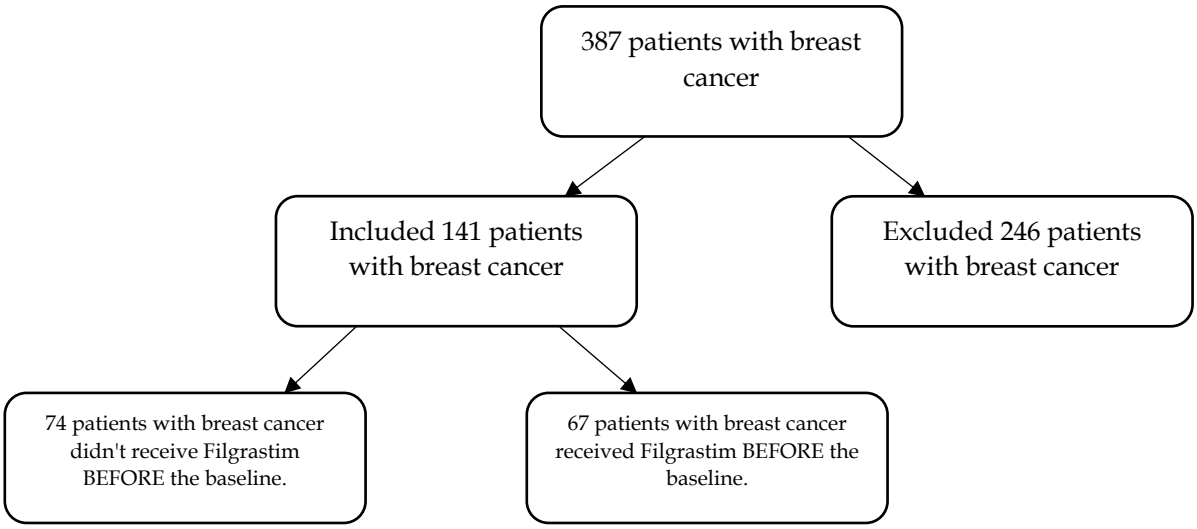


Figure 1: study population

Table 6. Demographic Information of Breast Cancer Patients Receiving Paclitaxel

Gender	**N:74**	**N:67**	**N**
Male	0	0	0
Female	74	67	141
Mean ± SD	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**
Age	50.64 ± 9.46	48.28 ± 7.96	49.52 ± 8.83
Body Surface Area (BSA)	1.75 ± 0.19	1.75 ± 0.19	1.75 ± 0.19
Weight	72.59 ± 14.47	72.56 ± 14	72.57 ± 14.20
Height	154.37 ± 5.69	152.68 ± 19.98	153.56 ± 14.35
BMI	31.47 ± 6.36	31.16 ± 5.34	31.32 ± 5.88

Table 7: The age distribution of the subjects			
Years	Frequency	Percent	Valid Percent
30-45	48	34.0	34.0
46-61	78	55.3	55.3
62-75	15	10.6	10.5
Total	141	100.0	100.0

Hemogram Parameters in Breast Cancer Patients Receiving Paclitaxel during Baseline, First Cycle, Second and Third Cycle while not receiving filgrastim at baseline.

The mean WBC of patients who didn't received filgrastim at baseline was 6.04 cells × 10^9/L (±5.76). However, the mean WBC in this group (n=74) decreased to 5.45 cells × 10^9/L (±1.79) following the first cycle of chemotherapy. Following the second cycle, the mean WBC was 5.95 cells × 10^9/L (± 3), which also decreased following the third cycle to 4.73 cells × 10^9/L (±1.69). Moreover, there was no statistically significant difference between baseline and first cycle of chemotherapy in terms of WBC variation (P-value = 0.384) as well as between baseline and second cycle (P-value = 0.897) nor between baseline and third cycle (P-value = 0.063). Yet, a statistically significant difference was noticed between the second and the third cycle of chemotherapy (P-value = 0.001) in terms of WBC variation. The Lymphocyte count mean of patients who didn't received filgrastim at baseline was 1.52 cells × 10^9/L (±0.7) which insignificantly increased during the first cycle and second cycle to 1.57 cells × 10^9/L (±0.62) and 1.58 cells × 10^9/L (±0.63) respectively. This mean decreased unremarkably during the third cycle of paclitaxel to reach 1.53 cells × 10^9/L (±0.65). There was no statistically significant difference between baseline and first cycle (P-value = 0.514) or between baseline and the second cycle (P-value = 0.386) in terms of lymphocyte count variation. In addition, no statistically significant difference was present between baseline and the third chemotherapy cycle (P-value = 0.894) as well as between the second and the third cycle (P-value = 0.389) in terms of lymphocyte count variation. In the group of patients who didn't received filgrastim at baseline (n=74), the mean granulocyte count was initially 3.47 cells × 10^9/L (±2.55). Whereas during the first, second and third cycle, the mean granulocyte count was respectively 3.35 cells × 10^9/L (±1.46), 3.91 cells × 10^9/L (±2.43) and 3.63 cells × 10^9/L (±7.52). Meanwhile, there was no statistically significant variation in terms of granulocyte count between baseline and the first cycle (P-value = 0.731), between baseline and the second cycle (P-value = 0.239), neither between baseline and the third cycle (P-value = 0.865) nor between the second and the third cycle (P-value = 0.759). On the other hand, RBC mean in patients who didn't receive

filgrastim at baseline decreased in a negligible way from 4.26 cells × 10^9/L (± 0.58) at baseline to 4.21 cells × 10^9/L (± 0.61) and 4.21 cells × 10^9/L (± 0.47) during the first cycle and the second cycle respectively, and undetectably increased during the third cycle to 4.22 cells × 10^9/L (±0.41). No statistically significant variation was present in terms of RBC mean between baseline and the first cycle (P-value = 0.283), and between baseline and the second cycle (P-value = 0.249). Also, no statistically significant difference was present between baseline and the third cycle (P-value = 0.298), and between the second and the third cycle (P-value = 0.896) in terms of RBC mean variation. In addition hemoglobin mean at baseline in patients who didn't receive filgrastim initially was 11.46 g/dl (±1.41). However, it remained approximately constant through the first, second and third cycle with a values of 11.21 g/dl (±1.35), 11.35 g/dl (±1.09) and 11.23 g/dl (± 0.96) respectively. A statistically significant difference in terms of hemoglobin mean was present between baseline and the first cycle (P-value = 0.044) but there was no statistically significant difference between baseline and the second cycle (P-value = 0.376), between baseline and the third cycle (P-value = 0.065) and between the second and the third cycle (P-value = 0.093) in terms of mean hemoglobin variation. Lastly, the mean of platelets count decreased from 328.32 cells × 10^9/L (± 93.02) during baseline to 294.32 cells × 10^9/L (±78.32) and 294.95 cells × 10^9/L (±64.07) during the first and second cycle respectively until it reached 291.47 cells × 10^9/L (±69.16) during the third cycle. Consequently, a statistically significant difference was present in terms of platelets count mean variation between baseline and the first cycle (P-value = 0.013) as well as between baseline and the second cycle (P-value = 0.007) and additionally between baseline and the third cycle (P-value = 0.001). However, there was no statistically significant difference between the second and the third cycle in terms of platelets count mean variation (P-value = 0.615) as seen in table 8.

Table 8. Hemogram parameters in breast cancer patients receiving Paclitaxel during baseline, first cycle, second and third cycle while not receiving filgrastim at baseline

	(N)	Mean ± SD	P-value (Baseline vs First Cycle)	P-value (Baseline vs Second Cycle)	P-value (Baseline vs Third Cycle)	P-value (Second cycle vs Third Cycle)
WBC (Baseline)	74	6.04±5.76	0.384	0.897	0.063	0.001
WBC (First cycle)	74	5.45±1.79				
WBC (Second cycle)	74	5.95±3				
WBC (Third cycle)	74	4.73±1.69				
LYMPH (Baseline)	74	1.52±0.7	0.514	0.386	0.894	0.389
LYMPH (First cycle)	74	1.57±0.62				
LYMPH (Second cycle)	74	1.58±0.63				
LYMPH (Third cycle)	74	1.53±0.65				
GRAN (Baseline)	74	3.47±2.55	0.731	0.239	0.865	0.759
GRAN (First cycle)	74	3.35±1.46				
GRAN (Second cycle)	74	3.91±2.43				
GRAN (Third cycle)	74	3.63±7.52				
RBC (Baseline)	74	4.26±0.58	0.283	0.249	0.298	0.896
RBC (First cycle)	74	4.21±.61				
RBC (Second cycle)	74	4.21±0.47				
RBC (Third cycle)	74	4.22±0.41				
HGB (Baseline)	74	11.46±1.41	0.044	0.376	0.065	0.093
HGB (First cycle)	74	11.21±1.35				
HGB (Second cycle)	74	11.35±1.09				
HGB (Third cycle)	74	11.23±.96				
PLT (Baseline)	74	328.32±93.02	0.013	0.007	0.001	0.615
PLT (First cycle)	74	294.32±78.32				
PLT (Second cycle)	74	294.95±64.07				
PLT (Third cycle)	74	291.47±69.16				

The Paired t-test test was used to assess the differences in hemogram parameters between the baseline and the first cycle or baseline and the second cycle or the first cycle and the second cycle

Hemogram Parameters in Breast Cancer Patients Receiving Paclitaxel during Baseline, First Cycle, Second and Third Cycle while receiving filgrastim at baseline.

The mean WBC of patients who received filgrastim at baseline was 6.35 cells × 10^9/L (±4.27). However, the mean WBC in this group (n=67) decreased slightly to 6.10 cells × 10^9/L (±5.33) following the first cycle of chemotherapy and then dramatically declined following the second cycle to 4.89 cells × 10^9/L (±1.68). Following the third cycle the mean WBC improved reaching 5.44 cells × 10^9/L (±3.49). Moreover, there was no statistically significant difference between baseline and first cycle of chemotherapy in terms of WBC mean variation (P-value = 0.758) as well as between baseline and third cycle (P-value = 0.202) and between the second and the third cycle (P-value = 0.156). Yet, a statistically significant difference was noticed between baseline and the second cycle of chemotherapy (P-value = 0.010) in terms of WBC variation. The Lymphocyte count mean of patients who received filgrastim at baseline was 1.34 cells × 10^9/L (±0.5) which slightly increased during the first cycle, second and third cycle to 1.58 cells × 10^9/L (±0.64), 1.49 cells × 10^9/L (±0.46) and 1.50 cells × 10^9/L (±0.52) respectively. There was a statistically significant difference between baseline and first cycle (P-value = 0.002), between baseline and the second cycle (P-value = 0.020) as well as between baseline and the third chemotherapy cycle (P-value = 0.024) in terms of lymphocyte count variation. In addition, no statistically significant difference was present between the second and the third cycle (P-value = 0.867) in terms of lymphocyte mean count variation. In the group of patients who received filgrastim at baseline (n=67), the mean granulocyte count was initially 4.51 cells × 10^9/L (±3.86) which decreased gradually to 4.04 cells × 10^9/L (±4.69), 3.02 cells × 10^9/L (±1.29) and 3.55 cells × 10^9/L (±3.03) respectively during the first, second and the third cycle. Meanwhile, there was no statistically significant variation in terms of granulocyte count mean between baseline and the first cycle (P-value = 0.524), between baseline and the third cycle (P-value = 0.127), neither between the second and the third cycle (P-value = 0.135). Though, there was a statistically significant difference between baseline and the second cycle in terms

of granulocyte count mean (P-value = 0.003). On the other hand, RBC mean in patients who received filgrastim at baseline decreased from 4.21 cells × 10^9/L (±1.1) at baseline to 4.06 cells × 10^9/L (±0.51) during the first cycle and then increased insignificantly to 4.1 cells × 10^9/L (±0.44) during the second cycle and to 4.15 cells × 10^9/L (±0.45) during the third cycle. No statistically significant variation was present in terms of RBC mean between baseline and the first cycle (P-value = 0.217), and between baseline and the second cycle (P-value = 0.333). Also, no statistically significant difference was present between baseline and the third cycle (P-value = 0.557), and between the second and the third cycle (P-value = 0.197) in terms of RBC mean variation. In addition hemoglobin mean at baseline in patients who did receive filgrastim initially was 11.26 g/dl (±1.1). However, it decreased through the first and the second cycle to 11.14 g/dl (±0.95) and 11.20 g/dl (±0.89) respectively and then increased to 11.27 g/dl (± 0.99) during the third cycle. No statistically significant difference in terms of hemoglobin mean was present between baseline and the first cycle (P-value = 0.211) as well as between baseline and the second cycle (P-value = 0.601), between baseline and the third cycle (P-value = 0.920) and between the second and the third cycle (P-value = 0.397). Lastly, the mean of platelets count increased from 254.82 cells × 10^9/L (±66.88) during baseline to 306.99 cells × 10^9/L (±84.53) during the first cycle. However, the mean platelets count then decreased gradually during the second and the third cycle to reach 280.58 cells × 10^9/L (±66.82) and 266.63 cells × 10^9/L (±62.89) respectively. Consequently, a statistically significant difference was present in terms of platelets count mean variation between baseline and the first cycle (P-value = 0.0001) as well as between baseline and the second cycle (P-value = 0.001) and additionally between the second and third cycle (P-value = 0.037). However, there was no statistically significant difference between baseline and the third cycle in terms of platelets count mean variation (P-value = 0.145) as seen in table 9.

Table 9. Hemogram parameters in breast cancer patients receiving Paclitaxel during baseline, first cycle, second and third cycle while receiving filgrastim at baseline

	(N)	Mean ± SD	P-value (Baseline vs First Cycle)	P-value (Baseline vs Second Cycle)	P-value (Baseline vs Third Cycle)	P-value (Second cycle vs Third Cycle)
WBC (Baseline)	67	6.35±4.27	0.758	0.010	0.202	0.156
WBC (First cycle)	67	6.10±5.33				
WBC (Second cycle)	67	4.89±1.68				
WBC (Third cycle)	67	5.44±3.49				
LYMPH (Baseline)	67	1.34±0.5	0.002	0.020	0.024	0.867
LYMPH (First cycle)	67	1.58±.64				
LYMPH (Second cycle)	67	1.49±0.46				
LYMPH (Third cycle)	67	1.50±0.52				
GRAN (Baseline)	67	4.51±3.86	0.524	0.003	0.127	0.135
GRAN (First cycle)	67	4.04±4.69				
GRAN (Second cycle)	67	3.02±1.29				
GRAN (Third cycle)	67	3.55±3.03				
RBC (Baseline)	67	4.21±1.1	0.217	0.333	0.557	0.197
RBC (First cycle)	67	4.06±0.51				
RBC (Second cycle)	67	4.1±0.44				
RBC (Third cycle)	67	4.15±0.45				
HGB (Baseline)	67	11.26±.1.1	0.211	0.601	0.920	0.397
HGB (First cycle)	67	11.14±0.95				
HGB (Second cycle)	67	11.20±0.89				
HGB (Third cycle)	67	11.27±.99				
PLT (Baseline)	67	254.82±66.88	0.0001	0.001	0.145	0.037
PLT (First cycle)	67	306.99±84.53				
PLT (Second cycle)	67	280.58±66.82				
PLT (Third cycle)	67	266.63±62.89				

The Paired t-test test was used to assess the differences in hemogram parameters between the baseline and the first cycle or baseline and the second cycle or the first cycle and the second cycle

The Use of Filgrastim during Baseline, First, Second and Third Cycle

67 patients representing 47.51 % of the sample received filgrastim at baseline. The number of patients requiring filgrastim dropped during the first cycle with 62 patients (43.97%) needing filgrastim. On the other hand, 63 patients (46.68%) received the drug during the second cycle and during the third cycle 61 patients that represent 43.26% of the study sample received filgrastim as seen in table 10.

Table 10. The use of Filgrastim at all Stages

Stage	Number of Patients N (%)
Baseline	67 (47.51%)
First Cycle	62 (43.97%)
Second Cycle	63 (46.68%)
Third Cycle	61 (43.26%)

Comparison of Hematological Toxicity between Baseline, First, and Second Cycle of Paclitaxel in patients who didn't receive filgrastim at baseline

In the group of patients who didn't receive filgrastim (n=74) at baseline, only one patient (1.35%) experienced grade 1 Lymphocytopenia at baseline. However, no patients experienced grade 2, grade 3 or grade 4 Lymphocytopenia at baseline. Moreover, none of the patients faced grade 1, grade 2, or grade 3 nor grade 4 Lymphocytopenia during the first cycle. Similarly, during the second cycle no patient undergone Lymphocytopenia with severity grade 1, grade 2, grade 3 or grade 4. Therefore, no statistical analysis could been obtained concerning various grade of Lymphocytopenia and differences between baseline and cycle one or baseline and second cycle. In addition, 4 patients representing 5.4 % of the study sample experienced grade 1 Neutropenia at baseline with no patient having grade 1 Neutropenia during the first cycle compared to two patients (2.7%) who experienced grade 2 Neutropenia at baseline and non during the first cycle. Likewise, none of the patients, underwent grade 1 or grade 2 Neutropenia during the second cycle. Therefore, statistically analysis could not be performed. Grade 3 Neutropenia was not detected in any patient during baseline, first cycle or second as well as no Grade 4 Neutropenia identified in any patient during baseline, first cycle or second cycle of Paclitaxel. Therefore, no statistical analysis performed to detect any change in terms of grade 2, 3 or grade 4 Neutropenia between baseline, first cycle or second cycle. Furthermore, 32 patients out of the 74 patients not receiving filgrastim in the study, that also represent almost half of the patients (43.2%), were facing grade 1 anemia at baseline. Whereas more patient, 36 patients (48.6%) were having grade 1 Anemia during the first cycle of Paclitaxel and also 36 patients representing 48.6 % of the study sample were experiencing grade 1 Anemia during the second cycle. However, no statistically significant change has occurred between baseline and the first cycle in terms of grade 1 Anemia as well as no statistically significant change occurred between baseline and the second cycle of paclitaxel also in terms of grade 1 Anemia with P value = 0.125 and P value = 0.125 respectively. Additionally, 4 patients corresponding to 5.4 % of the study population were having grade 2 Anemia at baseline and 4 patients representing 5.4 % were facing grade 2 Anemia during the first

cycle. However, no statistically significant change has occurred between baseline and the first cycle of Paclitaxel in terms of grade 2 Anemia since the number of patients remained the same during cycles. Only 2 persons that represent 2.7% of the study sample were suffering from grade 2 Anemia during the second cycle. Yet, there was no statistically significant change occurring between baseline and the second cycle of Paclitaxel in terms of grade 2 Anemia (P value = 0.5). At baseline, no patient had grade 3 Anemia. However, during the first cycle of Paclitaxel two patients representing 2.7% experienced grade 3 Anemia, with no further patient facing grade 3 anemia during the second cycle of Paclitaxel. Additionally, no patient ever faced grade 4 Anemia at baseline, during first cycle and neither during the second cycle of Paclitaxel. Therefore, no statistical analysis could have been assessed in terms of grade 3 or grade 4 Anemia between baseline and the first cycle as well as between baseline and the second cycle of chemotherapy. Lastly, in terms of Thrombocytopenia, none of the 74 patients had grade 1 Thrombocytopenia at baseline, during the first cycle neither during the second cycle of paclitaxel. Moreover, grade 2 Thrombocytopenia also was not detected in any patient at baseline, during the first cycle or during the second cycle of Paclitaxel. Similarly, grade 3 Thrombocytopenia was not seen in any patient at baseline, during the first cycle or during the second cycle of Paclitaxel as well as no presence of grade 4 Thrombocytopenia in any of the 74 patients included in the study at baseline, neither during the first cycle or during the second cycle of Paclitaxel. Therefore, in terms of Thrombocytopenia, no statistical analysis could been performed to compare between different grade and the cycle of chemotherapy as seen in table 11.

Table 11. Comparison of Hematological Toxicity between Baseline, Second and Third Cycle of Paclitaxel (N:74)							
Cancer Medications	**Hematological Toxicity**	**Grade**	**Baseline N (%)**	**First Cycle N (%)**	**P-value (Baseline vs First Cycle)**	**Second Cycle N (%)**	**P-value (Baseline vs Second Cycle)**
Paclitaxel	**Lymphocytopenia**	**Grade 1**	1(1.35)	-	-	-	-
		Grade 2	-	-	-	-	-
		Grade 3	-	-	-	-	-
		Grade 4	-	-	-	-	-
	Neutropenia	**Grade 1**	4(5.4%)	-	-	-	-
		Grade 2	2(2.7%)	-	-	-	-
		Grade 3	-	-	-	-	-
		Grade 4	-	-	-	-	-
	Anemia	**Grade 1**	32(43.2%)	36(48.6%)	0.125	36(48.6%)	0.125
		Grade 2	4(5.4%)	4(5.4%)	-	2(2.7%)	0.5
		Grade 3	-	2(2.7%)	-	-	-
		Grade 4	-	-	-	-	-
	Thrombocytopenia	**Grade 1**	-	-	-	-	-
		Grade 2	-	-	-	-	-
		Grade 3	-	-	-	-	-
		Grade 4	-	-	-	-	-

Comparison of Hematological Toxicity between Baseline, Second and Third Cycle of Paclitaxel in patients who didn't receive filgrastim at baseline

Out of the 74 patients who didn't receive filgrastim, only one patient (1.35%) experienced grade 1 Lymphocytopenia at baseline. However, no patients experienced grade 2, grade 3 or grade 4 Lymphocytopenia at baseline. Moreover, none of the patients faced grade 1, grade 2, or grade 3 nor grade 4 Lymphocytopenia during the third cycle. Therefore, no statistical analysis could have been obtained concerning various grade of Lymphocytopenia and differences between baseline and the third cycle or between the third cycle and the second cycle of Paclitaxel. Additionally, 4 patients representing 5.4 % of the study population were having grade 1 Neutropenia at baseline compared to only one patient (1.35%) who suffered grade 1 Neutropenia during the third cycle of Paclitaxel. There was no statistically significant difference between baseline and the third cycle of Paclitaxel in terms of grade 1 Neutropenia (P value = 0.25). In addition, no statistical analysis could have been conducted to detect changes between the second cycle and the third cycle of Paclitaxel in terms of grade 1 Neutropenia sine no patient experienced neutropenia during the second cycle. On the other hand, only 2 patients representing 2.7% were facing grade 2 Neutropenia at baseline, with no patients suffering from grade 2 Neutropenia during the third cycle of Paclitaxel. Moreover, none of the patients were having grade 3 or grade 4 Neutropenia at baseline as well as zero patient facing grade 3 or grade 4 Neutropenia during the third cycle of Paclitaxel. Therefore, in terms of Neutropenia, no statistical analysis could been performed to compare between different grade and the cycle of chemotherapy. Furthermore, compared to the 32 patient who were experiencing grade 1 Anemia at baseline, 37 patients representing also half of the study population 50% also suffered grade 1 Anemia during the third cycle of Paclitaxel. In conclusion, there was no statistically significant change occurring between baseline and the third cycle of Paclitaxel in terms of grade 1 Anemia (P value = 0.0625) as well as no statistically significant change occurring between the second and the third cycle of Paclitaxel in terms of grade 1 Anemia (P value = 0.5). In addition, in terms of grade 2 Anemia, 4 patients out of the 74 patients (5.4%)

suffered from grade 2 Anemia at baseline, whereas 2 patients out of the 74 patients (2.7%) experienced grade 2 Anemia during the third cycle of Paclitaxel. However, no statistically significant change occurred between baseline and the third cycle of Paclitaxel in terms of grade 2 Anemia (P value = 0.5). Since number of patients experiencing grade 2 anemia didn't changed between the second and the third cycle, no statistical analysis was performed. No further patient were facing grade 3 anemia at baseline neither during the third cycle of Paclitaxel. Similarly, grade 4 Anemia was not detected in any patients at baseline as well as no patients suffered grade 4 Anemia during the third cycle of Paclitaxel. Accordingly, no statistical analysis could been performed in order to assess the change between baseline and the third cycle of Paclitaxel as well as between the second cycle and the third cycle of Paclitaxel in terms of grade 3 and grade 4 Anemia. Lastly, in terms of Thrombocytopenia, none of the 74 patients had grade 1 Thrombocytopenia at baseline, during the second cycle neither during the third cycle of paclitaxel. Moreover, grade 2 Thrombocytopenia also was not detected in any patient at baseline, during the second cycle or during the third cycle of Paclitaxel. Similarly, grade 3 Thrombocytopenia was not seen in any patient at baseline, during the second cycle or during the third cycle of Paclitaxel as well as no presence of grade 4 Thrombocytopenia in any of the 74 patients at baseline, either during the second cycle or during the third cycle of Paclitaxel. Therefore, in terms of grade 1, grade 2, grade 3 and grade 4 Thrombocytopenia, no statistical analysis could been performed to evaluate the changes between baseline and the third cycle of Paclitaxel as well as between the second cycle and the third cycle of Paclitaxel as seen in table 12.

Table 12. Comparison of Hematological Toxicity between Baseline, Second and Third Cycle of Paclitaxel (N:74)						
Cancer Medications	**Hematological Toxicity**	**Grade**	**Baseline N (%)**	**Third Cycle N (%)**	**P-value (Baseline vs Third Cycle)**	**P-value (Second cycle vs Third Cycle)**
Paclitaxel	**Lymphocytopenia**	**Grade 1**	1(1.35)	-	-	-
		Grade 2	-	-	-	-
		Grade 3	-	-	-	-
		Grade 4	-	-	-	-
	Neutropenia	**Grade 1**	4(5.4%)	1(1.35)	0.25	-
		Grade 2	2(2.7%)	-	-	-
		Grade 3	-	-	-	-
		Grade 4	-	-	-	-
	Anemia	**Grade 1**	32(43.2%)	37(50%)	0.0625	0.5
		Grade 2	4(5.4%)	2(2.7%)	0.5	-
		Grade 3	-	-	-	-
		Grade 4	-	-	-	-
	Thrombocytopenia	**Grade 1**	-	-	-	-
		Grade 2	-	-	-	-
		Grade 3	-	-	-	-
		Grade 4	-	-	-	-

Comparison of Hematological Toxicity between Baseline, First, and Second Cycle of Paclitaxel in patients who did receive filgrastim at baseline

In the group of patients who did receive filgrastim (n=67) at baseline, only one patient (1.35%) experienced grade 1 Lymphocytopenia at baseline with also one patient (1.35%) experiencing grade 1 Lymphocytopenia during the first cycle. Grade 2, grade 3 or grade 4 Lymphocytopenia was not seen in any patients at baseline. Moreover, none of the patients faced grade 2, grade 3 nor grade 4 Lymphocytopenia during the first cycle. Similarly, during the second cycle no patient undergone Lymphocytopenia with severity grade 1, grade 2, grade 3 or grade 4. Therefore, no statistical analysis could been obtained concerning various grade of Lymphocytopenia and differences between baseline and cycle one or baseline and second cycle. In addition, 10 patients representing 14.9 % of the study sample experienced grade 1 Neutropenia at baseline with 4 patients (5.9%) having grade 1 Neutropenia during the first cycle. A statistically significant difference was seen between the baseline and the first cycle in terms of grade 1 Neutropenia (P value = 0.0312). Similarly 4 patients (5.9%) experienced grade 1 Neutropenia during the second cycle and a statistically significant difference was seen between the baseline and the second cycle in terms of grade 1 Neutropenia (P value = 0.031). Likewise, none of the patients, underwent grade 2 Neutropenia at baseline during the first or the second cycle. Therefore, statistically analysis could not be performed. Grade 3 Neutropenia was not detected in any patient during baseline, first cycle or second as well as no Grade 4 Neutropenia identified in any patient during baseline, first cycle or second cycle of Paclitaxel. Therefore, no statistical analysis performed to detect any change in terms of grade 2, 3 or grade 4 Neutropenia between baseline, first cycle or second cycle. Furthermore, 35 patients out of the 67 patients receiving filgrastim at baseline (52.2%) were facing grade 1 anemia at baseline. Whereas 40 patients (59.7%) were having grade 1 Anemia during the first cycle of Paclitaxel and 38 patients representing 56.7 % of the study sample were experiencing grade 1 Anemia during the second cycle. However, no statistically significant change has occurred between baseline and the first cycle in terms of grade 1 Anemia as well as no statistically significant

change occurred between baseline and the second cycle of paclitaxel in terms of grade 1 Anemia with P value = 0.0625 and P value = 0.25 respectively. Additionally, 2 patients corresponding to 2.9 % of the study population were having grade 2 Anemia at baseline and only one patient (1.35%) were facing grade 2 Anemia during the first cycle. However, no statistically significant change has occurred between baseline and the first cycle of Paclitaxel in terms of grade 2 Anemia with P value =1. No patient were suffering from grade 2 Anemia during the second cycle. At baseline, no patient had grade 3 Anemia, neither during the first cycle of Paclitaxel nor during the second cycle of Paclitaxel. Additionally, no patient ever faced grade 4 Anemia at baseline, during first cycle and neither during the second cycle of Paclitaxel. Therefore, no statistical analysis could have been assessed in terms of grade 3 or grade 4 Anemia between baseline and the first cycle as well as between baseline and the second cycle of chemotherapy. Lastly, in terms of Thrombocytopenia, none of the 67 patients had grade 1 Thrombocytopenia at baseline, during the first cycle neither during the second cycle of paclitaxel. Moreover, grade 2 Thrombocytopenia also was not detected in any patient at baseline, during the first cycle or during the second cycle of Paclitaxel. Similarly, grade 3 Thrombocytopenia was not seen in any patient at baseline, during the first cycle or during the second cycle of Paclitaxel as well as no presence of grade 4 Thrombocytopenia in any of the 67 patients included in the study at baseline, neither during the first cycle or during the second cycle of Paclitaxel. Therefore, in terms of Thrombocytopenia, no statistical analysis could been performed to compare between different grade and the cycle of chemotherapy as seen in table 13.

Table 13. Comparison of Hematological Toxicity between Baseline, first and second Cycle of Paclitaxel (N:67)							
Cancer Medications	**Hematological Toxicity**	**Grade**	**Baseline N (%)**	**First Cycle N (%)**	**P-value (Baseline vs First Cycle)**	**Second Cycle N (%)**	**P-value (Baseline vs Second Cycle)**
Paclitaxel	**Lymphocytopenia**	**Grade 1**	1(1.35)	1(1.35)	-	-	-
		Grade 2	-	-	-	-	-
		Grade 3	-	-	-	-	-
		Grade 4	-	-	-	-	-
	Neutropenia	**Grade 1**	10(14.9%)	4(5.9%)	0.0312	4(5.9%)	0.031
		Grade 2	-	-	-	-	-
		Grade 3	-	-	-	-	-
		Grade 4	-	-	-	-	-
	Anemia	**Grade 1**	35(52.2%)	40(59.7%)	0.0625	38(56.7%)	0.25
		Grade 2	2(2.9%)	1(1.35)	1	-	-
		Grade 3	-	-	-	-	-
		Grade 4	-	-	-	-	-
	Thrombocytopenia	**Grade 1**	-	-	-	-	-
		Grade 2	-	-	-	-	-
		Grade 3	-	-	-	-	-
		Grade 4	-	-	-	-	-

Comparison of Hematological Toxicity between Baseline, Second and Third Cycle of Paclitaxel in patients who didn't receive filgrastim at baseline

Out of the 67 patients who did receive filgrastim, only one patient (1.35%) experienced grade 1 Lymphocytopenia at baseline. However, no patients experienced grade 2, grade 3 or grade 4 Lymphocytopenia at baseline. Moreover, none of the patients faced grade 1, grade 2, or grade 3 nor grade 4 Lymphocytopenia during the third cycle. Therefore, no statistical analysis could have been obtained concerning various grade of Lymphocytopenia and differences between baseline and the third cycle or between the third cycle and the second cycle of Paclitaxel. Additionally, 10 patients representing 14.9% of the study population were having grade 1 Neutropenia at baseline compared to 4 patients (5.9%) who suffered grade 1 Neutropenia during the third cycle of Paclitaxel. Consequently, there was a statistically significant difference between baseline and the third cycle of Paclitaxel in terms of grade 1 Neutropenia (P value = 0.031). In addition, no statistical analysis could have been conducted to detect changes between the second cycle and the third cycle of Paclitaxel in terms of grade 1 Neutropenia sine same number of patients experienced neutropenia during the second and third cycle. On the other hand, no one was facing grade 2 Neutropenia at baseline, with no patients suffering from grade 2 Neutropenia during the third cycle of Paclitaxel. Moreover, none of the patients were having grade 3 or grade 4 Neutropenia at baseline as well as zero patient facing grade 3 or grade 4 Neutropenia during the third cycle of Paclitaxel. Therefore, in terms of Neutropenia, no statistical analysis could been performed to compare between different grade and the cycle of chemotherapy. Furthermore, compared to the 35 patients (52.2%) who were experiencing grade 1 Anemia at baseline, 33 patients representing almost half of the study population 49.2% also suffered grade 1 Anemia during the third cycle of Paclitaxel. In conclusion, there was no statistically significant change occurring between baseline and the third cycle of Paclitaxel in terms of grade 1 Anemia (P value = 0.5) as well as no statistically significant change occurring between the second and the third cycle of Paclitaxel in terms of grade 1 Anemia (P value = 0.0625). In addition, in terms of grade 2 Anemia, 2 patients out of the 67 patients (2.9 %) suffered from grade 2

Anemia at baseline as well as during the third cycle of Paclitaxel. However, since number of patients experiencing grade 2 anemia didn't changed between the baseline and the third cycle, no statistical analysis was performed. No further patient were facing grade 3 anemia at baseline neither during the third cycle of Paclitaxel. Similarly, grade 4 Anemia was not detected in any patients at baseline as well as no patients suffered grade 4 Anemia during the third cycle of Paclitaxel. Accordingly, no statistical analysis could been performed in order to assess the change between baseline and the third cycle of Paclitaxel as well as between the second cycle and the third cycle of Paclitaxel in terms of grade 3 and grade 4 Anemia. Lastly, in terms of Thrombocytopenia, none of the 67 patients had grade 1 Thrombocytopenia at baseline, during the second cycle neither during the third cycle of paclitaxel. Moreover, grade 2 Thrombocytopenia also was not detected in any patient at baseline, during the second cycle or during the third cycle of Paclitaxel. Similarly, grade 3 Thrombocytopenia was not seen in any patient at baseline, during the second cycle or during the third cycle of Paclitaxel as well as no presence of grade 4 Thrombocytopenia in any of the 67 patients at baseline, either during the second cycle or during the third cycle of Paclitaxel. Therefore, in terms of grade 1, grade 2, grade 3 and grade 4 Thrombocytopenia, no statistical analysis could been performed to evaluate the changes between baseline and the third cycle of Paclitaxel as well as between the second cycle and the third cycle of Paclitaxel as seen in table 14.

Table 14. Comparison of Hematological Toxicity between Baseline, Second and Third Cycle of Paclitaxel (N:67)						
Cancer Medications	**Hematological Toxicity**	**Grade**	**Baseline N (%)**	**Third Cycle N (%)**	**P-value (Baseline vs Third Cycle)**	**P-value (Second cycle vs Third Cycle)**
Paclitaxel	**Lymphocytopenia**	**Grade 1**	1(1.35)	-	-	-
		Grade 2	-	-	-	-
		Grade 3	-	-	-	-
		Grade 4	-	-	-	-
	Neutropenia	**Grade 1**	10(14.9%)	4(5.9%)	0.031	-
		Grade 2	-	-	-	-
		Grade 3	-	-	-	-
		Grade 4	-	-	-	-
	Anemia	**Grade 1**	35(52.2%)	33(49.2%)	0.5	0.0625
		Grade 2	2(2.9%)	2(2.9%)	-	-
		Grade 3	-	-	-	-
		Grade 4	-	-	-	-
	Thrombocytopenia	**Grade 1**	-	-	-	-
		Grade 2	-	-	-	-
		Grade 3	-	-	-	-
		Grade 4	-	-	-	-

CHAPTER IV

DISCUSSION

Cancer is a fatal condition characterized by unmatched heterogeneity and abnormal cell growth. One of the most prevalent cancers among women is breast cancer, a malignant development of epithelial cells lining the breast ducts or lobules, in addition to being the fifth-leading cause of cancer mortality in women worldwide. In 2020, 2.3 million females were estimated to have a positive diagnosis with breast cancer, accounting for 11.7% of all cancer cases with 685,000 passing away from the disease, making up 6.9% of all female cancer fatalities (Sung, H., et al., 2021). During the 1980s and 1990s, there was a sharp rise in the incidence of breast cancer in Northern America, Oceania, and Europe; this was most likely a result of increasing mammographic screening. Afterward, the incidence decreased or stabilized in the early 2000s. On the contrary, it had been rapidly rising across Africa, Asia, Central and South America (Torre, A., et al., 2017). According to estimates, roughly 20% of breast cancer cases worldwide result from modifiable risk factors like obesity, alcohol consumption, and physical inactivity. This suggests that promoting healthy behaviors could lessen the burden of disease (Danaei, G., et al., 2005). Moreover, age, early menstruation, late pregnancy, oral contraceptives, hormone replacement therapy, diet, family history, limited breastfeeding, and a history of benign breast cancer in the past are some of the additional risk factors for breast cancer (Bray, F., et al., 2013) (Brinton, A., et al., 2018). In addition, 10% of all breast cancers are hereditary, and the majority are caused by genetic variations that are passed down in an autosomal dominant manner (Howlader, M., et al., 2014). Hence, the largest risk factor for breast cancer is simply being a woman. Although men can develop breast cancer, women are around 100 times more likely than men to do so (Feng, Y., et al., 2018). Breast swelling, nipple pain, skin scraping, secretions, redness, or skin scraping of the breast or nipple are some of the early physical signs of breast cancer (Mangesi, L., & Zakarija-Grkovic, I., 2016).

In Iraq, the incidence rate of new cases of cancer has increased with time, from 52.00/100,000 in 2000 to 91.66/100,000 in 2019. Therefore, it is considered that the most prevalent kind of cancer in women in Iraq is breast cancer. According to the Children's Cancer Research Institute (CCRI), it is the most dominant malignancy in females and accounts for roughly a third of all cancer cases reported in the most recent Iraqi Cancer Register (IARC, 2013). Furthermore, For Iraqi women, breast cancer is the leading cause of death, accounting for nearly one-third of all cancer cases in the nation in 2019. Breast cancer was first among the top ten malignancies in terms of percentage of prevalence (34.08%, 35.95/100,000), and death incidence rate (22.58%, 6.22/100,000), all of which were highest in 2019 (Iraqi Cancer Board, 2019). Additionally, Iraq's Kurdistan Region has been exposed to a number of carcinogenic risks. Correspondingly, there was evidence of elevated cancer risks in the Iraqi Kurdistan Region. Hematological malignancies were the, most common cancer in men (21.13% of all cancer in men) whereas just behind breast cancer, Hematological malignancies were the second most prevalent cancer in women (18.8% of all cancer in women). Therefore, Kurdistan region was the region with the highest prevalence of breast cancer (Othman, T., et al., 2011). In 2000, the Ministry of Health (MOH), in collaboration with the World Health Organization (WHO), the Ministry of Higher Education and Scientific Research (MOHESR), and others, introduced the National Program for Early Detection and Down Staging of Breast Cancer. Since then, all of the major hospitals in Iraqi governorates have developed referral facilities and specialized clinics for the early discovery of breast tumor. The goal of Early Detection and Down Staging is to reduce the mortality rates from breast cancer by moving away from the diagnosis of the disease in its advanced stages (third and fourth), where recovery prospects are worse and treatment costs are higher, to the diagnosis of the disease in its earlier stages (first and second). This is done by conducting early detection and examinations for all women aged 20 and over. (Mualla, H., & Al-Alwan, A., 2014).

On the other hand, the overall survival of cancer patients has improved significantly during the past few decades. This is especially relevant given the growing number of diagnostic and treatment options available to these patients. Despite the significant

advancement in biological therapies, chemotherapy (CT) is still a key component of neo-adjuvant, adjuvant, and palliative care in cancer (Schelenz, S., et al., 2012). Although they have had a considerable effect on breast cancer, especially doxorubicin and epirubicin, anthracyclines have not significantly outperformed earlier regimens. The introduction of the taxanes has sparked fresh interest in this area. Therefore, in the fight against breast cancer, paclitaxel has become a crucial tool. Intense clinical research has been conducted globally as a result of this agent's effectiveness and tolerability as well as its lack of anthracycline cross-resistance (Perez, A., 1998). The Pacific yew tree Taxus brevifolia yields paclitaxel, that exhibit antineoplastic properties. Cell division is prevented by paclitaxel's binding to tubulin and blocking the disintegration of microtubules. By attaching to and deactivating the apoptosis inhibitor protein, this substance also causes apoptosis (Glass, E., 1995). Moreover, paclitaxel can be used with other medications in a variety of schedules and regimens.

Yet, bone marrow toxicity, is among the highest prevalent adverse events of chemotherapy, because the hematopoietic cells in the bone marrow produce and mature blood cells at a rapid rate, it is vulnerable to chemicals that target cells with a high potential for growth. Alongside, these toxicities reduce the formation of platelets (thrombocytopenia), white blood cells (neutropenia or granulocytopenia), and red blood cells (anemia), which might be fatal to the patient (Testart-Paillet, D., et al., 2007). Similarly, serious side effects including neutropenia and toxic effects on the bone marrow are paclitaxel's main disadvantages. Since the prognosis of neoplasms is limited by the possibility of hematotoxicity during chemotherapy. Knowing when toxicities will arise will help to avoid any interactions associated. Therefore, the aim of this study was to assess and compare the hematological toxicities of breast cancer patients receiving paclitaxel during its four cycles.

The majority of paclitaxel's reported side effects as a single chemotherapeutic agent were hematological in nature, with neutropenia topping the list and being followed by thrombocytopenia, and anemia. Hypersensitivity responses, neurotoxicity, including peripheral neuropathy, myalgia, gastrointestinal disturbances, alopecia, and hepatic indications were among recorded occurrences (Marupudi, I., et al., 2007). Neutropenia

continued to be the most common adverse event when it came to combination studies with paclitaxel, accounting for almost 90% of all cases. The effects on myelosuppression appeared to correspond well with dose and dosing schedule in the majority of studies where paclitaxel was either given as a monotherapy or in combination with other medications. Patients on paclitaxel are continuously checked for peripheral blood counts, and if neutropenia is found, the dosage will need to be changed for further therapy (Hamilton, E., et al., 2013). Opposite to these results, our study revealed that the most common hematological toxicity experienced by the patients during the four cycle of chemotherapy with paclitaxel was anemia followed by neutropenia where 67 patients (47.52%), 76 patients (53.90%), 75 patients (53.19%) and 70 patients (49.65%) experienced anemia respectively during the first, second, third and fourth cycle.

Anemia is a common side effect of cancer and cancer treatment that has been proven to have a strong correlation with patients' levels of energy and quality of life ratings as well as to affect prognosis in a number of cancer types, including breast cancer (Dubsky, P., et al., 2008). According to a 2001 prospective study, 62% of the 3,278 breast cancer patients experienced anemia at least once during the study's follow-up period (Ludwig, H., et al., 2004). These finding were similar to our results where 47.52% to 53.90% of the patients included in the study experienced anemia during the four cycles of paclitaxel. In addition, there was no statistically significant change in terms of anemia between baseline and the first cycle, baseline and second cycle as well as between first and second cycle and between baseline and third cycle. Demonstrating that anemia can occur at any stage of the treatment.

Furthermore, primary prophylaxis was linked to a 46 percent reduction in the risk of neutropenic fever, a 45 percent reduction in infection-related mortality, and a 40 percent reduction in all-cause mortality during the chemotherapy period, according to a meta-analysis that included 3493 patients treated in 17 randomized controlled trials. The effect of primary prophylaxis on survival with or without disease could not be examined by this meta-analysis (Kuderer, M., et al., 2007). In addition, the rates of documented infections and neutropenic fever were significantly lower in 148 trials of primary CSF prophylaxis in cancer patients and patients undergoing hematopoietic cell transplant

(HCT), but this meta-analysis was unable to confirm a decrease in short-term all-cause mortality or infection-related death (Sung, L., et al., 2007). Opposite to these findings, our results demonstrated that filgrastim use was not associated with a decrease incidence of Neutropenia. At baseline, 14 patients experienced neutropenia grade 1 with 2 patient experiencing neutropenia grade 2, although 67 patients received filgrastim. As the number of patients receiving filgrastim decreased during cycle 1 where 62 patients received filgrastim, the number of patients experiencing grade 1 neutropenia decreased to 4 patients that was translated by a statistically significant change between baseline and the first cycle (P value = 0.004), and during the second cycle 63 patients received filgrastim and similarly 4 patient's experienced only grade 1 neutropenia. Yet during the third cycle when number of patients receiving filgrastim decreased to 61 patients more patients where suffering from grade 1 neutropenia where 5 patients were documented to have grade 1 neutropenia.

During the study, the risk of grade 1 neutropenia appeared to be the highest during the first cycle of therapy. Similarly, a multicenter phase 3 study conducted internationally whereabouts 928 patients in all were randomly assigned to 88 sites throughout Europe and North America, in order to examine how well pegfilgrastim worked to lower the frequency of febrile neutropenia brought on by docetaxel in individuals having breast malignancy exposed that among the initial placebo group, 67% of all febrile neutropenia occurrences took place during the first treatment cycle. As a result, regardless of the tumor type or chemotherapy protocol, the risk of febrile neutropenia seems to be highest during the first two cycles of chemotherapy (Vogel, L., et al., 2005). Yet, also during the study when the number of patients receiving filgrastim during the fourth cycle of the treatment decreased to 61 patients, the number of patients who experienced grade 1 neutropenia increased to 5 patients and there was a statistically significant change between second and the third cycle of paclitaxel detected in terms of grade 1 neutropenia (P value = 0.004). Comparably, in a multicenter study evaluating the possibility of restricting G-CSF prophylaxis to the first two chemotherapy cycles as opposed to the current standard of continuous G-CSF prophylaxis throughout all chemotherapy cycles, individuals having cancer of the breast who were deemed suitable for 3 times per week

multiple chemotherapy but had a 20% hazard for FN were randomized to receive primary G-CSF prophylaxis only during the initial two chemotherapy cycles (experimental arm) or to receive initial G-CSF prophylaxis during all chemotherapy cycles (standard arm). It has been found that that the group receiving G-CSF for only the first two cycles had a considerably greater rate of febrile neutropenia (36 versus 10 percent) and therefore it is advised to continue primary G-CSF prophylaxis throughout each treatment cycle (Aarts, J., et al., 2013).

Limitations and Strengths of the study

This was one of the first studies to be conducted in Iraq, specifically in Kurdistan region, where no previous study has been conducted in order to assess the hematological toxicities in breast cancer patients despite its high prevalence among the population.

Moreover, this study has some limitations to be mentioned, first the study is a retrospective studies. Therefore, follow-up of the patients' cases was not possible. In addition, the study couldn't assess if the patients experienced any associated symptoms such as fever, fatigue associated with neutropenia or anemia cases.

Another limitation that should be mentioned, patients medical history including chronic diseases such as hypertension, diabetes mellitus, liver disease and kidney disease, thyroid disease could not be accessed during the study although any of the following condition could have affected the metabolism of the chemotherapy agent and therefore resulting in an increase chemotherapy associated hematological toxicities.

Furthermore, some drugs are also known to interact with the chemotherapy agent resulting in a reduced paclitaxel clearance and hence increasing the risk of chemotherapy associated hematological toxicities. All of which can interfere with the study results to a certain extend. Lastly, the study sample size was relatively low compared to the number of patients that were suffering from breast cancer and the study was performed in one center limiting the possibility to generalize these results. Therefore, future studies including larger number of patients from multiple center representing Kurdistan region is highly recommended while the inter-individual variability in hematological toxicity can also be addressed in an attempt to reduce the

charge of health care beside the burden toward patient for the ones who are at risk for hematological toxicities associated with other complications. External factors including medications and co-medications, can also be investigated and included in future models.

CHAPTER V

CONCLUSION

Paclitaxel a semi-synthetic taxane was discovered in the bark of the Pacific yew tree beside this by attaching to tubulin, this substance cause microtubule stabilization, mitotic arrest, and ultimately cell death. On the other hand, bone marrow toxicity, is among the greatest prevalent unfavorable outcome of chemotherapy including paclitaxel, because the hematopoietic cells in the bone marrow produce and mature blood cells at a rapid rate, it is vulnerable to chemicals that target cells with a high potential for growth in addition these toxicities reduce the formation of platelets (thrombocytopenia), white blood cells (neutropenia or granulocytopenia), and red blood cells (anemia), which might be fatal to the patient. In our study it has been found that anemia is the most prevalent chemotherapy associated hematological toxicity followed with neutropenia in breast cancer patients receiving paclitaxel. Moreover, anemia has the tendency to occur at any cycle of paclitaxel chemotherapy. Therefore, in order to treat patients more successfully, it would be beneficial to be familiar with such undesirable action while emphasizing on the importance of additional care to such effects, since hematological side effects are a major factor in people stopping their anticancer treatments and subsequent decline in rates of success and survival. Further studies in order to validate such findings are recommended while including larger sample size and different area in order to be able to generalize the findings.

CHAPTER VI

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APPENDIXES

Appendix I

Ethical approval by the Hospital

Monday, April 18, 2022

To: General Directorate of Health Sulaymaniyah

Subject: A request for permission of a study

To Whom It May Concern

We hereby request for your kind consideration of a study entitled '***Evaluation of Hematological Toxicity in Breast Cancer Patients Receiving Paclitaxel'***, which will be conducted by Shad Adil Noori (MSc Clinical Pharmacy candidate, Near East University, North Cyprus) under the supervision of Assist. Prof. Dr. Nevzat Birand, Near East University

The study aims to assess and compare the hematological toxicities of breast cancer patients receiving Paclitaxel in the oncology department of Hiwa Hospital, Sulaymaniyah, Iraq. In the Oncology Department of Hiwa Hospital in Sulaimaniyah, Iraq, cancer patients' information (Age, Gender, BSA, Cancer Stage, ECOG status) and their laboratory results (WBC, NEU, LYMPH, RBC, HGB, PLT) from the 1st, 2nd, 3rd, and 4th cycles of chemotherapy administration will be collected from the cancer patients' file. The study will be carried with full consideration and practice of ethical norms.

We kindly request the above-mentioned study to be evaluated and accepted to be carried in Hiwa Hospital in Sulaimaniyah

With respect,

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EDUCATION

YEAR	GRADE	UNIVERSITY	FIELD
2020-2023	3.94	Near East University	Clinical Pharmacy (MSc)
2015-2020	3.10	Cyprus International University	Pharmacy (Mpharm)
2015	946/700	Salahaddin High school for boys	High school

ACADEMIC EXPERIENCE

PERIOD	TITLE	DEPARTMENT	UNIVERSITY
2018-2020	Exchange Program officer, Project Manager, event organizer	Pharmacy	Cyprus International University

FIELD OF INTERESTS

FIELDS OF INTERESTS	KEY WORDS
Scientific knowledge, psychological support, Teamwork,Workshop, Photography, Traveling, self development, Marketing, supporting people, self awareness,	

Foreign Languages	**Reading comprehension**	**Speaking***	**Writing***
ENGLISH	EXCELLENT	EXCELLENT	EXCELLENT
KURDISH	EXCELLENT	EXCELLENT	EXCELLENT
ARABIC	GOOD	GOOD	GOOD
TURKISH	GOOD	GOOD	GOOD

COMPUTER KNOWLEDGE

Program	**Use proficiency**
MICROSOFT WORD	EXCELLENT
MICROSOFT EXCEL	EXCELLENT
SPSS	GOOD
MICROSOFT POWERPOINT	EXCELLENT