NEUTROPENIA IN BREAST CANCER PATIENTS ON CHEMOTHERAPY IN TANZANIA.

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By

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A Dissertation Submitted in (Partial) Fulfillment of the Requirements for the Degree of Masters of Medicine in (Clinical Oncology)

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CERTIFICATION

The undersigned certify that they have read and hereby recommend for acceptance of dissertation entitled *"**Neutropenia in breast cancer patients on chemotherapy in Tanzania"*** in fulfillment of the requirements for the degree of Master of Medicine (Clinical Oncology) of Muhimbili University of Health and Allied science.

_____

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Date

DECLARATION AND COPYRIGHT

I, **Theoneste Maniragaba**, declare that this **dissertation** is my own original work and that it has not been presented and will not be presented to any other university for a similar or any other degree award.

Signature: _____Date: _____

DEDICATION

I dedicate this thesis to my late Mum Mrs Nyiramivumbi GAUDENCE whose passing away during my teenage years left me with an unfulfilled gap in my heart. May your soul rest in peace Mum. I also dedicate this work to my late brother Mr Sinaruhamagaye EVARISTE whose role model of hard work to advance in school inspired me throughout all my studies.

To my father Iyamuremye Apollinaire for his support and prayers, my wife Chantal and children.

To Cousin Francois Xavier and Brother Hitimana Vianney who have raised me and always believed in me.

To my sisters, brothers and nephews, I dedicate this work.

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Last but not least, I thank my fellow residents for the amazing experiences we shared during the training period, and to all my friends for their moral support.

ABBREVIATIONS

ANC:	Absolute Neutrophil Count.
ASCO:	American Society of Clinical Oncology.
CHOP:	Cyclophosphamide-Adriamycin (Halotestin) Oncoverin (Vincristine) Prednisolone.
COPD:	Chronic Obstructive Pulmonary Disease.
CSF:	Colony Stimulating Factor.
CT:	Computerized Tomography Scan.
CXR:	Chest X-Ray.
ECOG:	European Cooperative Oncology Group.
EORTIC:	European Organization for Research and Treatment In Cancer.
FBP:	Full Blood Picture.
G-CSF:	Granulocyte Colony Stimulating Factor
GI:	Gastro-Intestinal System.
Hb:	Hemoglobin.
HIV:	Human Immunodeficiency Virus.
IDSA:	Infectious Disease Society of American.
LFT:	Liver Function Test.
MASC:	Multinational Association of Supportive Care in Cancer
MRSA:	Methicillin Resistant Staphylococcal Aureus.
NCCN:	National Comprehensive Cancer Network
NCI:	National Cancer Institute.
NHL:	Non-Hodgkin Lymphoma.
ORCI:	Ocean Road Cancer Institute
PLT:	Platelet.
PMN:	Polymorphonuclear Count.
TSH:	Tanzania Shilling.
UTI:	Urinary Tract Infection.
WHO:	World Health Organization.

ABSTRACT

Background:

Breast cancer is the second most common female cancer following cancer of the cervix in Tanzania (1). Chemotherapy plays a role in curative and palliative treatment; however, it may lead to life threatening complications if rigorous preventive and management measures are not taken. Neutropenic fever is an oncologic emergency among other common side effects. It is critical to recognize neutropenia early and to initiate empiric antibacterial therapy promptly in order to avoid progression to sepsis syndrome and possibly death. This study was aimed at showing the prevalence of chemotherapy-associated febrile neutropenia for cancer patients treated at Ocean Road Cancer Institute.

Aim:

To determine the prevalence of chemotherapy associated febrile neutropenia and associated factors in breast cancer patients treated with chemotherapy at ORCI

Material and Methods:

A retrospective cohort study was conducted from March 2019 to April 2019. Breast cancer patients who had received at least one drug of chemotherapy that is known to cause neutropenia were eligible. Data collected included details on patient demographics and, hematological and clinical characteristics pre and post chemotherapy administration. Categorization was done into mild, moderate and severe neutropenia as follows:

1.1-2x10^9/L, (mild), 0.5-1x10^9/L (moderate) and less than 0.5 x10^9/L (severe). Data were collected over three consecutive cycles**.** SPSS version 20 was used to analyze data using t-tests and linear regression analysis.

Results

This study involved 241 patients whose clinical data were abstracted from medical records. All patients were female, with mean age of 51 years and standard deviation of 13.7. The majority of patients were from coastal regions. Most (97.5%) had locally advanced breast cancer. Seventy-five percent of the study participants were prescribed chemotherapy as adjuvant treatment. Combination regimens including doxorubicin, cyclophosphamide,

Fluorouracil were the most commonly administered chemotherapy regimens. Administered doses for this regimen were respectively as follows: 60:600:50 mg/m^2.

The proportion of patients with neutropenia during the course of treatment was 27.4%. The pretreatment neutrophil count versus treatment neutrophil count for 3 cycles did not show significant association (2%). Among patients who had neutropenia before treatment (N=241), 16.6% were of advanced age, 51 years old and above. Pretreatment neutropenia was associated with having a neutropenia episode during the treatment with a p-value of 0.02. The average neutrophil count of each of three cycles were respectively 4.2%, 33.4%, and 62.2% meaning moderate and mild neutropenia respectively then normal neutrophil count. Pretreatment anemia was found to be associated with neutropenia during chemotherapy (p-value 0.06).

Conclusion

This study found that the prevalence of chemotherapy-associated neutropenia among breast cancer patients receiving chemotherapy at ORCI is high as compared to what is observed in developed countries in prospective studies; 37% versus 11.6% (2). Neutropenia in these patients is associated with low pretreatment hemoglobin, advanced age, and stage. Though strong clinical and treatment factors have been shown to be associated with neutropenia, specific chemotherapy drugs like taxanes, methotrexate and cyclophosphamide are the drugs most associated with neutropenia. Early identification of risk factors associated with neutropenia in history and physical exam before initiation of chemotherapy is necessary for better outcome

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DEFINITION OF KEY TERMS

Neutropenic fever:

Fever >38°C (>101°F) for 1 hour, with an absolute neutrophil count (ANC) of ≤500 cells/microliter, or an ANC of ≤1000 cells/microliter with a projected nadir of ≤500 cells/microliter.

Myelosuppression:

A condition in which bone marrow activity is decreased, resulting in fewer red blood cells, white blood cells, and platelets production.

Absolute neutrophil count:

Is a measure of the number of neutrophil granulocytes (also known as polymorph nuclear cells, PMN's, polys, granulocytes, segmented neutrophils) present in the blood. Neutrophils are type of white blood cell that fights against infections.

Lymphoma: a tumor of the lymphoid tissue. The major types of lymphoma are Hodgkin's disease and non-Hodgkin's lymphoma (NHL).

Cytotoxic drug: any pharmacological compound that inhibits the proliferation of cells within the body. Such compounds as the alkylating agents and the antimetabolites designed to destroy cells (with a high growth fraction) are commonly used in chemotherapy.

Performance Status:

Is a measure of how well a person is able to carry on ordinary daily activities while living with cancer?

Pulmonary embolism:

A condition in which one or more arteries in the lungs become blocked by a blood clot

Deep venous thrombosis:

A blood clot in a deep vein, usually in the legs

Paraneoplastic syndrome:

Rare disorders that are triggered by an altered immune system in response to a neoplasm.

Lumbar puncture:

Is a medical procedure in which a needle is inserted into the spinal canal, most commonly to collect cerebrospinal fluid for diagnostic testing?

Positive predictive value:

Is the probability that subjects with a *positive* screening test truly have the disease?

Immunosuppression:

Is a reduction of the activation or efficacy of the immune system?

Colony stimulating factors:

Family of cytokines that were initially identified by their ability to stimulate hematopoietic cells to form colonies in culture media

CHAPTER ONE: INTRODUCTION.

1.1 Background

Breast cancer is the second most common female cancer in Tanzania following cancer of the cervix (1). Systemic chemotherapy plays a major role in neoadjuvant or adjuvant treatment to reduce the risk of distant recurrence, since most of our patients present in advanced stages (3) . Cancer patients on chemotherapy are at high risk of developing subclinical infections secondary to myelosuppression, typically heralded by a neutropenic fever. In addition, the otherwise normal bacterial and fungal flora in the lower gastrointestinal tract may translocate and cause systemic infections (4) When the body's defense mechanisms are weakened due to immunocompromising factors such as chemotherapy, neutropenia can occur early with or without clinical manifestations(4). Neutropenia, defined as decreased neutrophil countless that 1500x 10^9 /liter of whole blood, remains a common life-threatening complication. Severe neutropenia is considered an oncologic emergency and should be dealt with accordingly.

1.1.1 Pathophysiology

Studies have shown that the host's endogenous flora is the major source of causative pathogens responsible for neutropenic fever. Before the advent of broad-spectrum beta-lactam antibiotics, gram-negative rods were the most prominent responsible pathogen, but now gram-positive cocci are mostly identified at (76% versus 15%). Anaerobes are found in <5% of cases, and fungi are found in 2% to 10% of at-risk patients (5)

1.1.2 Diagnostic approach

Clinical examination and investigations

Myelosuppression secondary to chemotherapy administration usually peaks (nadir effect) around 8 days. Patients with neutropenic fever often present with a temperature of 38.2°C (100.8°F) associated with an absolute neutrophil count of less than 500 cells /microliter. Patients present with signs of infection or subclinical manifestations due to inability to mount an inflammatory response(6). In managing febrile neutropenia, identifying the primary site or focus for infection is crucial. Careful attention should be paid to all skin surfaces, skin folds, bodily orifices, sinuses, prior surgical or biopsy sites, and intravenous lines as possible as

sources of infection. Multiple investigations are needed starting from laboratory tests then imaging. An initial serum laboratory evaluation including FBC with differential, urea, creatinine, LFTs, peripheral blood smear is done. Then central line blood cultures together with urinalysis, stool cultures, and lumbar puncture should be done when clinically indicated. Per ESMO guidelines, a chest x-ray should be done to rule out any lung infection and CT scan of the chest, abdomen and pelvis should be done on presentation if there are signs or symptoms suggestive of intra-abdominal abscess or biliary tract infection (7).

1.1.3 Treatment options.

Treatment choice and risk stratification is based on the Talcott system or the Multinational Association of Supportive Care in Cancer (MASCC) score (8)(9)(10)(11)(12). For cases of outpatients, oral ciprofloxacin or amoxicillin/clavulanate for 5-7 days is the first recommendation (13)(14). For medium- to high-risk patients, different monotherapy is recommended such as cefepime, ceftazidime, imipenem/cilastatin, or meropenem for 5-7 days (15) (16). Antibiotics should be continued for at least 48 hours more in patients with negative cultures, but for high-risk patients, antibiotics should be continued for a minimum of 2 weeks in cases where the patient is persistently neutropenic despite becoming afebrile (17).

The use of empirical granulocyte colony-stimulating factor (G-CSF) or granulocyte-macrophage colony-stimulating factor (GM-CSF) in patients with neutropenia is not recommended by many professional societies because many randomized studies have not shown a consistent benefit with respect to duration of antibiotic therapy and length of hospitalization, noting also none of the studies have demonstrated an improvement in mortality(18). Studies have documented an improvement in duration of neutropenia, duration of antibiotic therapy, and duration of hospitalization, but showed no difference in the time to defervescence or in overall mortality (11). (19)

1.1.4 Complications.

Complications of treatment include antibiotic-induced fungal infection, clostridium difficile colitis and multiresistant infections together with increased mortality rate. The risk of mortality is higher in patients who present with hypotension and documented bacteremia (17) (11) (20).

1.1.5. Prevention.

The mainstay is use of colony stimulating factor and prophylactic antibiotics which reduce the duration of neutropenia in patients at all risk levels and reduce the risk of hospitalization and infection(21)(22) (23)(24)(25)(26). Antibiotics have shown an effect of decreased incidence of neutropenic fever using prophylactic trimethoprim-sulfamethoxazole (22)(27) (28). No role of antifungals in prevention has been proven. (29)(30)(31).

1.2 Literature Review.

1.2.1. Epidemiology.

Neutropenia is one among common life threatening complications of cancer therapy (32). (32). In United States of America, it is estimated at 60,294 cases per year which is 7.83 cases per 1000 cancer patients (33). For patients treated for hematological malignancies, the incidence is higher; up to 43.3 cases per 1,000 patients. Neutropenia accounts for fifty percent of deaths in patients receiving chemotherapy for solid tumors (34). In case of breast cancer patients, chemotherapy-related neutropenia is estimated to be 11.06% for the first cycle. (35)

Different factors have been found to be associated with increased risk of neutropenia; these are classified into Sociodemographic, clinical, and treatment-related**.** Sociodemographic factors include older age of more than sixty five years as an independent risk factor and female gender(32)(11) Female and male gender are associated with a risk by odd ratio of 2.0 and 1.32 respectively. However, female gender is not associated with an increased risk of complications due to febrile neutropenia (35).

1.2.2 Clinical factors

Clinical factors play an important role in determining the outcome of febrile neutropenia in cancer patients. Amongst them type and stage of underlying malignancy, prior episodes of neutropenia, organ dysfunction, performance status and others should be taken care before initiation of treatment. Patients being treated for hematological malignancies have about 5 fold increased risk of developing febrile neutropenia compared with those treated for solid tumors or lymphoma(33).

Advanced stage of disease is a risk factor for both neutropenia and complications due to neutropenia. Patients with early stage disease or low disease burden with neutropenia may be candidates for outpatient treatment.

1.2.3 Treatment.

A history of previous chemotherapy-induced neutropenia predicts for recurrent neutropenia and neutropenic fever (36). Patients with pre-existing heart, liver and/or kidney disease are at increased risk of developing febrile neutropenia during chemotherapy (36). Patients with a worse European Cooperative Oncology Group (ECOG) performance status (PS) during chemotherapy are at increased risk of febrile neutropenia (37). A prospective trial of patients receiving chemotherapy for solid tumors and lymphoma showed that an ECOG PS more than one is associated with an increased prevalence of febrile neutropenia (11)

Evidence has shown a higher risk of neutropenia in patients receiving their first chemotherapy treatment but the risk is cumulative with ongoing cycles of therapy (11). The risk is also increased with low first cycle nadir cell counts ([ANC] <500.PMN/micro liter), prior history of neutropenia, prolonged duration of neutropenia, magnitude of neutropenia, low albumin level, associated anemia (<12 g/dL), bone marrow involvement, and pre-existing organ dysfunction (11)(8) (9).

In addition, dose and type of chemotherapy used is associated with higher risk of neutropenia. Among common cytotoxic agents, drugs like alkylating agents (cyclophosphamide), anthracycline (doxorubicin), antimetabolites (fluorouracil as 5FU) and methotrexate are highly

myelosuppressive (38)(39). We can cite also camptothecins, epipodophyllotoxins, taxanes and vinblastine in Hodgkin's lymphoma. Patients being treated with combined chemotherapy have an increased risk of neutropenia (40).

1.3 Problem statement.

In Tanzania, breast cancer is the second most common cancer in women and the second most common cause of mortality following esophageal cancer. The mean age of patients affected by the disease is estimated to be 45 years, which is a sensitive period for socio-economic development at family and national levels. Since the majority of patients present with advanced disease, systemic chemotherapy is an important part of the treatment for these patients. Among different chemotherapy regimens used to deal with the condition, several lead to febrile neutropenia, which is caused by myelosupression.

Febrile neutropenia is a major cause of increased morbidity, health care resource utilization due to prolonged hospitalization, and compromised efficacy resulting in delays and dose reduction in chemotherapy. Mortality remains significant, reaching overall rates of more than 5% in patients with solid tumors and 11% in hematological malignancies. The prognosis is worse in proven bacteremia with mortality rates of 18% in gram–negative and 5 % in gram-positive bacteremia (29). In Tanzania, many factors are highlighted namely lack of supportive care, little knowledge about the existing data in terms of associated factors and guideline for better management. The prevalence of neutropenia in Tanzania is not known. Our study aims to determine the prevalence and factors associated with neutropenia in breast cancer patients treated with chemotherapy at ORCI.

1.4. Rationale of the study.

By determining the underlying prevalence of neutropenia and associated factors, this project may impact strategies for neutropenia prevention efforts at Ocean Road Cancer Institute. Like many regions in sub-Saharan Africa, there is a paucity of data elaborating the challenge of neutropenia in cancer patients in general. Given the scarcity of data on neutropenia in sub-Saharan Africa, a retrospective evaluation of the prevalence and associated factors is necessary to define optimal management strategies for this common disease (breast cancer) in

this setting. Ultimately, research regarding neutropenia status and associated factors will potentially provide evidence needed to plan for capacity-building strategies focused on prevention, early detection and treatment of this life-threatening condition, as well as best practice guidelines for cancer management within Tanzania and sub Saharan Africa in general.

1.5 Research question and conceptual frame work.

1.5.1 Research question.

What is the prevalence of neutropenia and its associated factors in patients treated for breast cancer at ORCI?

1.5.2 Conceptual framework.

Exposure

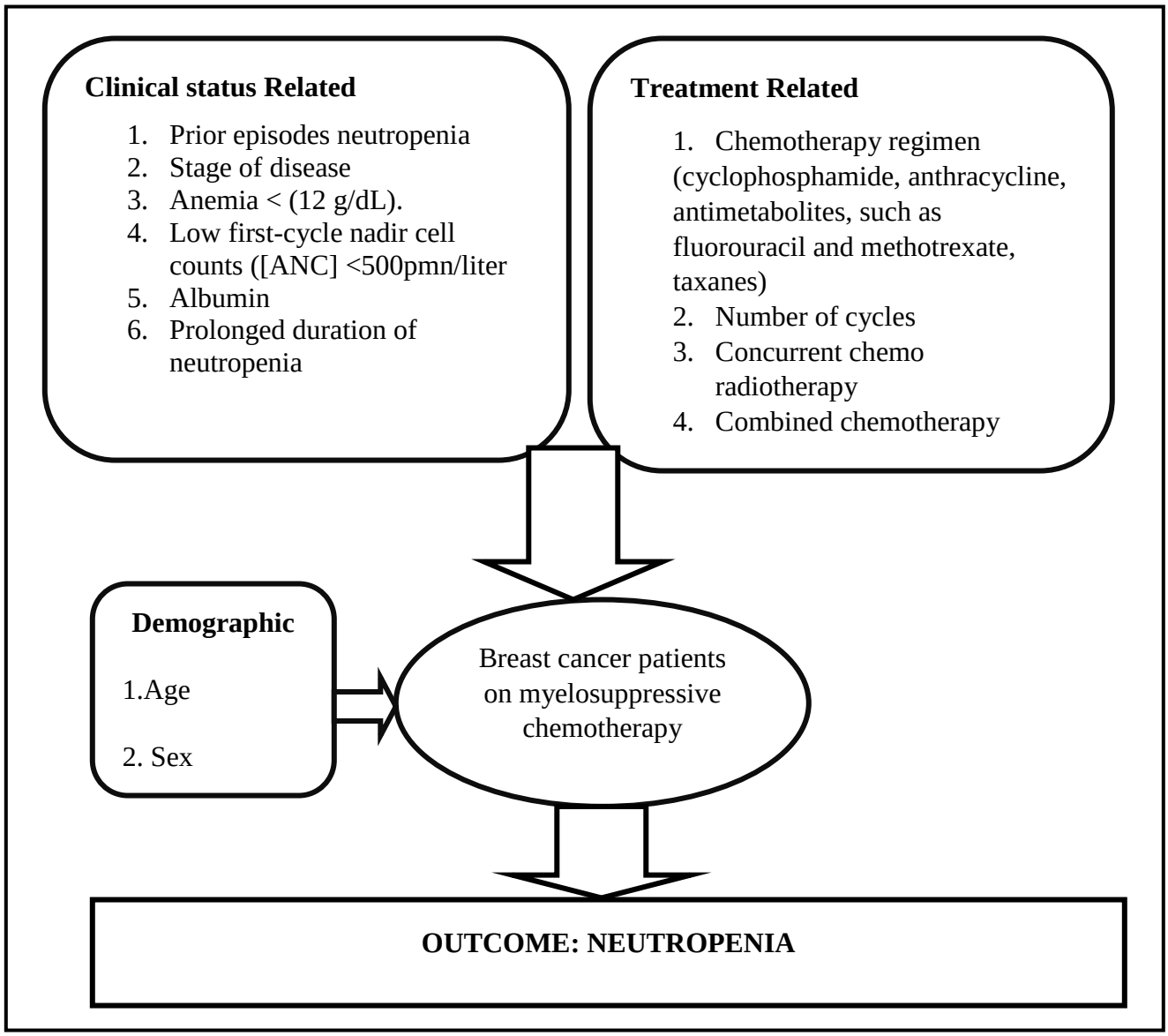


Figure 1: The conceptual framework

1.6. Objectives.

1.6.1 Broad objectives.

To determine the prevalence and factors associated with neutropenia in breast cancer patients treated with chemotherapy at ORCI.

1.6.2 Specific objectives.

1. To determine the prevalence of neutropenia in breast cancer patients on chemotherapy.
2. To determine the association between age and sex and neutropenia in breast cancer patients treated with chemotherapy at ORCI.
3. To determine the association between treatment factors and neutropenia in breast cancer patients treated with chemotherapy at ORCI.
4. To determine the association between clinical factors and neutropenia in breast cancer patients treated with chemotherapy at ORCI

CHAPTER TWO: MATERIAL AND METHODS.

2.1 Study design sample and data.

2.1.1 Study design.

This was a retrospective survey study.

2.1.2 Study population.

Female breast cancer patients treated with chemotherapy at ORCI during the year 2016 and 2017.

2.1.3 Inclusion criteria.

Patients more than 18 years of age

Patients with confirmed histology of breast cancer

Patients that have been prescribed chemotherapy as part of their treatment

2.1.4 Exclusion criteria.

Patients with HIV or any other immunosuppressive diseases (diabetes).

Male breast cancer patients.

2.1.5 Selection procedure.

From March through April 2019 files of patients with breast cancer confirmed on histology who have received at least 3 cycles of a chemotherapy regimen known to have at least one drug among the list cited below were enrolled in the study. Considered drugs were: antimetabolites like methotrexate, 5-Fluorouracil and capecitabine, anthracyclines like doxorubicin and epirubicin, Taxanes like paclitaxel and docetaxel together with others like cisplatin, carboplatin, cyclophosphamide and trastuzumab.

2.1.6 Sample size and sampling technique

This was calculated using the formula:

$$\text{Sample size} = \frac{Z_{1-\alpha/2}{}^2 p(1-p)}{d^2}$$

Where Z= statistical significance

P= proportion in previous study taken as reference

D=allowable error that is 5%

Hence, 1.96^2 x 21(100-21)/5^2 = 255

Adding 10% of missing response 26, the total sample size makes 280.

It was calculated by Reference to Bhavik D.Dhoshi at all as prevalence study from low income setting (31).

The sampling was by convenience that is also known as opportunity or accidental or haphazard where existing study subjects are used. It is a type of nonprobability sampling which involves the sample being drown from that part of the population which is close to hand.

2.1.7 Study variables

The following variables were considered in this study

Independent variables

Clinical related

i. Prior episodes neutropenia (<1.5×10^9/mL)
ii. Stage of disease
iii. Anemia < (12 g/dL).
iv. Albumin below 3.5 grams/dl
v. Prolonged duration of neutropenia(>10days)

Treatment related

i. Chemotherapy regimen
ii. Number of cycles

Dependent variables

Neutropenia

Mild: 1000-1500 cells/µL

Moderate: 500-1000/µL

Severe: lower than 500 cells/µL

2.1.8 Study Area.

Ocean Road Cancer Institute (ORCI) is located in Dar-es-Salaam and offers radiation therapy, medical oncology, palliative care, cancer prevention and screening programs. As such, it serves as the main referral center for cancer care in Tanzania. It is one of the oldest health institutions in Tanzania that since 1996 is autonomous in management. It is a national referral facility for comprehensive cancer services accessible by all Tanzanians and patients from neighboring countries.

2.1.9 Data collection.

Patients' files were retrieved and reviewed. The sampling was done by convenience. Demographics, pre-treatment neutrophil and hemoglobin counts and serum albumin levels were recorded. Treatment intent, disease stage, chemotherapy regime, cycles and dose range were extracted. Three consecutive post chemotherapy cycle evaluation FBP were traced and gathered a week post treatment

2.2 Data analysis, quality plan and ethical issues.

2.2.1 Data analysis.

Data were analyzed using SPSS version 20, and tallied in line with the objective of the study.

The pre-treatment neutropenia **S** were established by grouping the pre-treatment values of neutrophil count according to a grading system of mild, moderate, and severe neutropenia (41).

During the first three consecutive cycles of chemo administration, the full blood picture evaluation values were recorded. From these data, neutropenia classification was developed from the absolute neutrophil count obtained. Then the final neutrophil count which calculated

as arithmetic average of three. Then the measure of central tendencies was used to summarize and presented in tables and graph.

Table 1: Planed analysis of the specific objective

Objective	Analysis done
To determine the prevalence of neutropenia for breast cancer patients on chemotherapy.	Proportion
To determine how age and sex are associated with neutropenia in breast cancer patients treated with chemotherapy at ORCI.	Cross tabulation, frequency distribution
To determine treatment factors associated with neutropenia in breast cancer patients treated with chemotherapy at ORCI.	Percentage and frequency
To determine clinical factors associated with neutropenia in breast cancer patients treated with chemotherapy at ORCI	Percentage and frequency

Patients residential regions were categorized zone wise and presented in Figure.2. Chi square test analysis was used to establish the significance between dependent and independent variables with p-value less than 0.05 considered statistically significant.

2.2.2 Ethical consideration.

Ethical clearance was sought from the ethical committee (Institutional Review Board) of Muhimbili University of Health and Allied Sciences. Permission for file retrieval was obtained from Ocean Road Cancer Institute. Confidentiality was ensured by identifying data extraction sheets by using serial numbers, but not names of patients.

CHAPTER THREE: RESULTS.

The study recruited 241 patients. All patients were female, with a mean age of 51 years and standard deviation of 13. Majority of them came from coastal regions, with the least coming from the Lake Zone.

The proportion of patients with neutropenia in the overall course of treatment was 37.8% (Figure). A majority had advanced disease (97.5%), Table 2. Among patients who had neutropenia before treatment, 16.6% of them were 51 years old and above. (Table 4) The pretreatment neutropenia had an association with a neutropenic episode during the treatment (P value of 0.02, table 4.). Pretreatment anemia episode was found in 68% of patients and associated with inter-cycles neutropenia. p value of 0.06 (table 4.)

Approximately three quarters of the study participants were prescribed chemotherapy in the adjuvant setting. ACF chemotherapy was the most frequently administered regimen.

The average three cycles neutrophil count was generally found to be 4.2%(moderate), 33.4%(moderate) and 62.2%(normal neutrophil count). Mean hemoglobin values were 10.8g/L, 10.8g/L and 10.7g/L for the 1^{st}, 2^{nd}, and 3^{rd} cycles respectively. Standard deviation: 1.9, 1.7 and 1.7 in order of cycles. This average absolute neutrophil count of three cycles, stood as single entity in describing neutropenia while patient was on treatment. Table 3 and 4, describes the various proportion between these on treatment neutropenia and clinical and treatment factors.

Table 2: Baseline information of breast cancer study participants among breast cancer patients treated at ORCI during the year 2016/2017.

Variable	n (241)	%
Age(years)		
21-30	12	5
31-40	44	18.5
41-50	81	33.3
51-60	47	19.5
61+	57	23.7
Stage		
Early	6	2.5
Advanced	235	97.5
Pretreatment condition		
Neutrophil count (number/Microliter)		
<0.5(severe)	3	1.2
0.6-1 (mild)	5	2.1
1-1.5(moderate)	58	24.1
1.5 (normal)	175	72.6
Hemoglobin level (g/dl)		
<12	164	68
>12	77	32
Treatment intention		
Neoadjuvant	35	14.5
Adjuvant	205	85.5
Chemotherapy regime		
A/C/F	181	75.1
Others	60	24.9

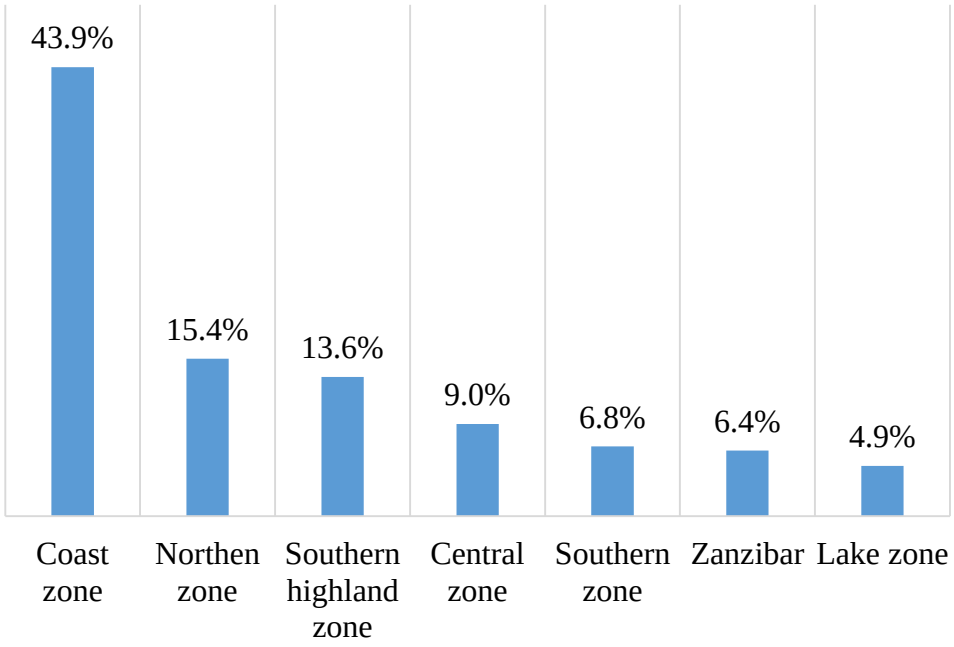
Key showing chemotherapy regimen:

C: cyclophosphamide, A: Anthracycline, F: 5 Fluorouracil

Early stage: stage: I, and II., Advanced stage: III and IV

This table shows mean age of 51 and standard deviation is 13.7. More than half of patients which is 56% are young of less or equal than 51 years While 97.5% are in advanced stage of disease (stage III and IV). A number of 27.3 % presented in neutropenic settings while 88% were anemic Anthracycline based therapy was common with 75.1%.

Figure 2: Zonal distribution of breast cancer patient treated at ORCI during the year 2016/2017



Key: *The country is divided into several regions which are distributed in seven zones as follows:*

Coast zone: Dar es salaam, Coast and Morogoro

Northern zone: Arusha, Kilimanjaro and Tanga.

Southern highland: Mbeya, Tabora, Iringa, Kigoma, Rukwa and Njombe.

Central zone: Dodoma and Singida.

Southern zone: Mtwara, Lindi and Ruvuma.

Zanzibar zone :Unguja and Pemba island.

Lake zone: Mwanza, Shinyanga, Mara and Kagera.

Coastal region is associated with many patients than lake zone.

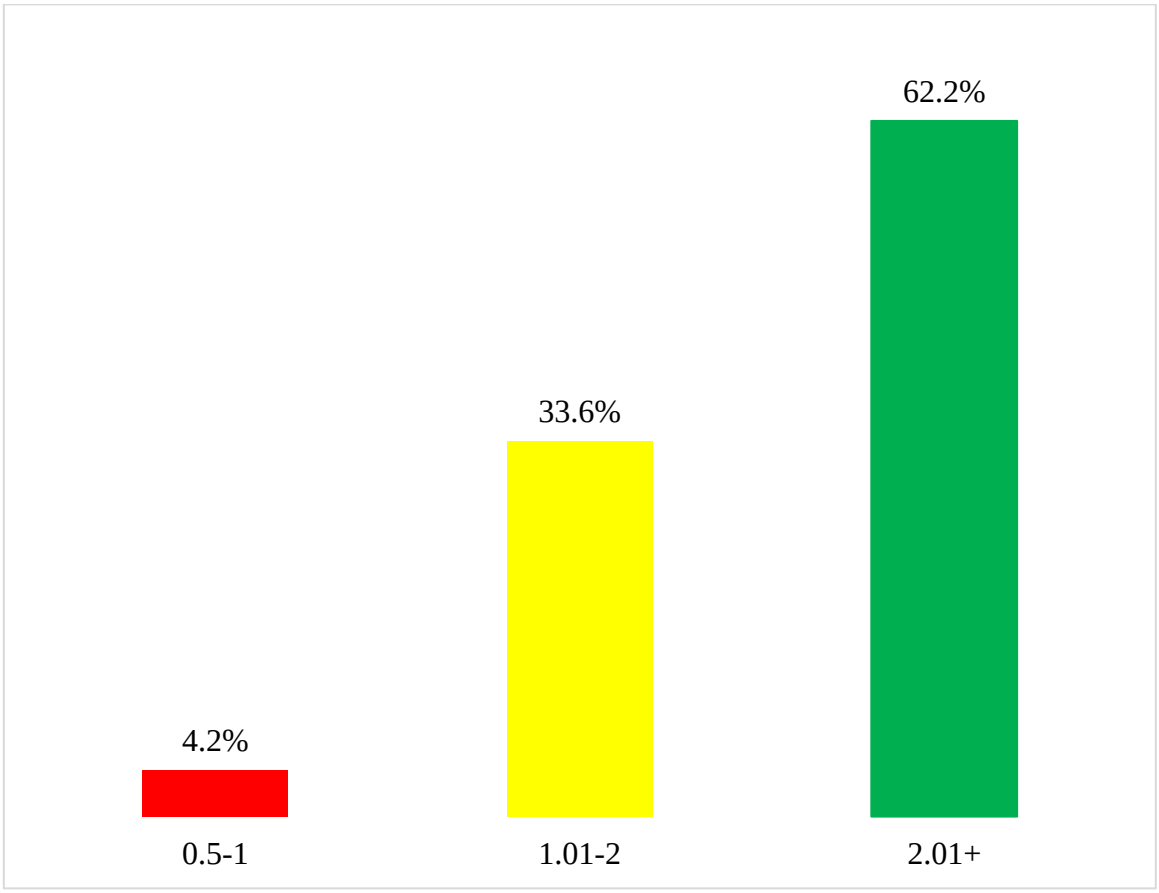
Table 3: Hematological and albumin results of three consecutive cycles among breast cancer patient treated at ORCI during the year 2016/2017.

	1st cycle		2nd cycle		3rd cycle	
	n	%	n	%	n	%
Neutrophil count ($x10^9$)						
<0.5	12	5.1	15	6.2	15	6.2
0.5-1	28	11.6	34	14.1	27	11.2
1.01-1.5	67	28.3	67	27.8	70	29
1.5+	130	54.9	125	51.9	129	53.5
Missing	3	1.2				
Total	241	100	241	100	241	100
Hb count						
<12	192	79.7	177	86.2	191	79.3
>12.1	49	20.3	559	22.8	50	20.7
Total	241	100	241	100	241	100
Albumin						
<3.5	64	53.3				
>3.51+	56	46.7		.		
Total albumin	120	100				

There is no much variation of neutropenia rate between among 1st, 2nd. And 3rd 45.2%, 48.1%, 46.4% respectively. Majority were anemic and no much variation among cycles (Hb less than 12g/dl) 79.7%, 86.2.79.3% for 1st, 2nd, and 3rd respectively. Around 53.3% of patients had low plasma albumin of less than3.5 g/d which is under normal range.

Figure 3: Mean neutrophil counts (number/Micro liter) among breast cancer patients after three cycles of chemotherapy (n=241).

This shows that overall neutropenia rate for three consecutive cycles of chemotherapy is 37.8 %.



Y axis: Level in percentage, X axis: Neutrophil /microliter

Green: Normal neutrophil count, Yellow: Mild neutropenia, Red: Moderate neutropenia

0.5-1 moderate neutropenia,1.1-1.5 mild neutropenia,1.5+ normal

Table 4: Average neutrophil count with respect to age, stage, and pretreatment episode.

		Neutrophil#			
	0.5-1	1.01-1.5	1.5+	total	
	p value				
Variable	n (%)	n (%)	n (%)	n (%)	
Age					
21-30	0	6(2.5)	6(2.5)	12(5)	
31-40	1(0.4)	16(6.6)	27(11.2)	44(28.3)	
41-50	4(1.7)	23(9.5)	54(22.4)	81(33.6)	
51-60	3(1.2)	16(6.6)	28(11.6)	47(19.5)	0.8
61+	2(0.8)	20(8.3)	35(14.5)	57(23.7)	
Total	10(4.1)	81(33.6)	150(62.2)	241(100)	
Stage					
Early	0	3(1.2)	3(1.2)	6(2.4)	
Advanced	10(4.1)	78(32.4)	141(61)	235(97.5)	0.74
Total	10(4.1)	81(33.6)	150(62.2)	241(100)	
Pretreatment neutrophil count					
Normal	6(2.5)	47(19.5)	122(50.6)	175(72.6)	
Mild	3(1.2)	29(12)	26(10.8)	58(24.1	
Moderate	1(0.4)	2(0.8)	2(2.8)	5(2.1)	
Severe	0	3(1.2)	0	3(1.2)	
0.002					
Total	10(4.1)	81(33.6)	150(62.2)	241(100)	
Pre-treatment hemoglobin count					
Hb<12	5(2.1)	49(20.3)	110(45.6)	164(68)	
Hb>12.01	5(2.1)	32(13.3)	40(16.6)	77(32)	0.06
Total	10(4.1)	81(33.6)	150(62.2)	241(100)	

There is an association between advanced age of 61 and above. There is high rate of neutropenia in advanced stage as opposed to early stage. We appreciate a high rate of neutropenia in patients with pretreatment neutropenia settings while low hemoglobin is associated with high rate of neutropenia however moderate category is common than severe one.

Table 5: chemotherapy regimen versus average neutrophil count of three cycles

Chemo	Neutrophil count			Total
	0.5-1	1.01-1.5	1.5+	
C/A/F	6 2.4%	65 27%	122 50.6%	193 80%
C/F/M	0 0.0%	6 2.5%	9 3.7%	15 6.2%
Others	4 1.7%	10 4.1%	19 7.9%	33 13.7%
Total	10 4.1%	81 33.6%	150 62.2%	241 100.0%

AC chemotherapy regimen was associated with high rate of neutropenia at ORCI.

(P value was 0.02.)

Regimen:

C/A/F= Cyclo, Adriamycin, 5-Fluorouracil, C/F/M= Cyclo, 5-FU, Methotrexates, C/F/d= Cyclo, 5-FU, Docetaxel, Others drugs included C/F, AD, Ad and vincristine

CHAPTER FOUR: DISCUSSION.

Breast cancer is a common malignancy among females in both developed and developing countries. Mortality from breast cancer can be associated with poor control of treatment-related complications.

This study recruited 241 patients. All patients were within age range of 21 and 61 years with standard deviation of 13.7 and all were female. This age range is concordant with what has been found by Burson et al in Tanzania., that a majority were found between 45 to 65.(1) It is quite different from Europe and other developed countries where patients who are diagnosed with breast cancer are more likely to be at advanced age at presentation.(45) Majority of patients reviewed revealed that most of them were from coastal regions, and Lake Zone had the least number of patients. This is concordant with most local studies in Tanzania, because most of our patients from the periphery come and reside in Dar es Salaam, and lake region is farther than most others mentioned above to consult Dar es Salaam. Also we think that most from that region consult at the nearest hospital, Bugando referral center.

Neutropenia is among the complications associated with chemotherapy in neodjuvant or adjuvant treatment settings. Accurate identification and prompt management are needed. During our study, we found that 37% of our patients treated with chemotherapy had neutropenia during the first three cycles of treatment.

Most of the study participants had advanced disease, showing similarities with most regional and continental study findings in similar settings (40)-(46). Reasons that could justify this difference may be among others: low levels of education and insufficient breast cancer screening which are uncommon in poor resource settings. The hypothesis for this delay is due to two possible reasons: lack of screening added to that of patients who come from far away that transfer/system delay doesn't allow them to present on time. Apart from the above reasons we have found that low levels of education and seeing a traditional healer first were significantly associated with a longer patient delay.(47)

Generally, pretreatment neutrophil counts appear normal which is expected since patients have not yet been exposed to chemotherapy. More than 96.7 % have quite normal neutrophils which later were affected by chemotherapy.

68% of patients had low pretreatment hemoglobin. According to Talcott et al. anaemia was found to be one among predictors of neutropenia in developed world. There is no study in the developing world showing the rate of pretreatment anemia, however it is known that anaemia is a common contributing factor in our environment due to inadequate nutrition (48). This is the same as compared to what has been shown in the Klasterky study showing the effect of low anemia for patients receiving chemotherapy (9)(11).

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We observed an increased rate of adjuvant chemotherapy compared to neoadjuvant treatment. We think that due to the reason that most our patients present to ORCI after surgery (mastectomy) from MNH and different hospitals which make chemotherapy to be given mostly in adjuvant settings rather than neoadjuvant. Among regimens used here, ACT combination was the most commonly given with 181 (75.4%). This goes with the common guideline of anthracycline based therapy considered as the first choice taking in consideration of co-morbidities.(49)

1. **Prevalence of neutropenia at ORCI**

Based on for first three cycles of treatment, 37.8% were found to be neutropenic. This is similar to what has been found by Doshi in India in solid malignancy, breast cancer included. (31) Dr Vanderpuye in Ghana found similar results with a median rate of 40 % of neutropenia in a prospective study(50). Comparing what has been found in developed countries, we see that there is bigger difference. Morrison in Canada found an estimated rate of 11.06%. The same result was found in Europe by Charles and colleagues; chemotherapy-associated neutropenia in breast cancer was estimated to be around 13%, which concurs with what has been reported by Morrison in North America (35)(22). Reasons why there is much difference from developed countries and less developed is thought to be advanced cases and lack of supportive care, especially low nutrition. This is confirmed by Miguela et al whose

study showed a ratio of 10-fold increase in infectious complications in low and middle income countries compared to high income countries due to lack of supportive care, diagnostic evaluations, trained personnel and adequate organizational structure (51).

2. **Age**

The literature shows that neutropenia rates increase with age of 60 years and above.(32)
During our analysis, we have found that 91 patients (37.7%) had neutropenia. we have found 16.9 % are above years. (p value of 0.8) .This concurs with what has been found by Ruth et all in UK that older age is mostly associated with increased risk of neutropenia.(32) The same results in older patients were confirmed by Bhavick et al. in India with increased rate of neutropenia in older patients. (31). (Table 4.)

3. **Treatment factors**

This being a retrospective study, we could not identify any history of previous neutropenia and performance status due to lack of information in files. All patients were treated by combination chemotherapy so it was not possible to compare the difference between single agents and combined chemotherapy. Rates of severe to mild neutropenia found were 5.8%, 12.3%, and 18.9% respectively. The rates were found to increase with consecutive cycles. This concurs with what J.H. Silber et al found in United States with increase in neutropenia by prospective chemotherapy cycles in prospective study.(36)(48)(49).

Our study found that more than 50% of our patients had low albumin of less than normal range (3.5 g/dl), a sign of liver co-morbidity especially poor nutrition. What needs to be highlighted here is that albumin was considered from first cycle and then for subsequent cycles there has been missing results of albumin measurement (2^{nd} and 3^{rd} cycles). Possible reasons for this are that albumin level is only routinely checked for patients on initial visits due to limitation in resources.

Drugs like anthracyclines (doxorubicin), cyclophosphamide and methotrexate were highlighted in multiple studies in Europe as showed by Sun D et al and this concurs to what

has been found here with antracyclines and docetaxel. (38) Lyman G H. at al. also found similar results in United states in Risk models for predicting chemotherapy-induced neutropenia.(39)(40) This goes to what was found during our study that Anthracycline and cyclophosphamide based chemotherapy were associated with high rate of neutropenia than other regimen

4.Clinical status Related

Advanced disease has a higher association with severe and high rate of neutropenia in our settings. In our study we found that more 34% of patients are of advanced stages. These results are common in most studies from sub-Saharan region that showed a high rate of metastatic cases at presentation which then contribute to the higher rates of severe neutropenia in these patients. This is different from what is found in developed settings in which Talcott, Klastersky J Lyman GH, et al. in United states with increased rate of neutropenia from those with advanced stages(III/IV).(8)(9)(37).

There were high rates of anemia with 81.8% having hemoglobin levels below the cut-off point of 12.0 g/dl. This pretreatment was associated with a neutropenia rate of 22.4% but was not statistically significant. (p value 0.06) This concurs to what have been shown in multiple literatures in multivariate analysis. Here we cite Lyman et al in Rochester ,USA where low baseline hemoglobin (less than 12 g/dl)was shown to be associated with chemotherapy associated neutropenia (39).This pretreatment low hemoglobin may be associated with organ dysfunction but most of the time it is associated with lack of support in nutrition which is common in low settings countries ,Tanzania included.(50)

STUDY LIMITATIONS

To our knowledge this is the first neutropenia study done in Tanzania at Ocean Road Cancer Institute. It provides baseline information about neutropenia status in breast cancer patients who constitute some of the most challenging cases in management.

This was a retrospective study that inherited some challenges primarily due to missing information in the patients' records.

This study was originally conceived as a prospective study that would give accurate data from thorough investigations and clinical records, but had to be amended into a retrospective one due to challenges in following up of patients and the limited time available for completion of this academic exercise. Hence the study was not able to collect data about fever occurrence.

Levels of neutropenia in cancer patients receiving chemotherapy are expected to be lowest during the 'WBC nadir phase'; unfortunately, the retrospective nature of this amended study was not able to pick up this information hence the results may not truly reflect neutropenia levels in this group of patients.

CHAPTER FIVE: CONCLUSIONS

Our study evaluated the rate of neutropenia in breast cancer patients in Tanzania. The prevalence of chemotherapy associated neutropenia is high compared to what is reported in developed countries. The study has shown a strong association of neutropenia with low pretreatment hemoglobin, advanced age and stage. Though strong clinico-treatment factors have been shown to be associated with neutropenia, specific chemotherapy like-taxanes, methotrexate and cyclophosphamide have been shown to be associated with high prevalence of neutropenia at Ocean Road cancer institute as our study has shown.

Recommendations

To The ministry of health and Ocean Road Cancer Institute

- To provide educative and screening program in order to decrease these most common cases of advanced stages which contributes to increased morbidity from many factors included.
- To conduct a prospective study that will help in capturing the accurate neutropenia and associated symptoms (febrile neutropenia).

To clinicians at MNH and other hospitals:

- To provide necessary clinical information for good evaluation and research and improve communication and collaboration between health professionals (nursing and lab technicians for proper management.

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APPENDICES.

Form A and B

Form A : First enrollment

Patient serial number:

1.SECTION A: **DEMOGRAPHIC FACTORS**	
Age	
2.SECTION B: **CLINICAL FACTORS**	
b)performance status in ECOG	
c)Disease stage	
d) Absolute neutrophil count	
e)Anaemia(HB)	
f) chemotherapy regimen	
g) Neoadjuvant/ Adjuvant	
h) chemotherapy intensity (dose range) in mg per body surface area	

Form B: Follow up

Item	**1st Follow up date:**	**2nd Follow up Date:**	**3rd Follow Date:**
b) FBP			
Neutrophil			
HB			
Platelets			
c)performance status			
c)Albumin<35g/l(3.5g/dl) sign of poor nutritional status			