INCIDENCE, RISK FACTORS AND MANAGEMENT OF NEUTROPENIA AMONG CANCER PATIENTS WITH SOLID TUMORS RECEIVING CHEMOTHERAPY AT KENYATTA NATIONAL HOSPITAL CANCER TREATMENT CENTRE

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U51/87583/2016

A thesis submitted in partial fulfillment of requirements for the award of the Degree of Master of Pharmacy (Pharmacoepidemiology and Pharmacovigilance), School of Pharmacy, University of Nairobi

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November, 2019

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Title of the work: Incidence, risk factors and management of neutropenia among cancer patients with solid tumors receiving chemotherapy at Kenyatta national hospital cancer treatment centre.

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DEDICATION

This work is dedicated to all cancer patients and to all healthcare practitioners who do their very best to care for cancer patients.

ACKNOWLEDGEMENTS

I would like to thank the staff at the cancer treatment centre, especially those working at the records department. Their kindness enabled me to access the data required in this study.

I am grateful to my research supervisors, Professor George Osanjo and Dr. Pegotty Mutai for mentoring and guiding me throughout this study.

I am grateful to Professor Faith Okalebo for her invaluable guidance and input.

I am thankful to my wife Winnie and son, Mwangi.

I am grateful to my colleagues and friends who walked through this journey with me and supporting me in different ways.

Most importantly, to God who is my ever present help: I am forever grateful for everything!

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LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AML	Acute Myeloid Leukemia
ANC	Absolute Neutrophil Count.
ASCO	American Society of Clinical Oncology
CA	Cyclophosphamide Adriamycin (Doxorubicin)
CAF	Cyclophosphamide Adriamycin Fluorouracil
CBC	Complete Blood Count
CIN	Chemotherapy Induced Neutropenia.
CMF	Cyclophosphamide Methotrexate Fluorouracil
CMVF	Cyclophosphamide Methotrexate Vincristine Fluorouracil
COPD	Chronic Obstructive Pulmonary Disease
CTCAE	Common Terminology Criteria for Adverse Events
CUA	Cost Utility Analysis
ESMO	European Society of Medical Oncology.
FN	Febrile Neutropenia
G-CSF	Granulocyte Colony Stimulating Factor
IAEA	International Atomic Energy Agency.
KNH-CTC	Kenyatta National Hospital Cancer Treatment Centre.
MASCC	Multinational Association for Supportive Care in Cancer
MDL	Myelodysplastic Leukemia
MOA	Measure of Association
NHIF	National Hospital Insurance Fund
OR	Odds Ratio
QALY	Quality Adjusted Life years
RDI	Relative Dose Intensity

DEFINITION OF OPERATIONAL TERMS

Absolute Neutrophil Count (ANC): is a measure of the number of neutrophil granulocytes present in the blood. The normal range is between 1.5* 10^9 cells/litre and 8.0* 10^9/cells/litre.

Chemotherapy-Induced Neutropenia (CIN): This is a condition characterized by low levels of white blood cells brought about by toxic effects of anti-cancer drugs. Patients with an absolute neutrophil count lower than 1.5* 10^9/cells/litre are after exposure to chemotherapeutics are considered to have developed CIN.

Fine needle biopsy: This is a type of procedure where a thin needle is inserted into an area of abnormal-appearing tissue or body fluid.

Oncological emergency: This refers to any acute potentially morbid or life threatening event directly or indirectly related to a patient's tumor or its treatment.

Laboratory abnormalities: These are laboratory results outside the reference range for a specific test within a particular laboratory.

Relative dose intensity: This refers to the amount of particular chemotherapy given over a specific time in relation to what is considered standard, such that a lower dose may be administered than is the standard due to toxicity.

ABSTRACT

Background: Cancer accounts for approximately 7-10% of deaths in Kenya. It is managed through surgery, chemotherapy, radiotherapy and hormonal therapy. Each of these interventions present benefits and risks.

Chemotherapeutics are known to cause a number of adverse effects. Chief among them is neutropenia. Neutropenia is considered the most serious hematologic toxicity. It is linked to serious infections, chemotherapy dose adjustments and delays that may compromise therapeutic outcomes. Few studies have been carried out to determine incidence of chemotherapy induced neutropenia (CIN) in Kenya.

Objectives: The main objective of the study was to determine the incidence and risk factors, and identify the interventional strategies and gaps in management of chemotherapy-induced neutropenia.

Methods: This was a retrospective observational cohort study. Participants were recruited from among adult cancer patients who received chemotherapy at the cancer treatment centre at KNH from January to March 2016. Data were abstracted from participants' files on their bio-data, type of cancer, co-morbidities, diagnosis for neutropenia and the strategy used to manage chemotherapy-induced neutropenia. Selected files were reviewed for a period of one year. Abstracted data were recorded into a pre-tested case record form.

Descriptive analysis was carried out using STATA version 13 and findings presented in form of proportions, ratios, pie-charts, histograms and tables. Logistic regression analysis was carried out using STATA version 13 to identify the combinations of risk factors most likely to have caused neutropenia.

Results. Forty seven (27.17%) of the 173 participants developed neutropenia during the period under review. The most important risk factor was administration of cyclophosphamide. 45.7% of all participants treated using cyclophosphamide developed neutropenia. Neutropenic effects were found to be age dependent. Internally standardized risk ratio for participants aged 50 years and above was 4.71(2.27-9.77). In participants aged below 50 years, the neutropenic effect was minimal with a risk ratio of 0.92(0.41-2.04). Participants aged 50 years and above were almost five times at risk of developing neutropenia compared to participants aged 50 years and below.

Doxorubicin had a protective effect which confounded the association between cyclophosphamide and neutropenia. The odds ratio of developing neutropenia after administration of cyclophosphamide reduced from 9.23(2.6-32.80) to 2.02(0.16-25.73) after adjusting for the protective effects of doxorubicin. Although breast cancer had the highest incidence of neutropenia, this was attributed to its treatment with cyclophosphamide.

The main intervention for chemotherapy-induced neutropenia was administration of a granulocyte colony stimulating factor for 29(61.7%) of participants.

Conclusions and recommendations. The number of new cases of neutropenia was high at 27.2% of the participants. The risk of neutropenia varied with age. Patients aged 50 years and above may require close monitoring for neutropenic effects especially those treated using risky regimens.

Cyclophosphamide was found to present a significant risk of developing neutropenia. A protocol for determining risk profiles of patients on cyclophosphamide should be developed. Such a protocol should include strategies for managing neutropenia if, and once it develops.

Majority of participants developing neutropenia were managed using a granulocyte colony stimulating factor (GCSF). The rest were treated with antibiotics or had their chemotherapy deferred.

CHAPTER ONE: INTRODUCTION

1.1 Background

Cancer is one of the leading causes of death alongside infectious and cardiovascular diseases. It was ranked as the second leading cause of deaths in the United states in 2015 (1). Most cancer deaths occur in Asia and Africa, which, combined, accounted for 64.6% of all cancer deaths in 2018. This could be attributed to a higher incidence of cancers with poor prognosis, and relatively poorer outcomes of diagnosis and management (2). In Kenya, the annual incidence of cancer is 37000 new cases and about 28000 cases of mortality from cancer are recorded yearly (3).

During management of cancer, drugs are administered following established protocols that have been carefully pre-evaluated. The more complex the drug therapy, the likelier the chance for occurrence of drug related problems including adverse drug reactions. Furthermore, anti-cancers have a narrow therapeutic index and adverse drug reactions (ADRs) to these medications are higher compared to other classes of drugs.

Anti-cancers are targeted on those cells that are abnormally actively dividing. Normally but actively dividing cells are also affected leading to adverse effects. The mouth, intestines, skin, hair and the bone marrow are the most often affected by chemotherapy (4).

1.2 Problem statement

As the incidence of cancer has increased, so has the types and sources of chemotherapeutic drugs. The complex nature of cancer has called for use of equally complex protocols. Therefore, the predictability of likely adverse effects from anti-cancers is not obvious. Furthermore, cytotoxic agents have a narrow therapeutic window and a complex pharmacological and pharmacokinetic profile leading to a higher chance of experiencing adverse drug reactions (ADRs) (5).

Bone marrow suppression is one of the most common adverse reaction resulting from chemotherapy (6). Myelosuppression is the most significant dose limiting factor in patients undergoing chemotherapy (7). It can cause delays in the initiation of therapy or substitution with clinically inferior regimens.

A study on optimal delivery of anthracycline-based chemotherapy among breast cancer patients at University of Valencia hospital(Spain), in 2007, reported that the onset of administration of chemotherapy could be delayed by 5-7 days even in cases where neutropenia was not severe (8). This may compromise optimum outcome of management (7).

Bone marrow suppression affects hematopoiesis, the process by which blood cells are normally formed. This leads to a decrease in the production of white blood cells, platelets and red blood cells. This further causes neutropenia, anemia and thrombocytopenia, all of which place patients at risk of severe infections, bleeding and cardiovascular disorders (9).

Of these three, neutropenia is the most prevalent among cancer patients receiving chemotherapy. Occurrence of neutropenia can cause life-changing adverse effects. Physicians may prefer to manage the condition before continuing with chemotherapy. Alternatively, they may adjust dosages of chemotherapy to try and achieve a risk-benefit balance. Either intervention has a likelihood of compromising optimum clinical outcome of chemotherapy.

A study on mortality among participants with and those without febrile neutropenia(FN) based on data from the national death index in the US in 2010, recorded a 35% increase in early mortality among cancer patients with FN (10).

Management of neutropenia results in additional costs for the patient and healthcare providers. New medications and lengthened hospital stays lead to an additional financial burden for the patients and their guardians. Higher chances of morbidity and mortality weigh down the patients causing them emotional agony and physical pain (11).

1.3 Research questions

1. What is the incidence of Chemotherapy-induced neutropenia among cancer patients with solid tumors receiving chemotherapy at Kenyatta National Hospital- Cancer Treatment Centre (KNH-CTC)?
2. What are the risk factors associated with chemotherapy-induced neutropenia among cancer patients with solid tumors receiving chemotherapy at KNH-CTC?
3. What are the interventions against chemotherapy-induced neutropenia among cancer patients with solid tumors who have received chemotherapy at KNH-CTC?

1.4 Study objectives

1.4.1 General objective

The main objective in this study was to determine the incidence and management of chemotherapy-induced neutropenia among cancer participants who had received their first course of chemotherapy at Kenyatta National Hospital- Cancer Treatment Centre (KNH-CTC).

1.4.2 Specific objectives

The specific objectives of the study were;

i. To determine the incidence of neutropenia among cancer patients with solid tumors who had received chemotherapy at KNH-CTC between January and March 2016.
ii. To identify the risk factors associated with chemotherapy-induced neutropenia among cancer patients with solid tumors receiving chemotherapy at KNH-CTC.
iii. To identify the management strategies used to manage chemotherapy-induced neutropenia among cancer patients with solid tumors at KNH-CTC.

1.5 Justification of the study

Chemotherapy-induced neutropenia (CIN) is not a new problem among cancer patients. Due to their compromised immunity, cancer patients remain at high risk of infection.

Not all cancer patients suffer from neutropenia. A 2017 study among cancer patients with solid tumors at Moi Teaching and Referral Hospital (MTRH) found a prevalence of neutropenia of 10.5% (12). There have been few if any, studies on incidence of neutropenia in African and specifically Kenyan settings, making this study timely.

Prevalence rates vary depending on several local factors. Key among them is the type of chemotherapy administered. Age, nutritional status, co-morbidities are other key factors. Collection of data regarding nutritional factors and other key lifestyle factors such as smoking and alcohol consumption was key in informing recommendations from this study.

This study aimed at ascertaining the incidence of CIN among cancer participants on chemotherapy in KNH. Management strategies used for CIN were also derived.

CHAPTER TWO: LITERATURE REVIEW

2.1 Introduction

Hematopoiesis is the process by which blood cells are formed in the bone marrow and the lymphoid tissue. Formation of white blood cells in the bone marrow is an active and continuous process (13). Decrease in the formation of neutrophils, one of the types of white blood cells, leads to neutropenia.

Neutropenia refers to a decrease in the number of white blood cells in the body. It is specifically defined as an absolute neutrophil count (ANC) of 1.5 $*10^9$ cells/litre or an ANC that is expected to decrease to below 1.5 $*10^9$ cells/litre over the next 48 hours (14). Since white blood cells form the main line of defense against infection, neutropenia increases one's risk to infection (11)

Neutropenia is mostly accompanied by fever. This type of fever refers to a single oral temperature above or equal to 38.3° C or a temperature above or equal to 38.0°C sustained over a period of one hour.

Neutrophils are a type of white blood cells representing 40-70% of all WBCs. They form the primary line of defense. Upon infection or inflammation, neutrophils migrate to the affected site and intervene by producing lytic enzymes and phagocytosis (15).

Neutropenia arises from disorders secondary to impairment in the production, distribution or rapid breakdown of neutrophils. Of these, the main causative factor is decreased production.

2.2 Epidemiology of chemotherapy induced neutropenia

Morbidity and mortality from CIN vary from one group of patients to another depending on their cancer type and chemotherapy administered (16). Further, the risk of neutropenia may depend on one's ethnicity, with Africans at greatest risk (17).

A study on incidence of CIN in two Indian hospitals, in 2012,reported that 46% of all cancer participants had grade 3 or 4 neutropenia while 15 % had febrile neutropenia (18).

Reporting their findings in 2007, after a three-year prospective study, researchers at an Italian children hospital estimated that fever complicated 34% of all cases under study and that less than one febrile episode occurred for every 30 neutropenic days at risk. They further observed that the incidence and rate of febrile complications varied with the phase of treatment (19).

Fever occurs frequently in CIN in 80% of participants with hematological malignancies. Between 10% to 50% of patients with solid tumors develop fever during more than one of their chemotherapy cycles (20).

Clinical manifestations of infections have been detected and recorded in 20-30% of patients with FN with bacteremia being detected in 10-25% of patients with neutropenia(21). The risk of early mortality due to FN is around 35% (10).

2.3 Types of neutropenia

Neutropenia can be classified as that which arises from intrinsic and extrinsic factors. Intrinsic factors refer to a primary hematological disease while extrinsic factors include infection, drugs and radiation. Neutropenia due to drug toxicity is the most frequent (22). A classification of causes is tabulated below (Table 2.1).

Table 2 1: Causes of neutropenia and corresponding examples (23)

Cause	Example
Primary hematological disease	
Congenital	Kostmann's syndrome Cyclic neutropenia
Acquired	Acute myeloid leukemia Chronic lymphocytic leukemia Aplastic anemia
Secondary disorders	
Immune	Allo-immune neutropenia Iso-immune neutropenia Autoimmune neutropenia As part of autoimmune diseases
Infections – viral, bacterial and protozoan	Cytomegalovirus, HIV, Brucellosis
Drugs- anticonvulsants, antipsychotics, anti-rheumatic, antimicrobial.	Carbamazepine Penicillins Sulphonamides olanzapine
Nutritional deficiency	Vitamin B 12 deficiency Folic acid deficiency

2.4 Grades of neutropenia

The common toxicity criteria designed by the US National Cancer Institute is the most frequently used criteria for grading CIN (16).

Table 2 2: Grades of neutropenia.

GRADE	ABSOLUTE NEUTROPHIL COUNT($\times 10^9$)
0	Within normal limit
1	≥1.5<2.0
2	≥1.0<1.5
3	≥0.5<1.0
4	<0.5

2.5 Chemotherapy induced neutropenia (CIN)

Chemotherapy-induced neutropenia and febrile neutropenia are the most frequent hematologic complications in patients undergoing chemotherapy. They cause one's dose to be adjusted thereby affecting optimum clinical outcomes. Some patients may develop higher susceptibility to infections and hence short-term mortality (18).

Despite new interventions, FN and CIN remain oncological emergencies. FN causes complications that are life threatening often leading to high cases of morbidity, mortality and costs. The result is a reduction in relative dose intensity or a complete change to a lesser optimum protocol for the specific malignancy. Optimal patient outcomes are therefore delayed or missed altogether (24).

2.5.1 Signs and symptoms of CIN

Patients who might have developed neutropenia may not be aware of their condition. They normally find out after a blood test. A minor infection can turn fatal. Various signs and symptoms enable clinicians to make an initial diagnosis of neutropenia (13).

A fever which is 38°C or higher coupled with chills and profuse sweating are pointers to an infection. The patient might also complain of a sore throat and toothaches. Other symptoms include infections of the middle ear, tonsillitis, skin abscesses and ulcers of the oral mucosa (25).

Occasionally, patients will complain of painful urination and abdominal pain. Some of this pain may be alleviated for a short period and then re-occur.

Approximately half the patients who have developed neutropenia will have a cough with shortness of breath. A careful inspection will reveal inflammation around small cuts and wounds and unusual vaginal discharges in some female patients.

Patients who are hospitalized with neutropenia are at risk of nosocomial infections arising from clostridium defficile infection (26).

2.5.2 Pathophysiology of CIN

Various mechanisms are involved in development of Chemotherapy-induced neutropenia.

Reduction in the efficient production of white blood cells due to a problem in the bone marrow: This is the foremost explanation for a reduction in white cell count (27). An initial examination using a fine needle biopsy would reveal possible malfunction of the bone marrow. Although advances have been made in the practice of fine needle biopsy, the procedure is prone to risks. Hemorrhage, infection and needle related incidents have been reported (28).

Margination: This results from the migration of circulating neutrophils from blood vessels to tissues. The process of transmigration may be triggered by various factors including injury and infection. Migration of neutrophils is aided by leucocyte-endothelial adhesion molecules. These include selectins, integrin and immunoglobulins (29). This migration is common in splenomegaly. A physical examination of the spleen or an x-ray of the spleen may be necessary.

Immune mediated destruction of neutrophils: This happens where drug molecules or its reactive metabolite binds onto the neutrophil membrane leading to its death.

Direct toxicity on granulocytic precursors: Some drugs bind directly and damage myeloid precursors in the bone marrow.

2.5.3 Risk factors for CIN

Different risk factors have been found to increase the likelihood of developing CIN and FN. These factors may be inherent in the nature of the patient or the tumor.

These risk factors can be classified as patient specific and treatment specific (30).

Patient specific risk factors

Age: Various studies have found higher age to be a general risk factor for severe neutropenia and accompanying complications. The overall functional efficiency of multiple organs is marginally reduced as one grows old. A decline in glomerular filtration rate is mostly observed. This affects the excretion of some cytotoxic drugs leading to a higher concentration in the body. Such drugs include methotrexate, bleomycin and carboplatin. Cancer patients with advanced age are usually treated with lower doses of chemotherapy to minimize chances of suffering from neutropenia (31).

Co-morbidities: Heart disease and renal disease have been shown to increase the risk of neutropenia in certain categories of cancer patients. Heart, liver and kidney diseases were particularly useful predictors of the risk of neutropenia among patients who have been diagnosed with breast cancer (32). Blood cell counts has been observed to reduce significantly in patients with chronic kidney injury. White cell count also tends to decrease, leading to neutropenia (33). Hypertension has been found to increase the risk of serious neutropenic effects and therefore high risk of morbidity (34).

HIV infection has been found to be an important risk factor for neutropenia (35). This is because the infected patient's immune system is compromised leading to neutropenia. The synergy from cytotoxic effects of chemotherapy leads to enhanced myelosuppression (36).

Patients who have a prior history of bacterial, viral or fungal infection or previous hospitalization have been found to be at a higher risk of neutropenia. Generally, older patients have more co-morbidities. These co-morbidities exert a negative influence on survival (37).

Performance status: Performance status refers to one's physiological age or frailty. It tends to decrease as one's actual age increases. Performance status of a patient may be classified as poor or good. If poor, the patient may be at higher risk of developing neutropenia.

Laboratory abnormalities: Previous white blood cell counts are predictive of the likelihood of neutropenia. Hemoglobin levels below 12g/dl can also guide one in predicting neutropenia. High low density lipoprotein (LDL) levels are also useful markers for determining the likelihood of neutropenic episodes.

Treatment specific factors

Type of chemotherapy regimen: Some chemotherapy regimens are more intense than others and therefore a higher chance of neutropenia. Those regimens that contain cyclophosphamide and anthracycline have been identified as presenting the highest risk (38).

The first cycle of chemotherapy presents a higher risk of developing neutropenia than subsequent cycles (39). This may be due to lower tolerability levels at the onset of chemotherapy.

Higher dose intensity also exposes the patients to higher risks of developing neutropenia.

Administration of colony stimulating factor (CSF): Several studies have shown that administration of a CSF leads to decreased chances of developing neutropenia.

2.6 Grading of febrile neutropenia- Common Terminology Criteria for Adverse Events (CTCAE)

CTCAE is formulated by the U.S Department of health and human services' National

Institutes of Health and the National Cancer Institute.

This grading system classifies Adverse Events (AEs) into 5 grades; Mild AEs are placed in

Grade 1, moderate Grade 2, severe Grade 3, life threatening Grade 4 and death related Grade 5.

Febrile neutropenia is graded as tabulated below.

Table 2 3: Grading of Febrile neutropenia according to the Common Terminology Criteria for Adverse Events (40)

Febrile neutropenia	Grade	Characteristics	Nature
	1	-	
	2	-	
	3	ANC 38.3 degrees C (101 degrees F) or a sustained temperature of >=38 degrees C (100.4 degrees F) for more than one hour.	severe
	4	Life-threatening consequences; urgent intervention indicated	Life-threatening
	5	Recovery is improbable	Death-related

2.7 Diagnosis of neutropenia

Neutropenia is defined as an absolute neutrophil count of less than 1.5 $*10^9$ /litre. A laboratory determination of neutropenia can be done by carrying out a complete blood count (CBC), bone marrow examination, neutrophil antibody and antigen testing and genetic testing (41).

2.7.1 Complete blood count (CBC)

Complete blood count is the primary test for determining if one has neutropenia. A leukocyte differential count is done in addition to the CBC in patients with acute or mild fevers or for general check-up. In patients with mild neutropenia and no other underlying factors, a repeat CBC is necessary.

Severity and duration of neutropenia is made by at least three or more determinations over a three month period. Studies among Africans have revealed different laboratory results (42).

2.7.2 Examination of the bone marrow

Examining the bone marrow is essential to determine the cause of myelo-suppression in neutropenic patients.

A bone marrow smear is particularly helpful in staging the defect causing the neutropenia. A cytogenic examination may also be helpful to reveal complications such as MDL and AML.

2.7.3 Neutrophil antibodies and antigens

Anti-neutrophil antibodies may be tested by immuno-florescence, flow cytometry or agglutination. This test may be helpful to detect auto-immune neutropenia. Determination of parental neutrophil antigens may be necessary to diagnose neonatal allo-immune neutropenia (43).

2.7.4 Other laboratory tests

Additional laboratory tests are necessary to determine nutritional deficiencies such as vitamin B12, folate or copper. They also reveal Immune deficiencies, such as quantitative immunoglobulins and rheumatologic disorders.

2.8 Management of neutropenia

2.8.1 European Society of Medical Oncology (ESMO) guidelines

Febrile neutropenia is defined by ESMO as an oral temperature that is higher than 38.5° C or two consecutive readings that are higher than 38° C for 2 hours or a neutrophil count below 0.5 x 10^9/l (44). Successful management of FN requires prompt detection and treatment.

Patients should be educated on how to monitor their body temperatures and where to seek medical attention. An initial assessment is vital to determine the type of chemotherapy, prior antibiotics taken for prophylaxis and any allergies patients might have. Recent surgical history is also key.

Initial assessment and investigations also involves the assessment of signs and symptoms suggesting any infections in regards to the respiratory, gastrointestinal and central nervous systems, and the skin. A comprehensive assessment will involve examination of previous microbiological results and routine investigations.

Routine examinations involve testing of the blood to assess the competency of the bone marrow. Further tests may be done to deduce the kidney and liver function. A stool test and urinalysis may also reveal an infection. Examination of skin lesions and the chest using a chest radiography are also key. Coagulation screening may also be done during routine examination. Further investigations may be done as needed.

After assessment, an MASCC (Multinational Association for Supportive Care in Cancer) scoring index is used to classify patients as either low or high risk. The MASCC scoring index is as tabulated below.

Table 2 4: The MASCC scoring index for patients at risk of neutropenia (45).

	Score
Burden of illness: no or mild No hypotension (systolic BP >90 mmHg)	5
Burden of illness: moderate symptoms	3
Symptoms Burden of illness: severe symptoms	0
No chronic obstructive pulmonary disease	4
Solid tumor/lymphoma with no previous fungal infection	4
No dehydration	3
Outpatient status (at onset of fever)	3
Age <60 years	

Scores > 21 are at low risk of complications.

Low risk patients

These are managed at outpatient settings using a fluoroquinolone or in combination with amoxicillin/clavulanic acid. The combination is preferred due to the risk of infection from gram-positive as well as gram-negative bacteria.

High risk patients

They are normally treated within the hospital using antibiotics effective against gram positive and gram negative bacteria. Antibiotics are selected depending on culture results and susceptibility to resistance. Once a day antibiotics such as teicoplanin are considered. If the neutrophil count is above 0.5 * 109/l and the patient is afebrile for more than 48 hours, and the blood cultures are negative for bacteria, antibiotics can be discontinued.

2.8.2 American Society of Clinical Oncology (ASCO) guidelines

ASCO recommends that antibacterial and antifungal prophylaxis be given only to patients whose neutrophil count is less than $1.0* 10^9$/litre for more than 7 days. This is applicable where no other risk factors are assessed (46).

Patients with a MASCC score of more than 21 and are placed in Talcott group 4 with no other secondary risk factors are considered low risk hence managed in an outpatient setting.

For this cohort of patients, an empirical treatment with a fluoroquinolone for bacterial prophylaxis and an oral tri-azole for fungal prophylaxis are considered. Amoxicillin plus clavulanic acid (or clindamycin for patients allergic to penicillin) should be added to the fluoroquinolone unless a fluoroquinolone had been used prior to the onset of the fever.

2.8.3 Granulocyte colony stimulating factor (G-CSF)

Routine administration of G-CSF to afebrile patients with severe neutropenia can be helpful. It serves to reduce the duration of neutropenia among these patients thereby decreasing the number of days one would require hospitalization (47). Adding a G-CSF to the patient's treatment plan has been found to reduce cases of febrile neutropenia by up to 50% (48).

The use of relative dose intensive (RDI) chemotherapeutic regimens leads to an increased risk of myelo-suppression. In these circumstances, it has become necessary to administer recombinant colony stimulating factors to enhance production of granulocytes. This may be done during the period the patient would be expected to develop neutropenia. Use of a G-CSF is especially essential where limiting the dose of chemotherapy that causes neutropenia, would be detrimental (49).

When used together with prophylactic antibiotics, CSFs have been found effective in severe febrile neutropenia. However, they have not been shown to reduce mortality rates or hospital stay durations. Therefore, despite a number of physicians prescribing them, ASCO has not recommended routine use of CSFs in febrile neutropenia.

2.8.4 Prophylactic antibiotics and anti-fungals

CIN and FN can be life-threatening conditions which may require administration of empirical broad-spectrum antibiotics (50).

The infectious diseases society of America (IDSA) has recently recommended use of antibiotics for prophylaxis against neutropenia among cancer patients. High risk patients ought to have antibiotics empirically administered in the inpatient settings while low risk patients can have the antibiotics administered from an outpatient settings (51). The determination of the risk levels is done through a scoring mechanism such as MASCC scoring index.

Administration of antibiotics should be done with caution because of the risk of renal injury associated with many antibiotics. This is an important considering the reverse risk renal injury has on neutropenia.

The IDSA guidelines recommend commencement of antifungal therapy for patients whose febrile neutropenia exceeds 5 days. Amphotericin is considered the first line drug of choice. However, other anti-fungal drugs such as itraconazole, voriconazole and caspofungin may be chosen (52).

2.8.5 Deferral of chemotherapy

Due to the risk of bone marrow suppression following administration of chemotherapy, some patients inevitably develop neutropenia. Sometimes the neutropenic effects may be so severe as to lead to deferral of their chemotherapy. Deferral in treatment may lead to deterioration in the health of the patient in addition to psychological effects and additional financial costs.

Despite the risk of cancer progression, most clinicians would be wary to continue chemotherapy until the patient has recovered from neutropenia.

Such a deferral would be necessary to allow time to boost the levels of neutrophils which are the first line of defense against infection (52). Deferral can also be helpful in that it allows time for the patients to cope with adverse effects of chemotherapy.

CONCEPTUAL FRAMEWORK.

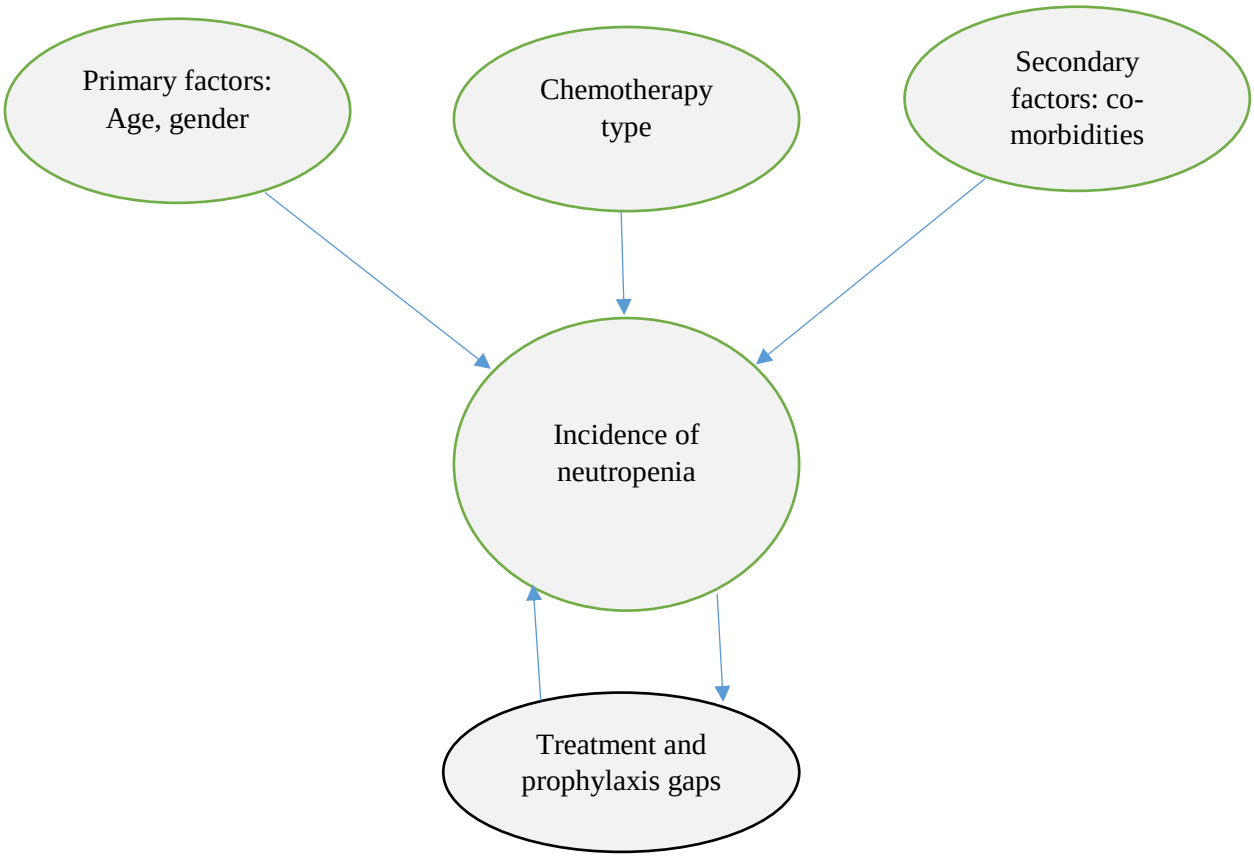

Figure 2.1: Conceptual framework

This study was anchored on four areas. These are; determination of incidence, identification of risk factors for developing chemotherapy-induced neutropenia, management strategies and gaps in management of CIN.

The incidence of chemotherapy-induced neutropenia is dependent on primary and secondary risk factors as well as the chemotherapy type administered. A higher incidence will be associated with gaps in treatment and prophylaxis, and vice versa.

CHAPTER THREE: METHODOLOGY

3.1 Study design

This was a retrospective observational cohort study to assess the incidence and management of CIN among cancer patients with solid tumors who were started on chemotherapy in the months of January, February and March 2016. The participants' records were reviewed for a period of one year or until the date of discharge if the participant was discharged before one year elapsed.

3.2 Study setting

The study was conducted at the Kenyatta National Hospital between May 2018 and August 2018. The hospital is a referral university hospital with a bed capacity of 2000. It is located in Nairobi serving a population of over 4 million people. It is one of the few public health facilities in Kenya where patients can obtain advanced comprehensive treatment for cancer. It therefore has high demand for services. Records indicate that there are approximately 30 new cancer patients every week, with 50 patients admitted into the oncology wards and about 100 patients attended at the outpatient clinic daily.

3.3 Participant selection

All patients who met the criteria and who were attended to between January and March 2016 were selected to participate in this study.

3.3.1 Target population

The study targeted cancer patients on chemotherapy who were aged 18 years above, and being attended to at the Kenyatta National Hospital Cancer Treatment Center (KNH-CTC).

3.3.2 Participant's inclusion criteria

Participants were enrolled into this study if they met the following criteria:

i. Availability of participants' records.
ii. Participant aged between 18 years and above.
iii. Participants that had confirmed diagnosis of a malignant solid tumor by histopathology.
iv. Participants who were on their first cancer treatment regimen.
v. Participants who had not been diagnosed with neutropenia prior to starting their chemotherapy.

3.3.3 Exclusion criteria

i. Participants who had a prior exposure to chemotherapy.
ii. Participants whose absolute neutrophil count was <1.5 x10^9/l prior to administration of chemotherapy

3.4 Sampling and sample size determination

A study by Kawinzi in 2015 in a Kenyan setting found a prevalence rate of 10.5% of chemotherapy induced neutropenia(12).

The sample size for this study was estimated using the formula suggested by Cochran (53).

$$n = \frac{pqz^2}{e^2}$$

Where

n is the sample size

p is the prevalence of neutropenia

q is the level of precision that is 1-p

z is the standard deviation for 95% confidence interval which is 1.96

e is the allowable margin of error that is 5%

$$n = \frac{0.105\ x\ (1-0.105) x\ 1.96^2}{0.05^2}$$

= 144

Adjusting for a 20% attrition rate

$$n = \frac{120}{100} x\ 144 \quad = 173 \text{ files}$$

Convenient sampling was done until the desired sample size is achieved.

3.5 Data collection

A data abstraction form (appendix B) was used for data collection. The information collected included data on participants' biodata, type of cancer, neutrophil count, type of chemotherapy, co-morbidities and interventions for neutropenia.

3.6 Participant selection

The head of the records department was requested to provide a list of all patients seen at the cancer treatment centre between January and March 2016. These files were quickly perused to determine if the patients met the eligibility criteria.

Records of the full haemogram before initiation of chemotherapy were used to exclude those who had neutropenia prior to initiation of chemotherapy.

3.7 Data management

Once data was collected, it was entered into an excel sheet within 24 hours of data collection. Double data entry was conducted. The entered data was coded with the guide of a code book. The data was password-protected to ensure confidentiality. The database was evaluated for inconsistencies and any discrepancies reconciled after checking the source documents.

All hard copies were stored in a lockable cabinet by the investigator with restricted access. The data was backed-up daily in a google cloud that is password-protected. Additional back-up was done onto a CD-ROM and stored in a site different from the primary data.

The primary data set did not have participant identifier information such as the name, address, and telephone number. Identifier information was stored separately by the principal investigator.

3.8 Data analysis

Descriptive data analysis was carried out using Stata® version 13(Stata Corp, USA). Categorical variables were summarized as frequencies and proportions. Continuous variables were first tested for normal distribution using the shapiro-wilk test. Variables that were normally distributed were summarized as the mean and standard deviation of the mean. Variables that were not normally distributed were summarized as the median and interquartile range.

Exploratory data analysis was conducted whereby the traits of participants who experienced neutropenia and those who did not were compared. Cox regression analysis was conducted to identify the key risk factors for the first episode of neutropenia. Multi-variable analysis was done to adjust for confounding. The main co-variates of interest were socio-demographic characteristics, neutrophil counts and other variables that were statistically significant on exploratory data analysis.

Survival analysis was done for participants on the most risky chemotherapy regimens. Data analysis was done using STATA version 13. The level of significance was set at 5%.

3.9 Ethical approval

Approval for the study was sought and granted by the Kenyatta National Hospital/University of Nairobi Ethics and Research Committee (KNH-UoN-ERC) (Approval number -KNH-ERC/A/160).

To ensure privacy and confidentiality, information collected was not directly linked to the respective participants, names of participants were not used. Codes were used as identifiers. In addition, all information collected was kept under lock and key by the researcher.

With regards to risks, this was low-risk study because it was retrospective and there were no interventions on the participants. The only potential risk to the participants was loss of privacy. However, this was safeguarded by only extracting information in the records department and putting in place prudent data management systems.

There were no direct benefits to the participants but the findings of the study can be used by cancer caregivers and policy makers to improve management of cancer patients.

CHAPTER 4: RESULTS

4.1: Participant selection

A total of 200 participants were initially selected. Out of these, only 173 were included, having met the inclusion criteria. The reasons for exclusion of the remaining files are presented in the Consort diagram in Figure 4.1.

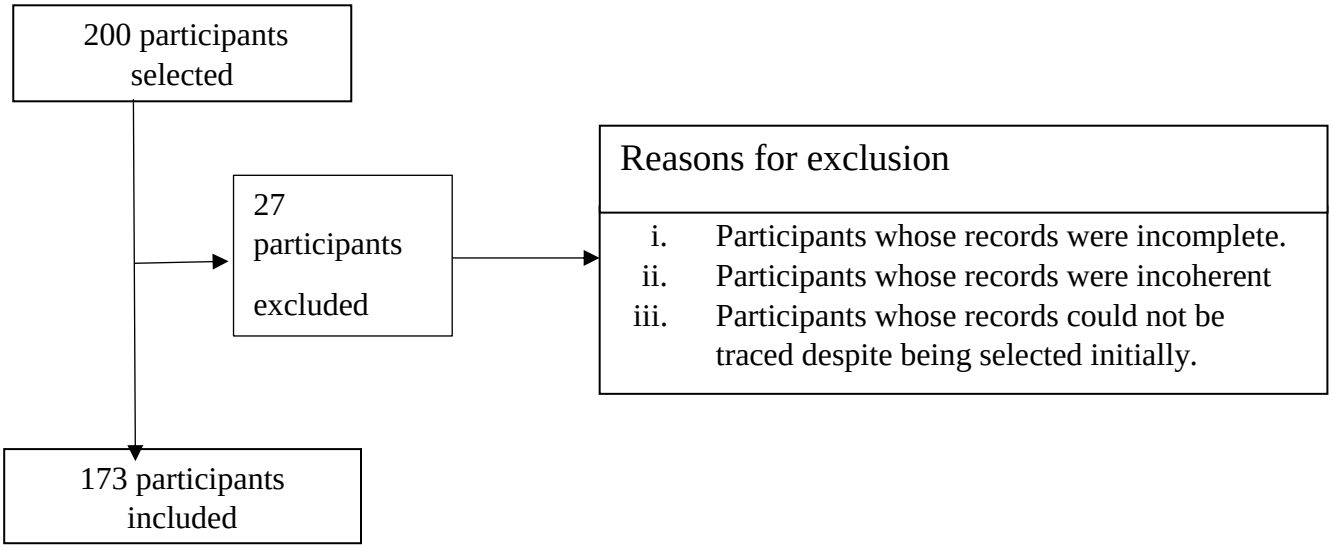

Figure 4.1: Consort diagram for recruitment of participants

4.2: Socio-demographic characteristics of participants on chemotherapy

The mean age of participants diagnosed with cancer was 53 years while the median age was 51 years. Majority of participants were aged 50 years and above (50.9%).

Most participants had a normal body mass index (70, 40.5%). Majority reported being married (108, 62.4%). Regarding levels of education, most reported having only attained a primary or lower level of education (95, 54.9%). In terms of residence, the majority reported to have lived in a rural-urban or completely urban setting in the preceding two years (83, 48%). The socio-demographic characteristics of the participants are summarized in Table 4.1.

Table 4 1: Socio-demographic characteristics of participants

Variable		**n**	**Percent (%)**
Age:	18-≤35 years	17	9.8
	35-≤50 years	68	39.3
	>50-≤65 years	55	31.8
	>65years	33	19.1
	Total	**173**	**100**
Gender:	Male	74	42.8
	Female	99	57.2
	Total	**173**	**100**
Marital status	Single	43	24.9
	Married	108	62.4
	Divorced	4	2.3
	Widowed	18	10.4
	Total	**173**	**100**
Education	Primary	95	54.9
	Secondary	55	31.8
	College and university	23	13.3
	Total	**173**	**100**
Occupation	Unemployed	58	33.5
	Housewife	28	16.2
	Self-employed	66	38.2
	Employed	21	12.1
	Total	**173**	**100**
Residence	Rural	83	48
	Rural-Urban	50	28.9
	Urban	40	23.1
	Total	**173**	**100**
BMI	Underweight, <18	35	20.2
	Normal, 18-25	70	40.5
	Overweight, 25-30	37	21.4
	Obese > 30	31	17.9
	Total	**173**	**100**

4.3: Types of cancer and co-morbidities among the participants

The types of cancers diagnosed among patients recruited in the study were as tabulated in table 4.2.

Table 4.2: Summary of main cancer types diagnosed among participants

Cancer type	Number	percentage
Breast	48	27.8
Cervical	23	13.3
Colon	21	12.1
Prostate	14	8.1
Nasopharyngeal	11	6.4
Esophageal	9	5.2
Lung	6	3.5
Bladder	6	3.5
Neuroendocrine	4	2.3
Buccal	3	1.7
Tongue	3	1.7
Uterine	2	1.2
Kaposi sarcoma	2	1.2
Stomach	2	1.2
Ovarian	2	1.2
Unknown origin	2	1.2
TOTAL	173	100

Most participants were diagnosed with breast (27.75%), cervical (13.29%), colon (12.14%), prostrate (8.09%) and nasopharyngeal cancer (6.36%). Breast, cervical and colon cancers accounted for more than half of all cancer cases in this study (53.44%).

4.4: Co-morbidities among participants

Nearly 90% of the participants did not have co-morbidities (152, 88.4%) recorded in their files. Out of the remaining participants, hypertension was the most prevalent at 8 (4.7%) followed by diabetes (4, 2.3%). Figure 4.2 summarizes the co-morbidities recorded in the participants' files.

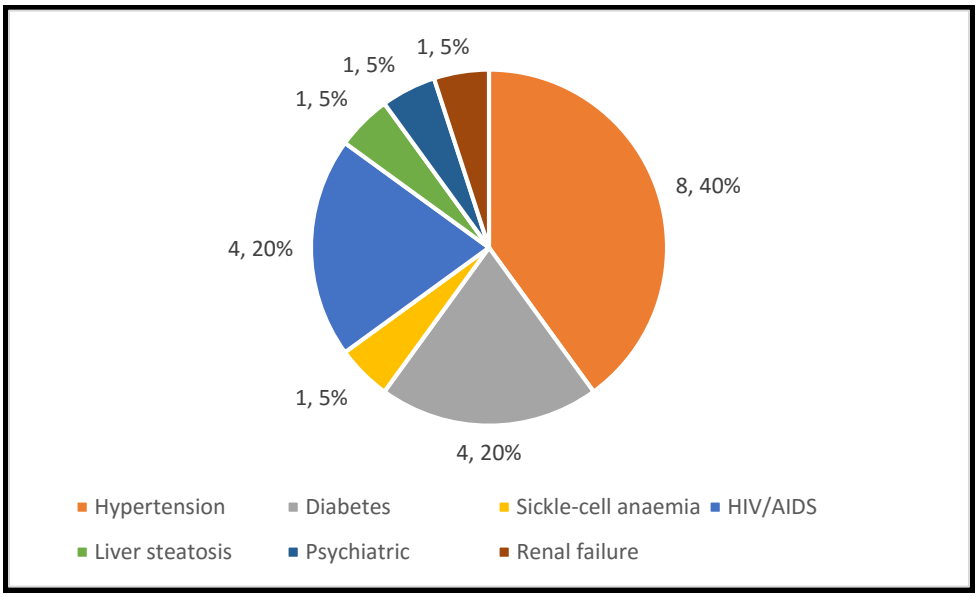

Figure 4. 2: Co-morbidities diagnosed among participants

The participants in this study who might have these co-morbidities were also assigned to other clinics and so the records of their actual ailments were mostly missing in their cancer treatment files.

4.5: Types of chemotherapeutic regimens

Most participants were treated with cisplatin-paclitaxel combination (31, 17.9%), cyclophosphamide-doxorubicin (20, 11.6%) and paclitaxel-carboplatin (12, 6.9%). Some participants were treated with one chemotherapeutic agent. Paclitaxel (31, 17.9%) and Cisplatin (16, 9.2%) were the most commonly used individual agents. Table 4.3 provides a summary of the types of chemotherapy that were administered on the participants.

Table 4 3: Combinations of chemotherapeutic agents used for cancer management

Chemotherapy	n	Percent	Totals per regimen
Cisplatin-based regimens			
Cisplatin + oxaliplatin + epirubicin + capecitabine	1	0.6	
Cisplatin + epirubicin+ capecitabine	3	1.7	53 (30.6%)
Cisplatin + docetaxel+ fluorouracil	1	0.6	
Cisplatin+ paclitaxel	31	17.9	
Cisplatin+ docetaxel	1	0.6	
Cisplatin alone	16	9.2	
Cyclophosphamide-based regimens			
Cyclophosphamide + doxorubicin + 5- Fluorouracil	10	5.7	
Cyclophosphamide + doxorubicin + docetaxel	3	1.7	37 (21.4%)
Cyclophosphamide + doxorubicin	18	10.4	
Cyclophosphamide + 5-fluorouracil	2	1.2	
Cyclophosphamide + fluorouracil + methotrexate	4	2.4	
Paclitaxel-based regimens			
Paclitaxel+ docetaxel	1	0.6	
Paclitaxel + carboplatin	12	6.9	44 (25.4%)
Paclitaxel only	31	17.9	
Oxaliplatin-based regimens			
Oxaliplatin + 5-fluorouracil	10	5.7	
Oxaliplatin + capecitabine	8	4.6	29 (16.7%)
Oxaliplatin + gemcitabine	4	2.3	
Oxaliplatin + epirubicin	7	4.0	
Gemcitabine-based regimens			
Gemcitabine + carboplatin	4	2.3	6 (3.4%)
Gemcitabine + docetaxel	2	1.2	
Docetaxel-based regimens			
Docetaxel + carboplatin	4	2.3	4 (2.3%)

The drugs most frequently administered were used as the base drugs upon which the analysis of regimens was done. Cisplatin, cyclophosphamide and paclitaxel were the most frequently administered.

The main regimens used to manage breast cancer were cyclophosphamide-doxorubicin (CA) (20/48%) and cyclophosphamide-Adriamycin-5-fluorouracil (CAF) (14/48%). Other regimens were paclitaxel and cisplatin as monotherapies or in combination. Due to a small sample and the narrow scope of this study, it was not possible to get a clear trend on all the regimens used to treat breast cancer.

4.6: Incidence of neutropenia amongst participants on chemotherapeutic regimens

Neutropenia was diagnosed in participants whose ANC fell below $1.5 * 10^9$ cells/litre. In this study 47 (27.2%) of the 173 participants studied over a period of one year between January 2016 and March 2017, developed neutropenia. The variation in the incidence of neutropenia by weight category, age and gender is summarized in the bar chart in Figure 4.3.

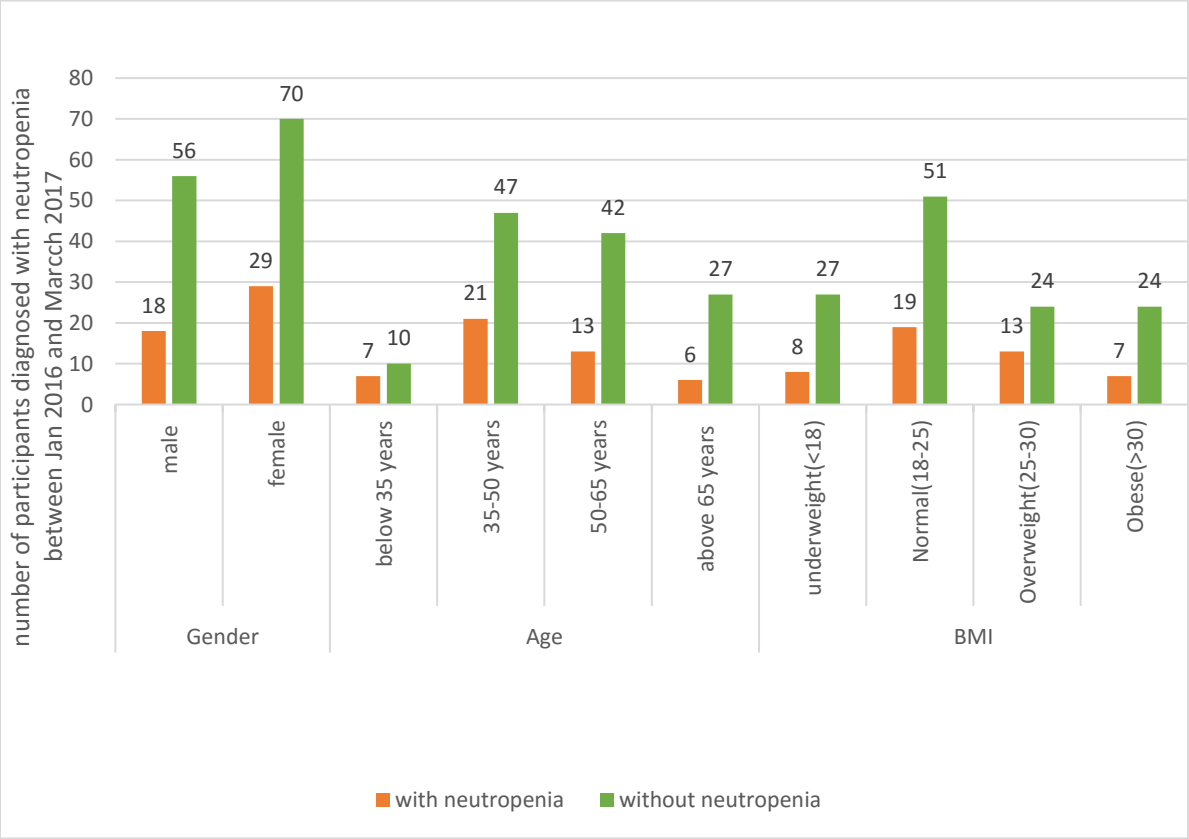

Figure 4. 3: Incidence of neutropenia by gender, age and body mass index.

Most participants with neutropenia were women (61.7%). The majority of patients with neutropenia (85.1%) were aged 35 years and above and most had a normal body mass index (53%).

4.7: The Incidence and association between individual chemotherapeutic agents and neutropenia

Table 4 4: Bivariate analysis of chemotherapeutics and neutropenia.

Chemotherapy	Percentage developed neutropenia between Jan. 2016 and March 2017	Crude odds ratio(95% CI)	P value
Cyclophosphamide	16 (34.04%)	2.91 (1.34, 6.32)	0.007
Doxorubicin	15 (31.91)	2.34 (1.08, 5.07)	0.031
Cisplatin	13 (27.66)	0.74 (0.35, 1.54)	0.42
Paclitaxel	12 (25)	0.86 (0.40, 1.84)	0.691
Carboplatin	4 (18.18)	0.56 (0.18, 1.74)	0.316
Oxaliplatin	10 (21.28)	1.52 (0.65, 3.57)	0.334
Docetaxel	1 (2.13)	0.115 (0.02, 0.88)	0.038
Epirubicin	4 (8.51)	1.37 (0.39, 4.79)	0.620

Table 4.4 presents the incidence of neutropenia by chemotherapeutic agent. It also presents the crude measure of association between individual agents and neutropenia.

Nearly a third of participants treated with either cyclophosphamide (34.04%) or doxorubicin (31.91%) developed neutropenia as presented in Table 4.4. There was a strong positive association between each of these two drugs and neutropenia with crude OR of 2.91 (95% CI 1.34-6.31; p= 0.007) and 2.34 (95% CI 1.08-5.07; p=0.031) respectively. This indicates that these two drugs were the most important predictors of neutropenia.

A negative association is indicative of a protective effect; suggesting that drugs that show a negative association with neutropenia reduce the risk of this adverse effect.

The drugs for which a negative association was observed were cisplatin, carboplatin, paclitaxel, and docetaxel. The only agent whose protective effect was statistically significant was docetaxel, OR 0.12 (95% CI 0.02, 0.88 p= 0.038).

With regards to classes of agents, among the taxanes, paclitaxel was negatively associated with neutropenia. Amongst the platinum-based compounds, an intra-class difference was noted. Cisplatin and carboplatin were less likely to cause neutropenia as opposed to oxaliplatin which was positively associated with neutropenia. The alkylating agent cyclophosphamide was the most myelo-suppressive.

4.8:Multi-variable logistic regression analysis for identification of the most risky chemotherapeutic regimens for neutropenia

Table 4.5 represents the analysis of chemotherapeutic regimens causing neutropenia. The frequency of use, average number of cycles per regimen, mean duration of treatment before diagnosis of neutropenia and intervention most administered are indicated.

The risk of causing neutropenia is presented as the odds ratio. Only three regimens were found to have a significant odds of causing neutropenia. These were, Carboplatin and gemcitabine; OR 11.63 (95% CI: 1.26, 106.91; p=0.03), Cyclophosphamide, doxorubicin and fluorouracil; OR 4.46 (95% CI: 1.2, 16.60; p=0.026), and Cyclophosphamide, 5-fluorouracil and methotrexate OR 11.63 (95% CI: 1.26, 106.91; p=0.03)

Table 4.5: Analysis of risk of neutropenia per regimen

Regimen	Frequency	Average number of Cycles	Mean duration(in days) to neutropenia	Modal Intervention	Crude odds ratio	P value
Carboplatin + gemcitabine	3	6	42	Gcsf	11.63 (1.26-106.91)	0.030
Paclitaxel + cisplatin	10	3.5	55	Gcsf	1.52 (0.65 – 3.57)	0.334
Cyclophosphamide + doxorubicin	11	4.3	43	Gcsf	1.66 (0.61 – 4.52)	0.319
Cyclophosphamide+doxorubicin+ 5 fluorouracil	4	5	36	Gcsf	4.46 (1.2 – 16.60)	0.026
Cyclophosphamide+ 5-fluorouracil + methotrexate	1	2	21	Deferral	11.63 (1.26 - 106.91)	0.030
Paclitaxel+carboplatin	1	2	30	None	1	-
Paclitaxel	2	2	21	Gcsf	1.35 (0.12-15.22)	0.809
Cisplatin+epirubicin +capecitabine	2	4	70	Gcsf	5.56 (0.49 - 62.76)	0.166
Epirubicin+ oxaliplatin	1	5	33	Gcsf	2.72 (0.17 - 44.35)	0.483
Epirubicin +oxaliplatin +capecitabine	1	3.5	26	Gcsf	0.89 (0.09-8.79)	0.921
Gemcitabine + oxaliplatin	2	5	32	None	2.76 (0.38 - 20.15)	0.318
Gemcitabine +vinorelbine	1	6	7	Gcsf	2.72 (0.17 - 44.35)	0.483
5-fluorouracil +oxaliplatin	5	3	26	Deferral	1.86 (0.50 - 6.91)	0.354
Doxo+bleomycin+vinblastin	1	6	13	Gcsf	1	-
Oxaliplatin +capecitabine	1	6	19	Gcsf	0.89 (0.17 – 4.56)	0.888
Capecitabine	1	5	27	Deferral	2.72 (0.17 - 44.35)	0.483

4.9 Survival analysis for participants on regimens with significant risk

Survival analysis was done for the risky regimens to determine the proportion of participants surviving without neutropenia over a duration of time. The results were presented using Kaplan-Meier survival curves. Survival curves are helpful in determining the most appropriate time during treatment to watch out for likely adverse effects (54).

4.9.1 Survival of participants on cyclophosphamide-doxorubicin-fluorouracil (CAF) regimen.

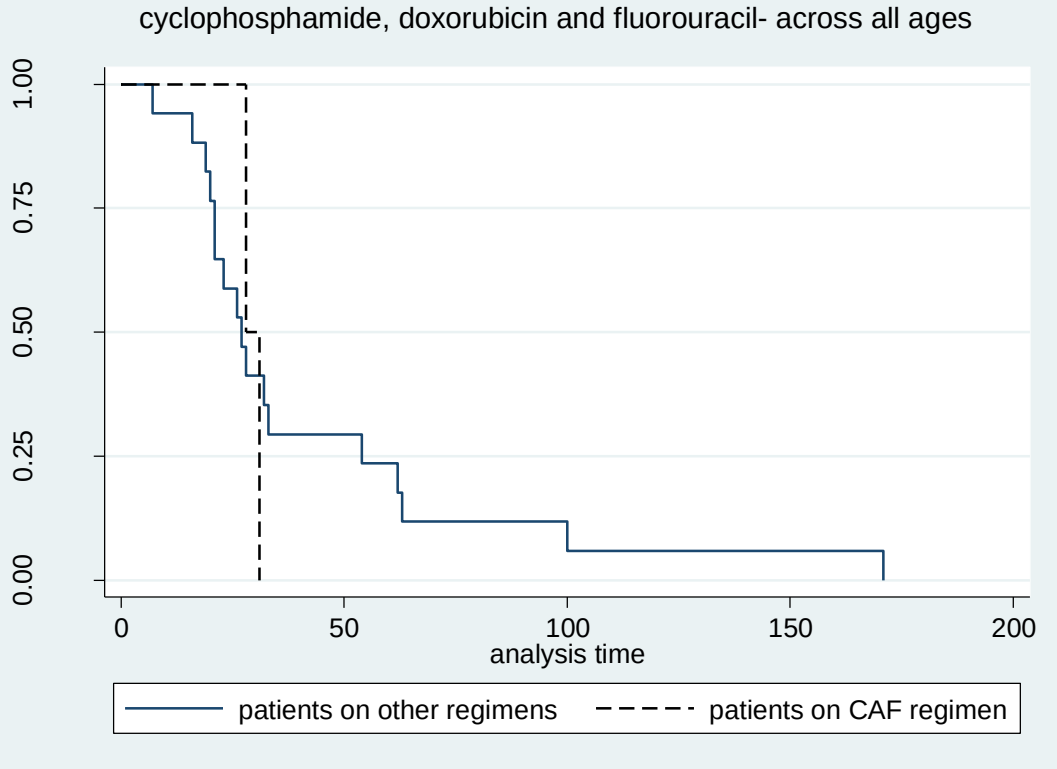

Figure 4.4: survival curve of participants on CAF regimen aged 50 years and above.

Figure 4.4 represents a survival curve for patients on the risky regimen cyclophosphamide-doxorubicin-5-fluorouracil versus patients on alternative regimens.

Although participants on this regimen survive without neutropenia for some time, most develop neutropenia after an average of 30 days. Cyclophosphamide posed considerable risk but when used in combination with doxorubicin, the risk was markedly reduced (from OR 6.64 (95% CI: 0.66, 67.15; p=0.109) to OR 2.91 (95% CI: 1.34, 6.31; p= 0.007). Addition of fluorouracil resulted in a high risk of neutropenia (OR 4.46 (95% CI; 1.12, 16.60, p=0.026).

The additive neutropenic effects of cyclophosphamide and fluorouracil explain the steep survival curve.

4.9.2 Survival of participants on cyclophosphamide-5-fluorouracil-methotrexate (CMF) regimen.

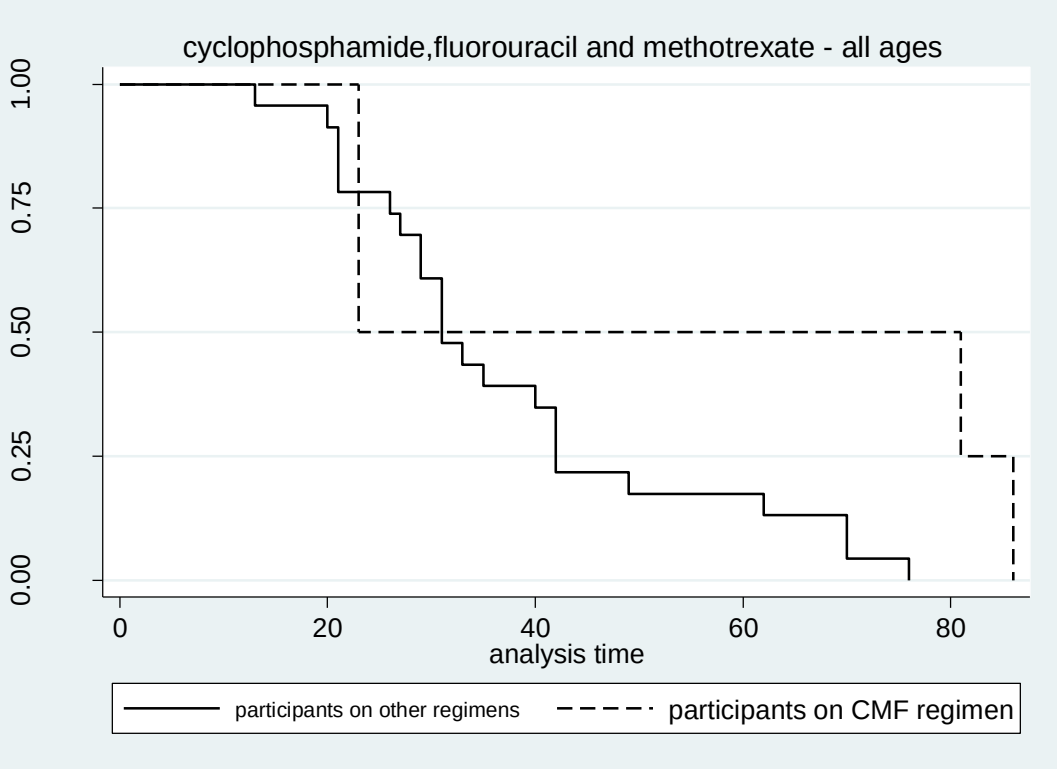

Figure 4.5: survival curve of participants on CMF regimen.

Figure 4.5 represents participants on cyclophosphamide, fluorouracil and methotrexate regimen versus patients on alternative regimens. 50% of the participants developed neutropenia within 25 days while the rest were affected between 80^{th} and 85^{th} day.

4.9.3 Survival of participants on gemcitabine-carboplatin regimen

Figure 4.6 represents the survival of participants treated with carboplatin and gemcitabine and those not on this combination for all ages. 50% of all participants on this combination had developed neutropenia by day 23. This is in comparison to the patients on other regimens who developed neutropenia after the 30th day of treatment.

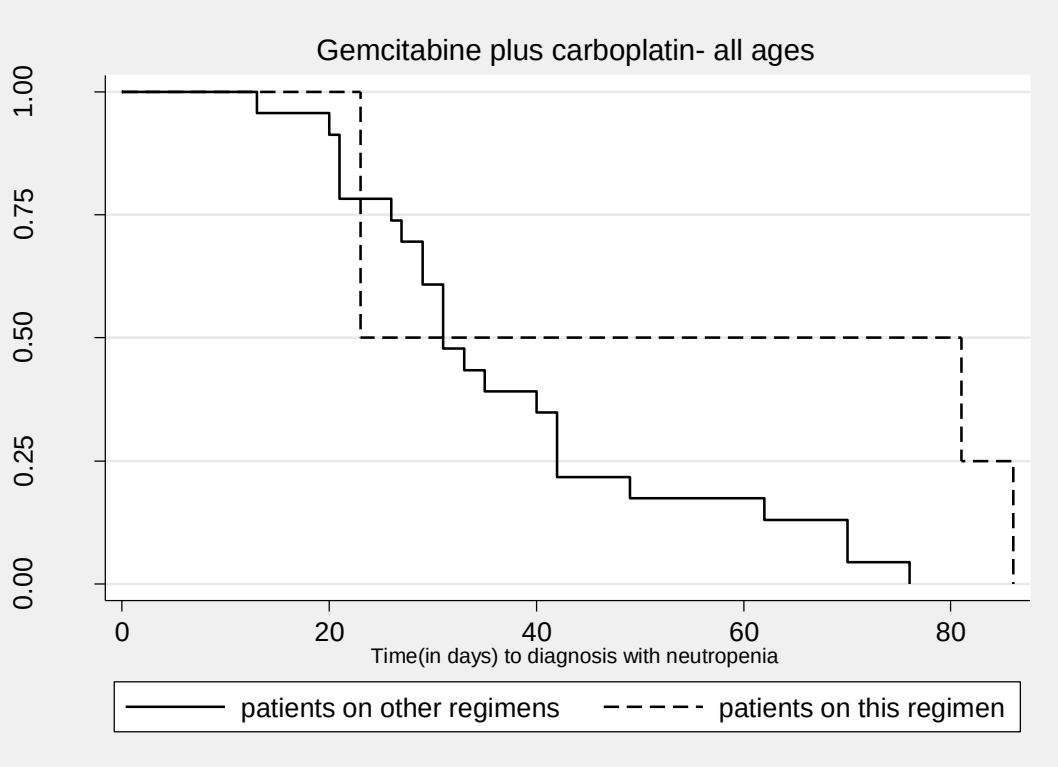

Figure 4.6: survival curve of participants on gemcitabine-carboplatin regimen across all ages.

4.10: Multivariable logistic regression analyses for the identification of key risk factors for neutropenia

To identify the most important risk factors for neutropenia, multi-variable logistic regression was conducted. The predictor variables were divided into three categories, namely: socio-demographic characteristics, type of cancer, and chemotherapeutic agent. Only variables that had a statistically significant association with neutropenia were included in the analysis. The findings are presented in Table 4.6.

Table 4 6: Multi-variate analysis of key risk factors for neutropenia

CHARACTERISTIC	RISK FACTOR	CRUDE OR		ADJUSTED OR	
		OR,95% CI	P-VALUE	OR,95% CI	P-VALUE
Socio-demographic	Age > 50 years	0.47 (0.24 , 0.93)	0.030	0.22 (0.09, 0.54)	0.001
Type of cancer	Breast cancer	1.99 (0.97, 4.07)	0.061	-	-
	Cervical cancer	0.60 (0.32, 1.13)	0.114	-	-
Chemotherapeutic agent	Cyclophosphamide	2.91 (1.34, 6.32)	0.007	0.80 (0.24, 2.69)	0.715
	Doxorubicin	2.34 (1.08, 5.07)	0.031	-	-
	Docetaxel	1.37 (0.39, 0.88)	0.038	0.98 (0.96, 1.00)	0.037
Statistical interaction term	Age>50 and cyclophosphamide	-	-	12.18 (2.27, 65.37)	0.004

The significant finding was the interaction between age and use of cyclophosphamide. To understand the interaction, the incidence of neutropenia was stratified by age and use of cyclophosphamide.

The statistical interaction implied that the effects of cyclophosphamide were more intense in one age group than the other. To provide more evidence to support the interaction, the Maintel-Hanzel test for homogeneity for stratum specific measure of association (MOA) was conducted.

The MOA between cyclophosphamide and neutropenia was very high (OR 9.24, 95% 2.60, 32.80) in the age group above 50 years. Amongst participants aged below 50 years (who made up most of the cohort) there was no association between cyclophosphamide and neutropenia (OR 0.89, 95% CI 0.21, 3.31).

4.10.1 Confounding between the effects of cyclophosphamide and doxorubicin

On bivariate regression analysis, there was a strong positive association between being on doxorubicin and neutropenia. However, on multi-variable analysis, when adjusting for confounding, the effects of doxorubicin became insignificant. In the case of doxorubicin, we found evidence of qualitative confounding. The crude MOA showed that being on doxorubicin increases the risk of neutropenia but on adjusting for confounding, doxorubicin was found to have a negative association with neutropenia; adjusted OR 0.41 (95% CI:0.04, 4.20; p=0.453). A strong qualitative confounding effect was observed.

On repeating multivariable analysis with age and doxorubicin, and cyclophosphamide alone, the adjusted measure of association between neutropenia and cyclophosphamide increased from 2.91 (95% CI: 1.34, 6.31; p= 0.007) to OR 6.64 (95% CI: 0.66, 67.15; p=0.109). This was more than a two fold increase. This seems to suggest that co-administration of cyclophosphamide and doxorubicin results in a reduction of the toxic effects of cyclophosphamide.

4.10.2 Confounding between Breast cancer and cyclophosphamide

The crude MOA between breast cancer and neutropenia showed a positive correlation, OR 3.35 (95% CI: 0.93, 12.04; p=0.065).

On multivariable analysis with cyclophosphamide and breast cancer as predictor variables, the effect of breast cancer became insignificant (p=0.786). Hence, most of the neutropenia diagnosed among participants with breast cancer could be due to administration of cyclophosphamide rather than their type of cancer.

4.11: Management of neutropenia

Figure 4.4 represents the various strategies used to manage neutropenia.

Most participants with neutropenia were managed with a granulocyte colony stimulating factor (29, 61.7%)). Only 2 (4%) were treated with antibiotics. Among 15% of the participants diagnosed with neutropenia, chemotherapy was deferred until they recovered. The 7 participants who had their chemotherapy deferred, recovered and the treatment was continued.

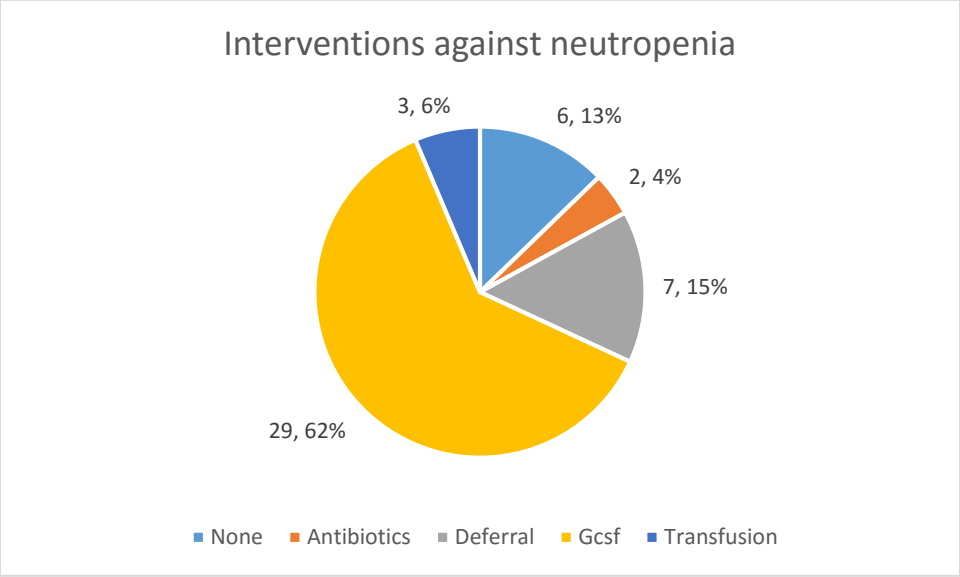

Figure 4.7: Strategies used to manage chemotherapy-induced neutropenia.

This study found that 6 participants who had a diagnosis for neutropenia, chemotherapy was continued without appropriate management of neutropenia being instituted. Amongst these 6, 3, participants had a switch on their regimens, while the rest were lost to follow up.

CHAPTER 5: DISCUSSION

The age composition of participants in this study compared well with that of a study done in Nigeria in 2008 among cancer patients, where ages ranged from 23 to 85 years with a mean age of 48±12.3 years (46). The age range 35-65 years accounted for more than 70% of all the participants. This correlates well with the onset of most cancers. Some like breast cancer are mostly diagnosed in the pre-menopausal stage among African women (55).

In our study setting, more women (57.2%) than men were diagnosed with cancer. This finding differs with various studies that have shown a higher likelihood of men to develop cancer than women (56). Various factors could have led to this result. These include the recent campaigns for screening for cancers that mostly affect women, such as breast and cervical cancers. Women also tend to have a better health seeking behavior than men (57).

The findings on prevalence of cancer cases are comparable with data at the Nairobi cancer registry 2002 which recorded 23.3%, 20% and 9.4% for breast, cervical and prostate cancer respectively, of all the cancers reported (58).

Most cancers are diagnosed among middle and upper age categories. Advanced age predisposes patients to a myriad of ailments and chronic illnesses. Key among them are hypertension, diabetes, chronic pulmonary obstructive disease (COPD), kidney and liver diseases (37).

Various regimens were used in treatment of various types of cancer. Cyclophosphamide-doxorubicin (CA) (20/48%) and cyclophosphamide-doxorubicin-5-fluorouracil (CAF) (14/33.6%) were the main regimens used to manage breast cancer. These regimens are comparable to those used among participants selected in a study among Nigerian patients with breast cancer where the main regimens included cyclophosphamide-methotrexate-5-fluorouracil(CMF) (79.3%) and cyclophosphamide-adriamycin-5-fluorouracil (CAF) (11.2%) (55).

Neutropenia was the main outcome of interest in this study. Diagnosis for neutropenia was made for those participants whose absolute neutrophil count fell below $1.5*10^9$ /litre. A total of 47 of the 173 participants, developed neutropenia during the period of this study. This represents an incidence of 27% over the one year study period.

A study by Doshi (2012) found an incidence of neutropenia of 46% of all new cancer patients recruited during the year (18). A study by Kawinzi (2017) among cancer patients in a Kenyan hospital found a prevalence of 10.5% (12).

Most participants with neutropenia were women (61.7%). Few studies seem to link one's gender to development of neutropenia. However, a study by Kloess (1999) reported that being female was a significant factor in development of neutropenia (34).

The majority of participants with neutropenia (85.1%) were aged 35 years and above. Older age is associated with development of neutropenia. This may be due to compromised immunity as one advances in age (34).

The majority of participants with neutropenia were of normal body mass index (53%). The rest were either underweight, overweight or obese. Studies have reported a significant risk of certain cancers such as colon and postmenopausal breast cancer among the overweight and obese. This in turn increases the risk of neutropenia (59)

Cyclophosphamide presents a high risk of bone marrow suppression. It is an immunosuppressant that alkylates DNA, thereby interfering with its synthesis and function, particularly in proliferating lymphocytes (60). In some patients, it has had to be discontinued due to severe cases of neutropenia. Some studies have reported high rates of neutropenia when patients are put on a cyclophosphamide-based regimen (61). Our study found an odds ratio of 6.64 (95% CI: 0.66, 67.15; p=0.109) of developing cyclophosphamide induced neutropenia.

Some studies have shown that cyclophosphamide presents a high risk of neutropenia even at relatively low doses (62).Therefore, cyclophosphamide should be used with close monitoring for likely neutropenic adverse effects.

Multi-variable analysis revealed that the risk of cyclophosphamide-induced neutropenia in the age group above 50 years was far higher than among participants aged below 50 years. It can be concluded therefore, that though cyclophosphamide increases the risk of neutropenia, its effects are age dependent. Younger patients have a lower risk of neutropenia compared to those of advanced age (63)

An analysis of risk among participants with breast cancer revealed a positive association for cyclophosphamide and a negative association with breast cancer as predictor variables.

This finding is clinically significant as treatment with cyclophosphamide clearly increases the risk of neutropenia, and explains the higher incidence of neutropenia among breast cancer patients.

Use of platinum based chemotherapeutics such as cisplatin and carboplatin revealed a protective effect of neutropenia. The protective effects were however not statistically significant. Use of an anti-folate such as permetrexed together with a platinum based drug such as cisplatin is beneficial in mitigating hematologic toxicities (64).

Taxanes used to treat participants included paclitaxel and docetaxel. Their odds ratio of causing neutropenia were OR 0.86 (95% CI: 0.40, 1.84; p=0.691) and OR 0.12 (95% CI: 0.02, 0.88; p=0.038) respectively. The protective effect from docetaxel was statistically significant. The number of patients on docetaxel in this study was relatively quite small so a solid conclusion on its protective effects could not be drawn. However, use of docetaxel with cyclophosphamide has been associated with overall survival benefit compared to doxorubicin and cyclophosphamide (65).

Further analysis revealed that three regimens were significantly implicated in resulting in neutropenia. These were; Carboplatin and gemcitabine; OR 11.63 (95% CI:1.26 ,106.91; p=0.03), Cyclophosphamide, doxorubicin and fluorouracil; OR 4.46 (95% CI;1.20, 16.60 ;p=0.026), and Cyclophosphamide,5-fluorouracil and methotrexate OR 11.63 (95% CI :1.26,106.91 ;p=0.03).

Survival analysis was necessary to determine the number of participants surviving without neutropenia at specific time intervals.

Most of the participants on CAF developed neutropenia after approximately 30 days. Cyclophosphamide has been reported to pose a considerable risk of neutropenia. However, the risk reduced considerably when used in combination with doxorubicin, (from OR 6.64 (95% CI: 0.66, 67.15; p=0.109) to OR 2.91 (95% CI: 1.34, 6.31; p= 0.007), addition of fluorouracil increased risk of neutropenia disproportionately. Perhaps that explains why the risk of the three drug regimen is high at OR 4.46 (95% CI; 1.20, 16.60, p=0.026). Fluorouracil has been found to pose a high risk of febrile neutropenia that may be fatal (66).

Methotrexate has been found to cause serious neutropenic effects even at low doses (67). The additive neutropenic effect of cyclophosphamide, fluorouracil and methotrexate in the CMF regimen was responsible for the short survival span of all patients on this regimen. 50% of the participants aged 50 years and above on this regimen developed neutropenia within 30 days of treatment.

Use of gemcitabine-carboplatin regimen has been shown to have overall survival benefits among advanced ovarian cancer patients. This is because of the reduced likelihood of neurotoxicity compared to single agent carboplatin regimens. Gemcitabine seems to confer survival benefit to this regimen in the long run (67).

Gemcitabine has been found to cause significant hematologic adverse effects including neutropenia when used singularly(68). Carboplatin, when used in combination with other drugs has been found to cause neutropenia (69).

This study found that across the whole age spectrum, for half the number of participants on gemcitabine-carboplatin, neutropenia was diagnosed within a month of starting treatment. The other half survived for nearly 90 days without neutropenia.

Concerning management of participants who developed neutropenia, most were treated with a GCSF. Some were managed using antibiotics. A few had their chemotherapy deferred. The National Hospital Insurance Fund (NHIF) covered for the costs of management for most participants who are enrolled members of the fund. The main challenge was lack of medication and other inputs, which forced them to buy them outside the hospital at higher costs.

GCSF is a glycoprotein that promotes proliferation and survival of granulocytes (70)**.** GCSF is also responsible for the activity of mature granulocytes (71). It was evident that all the cases treated with a GCSF were as a secondary intervention rather than primary prophylaxis.

Studies have shown that primary prophylaxis with a GCSF may be beneficial during treatment for different cancers depending on the risk of developing neutropenia (72). One of the main challenges for patients who could benefit from GCSF is the cost of buying the medication. However, cost effectiveness studies have shown that the benefits of reduced hospitalization, and reduced need for antibiotics outweigh the costs (73).

Use of antibiotics for prophylaxis and management was limited in participants selected for this study. Empirical management of CIN using appropriate antibiotics can be beneficial in averting likely cases of fatalities (50). Prophylactic antibiotics should be timed with the survival period of patients so that they benefit most at the time they are most likely to develop neutropenia.

Deferral should only be considered in exceptional cases where the risks outweigh the benefit of continuing treatment. In some instances, deferral may derail the whole treatment plan where a rare drug is no longer available on reinstating treatment. Often times, the patient may later on suffer from other diseases that may lead them to discontinue treatment altogether.

STUDY LIMITATIONS

The study relied heavily on pre-recorded information within the participant' files.

The major limitation was that some participants' files were either missing from the filing area or did not contain necessary information that should otherwise be recorded. Some of the records were not filed sequentially or were missing leading to difficulties in obtaining all the necessary information.

CHAPTER 6: CONCLUSION AND RECOMMENDATIONS

6.1: CONCLUSION

This study found an incidence of neutropenia of 27.2% over January 2016 to March 2017 study period. Although there may be specific reasons for this relatively high incidence, special attention needs to be paid to this finding. Strategies need to be put in place to ensure that fewer patients suffer from neutropenia where this could be avoided or risk minimized.

Cyclophosphamide was found to present a significant risk of developing neutropenia. A protocol for determining risk profiles of patients on cyclophosphamide should be developed. Such a protocol should include strategies for managing neutropenia if, and once it develops.

Apart from cyclophosphamide based regimens, gemcitabine-carboplatin regimen has been found to pose significant risk of neutropenia.

Majority of participants developing neutropenia were managed using a granulocyte colony stimulating factor (GCSF). The rest were treated with antibiotics or had their chemotherapy deferred.

6.2: RECOMMENDATIONS

It would be necessary to document uniform protocols for managing neutropenia. The hospitals should be well equipped for admission and provision of necessary medication such as antibiotics and granulocyte colony stimulating factors (GCSFs).

Clinical practice guidelines for use of antimicrobial agents among neutropenic patients should be formulated. These should be updated regularly (74).

Continuous medical education is necessary in this area to healthcare workers attending to cancer patients in order to promptly diagnose and manage chemotherapy-induced neutropenia.

The National Hospital Insurance fund (NHIF) should give support to patients who cannot afford the regular laboratory tests as well as medication used to manage neutropenia once diagnosed. The fund managers should also consider lowering the cost of premiums from the current minimum of five hundred shillings. Some participants who might not afford may have been forced to default on treatment (75).

In their support of cancer programs, donors should consider placing a special emphasis on provision of support to cancer patients at risk or already suffering from neutropenia.

A cost utility analysis is important to determine whether primary prophylaxis is a better alternative to secondary management with a GCSF and how this can be formulated as a policy. Such a study would have to look at the direct as well as indirect costs. A CUA in this scenario would also include quality of life expressed as quality adjusted life years (QALYs) in quantifying the benefit obtained from each intervention. A paradigm shift has been observed where active and preventive is preferred to passive management which is instituted after the outcome.

Future studies should focus on coming up with an algorithm for predetermining risk of neutropenia among patients on various regimens.

REFERENCES

1. Heron M. Leading causes of deaths. National Vital Statistics Reports 2015-2017; 66(5).
2. Bray F, Ferlay J, Soerjomataram I. Global cancer statistics: GLOBOCAN; Estimates of Incidence and mortality worldwide for 36 cancers in 185 countries 2018; 394-424.
3. Ministry of Health and Sanitation and Ministry of Medical Services, National cancer control strategy 2011-2016; 2012; 1-35.
4. Sharma A, Kumari KM, Maohar HD, Bairy KL, Thomas J. Patterns of adverse drug reactions due to cancer chemotherapy in a tertiary care hospital in South India. Perspective Clinical Research 2015; 6(2):109-15.
5. Ayalew Sisay E. Drug Related Problems in Chemotherapy of Cancer Patients. Journal of Cancer Science and Therapy 2015; 07(02):55-9.
6. Lin H, De Stanchina E, Zhou XK, Hong F, Seidman A, Fornier M. Maitake beta-glucan promotes recovery of leucocytes and myeloid cell function in peripheral blood from paclitaxel hematotoxicity. Journal of cancer Immunology and Immunotherapy 2010; 59(6):885-97.
7. Wang Y, Probin V, Zhou D. Cancer therapy-induced residual bone marrow injury-Mechanisms of induction and implication for therapy. Current Cancer Therapy Reviews 2006 2(3):271-9.
8. Chirivella I, Bermejo B, Insa A, Perez-Fildago A, Magro A, Rosello S. Optimal delivery of anthracycline-based chemotherapy in the adjuvant setting improves outcome of breast cancer patients. Journal of Breast Cancer Research and Treatment 2009; 114(3):479-84.
9. Tia L, Lui A, Chua N, Strebel H. (2015) Chemotherapy-induced neutropenia, anemia and thrombocytopenia among Filipino breast cancer patients on adjuvant chemotherapy. Acta Medica Philipina, 2015; 49(2):26-31.
10. Lyman GH, Michels SL, Reynolds MW, Barron R, Tomic KS, Yu J. Risk of mortality in patients with cancer who experience febrile neutropenia. Cancer 2006; 116(23): 5555-63.
11. Kuderer NM, Dale DC, Crawford J, Cosler LE, Lyman GH. Mortality, morbidity and cost associated with febrile neutropenia in adult cancer patients. Cancer 2006; 106(10):2258-66.

12. Kawinzi C, Okoth J, Mutai C. Prevalence of Neutropenia among Patients with Solid Tumors undergoing chemotherapy at Moi Teaching and Referral Hospital, Kenya. International Journal of Life Sciences 2012; 6(3):91-5.
13. Division for cancer prevention and control, Centre for Disease Control and Prevention, Fact-sheet on neutropenia and risk for infection. Last Review 5th November 2018.
14. Hsieh MM,Tisdale JF, Rodgers GP, Branch CH, Young NS, Branch H. Neutrophil count in African Americans: Lowering the target cut-off to initiate or resume chemotherapy. Journal of Clinical Hematology 2010; 28(10):1633-7.
15. Abdul B, Hassan R, Binti Z, Yusoff M, Othman S Bin. A close look at neutropenia among cancer patients- Risk Factors and Management, 2015; 1-24.
16. Shelenz S, Giles D, Abdallah S. Epidemiology, management and economic impact of febrile neutropenia in oncology patients receiving routine care at a Regional UK cancer centre. Annals of Oncology 2012; 23(7):1889-93.
17. Denic S, Narchi H, Mekaini LA, Al-hammadi S, Jabri On. Prevalence of neutropenia in children by nationality. BMC Hematology 2016; 1-7.
18. Doshi BD, Pandya NM, Shah CA, Gupta AK, Makwana MV. Chemotherapy-induced Neutropenia in cancer patients with solid tumors in India. Der Pharmacia Lettre 2012; 4(2):584-90.
19. Castagnola E, Fontana V, Caviglia I, Caruso S, Faraci M, Fioredda F. A prospective study on the epidemiology of febrile episodes during chemotherapy-induced Neutropenia in children with cancer or after hemopoietic stem cell transplantation. Journal of Clinical Infectious Diseases 2007; 45(10):1296-304.
20. Klasterskey J. Management of fever in neutrogenic patients with different risks of complications. Journal of Clinical Infectious Diseases 2004; 39 Suppl 1:32-7.
21. Ramphal R. Changes in the etiology of bacteremia in febrile neutropenic patients and the susceptibilities of the currently isolated pathogens. Journal of Clinical Infectious Diseases 2004; 39:S25-31.
22. Schouten HC. Neutropenic management. Annals of Oncology 2006; 17; S10:85-9.
23. Capsoni et al. Primary and secondary autoimmune neutropenia. Athritis Research and Therapy 2005; 7:208-2014.

24. Lalami Y, Klastersky J. Impact of chemotherapy-induced neutropenia and febrile neutropenia on cancer treatment outcomes: An overview about well-established and recently emerging clinical data. Critical Reviews in Oncology (Hematology) 2017; 120 (October): 163-79.
25. Cottle T, Edwards C. Understanding severe chronic neutropenia, A Handbook 2017; 1-65.
26. Glasmacher A, Hahn C, Schakowski F, Ziske C, Molitor E. Clostridium defficile infection in patients with neutropenia. Clinical Infectious Diseases 2001; 33(April 1991).
27. Kath R, Hoeffken K. Oncologist emergencies, Intensivmed und notfallmedizin 1997; 34(5):480-90.
28. BainBJ, Mary S, Medicine F, College I. Bone marrow biopsy morbidity and mortality. British Journal of Hematology 2003; 612:949-51.
29. Klaus Ley, Molecular mechanisms of leucocyte recruitment n the inflamamatory process. Cardiovascular Research 1996; 32:733-42.
30. Schwenkglenks M, Pettengell R, Jackisch C, Paridaens R, Constenla M, Bosly A. Risk factors for the chemotherapy-induced neutropenia occurrence in the breast cancer patients: Data from the the INC-EU Prospective Observational Europena Neutropenia Study. Support Care Cancer 2011; 19(4): 483-90.
31. Lyman GH, Dale DC, Friedberg J, Crawford J, Fisher RI. Incidence and predictors of low chemotherapy dose-intensity in aggressive non-Hodgkin's lymphoma,A nationwide study. Journal of Clinical Oncology 2004; 22(21):4302-11.
32. Keswara M, Sudarsa I, Golden N. The Risk Factor of Neutropenia on locally Advanced Breast Cancer Patients Treated with First Cycle with Cyclophosphamide, doxorubicin, 5-Fluorouracil chemotherapy at Sanglah General Hospital. Bali Medical Journal 2012; 1(3):116-20.
33. Suresh M, Mallikarjuna N, Bandi HK, Shravya G. Hematological Changes in Chronic Renal failure. International Journal of Scientific and Research publications 2012; 2(9):1-4.
34. Gary HL, Christopher HL, Olayemi A. Risk models for predicting chemotherapy induced neutropenia. The Oncologist 2005; 427-37.

35. Iuliano AD, Weidle PJ, Brooks JT, Masaba R, Girde S, Ndivo R. Neutropenia in HIV-infected Kenyan women Receiving triple antiretroviral prophylaxis to prevent mother-to-child HIV transmission is not associated with serious clinical Sequele. Journal of International Providers of Aids care 2014; 14(3):261-8.
36. Ngidi S, Rad FC, Sa O, Magula N. Incidence of Chemotherapy-Induced neutropenia in HIV-infected and uninfected patients with breast cancer receiving adjuvant chemotherapy. South African Medical Journal, 2017; 107(7):595-601.
37. Extermann BM, Overcash J, Lyman GH, Parr J, Balducci L. Co-morbidityand Functional Status are independent in Older Cancer Patients. Journal of Clinical Oncology, 1998 ;(April):1582-7.
38. Ouyang Z, Peng D, Dhakal DP. Risk factors for hematological toxicity of chemotherapy for bone and soft tissue sarcoma. Oncology Letters, 2013; 5(5):1736-40.
39. Limpovorapitak W, Khawcharoenporn T. Incidence, risk factors and outcomes of febrile neutropenia in Thai hematologic malignancy patients receiving chemotherapy: Asian Pacific Journal of Cancer 2015;16:5945-50.
40. Cirillo M, Venturini M, Ciccarelli L, Coati F, Bortolami O, Verlato G. National Cancer Institute- Common Terminology Criteria for Adverse Events during chemotherapy: results of a comparison based on patient's self-reported questionnaire July 2009: 1929-35.
41. Newburg PE, Dale DC. Evaluation and Management of patients with isolated neutropenia. Seminars in Hematology 2013; 50(3): 198-206.
42. Miri-dashe T, Osawe S, Tokdung M, Daniel N, Chonji RP, Mamman I et al . Comprehensive references Ranges for Hematology and clinical Chemistry Laboratoey parameters derived from normal Nigerian Adults, PLoS ONE 2014;9(5).
43. Shwartz R, Harlan M. A Monoclonal Required 1985; 65(6):1553-6.
44. De Naurois J**,**Norvitzky-Basso I, Gill MJ, Marti FM, Cullen MH, Roila F. Management of febrile neutropenia: ESMO clinical Practice Guidelines. Annals of Oncology 2010; 21(5):252-6.

45. Klastersky BJ, Paesmans M, Rubenstein EB, Boyer M, Elting L, Feld R, et al. Multinational Association for Supportive Care in Cancer in Care Risk Index: A Multinational Scoring System for Identifying Low-Risk Febrile Neutropenic Cancer Patients, Journal of Clinical Oncology 2014; vol 18, No 16.
46. Flowers CR, Seidenfel J, Bow EJ, Karten C, Gleason C, Hawley DK, et al. Antimicrobial prophylaxis and outpatient management of fever and neutropenia in adults treated for malignancy: American society of clinical oncology practice guideline. Journal of Clinical Oncology 2013; 31(6):794-810.
47. Ynn L, Artmann CH, Schetter OKT, Homas T, Abermann MH, Arry L, et al.Granulocyte Colony stimutating Factor in severe Chemotherapy-Induced Afebrile Neutropenia. The New England Journal of Medicine 1997; 1776-80.
48. Schouten HC. Neutropenia Management. Annals of Clinical Oncology; 2018; 85-9.
49. Greil R, Jost LM. ESMO recommendations for the application of hematopoietic growth factors. Annals of Oncology 2005; 16(1):80-2.
50. Klastersky BJ, Paesmans M, Rubenstein EB, Boyer M, Elting L, Feld R et al. Multinational Association for Supportive Care in Cancer in Care Risk Index: A Multinational Scoring System for Identifying Low-Risk Febrile Neutropenic Cancer Patients, Journal of clinical oncology 2016; vol 18,No 16,:3038-51.
51. Freifeld AG, Bow EJ, Sepkowitz KA, Boeckh MJ, Ito JI, Mullen CA, et al. Clinical Practice Guideline for the Use of Antimicrobial Agents in Neutropenic Patients with cancer. Clinical Infectious Diseases 2011; 52(4): 427-31.
52. Sylvester RK, Blamble D, Kelly HW. Infections in patients with cancer. Pharmacotherapy self-assessment program, 5th edition, 147-164.
53. Barlett JE, Kotrlik JW, Higgins CC. Organizational research: Determining Appropriate Sample Size in Survey Research. Information Technology, Learning and Performance Journal 2001; 19(1):43-50.
54. Guyot P, Ades AE, Ouwens MJ, Welton NJ. Enhanced secondary analysis of survival data: Reconstructing the data from published Kaplan-Meier survival curves. BMC Medical Research Methodology 2012; 12(9).
55. Adisa A, Lawal O, Adesunkanmi A. Evaluation of patients' adherence to chemotherapy for breast cancer. African Journal of Health Sciences 2008; 15(1):22-7.

56. Hsieh MM, Everhart JE, Byrd-Holt DD, Tisdale JF, Rodgers GP. Prevalence of neutropenia in the US population: Age, sex, smoking status, and ethnic differences. Annals of Internal Medicine 2007; 146(7):486-92.
57. Ali I, Hogberg J, Hsieh J, Auerbach S, Korhonen A, Stenius U, et al. Gender differences in cancer susceptibility: role of oxidative stress. Oxford University Press 2016; 37(10): 985-92.
58. Ministry of Health and sanitation (Kenya) and Ministry of Medical Services (Kenya). National cancer control strategy, Guidelines 2011-2016.
59. Dignam JJ, Polite BN, Yothers G, Raich P, Colangelo L, Connel MJO, et al. Body Mass Index and outcomes in Paients who Recieve Adjuvant Chemotherapy for Colon cancer. Journal of National Cancer Institute 2007; 98(22); 1647-54.
60. Dale DC, FAuci AS, Wolff SM. The effect of cyclophosphamide on leucocyte kinetics and susceptibility to infection in patients with wegener's granulomatosis. Journal of Arthitis and Rheumatism 1973; 16(5):657-64.
61. Moore AS, Cotter SM, Rand WM.,et al . Evaluation of a Discontinous Treatment protocol (VELCAP-S) for Canine Lymphoma. Journal of Veterinary Internal Medicine 2001; 15(4):348-54.
62. Zuluaga AF, Salazar BE, Rodriguez CA., et al. Neutropenia induced in outbred mice by a simplified low-dose cyclophosphamide regimen: characterization and applicability to diverse experimental models of infectious diseases. BMC Infectious Diseases 2006; 10:1-10.
63. Balducci, Al-Halawani, Charu et al. Elderly Cancer Patients Receiving Chemotherapy Benefit from First-Cycle Pegfilgrastim. The oncologist 2007; 12: 1416-24.
64. Volgelzang BNJ, Rusthoven JJ, Symanowski J, Denham C, KAukel E, Ruffie P., et al. Phase 3 study of Permetrexed in Combination with Cisplatin Versus Cisplatin alone in Patients with Malignant Pleural Mesothelioma. Journal of Clinical Oncology 2003; 21(14): 2636-44.
65. Stephen J, Holmes FA, et al. Docetaxel with cyclophosphamide is associated with an overall survial compared with Doxorubicin and Cyclophosphamide: A 7-year Follow-up of US oncology Research Trial. Journal of Clinical Oncology 2017; 27(8): 1177-83.

66. Mugada V, Ramineni H, Padala D. A case report, 5-Fluorouracil-induced Febrile Neutropenia and Death. Journal of Young Pharmacists 2017; 9(1): 133-44.
67. Jacobus P, Marie P, et al. Gemcitabine plus Carboplatin compared with carboplatin in patients with platinum-sensitive recurrent ovarian cancer: An intergroup trial in patients with Platinum- sensitive Recurrent Ovarian cancer. Journal of Clinical Oncology 2016; 24:4699-07
68. Sun YR, Hei CJ, et al. An Association between RRM1 haplotype and Gemcitabine-Induced Neutropenia in breast cancer patients. The Oncologist 2007; 2:622-630.
69. Vasey PA, Jayson GC, et al. Phase III Randomized Trial of Docetaxel–Carboplatin Versus Paclitaxel–Carboplatin as First-line Chemotherapy for Ovarian Carcinoma. Journal of the National Cancer Institute 2004; 96(22):1682-91.
70. G-CSF Supplement Union for International Cancer Control. Review of Cancer Medicines on WHO List of Essential Medicines. Report. 2014.
71. Czygier M, Dakowicz L, Szmitkowski M. The effect of Granulocyte Colony-Stimulating Factor (G-CSF) on the activity of granulocyte enzymes in children with cancer who developed neutropenia after chemotherapy. Advances in Medical Sciences 2008; 53(2):278-82.
72. Whyte S, Cooper KL, Stevenson MD, Madan J, Akehurst R. Cost effectiveness of granulocyte colony-stimulating factor for febrile neutropenia in breast cancer in the the United Kingdom. Value in Health 2011; 14(4): 465-74.
73. Michon J, Milpied N, Boiron JM, Bourhis JH. Cost effectiveness of 5-day G-CSF (lenograstim s) administration after PBSC transplantation: results of a SFGM-TC randomized trial. Bone Marrow Transplantation 2005; 36:547-52.
74. Freifeld AG, Bow EJ, Sepkowitz KA, Boeckh MJ, Ito JI, Mullen CA, et al. Executive summary. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infectious Diseases society of America. Journal of Clinical Infectious Diseases 2011; 52(4): 427-31.
75. Mostert S, Njuguna F, Ven PM, Olbara G, Kemps L, Musimbi J, et al. Infulence of Health-Insurance Access and Hospital Retention Policies on childhood Treatment in Kenya. Journal of Paediatric Blood Cancer 2014; 61:913-8.

Appendix A: ELIGIBILITY CHECK LIST

PART A: ELIGIBILITY CHECKLIST

	YES	NO
1. Age 18 years and above	☐	☐
2. Confirmed diagnosis of a malignant solid tumor	☐	☐
3. Participant on first chemotherapy regimen	☐	☐
4. Participant not previously diagnosed with neutropenia	☐	☐

If excluded reasons for exclusion……

……

APPENDIX B: DATA ABSTRACTION FORM.

DATE OF DATA COLLECTION --------- CODE NUMBER _____

PART A: PARTICIPANT'S BIO-DATA

Date of Birth: Day…….month …… year…….

Age in years (at treatment initiation)

……..

Gender Male ☐ Female ☐

Weight at diagnosis in (kg)……

Height ……..cm

Usual residence in the last 2 years

Urban ☐ Rural ☐ Rural-urban ☐

Level of education?

Primary ☐ secondary ☐ college ☐ university ☐

Occupation

Unemployed ☐

Housewife ☐

Employed ☐

If employed, state the profession _____

Marital status:

Single ☐

Married ☐

Divorced ☐

Widow/widower ☐

Does participant smoke? Yes ☐ No ☐

Does participant take alcohol? Yes ☐ No ☐

DATE OF DATA COLLECTION --------- CODE NUMBER _____

PART B: HISTORY OF PRESENTING ILLNESS.

Date diagnosed with cancer ……..

Type of cancer diagnosed

Type of cancer	Tick as appropriate
Breast cancer	
cervical	
Prostate cancer	
Lung cancer	
Hodgkin's lymphoma	
Non-Hodgkin's lymphoma	
Uterine cancer	
Colon cancer	
Other types (specify)	

Stage of cancer at diagnosis given? Yes no

If yes, stage 1. ☐ 2 ☐ 3 ☐ 4 ☐ other (state)……

Has tumor metastasized? Yes ☐ No ☐

PART C: PAST MEDICAL HISTORY.

Has known chronic co-morbidities

Diabetes Yes ☐ No ☐

Hypertension Yes ☐ No ☐

Renal failure Yes ☐ No ☐

HIV Yes ☐ No ☐

Tuberculosis Yes ☐ No ☐

Asthma Yes ☐ No ☐

Others (specify)……

Likely cause of co-morbidities……..

Genetic ☐

Lifestyle ☐

Infection ☐

DATE OF DATA COLLECTION --------- CODE NUMBE----------

PART D: CANCER TREATMENT MODALITIES INSTITUTED

Surgical removal of tumour	Yes ☐ No ☐	If yes, date conducted:	
Radiotherapy	Yes ☐ No ☐	Date started:	
Herbal therapy	Yes ☐ No ☐	Date administered	
Hormonal therapy	Yes ☐ No ☐	Date started	

If radiotherapy done, answer the following;

Number of sessions……

Was radiotherapy done concurrently with chemotherapy? Yes ☐ No ☐

Was radiotherapy instituted before chemotherapy if not concurrent Yes ☐ No ☐

Dose of radiotherapy……

PART E: CHEMOTHERAPEUTIC AGENTS ADMINISTERED.

Cycle	Date of initiation	Drugs	Was dose adjusted?	Specify dose adjustment
First				
Second				
Third				
Fourth				
Fifth				
Sixth				

DATE OF DATA COLLECTION --------- CODE NUMBER _____

PART F: NEUTROPHIL COUNTS

Cycle	Chemotherapy administered	Pre-chemotherapy count	Post-chemotherapy count	Neutropenia detected (Yes/No)
1st cycle				
2nd cycle				
3rd cycle				
4th cycle				
5th cycle				
6 th cycle				

Neutropenia present if counts are less than an ANC <500 cells/mm^3

Has patient developed any of the following signs of neutropenia?

Sign/symptom	Tick as appropriate	Date of onset
Febrile illness		
Oral candidiasis		
Painful urination		
Abdominal pain		
Shortness of breath/ cough		
Inflammation around cuts/ bruises		
Vaginal discharge		
Others (specify)		

INTERVENTIONS AGAINST THE SIGNS AND SYMPTOMS.

Intervention	Tick as appropriate
Antipyretics	
Antibiotics	
Antifungals	
Admissions	
Others(specify)	

DATE OF DATA COLLECTION --------- CODE NUMBER _____

PART G: INTERVENTION AGAISNT NEUTROPENIA.

a. Complete cessation of chemotherapy ☐
b. Adjustment of dosages of causative drug ☐
c. Antibiotics (specify) ☐
d. Administration of a granulocyte- colony stimulating factor ☐
e. Transfusion ☐
f. No intervention ☐
g. Other intervention
(specify)……

……
……...