EFFECTIVENESS AND ADVERSE EFFECTS OF ETOPOSIDE, METHOTREXATE, ACTINOMYCIN D, CYCLOPHOSPHAMIDE AND VINCRISTINE REGIMEN AMONG GESTATIONAL TROPHOBLASTIC NEOPLASIA PATIENTS AT KENYATTA NATIONAL HOSPITAL.

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A Research Dissertation Submitted in Partial Fulfillment of the Requirements for the Award of the Degree of Master of Pharmacy in Clinical Pharmacy in the School of Pharmacy of the University of Nairobi

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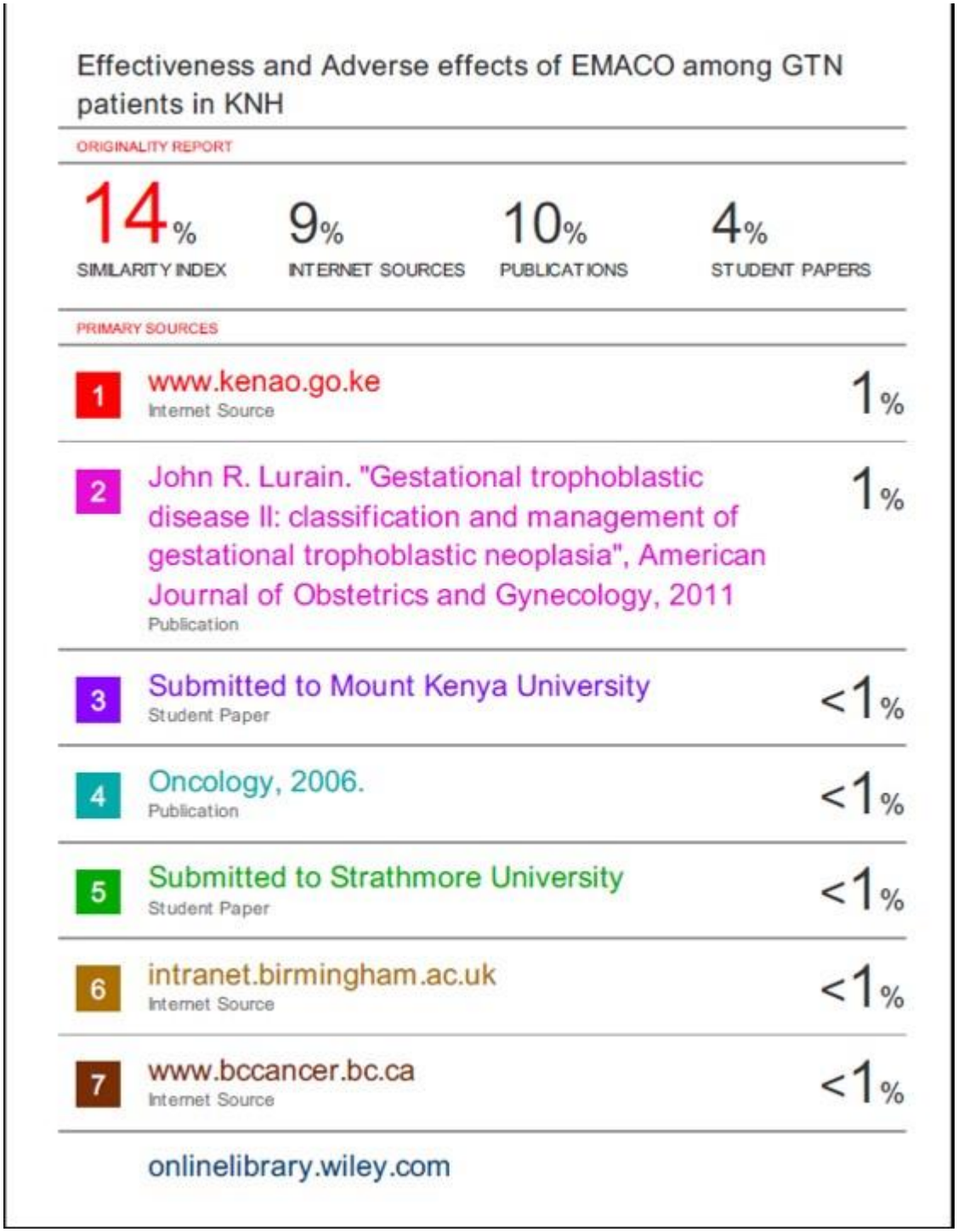

Effectiveness and Adverse effects of EMACO among GTN patients in KNH

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Dedication

This research dissertation is dedicated to my father, Mr. Kipsang Keter, who from an early age impressed on me the wonders of science and its influence on the world we live in, thus shaping the paths that led me to my career. Thank you for giving me the best foundation a parent could give his child, I love you.

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Table of contents

List of Figures and Tables

List of figures

List of tables

Abbreviations and acronyms

ASCO	-	American Society of Clinical Oncology
BCCA	-	British Columbia Cancer Agency
CHAMOCA	-	Cyclophosphamide, Hydroxyurea, Actinomycin D, Methotrexate, Vincristine and Doxorubicin
DMARDs	-	Disease-Modifying Antirheumatic Drugs
DNA	-	Deoxyribonucleic Acid
EMACO	-	Etoposide, Methotrexate, Actinomycin-D, Cyclophosphamide, Vincristine
EMAEP	-	Etoposide, Methotrexate, Actinomycin-D, Etoposide, Cisplatin
EORTC	-	European Organization for Research and Treatment of Cancer
ESMO	-	European Society for Medical Oncology
FIGO	-	International Federation of Gynecology and Obstetrics
GCSF	-	Granulocyte Colony Stimulating Factor
GTD	-	Gestational Trophoblastic Disease
GTN	-	Gestational Trophoblastic Neoplasia
HCG	-	Human Chorionic Gonadotrophin
HIV	-	Human Immunodeficiency Virus
KNH	-	Kenyatta National Hospital
MAC	-	Methotrexate, Actinomycin-D, and Cyclophosphamide or Chlorambucil

NCCN	-	National Comprehensive Cancer Network
NSAIDS	-	Non-Steroidal Anti-Inflammatory Drugs
RDI	-	Relative Dose Intensity
UON	-	University of Nairobi
WHO	-	World Health Organization

Operational definition of terms

Gestational Trophoblastic Disease (GTD) - It refers to a group of neoplastic disorders arising from the placental trophoblastic tissue after normal or abnormal fertilization. It includes hydatidiform mole and GTN.

High-risk GTN – Disease at stage II, III or IV with a WHO prognostic score equal to or greater than 7.

Low-risk GTN – Disease at stage II and III with a WHO prognostic score equal to or less than 6.

Primary Filgrastim prophylaxis - Filgrastim use starting in the first cycle of chemotherapy and in the subsequent cycles.

Secondary Filgrastim prophylaxis - Use of filgrastim where there is an experience of a neutropenic complication in a previous cycle of chemotherapy.

Adverse effect – An undesired harmful effect resulting from a medication

High dose density – This refers to administration of chemotherapy with less time between treatments.

Dose intensity - It is the dose of chemotherapy given per unit body surface area, per unit time ($mg/m^2/week$). It is the maximum tolerable dose at each administration.

Relative dose intensity - The ratio of the dose intensity actually delivered, to the standard dose intensity established for a chemotherapy regimen. It is a percentage of the dose intensity that is given as a portion of the dose that is planned.

Rising HCG levels - It is defined as two consecutive increase in HCG of 10% or more over at least two weeks (days 1, 7 and 14).

Plateau – It is four or more equivalent values of HCG over at least three weeks (days 1, 7, 14 and 21).

Single - This refers to a woman who does not have a husband.

Married - This refers to a woman who has a husband.

Oral Hormonal Contraceptives - These include Combined Oral Contraceptives, Progestin-Only Contraceptives, Postcoital or Emergency Contraceptives

Non-oral Hormonal Contraceptives - These are transdermal, transvaginal and injectable preparations which include Depo-Provera and intra-uterine devices.

Barrier Contraceptives - These include condoms, diaphragms, and cervical cap and contraceptive sponges.

Sterilization - These include vasectomy and tubal ligation

Abstract

Background: Etoposide, methotrexate, actinomycin D, cyclophosphamide and vincristine (EMACO) regimen is used in the management of gestational trophoblastic neoplasia (GTN) to achieve cure. It has been shown to be highly effective. It is associated with a variety of adverse effects that are influenced by sociodemographic factors, co-morbidities, and concomitant therapy.

Objective: The aim of this study was to determine effectiveness and adverse effects of EMACO regimen among GTN patients in Kenyatta National Hospital.

Methodology: A longitudinal study was conducted on GTN patients treated with EMACO regimen in Kenyatta National Hospital (KNH), between March 2013 and April 2018. The sample size was determined using Cochrane formula for finite populations. Universal sampling was employed and sixty-eight participants were included in the study. Data on β-HCG levels, adverse effects, co-morbidities, concomitant therapy, diet and use of filgrastim prophylaxis was obtained from patient records. Data was entered into Microsoft Excel Spreadsheet and imported to STATA version 14 for analysis. The outcome of interest, beta HCG levels were used to construct the HCG regression nomograms, which enabled the determination of the effectiveness of EMACO regimen. The prevalence of adverse effects of EMACO regimen and use of filgrastim prophylaxis was determined. Bivariate analysis was done to show the outcome variable of interest across different arms of predictor variables. The outcome variable, adverse effects were regressed against potential predictor variables; age, nutritional status, co-morbidities, and concomitant therapy. Permission to conduct research was granted by KNH-UON Ethics and Research committee.

Results: EMACO regimen was effective in 88% participants (59/68). Adverse effects were reversible and tolerable with myelosuppression being the most prevalent in (62,91.2%) participants. Other prevalent complications of EMACO regimen included extravasation (61,89.7%), nausea and vomiting (59,86.7%), alopecia (57,83.8%), diarrhea (47,69.1%), mucositis (43,63.2%) and loss of appetite in (38,55.9%). Increased occurrence of adverse effects was seen in the previous use of chemotherapy and metastatic disease. Filgrastim prophylaxis was administered to (29, 42.6%) participants who developed chemotherapy-induced neutropenia.

Conclusion: EMACO regimen achieves high remission rates for early GTN. A positive history of chemotherapy use and metastatic disease is associated with an increased tendency to develop adverse effects of EMACO regimen. Filgrastim prophylaxis maintained the treatment schedule among these patients.

Recommendations: Adverse effects should be actively monitored especially in patients with metastatic disease and where chemotherapy has previously been used. Health workers administering chemotherapy should be well trained to minimize adverse effects.

CHAPTER ONE: INTRODUCTION

1.1 Background

Gestational Trophoblastic Neoplasia (GTN) is a group of invasive tumors that arise from the trophoblastic epithelium. They include invasive mole, gestational choriocarcinoma, placental-site trophoblastic tumors, and epithelioid trophoblastic tumor. The incidence of GTN varies in different parts of the world based on racial and environmental factors. Incidence in the developed countries is low; choriocarcinoma is seen in 1 in 45000 pregnancies (1). It, however, has a higher occurrence in Asia, South America, and Africa. In Asia and South America incidence is 1 per 120 pregnancies while in Africa epidemiological studies are scanty. In a study of Gestational Trophoblastic Disease (GTD) in Nigeria, incidence was estimated to be 3.8 per 1000 in the North Eastern part of the country and 4.7 per 1000 in the Southeast (2). Studies carried out in single GTN treatment centers in Rwanda, Ethiopia and Kenya have shown that a significant number of women are affected (3) (4) (5).

Patients with GTN are divided into two groups; International Federation of Gynecology and Obstetrics (FIGO) stage II, III or IV and a World Health Organization (WHO) prognostic score ≥7, is high risk while FIGO stage II and III and a WHO score ≤6 is low risk.

Table 1 - FIGO anatomic staging

Stage	Extent of disease
Stage I	The disease is confined to the uterus
Stage II	Disease extends outside the uterus but is limited to the genital structures
Stage III	Disease extends to the lungs with or without genital tract involvement
Stage IV	Tumor metastatic to any other site

Table 2 - Modified WHO prognostic scoring for GTN

Prognostic factor	0	1	2	4
Age	<40	≥40	-	-
Antecedent pregnancy	Mole	Abortion	Term	-
Interval months from index pregnancy	<4	4-6	7-12	>12
Pre-treatment serum β-HCG (IU/liter)	<1000	<10000	<100000	>100000
Largest tumor size in cm (including uterus)	<3	3-4	≥5	-
Site of metastases	Lung	Spleen, Kidney	Gastrointestinal	Liver, Brain
Number of metastases	-	1-4	5-8	>8
Previously failed chemotherapy	-	-	One drug	≥2 drugs

EMACO is a multidrug regimen consisting of etoposide, high dose methotrexate with folinic acid supplementation, actinomycin D, cyclophosphamide, and vincristine. It was formulated by Newlands et al in London when it was established that etoposide was highly effective in management of gestational trophoblastic neoplasia. In their study, 76 GTN patients were put on EMACO and high clinical response rates (80%) and survival rates (82%) were reported (6). Kim et al compared the earlier multiagent regimens MAC and CHAMOCA with EMACO and reported remission rates of 67.5%,76.2%, and 90.6% respectively, validating EMACO as the most appropriate regimen for the management of high-risk GTN (7).Several groups worldwide reported findings that concur with Newlands et al with regards to efficacy and safety of EMACO regimen. Bolis et al from Italy carried out a study on seventeen patients on EMACO regimen and observed a 94% response rate. Only one participant was unresponsive and during follow up there were three cases of relapse. Overall the patients achieved a survival rate of 88%

(8).Schink et al from the U.K. reported initial findings on the effectiveness and adverse effects when EMACO regimen was used as first line management for patients with high-risk metastatic GTN in 1992. Ten (93%) of the first 12 patients we treated achieved complete remission with EMACO. Severe adverse effects were not reported, except for neutropenia which developed in 12% of the chemotherapy cycles and interrupted treatment for one week (9). An Australian study investigated 35 patients with metastatic disease being managed with EMACO regimen. The rate of survival was 89% with a total of four deaths. These patients had brain and liver metastases. One of them had a diagnosis of placental site trophoblastic tumor (10). In 1997, Bower et al managed 272 high risk GTN patients with EMACO regimen. Of these, 214(78%) were responsive to treatment. Among the 47(22%) unresponsive cases, 33(12%) responded to additional treatment modalities such as surgery and second-line cisplatin-based chemotherapy. However, 11(4%) succumbed to the disease (11). Similarly, Turan et al. from Turkey, Lu et al. from China, and Cagayan from the Philippines reported remission rates of 82%, 78% and 72% and survival rates of 91%, 93% and 86%, respectively, when the EMA-CO chemotherapy regimen was used as primary therapy for the management of high-risk GTN (12)(13)(14). In more recent studies (2012), Priyanka et al did a study in Asia and reported that EMACO achieved remission in 77% of the patients, resistance in 23% and overall survival rates of 95%. They concluded that EMACO is the preferred multiagent chemotherapy regimen as it is highly effective, well tolerated and it conserves fertility (15). In Africa, EMACO regimen has been used widely. A study in Rwanda reported the use of EMACO among patients unresponsive to single-agent methotrexate and among high-risk GTN patients. The rates of remission were reported to be 77% (3).Other countries which have carried out studies on EMACO include Ghana, Senegal, and Nigeria. According to the National Guidelines for Cancer Management, Kenya EMACO has been adopted as first line regimen in management of high risk GTN (16). In KNH, the regimen is used as primary treatment for GTN patients in FIGO stage II, III or IV with a WHO prognostic score >7. It is also used when patients are unresponsive to either methotrexate or actinomycin D. It is administered every 14 days as etoposide 100mg/m² days 1 and 2, methotrexate 300mg/m² day 1 and actinomycin D 0.5 mg IV bolus day 1 and 2. Four doses of folinic acid 15 mg 12 hourly are also administered from day 2 starting from 24 hours after commencement of methotrexate. The EMA alternates with cyclophosphamide 600mg/m² and vincristine 1mg/m² on day 8. The second cycle begins on day 15. Treatment is initiated among patients whose hematological profile is within normal range. A white cell counts greater than 3000, granulocyte count greater than 1500 and platelet count greater than 100,000 per microliter are the requirements. Subsequent doses are administered if granulocyte count is

greater than 1000 per µl and platelets above 75000 per µl. It has been shown to achieve high rates of remission (6).In addition, it is well tolerated and conserves fertility (17). However, it has been reported to result in development of toxic effects. The individual drugs within the regimen have a range of toxic effects. Cumulative toxicity occurs when similar adverse effects are caused by different individual drugs in the regimen. These drugs act on the proliferating cycle of the cell. Exposure of tumor cells to these drugs leads to activation of tumor cell apoptosis pathways. GTNs are generally rapidly proliferating and are usually highly chemosensitive. Normal cells in the body with a high growth fraction that tend to be injured the most due to chemotherapy. Those cells include the bone marrow, gastrointestinal tract, hair follicles, and reproductive organs. The resulting symptoms include myelosuppression, emetic potential due to disruption of cells in the stomach which causes nausea and vomiting and alopecia. Adverse effects of chemotherapy may lead to reduced bioavailability of drugs. It is estimated that between 9% and 33% of GTN resistance to single-agent chemotherapy may be ascribed to severe side effects of the chemotherapy agents necessitating multi-agent regimen (18).Similarly, skipped courses, increasing dosing intervals and administration of sub-therapeutic doses of the chemotherapeutic agents allow growth of the tumor especially tumor cell subpopulations with potential resistance to the agents. Delayed initiation of treatment due to any cause allows further progression of the tumor.

Predominant toxic effects of EMACO include myelosuppression, alopecia, and mucositis. Some adverse effects are unique to a particular drug in the regimen. Etoposide is associated with allergic reactions and a risk of developing leukemia. Nephrotoxicity, dry cough, and hemiparesis are seen when methotrexate is used. Nausea and vomiting are frequently reported when actinomycin D is used. Cyclophosphamide can cause bladder injury which manifests as haematuria. Vincristine has been associated with peripheral neuropathy. Hepatic derangements are exacerbated by all the five drugs in the regimen. The low neutrophil count is a common occurrence among patients on EMACO (19). Neutrophil count in normally healthy individuals is approximately above 2000 cells per µl. Values below this count indicate neutropenia which is classified according to severity. Neutropenia puts the patient at risk for bacterial, fungal and viral infections. Febrile neutropenia (FN) may also occur. It is a serious and potentially fatal condition characterized by body temperature above 38˚C for more than one hour while having neutrophil counts less than 500 cells per µl (20). Febrile neutropenia (FN) is a major contributor to morbidity and mortality. Management of both FN and infections may necessitate hospitalization and intravenous antibiotics leading to high costs of treatment (21). Adverse

effects may also limit the total dose of chemotherapy that can be delivered or delay chemotherapy treatment schedule thereby compromising treatment outcome (22).

Table 3 - Risk factors for adverse effects

<table>
<tr><td colspan="3">Factors associated with adverse effects</td></tr>
<tr><td>Type of malignancy</td><td>Chemotherapy regimen</td><td>Patient risk factors</td></tr>
<tr><td rowspan="7"></td><td rowspan="2">Treatment intent; curative versus palliative.</td><td>Age>65 years</td></tr>
<tr><td>Poor performance status, ECOG>2</td></tr>
<tr><td rowspan="2">Number of myelosuppressive agents used >2</td><td>Poor nutritional status</td></tr>
<tr><td rowspan="5">Co-morbidities (Hypertension, Tuberculosis, HIV)</td></tr>
<tr><td rowspan="5">Extensive prior treatment</td></tr>
<tr><td>Bone marrow involvement</td></tr>
<tr><td>Advanced disease</td></tr>
<tr><td>Concomitant medications</td></tr>
</table>

The type, frequency and total dose of chemotherapy agents influence the likelihood of developing undesirable toxic effects (20). Patients may be on other medications like antibacterials, antihypertensives, antipsychotics and anti-epileptic drugs which may potentiate the toxic effects of EMACO. It has been established that changes occur in bone marrow reserves with increasing age (23). Infectious diseases such as tuberculosis, human immunodeficiency virus (HIV), viral hepatitis, cytomegalovirus, and Epstein-Barr virus have also been associated with adverse effects (24) (25). Co-morbidities which may be chronic are associated with declining renal and hepatic function and have also been shown to influence the occurrence of adverse effects (25). Other risk factors include poor performance status and nutritional deficiency (26).

Granulocyte Colony Stimulating Factor (filgrastim) is the standard treatment of chemotherapy-induced neutropenia. It is a hematopoietic glycoprotein which regulates production and function of neutrophils. It controls the proliferation of committed progenitor cells and influences their maturation into mature neutrophils. Filgrastim also stimulates the release of neutrophils from bone marrow storage pools and reduces their maturity time. It also increases the phagocytic activity of mature neutrophils. In patients receiving cytotoxic chemotherapy, filgrastim can accelerate neutrophil recovery, reducing the duration of the neutropenic phase. Filgrastim has been used to shorten the duration of neutropenia in patients who have undergone chemotherapy. Filgrastim is expensive and its use could increase the overall treatment cost of the patient.

Several guidelines have been developed to ensure patient needs are met at the minimum cost. They guide the use of colony-stimulating factors in the management of chemotherapy-induced neutropenia on the basis of disease, patient, and regimen characteristics. They include the American Society of Clinical Oncology (ASCO), British Columbia Cancer Agency (BCCA), and European Organization for Research and Treatment of Cancer (EORTC), European Society for Medical Oncology (ESMO) and National Comprehensive Cancer Network (NCCN). EORTC, ASCO and NCCN guidelines all recommend prophylactic use of filgrastim in high-risk regimens (27). A review of these guidelines by Cancer Care Ontario categorized EMACO as a high-risk regimen (28). A systematic review of randomized controlled trials has shown that prophylactic use of filgrastim has led to a 46% decrease in incidents of neutropenia during chemotherapy. Other studies have shown that the use of filgrastim for prophylaxis has led to better outcomes and reduced prolonged hospitalization (22).

1.2. Problem statement

EMACO regimen has been associated with a wide variety of adverse effects. Studies in different settings have reported that alopecia, nausea, and vomiting, loss of appetite, reversible neurotoxicity and myelosuppression occur early in patients on EMACO regimen (29). Pritchett et al also reported generalized pain and weakness, diarrhea and mucositis (3). Different studies have found cases of peripheral neuropathy among patients(17)(30). Shrivastava et al reported liver derangements that resulted in treatment delay (31). Secondary malignancies, such as acute myeloid leukemia has been reported as a late adverse effect of EMACO regimen (32)(33).In our setting, only myelosuppression and alopecia have been reported.The prevalence of other adverse effects of EMACO regimen is unknown. This is because they are under-reported (5). A number of studies have shown that as age, diet and performance status have an effect on

physiological processes. These factors may influence the severity of adverse effects in patients receiving chemotherapy (34)(35)(36). Concomitant therapy and comorbidities may make patients susceptible to adverse effects of chemotherapy. The effectiveness of EMACO regimen has been evaluated in different settings worldwide, with different outcomes(3)(9). Its effectiveness, however, has not been determined in our setting. Prophylactic filgrastim is not used in these patients and neutropenia is managed once it sets in, despite previous studies done in KNH recommending filgrastim prophylaxis use to reduce incidences of interruption of therapy (19). Treatment delays are undesirable because it compromises outcomes resulting in reduced overall survival. In addition, it may allow growth of tumor cell subpopulations with potential resistance to EMACO. Introduction of resistance will necessitate salvage combination therapy with EMAEP (etoposide, methotrexate, actinomycin-D, etoposide, cisplatin) which are more toxic (14) (37).EMACO is categorized as high-risk regimen and the use of prophylactic filgrastim adjuvant therapy is advised (28). Unfortunately, in KNH, EMACO is often administered without filgrastim prophylaxis among GTN patients. The purpose of this study is to evaluate the effectiveness and adverse effects of EMACO regimen. It also aims to determine the prevalence of filgrastim prophylaxis among GTN patients on EMACO at KNH.

1.3. Objectives

1.3.1. General objectives

i. To determine the effectiveness and adverse effects of EMACO regimen among GTN patients in KNH.

1.3.2 Specific objectives

i. To determine the prevalence of adverse effects of EMACO regimen among GTN patients
ii. To identify the risk factors for adverse effects of EMACO regimen among GTN patients
iii. To evaluate the trend of β-HCG levels in GTN patients on EMACO regimen
iv. To determine the prevalence of prophylaxis of neutropenia with filgrastim among GTN patients on EMACO regimen

1.4 Research questions

i. What is the prevalence of adverse effects of EMACO regimen among GTN patients on EMACO in KNH
ii. What are the risk factors for adverse effects of EMACO among GTN patients in KNH?
iii. What is the trend of β-HCG levels in high-risk GTN patients on EMACO in KNH?
iv. What is the prevalence of prophylaxis of neutropenia with filgrastim among GTN patients on EMACO?

1.5 Justification of the study

Earlier studies in different groups worldwide have reported adverse effects of EMACO regimen. In our setting, toxic undesirable effects of EMACO have been reported to be anemia, neutropenia, and thrombocytopenia. A major issue among our patients is treatment delay due to hematological, renal or liver derangements. This has contributed significantly to instances of treatment resistance, morbidity, and mortality. This study seeks to identify risk factors that predispose to adverse effects of EMACO among our GTN patients. It also seeks to determine the effectiveness of EMACO, the prevalence of all adverse effects. The results of the study will guide the clinicians on measures to take before or during treatments to improve outcomes.

1.6 Significance and anticipated output

The beneficiaries of this study are GTN patients being treated with EMACO. The findings on risk factors predisposing to adverse effects of EMACO will give guidance on the preventive measures to be taken. This will enable delivery of a full dose EMACO regimen without interruptions to achieve complete remission. This will be cost effective for the patient since unnecessary hospitalizations and treatment of other infections will be avoided. In addition, it will relieve anxiety in the patient since complete remissions will be achieved after a few cycles of chemotherapy. The findings of this study will be useful to caregivers of these patients since they will be able to ameliorate EMACO-induced adverse effects by identifying risk factors, modifying them where possible and administering filgrastim support. This will enable a better prognosis reducing unnecessary hospitalization and increased treatment costs leading to improved quality of life. It will be useful for medical students as a primary source of information on adverse effects of EMACO regimen among GTN patients at KNH.

1.7 Delimitations

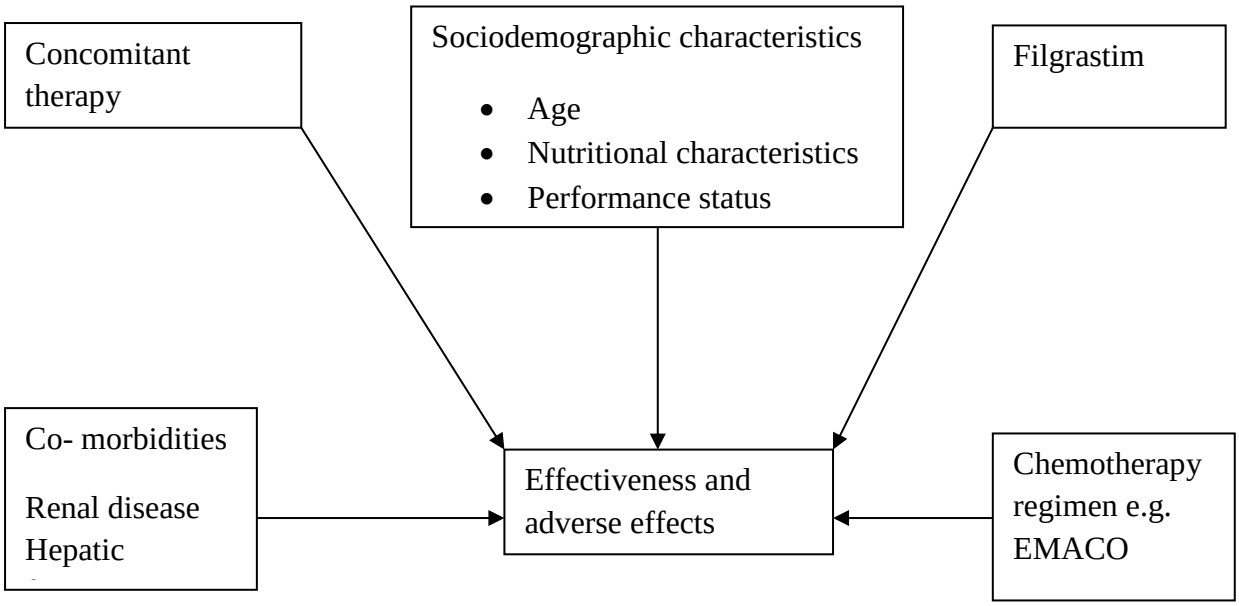
EMACO is a well-tolerated regimen that has been associated with adverse effects. This study aims to determine the prevalence of these adverse effects without including the management of adverse effects.

1.8 Limitations

Study subjects will be sampled from those seeking treatment in KNH and this may introduce selection bias. GTN patients being treated using EMACO in KNH are few; this may limit the statistical power of the study.

1.9 Conceptual/Theoretical framework

Figure 1 - Conceptual/Theoretical framework



In a study determining the efficacy and adverse effects of EMACO regimen, an attempt is made to explain the effect of independent variables on adverse effects. Effectiveness and adverse effects of EMACO regimen is the dependent variable. The independent variables include sociodemographic characteristics, chemotherapy regimen, concomitant therapy, co-morbidities, and filgrastim prophylaxis. Adverse effects of EMACO include myelosuppression, alopecia, stomatitis and mucositis among others. The individual drugs in the regimen have a range of toxic effects. Cumulative toxicity occurs when different drugs cause similar adverse effects. These toxicities predominate when patients are put on EMACO.

Sociodemographic characteristics include increasing age, nutritional status and performance status. Elderly age is associated with a range of physiologic changes. This may result in an increased prevalence of comorbid ailments such as hypertension, diabetes and congestive heart disease among others. Metabolic functions of the liver and excretion function of the kidneys are diminished resulting in altered pharmacokinetic profile. Increasing age is also associated with hematological toxicity due to reduced bone marrow regeneration. Diet deficient in cobalamin, iron and folic acid contribute to adverse effects such as hematologic toxicity. Poor performance status is also a risk factor of adverse effects of EMACO regimen.

Filgrastim, a recombinant human granulocyte colony-stimulating factor is a hematopoietic growth factor which regulates the production and function of neutrophils. Filgrastim controls the proliferation of committed progenitor cells and influences their maturation into mature neutrophils. Filgrastim prophylaxis is used among patients on myelosuppressive dose-dense chemotherapy regimens like EMACO, to minimize treatment interruption and dose adjustments.

Concomitant therapy is common among cancer patients. Use of these drugs may exacerbate the adverse effects of EMACO. Drugs can cause myelosuppression, and they are indicated in neutropenia. Medications that have been associated most frequently with neutropenia include propylthiouracil, erythromycin, and procainamide. Drugs act through different mechanisms. They may have cytotoxic effects on the undifferentiated pluripotent cells or myeloid precursor's e.g. antipsychotics (phenothiazines), antidepressants and chloramphenicol. Others may act by an immune-mediated mechanism where a drug acts as a hapten which induces antibody formation. These antibodies are subsequently destructive to the granulocytes even in the absence of the drug. Drugs which act in this way includes gold, aminopyrine, and propylthiouracil. Drugs may also form immune complexes which attach to the neutrophils, for example, quinidine. Other drugs that have been implicated in immune-mediated neutropenia include cephalosporins, penicillins, sulphonamides, phenothiazines, and hydralazine. Some drugs may employ both mechanisms.

Co-morbidities like underlying renal failure and heart disease may exacerbate the chemotherapy-induced adverse effect. Autoimmune conditions like rheumatoid arthritis may be associated with the body's immune system targeting neutrophils for destruction. It also includes bacterial infections (typhoid fever, shigella enteritis, brucellosis, and tuberculosis), viral infections (HIV, viral hepatitis, and cytomegalovirus), and parasitic infections (malaria).

CHAPTER TWO: LITERATURE REVIEW

2.1 Introduction

Studies on the effectiveness of EMACO have shown high rates of remission accompanied by toxic effects. Adverse effects of EMACO regimen among GTN patients have not been investigated in our setting. Previous studies on GTN patients on EMACO regimen have shown that myelosuppression and mucositis are among the dose-limiting toxicities. It is important to ascertain the presence of factors that predispose to adverse effects in this population. This will provide guidance for use of supportive measures like colony-stimulating growth factors.

2.2 Adverse effects of EMACO

EMACO regimen has been associated with several adverse effects. DNA damage has been linked to several side effects. Akyol D et al reported a positive association between the extent of DNA damage and that of the toxic effects of EMACO. The side effects and their frequency of occurrence were fever 71.4%, leucopenia 57%, elevated liver enzymes 57%, thrombocytopenia 57% and anemia 57% (38).

Myelosuppressive effect of EMACO in GTN patients has been established in a number of studies. Priyanka et al found that grade 1 anemia was the most common toxicity affecting 24 of the 25 patients in the study. Grade 1 FN also caused significant toxicity affecting 11 of the 25 patients. Neutropenia was observed in 8 patients. The second most common toxicity was grade 1 oral mucositis which was seen in 5 (24%) patients. Liver toxicity was observed in 3 patients but 1 succumbed. Thrombocytopenia and alopecia were both seen in 2 patients (15).In another study, Schink et al found that neutropenia interrupted treatment in 12% of cycles by a period of one week (6). Anjana et al reported grade 1 and 2 hematological toxicity as being the most common affecting 50% of study subjects(17). Neutrophils are the main cells in innate immunity and are also involved in inflammatory response. Low neutrophil counts allow bacterial invasion and multiplication and blunt the inflammatory response. Complications include life-threatening infections and fever. They are associated with substantial morbidity, mortality and treatment costs (39). Neutropenia may necessitate dose reduction and delay which is undesirable since EMACO use in high-risk GTN is with curative intent; which is achieved when it is administered at short intervals without interruption. Several studies on treatment of GTN with EMACO found that neutropenia was the most common dose-limiting toxicity leading to treatment delay (6) (17) (15). Another study by Clasien et al on adverse effects of EMACO among GTN patients

in the Netherlands reported that anemia was common with 7 of 50 patients having WHO grade 3 anemia with 23 patients (54%) receiving transfusions. WHO grade 3 and 4 neutropenia was observed in 24 (57%) of the patients. Treatment delay developed in 15 of these patients. Neuropathy was reported by 16 (38%) of the patients leading to dose reduction or stopping the use of vincristine in 11 of them. One case of acute myeloid leukemia was seen during the follow up after remission (40). A study on GTN patients in KNH reported neutropenia among 63% of the patients, treatment had to be interrupted and the patients put on filgrastim. This led to treatment delay (5). Shina et al reported that bone marrow suppression was the most common adverse effect among GTN patients being treated with EMACO regimen. Treatment delay for 2-3 weeks resulted from grade 2-3 neutropenia and filgrastim prophylaxis was required by these patients (41). Another study in a Rwandan hospital reported one incidence of grade 3 anemia and two patients on methotrexate had grade 3 neutropenia. A higher number of cases of toxicity were observed with EMACO regimen. Grade 3 to 4 anemia affected 39% while neutropenia was seen in 72% of the patients. Grade 3 and 4 neutropenia was seen in 28% and 44% of the patients respectively. Treatment delay was experienced by 13 patients on EMACO and 2 patients on methotrexate due to neutropenia and elevated liver enzymes respectively. Other adverse effects generalized pain, loss of appetite and weakness (3).According to a study by Ken Kobayashi et al, etoposide is associated with myelosuppression, particularly neutropenia limiting its current use in chemotherapy (39). Another study by Mayall B et al found that neutropenia is seen when there is a reduced clearance of methotrexate due to impaired renal function or concomitant therapy (42). A study on chemotherapy-induced myelosuppression by Otieno -Abinya et al observed grade 4 neutropenia in 22.6% of patients on CHOP regimen. The study observed that severe anemia and thrombocytopenia rarely affected patients with solid tumors on chemotherapy (19). Matsui et al reported that MEA regimen without cyclophosphamide or vincristine is used on high-risk GTN patients due to reduced toxicity. Grade 4 leukocytopenia was seen in 5.3% of the 39 high-risk GTN patients who took part in the study (43). Complications of neutropenia can increase cancer-related morbidity. Deaths attributed to sepsis have been reported in various studies (19).

Treatment interruption or dose reduction and use of supportive measures allow the neutrophil count to rise above 1000 cells/mm^3 so that treatment can be continued. Treatment reduction and delay may compromise long-term disease control and reduce chances of survival (24). Alopecia is a common side effect of most chemotherapeutic agents. Hair follicles are rapidly dividing cells similar to the targeted tumor cells. Alopecia is largely reversible and it may be complete

or partial. Shrivastava et al conducted a 6-year retrospective study and reported that alopecia was seen in all patients treated with EMACO regimen. A significant number of patients experienced hematological side effects like anemia, neutropenia, and thrombocytopenia. Only 1 person had grade 3 mucositis after the first cycle of the regimen (29). Another study by Burrows A et al reported nausea, vomiting, and alopecia among GTN patients on EMACO regimen (44).

EMACO regimen is associated with a risk of secondary malignancies due to its etoposide component. G.J. Rustin et al observed a slight increase in risk for secondary tumors particularly leukemia when etoposide was a component of combination therapy for GTN (45). Methotrexate is metabolized by the liver and is associated with elevated liver enzymes. It is the drug of choice in the treatment of low-risk GTN, but in the case of hepatic dysfunction, actinomycin D should be used. A study carried out in Northern Thailand Tertiary Care Center reported that a significant side effect of methotrexate was liver dysfunction and mucositis (46) (11). Methotrexate has also been associated with acute tubular necrosis, meningeal irritation, encephalopathy, and temporary or permanent paralysis.

Actinomycin D has more adverse effects compared to methotrexate hence is the secondary agent in the management of low-risk GTN. C. Aghajanian reported that actinomycin is associated with myelosuppression, nausea, and alopecia (47). A Cochrane review that included five randomized clinical trials (RCT) in 2014, both actinomycin D and methotrexate had statistically comparable side effect profiles. Nausea, vomiting, alopecia, diarrhea, and anemia were observed.

Cyclophosphamide is associated with mucositis especially of the bladder which manifests as hematuria. Adequate rehydration to improve the flow of urine or administration of mesna can be used to manage this side effect. Vincristine is associated with peripheral neuropathy.

2.3 Risk factors for adverse effects

Risk factors include patient and regimen characteristics. Predictive models that are used to assess patients for characteristics that may predispose them to adverse effects of EMACO have been developed (34). The models are based on either unconditional factors such as pre-treatment measures or on conditional factors such as the patient's hematologic response in the first cycle of treatment. Conditional models have been shown to be better predictors of chemotherapy-induced adverse effects, dose reduction or delay than pre-treatment models (48). Patients at risk

of adverse effects are managed using preventive strategies that reduce occurrences of myelosuppression and its complications (27).

2.3.1 Sociodemographic characteristics

The disparity in hematologic indexes has been established among racial and ethnic groups. Saxena S. and Wong E.T. reported that higher red blood cell counts and hemoglobin levels among Asians compared to blacks and Latin Americans (49). Hsieh et al compared different races in the United States population and found the incidence of neutropenia among whites at 0.25%, blacks 4.05%, Mexican-American 0.35%, and others at 0.98% (39). Lower neutrophil counts have been established in Africans in comparison to Europeans and Americans (50). Studies in Africa have also shown variation in neutrophil counts among people from different ethnic groups. In a study on the causes of neutropenia, ethnicity accounted for 7.2% of the cases (24).

Older age has been identified as an independent risk factor for adverse effects. It is associated with changes in the bone marrow microenvironment resulting in hematologic toxicity (27). Aging has been shown to cause decreased production of regulatory growth factors resulting in reduced bone marrow reserves (51). Salive et al observed that there is a general increase in the proportion of anemic patients with increasing age (35). The median baseline absolute neutrophil count (ANC) of a population with a median age of 60-year-old patients was found to be 140 cells/mm^3 in a study (52). In a systematic review, different studies reported that low baseline blood counts and a precipitous, early drop in counts of all hematopoietic cell types in cancer patients are strong predictors of myelotoxicity (53). Patients older than 65 years are twice as likely as younger patients to suffer febrile neutropenia. Hsieh et al stratified patients by age and observed that the incidence of neutropenia was highest among patients aged 65 years older (54).

Aging can also exacerbate mucositis as a result of treatment with EMACO regimen. It has been associated with changes in the physiology of the gastrointestinal system resulting in increased mucosal damage (35).

Poor nutrition has also been associated with adverse effects (55). A study on the influence of malnutrition on acute hematologic toxicity found that altered nutritional status correlates with increased risk of severe hematological toxicity following chemotherapy (56). Poor performance status has been shown to predispose to chemotherapy-induced adverse effects (57). The European Cancer Anemia Survey reported that anemia significantly correlates with poor

performance status (35).

2.3.2 Type of cancer and chemotherapy

The type of cancer determines the level of adverse effects. Hematopoietic cancer results in severe myelosuppression. Similarly, the more severe the disease is the greater the incidences of toxicity. Different types of chemotherapy agents cause adverse events to varying degrees. Among the chemotherapy agents for GTN, platinum-based agents are considered the most myelotoxic and are associated with grade 3 or 4 neutropenia (37). P.G. Rose conducted a study on etoposide, evaluated its toxicity profile and found that grade 3 and 4 hematologic toxicity was common with 41.2% leucopenia, 45.4% neutropenia, 13.4% anemia, and 9% thrombocytopenia. One patient was reported to develop leukemia (35). Tonanont et al studied the toxicity of methotrexate among 94 intermediate and low-risk GTN patients and reported that the most common toxicities were mucositis and hepatotoxicity in 6.4% of patients. Neutropenia affected 3 patients while thrombocytopenia, hyperpigmentation, nausea, and vomiting affected 1 patient each (58). Prapaporn et al also studied GTN patients on single-agent chemotherapy and reported that methotrexate showed no alopecia, but had a few cases of nausea and vomiting. Six patients experienced hepatic dysfunction and mucositis and their chemotherapy was changed to actinomycin D (59). A study on toxic effects of actinomycin D among GTN patients in Istanbul University, Turkey found that it was associated with nausea and vomiting while methotrexate caused severe stomatitis in 8 of 18 (44%) low-risk GTN patients. In high-risk GTN patients managed with EMACO regimen, myelosuppression was significant affecting 39% of the patients, with 2 cycles being complicated by neutropenic sepsis and thrombocytopenia that was managed with platelet transfusion (12). Covens et al reported that adverse effects of actinomycin D are gastrointestinal toxicity and alopecia. This was characterized by mucositis, nausea, and vomiting. Alopecia affected all the women enrolled in the study (60). L.S Dobson et al carried out a study on efficacy and toxicity of MEA regimen among high-risk disease patients and EA regimen among low-risk patients and found that 64% grade III or IV neutropenia,51% experienced grade II/III anemia and 8% grade II or higher neutropenia. Nausea, emesis, and stomatitis were observed in 29%, 30% and 37% of the patients respectively. Alopecia affected all the study subjects (61). Cyclophosphamide, etoposide, and vincristine have also been shown to cause myelosuppression, alopecia, and mucositis. Most treatment regimens have these drugs in combination potentiating their individual toxicities (19). The doses of the drugs, the administration schedule of the treatment regimen influence adverse effects. Increasing the dose density, dose intensity, and relative dose intensity increase the

potential for developing toxicity (62). Several reviews including Cancer Care Ontario Review have attempted to categorize regimens according to the degree of risk of adverse effects and EMACO is considered a high risk due to high dose intensity and its dose-dense treatment schedule (28). Pre-existing myelosuppression from previous cycles of treatment predisposes to low blood cell counts. Studies have reported that myelosuppression is most severe after the first cycle of chemotherapy probably because of the bone marrow capacity to supply mature neutrophils to the peripheral blood for up to 8 days (19).

2.3.3 Concomitant therapy

Current or previous therapies may predispose to adverse effects. The incidence of thrombocytopenia attributed to drugs is estimated to be 10-18 cases per million. Autoimmune hemolytic anemia is estimated to be 10 times more than drug induced. Methyldopa, intravenous penicillin, and cephalosporins (cefotetan and ceftriaxone) have been implicated as causes of drug-induced hemolytic anemia. Piperacillin and hydrocortisone have also been associated with drug-induced hemolytic anemia (63). Johnson et al carried out a 20-year retrospective study on serology of drugs associated with drug-induced immune hemolytic anemia and reported that 52% were due to cephalosporins (cefotetan), penicillin and its derivatives, NSAIDS, quinine, and quinidine caused anemia (64). Lars et al reviewed causes of thrombocytopenia and anemia and reported that drugs such as oral diuretics, analgesics, and diuretics were implicated in 25%-36% of cases (65). A study on the causes of neutropenia found that 2.1% of cases of neutropenia in the population under study were drug related (24). A study in England and Wales involving 3224 patients found that the risk of neutropenia was 34.7 for users of antithyroid drugs, 9.5 for users of disease-modifying antirheumatic drugs (DMARDs) and 7.6 for aminosalicylates. Other drugs that had statistically significantly increased risks of neutropenia include antibacterials, non-opioid analgesics, non-steroidal anti-inflammatory drugs (NSAIDS), antidepressants, proton-pump inhibitors, and anti-epileptics. Increase in the risk of adverse effects predominantly occurred during the first months of treatment (66). Other drugs that have been shown to exacerbate EMACO regimen induced adverse effects include. Mucositis, a dose-limiting toxicity influences nutritional intake and generally, it determines the ability of the patient to tolerate chemotherapy. It is exacerbated by states of neutropenia which allow invasion of gram-negative bacteria and fungi. Drugs that predispose to neutropenia such as phenothiazines, diuretics and immunosuppressive agents should be avoided. Antidepressants have been associated with xerostomia and mucositis due to anticholinergic activity. Other drugs that have been shown to cause mucositis include antihypertensives, sedatives, opiates, and

antihistamines. Other factors that exacerbate mucositis include smoking, alcohol consumption, poor nutritional status and poor oral hygiene (67). Duncan et al conducted a review on oral and intestinal mucositis and reported that it is caused by drugs associated with free radical damage, DNA damage, cell cycle arrest and disturbance of cell interactions. Anti-inflammatory agents like indomethacin may exacerbate mucositis in a review on oral and intestinal mucositis (68).

2.3.4 Co-morbidities

Adverse effects can also occur due to underlying medical conditions and infections. Increasing age is associated with increased frequency of comorbidities. Anemia is a complication of nephrotoxicity due to diminished ability to synthesize erythropoietin. I. MacDougal reported that uremic toxins exacerbate anemia (69). A study on the causes of neutropenia in adults found that infectious diseases accounted for 9.3%, autoimmune diseases 9.3%, hematological disease 9.3% and thyroid disease 8.2% (24).HIV infection in Africa is widespread and there is a chance of finding patients with concurrent GTN and HIV infection. Hematologic toxicity of EMACO may further compromise immunity in these patients leading to increased morbidity and mortality. Moodley et al (55) carried out a study on 78 women with GTD. Among them, 24 (31%) were seropositive. Neutropenia affected 52% of the patients; thrombocytopenia affected 11.5% and 6.4% experienced renal failure. The rate of mortality was higher among patients who had abnormal blood profiles particularly anemia (42%) before commencing treatment and other comorbidities such as hyperthyroidism (35%). Fifteen patients succumbed due to widespread disease, multiorgan failure, septicemia, and neutropenia; of these 4 were related to adverse effects of chemotherapy (70). A study by Shari Chen et al reported that neutropenia hospitalizations were common among older adults with comorbidity. Adverse effects of HIV may be due to viral toxicity to hematopoietic tissue. The use of antiretroviral (ARV) drugs which may be myelotoxic, complications with secondary opportunistic infections and malignancies may also contribute to neutropenia (71). In tuberculosis infection, use of isoniazid exacerbates adverse effects. Co-morbidities are associated with a decline in hepatic or renal function leading to accumulation of toxins and this may further contribute to adverse effects. Depressive disorders are a common complication among cancer patients. Antidepressants have an anticholinergic activity which contributes to xerostomia leading to mucositis (67).

2.4 Beta HCG

HCG is a hormone secreted by tumor cells in GTN and has been employed as a reliable tumor marker (72). HCG levels have been used to diagnose GTN following an evacuation in patients with GTD. Soheila et al found that HCG levels were significantly higher among women with GTN and reported that it strongly indicates early disease (73).HCG levels indicate the extent of growth of the tumor, with pretreatment levels >100,000 indicating advanced disease. It is estimated that 10^9 tumor cells secrete 10^5 IU of HCG per day, showing that HCG levels have a linear relationship with tumor size (5). When treatment is initiated, the extent of HCG regression can be used to estimate how responsive GTN is to chemotherapy. Burrows et al observed HCG decay curves of GTN patients on single-agent chemotherapy and multiagent chemotherapy and concluded that HCG regression curves can help determine the chemosensitivity of the tumor and will enable early changes in chemoresistant tumors (74). Early disease may respond to single-agent chemotherapy agents while advanced disease responds to different multiagent combinations of chemotherapy. When treatment is successful, HCG levels decline to undetectable levels in most of the population under study. Wolfberg et al found that the risk of recurrence of GTN among women who achieve undetectable GTN levels after treatment is very low (75). Rising HCG levels or a plateau is usually an indication of persistent GTN. During treatment, serial HCG measurements are taken every week to monitor the progress of the patient. When remission is achieved, following completion of chemotherapy follow up is done by taking monthly HCG levels for up to one year due to the risk of relapse within the first year following remission (29). Women who become pregnant during the follow-up period are evaluated for molar pregnancies since HCG levels are higher in GTN compared to normal pregnancy(73).

2.5 Filgrastim use in GTN patients

Filgrastim has commonly been used to manage neutropenia that sets in during treatment in GTN patients on EMACO (15) (24). It shortens the duration of neutropenia allowing treatment to be continued as per schedule (19) (76). In KNH, filgrastim use in high-risk GTN patients to manage neutropenia when it sets in has resulted in undesirable treatment delay (5). A study by Hartmann et al found that filgrastim treatment for neutropenia is not as effective in preventing neutropenic complications as filgrastim prophylaxis before neutropenia develops (77). This is because there is a risk of occurrence of neutropenic complications that the filgrastim intended

to prevent resulting in inefficiency. ASCO guidelines recommend primary filgrastim in patients who have approximately 20% or higher risk of FN on the basis of the patient, disease, and treatment-related factors and in patients receiving dose-dense chemotherapy. Secondary prophylaxis is recommended where FN occurs in a previous cycle of chemotherapy in which treatment delay may compromise outcome (78).EORTC guidelines recommend prophylactic filgrastim in subsequent cycles of chemotherapy following an episode of febrile neutropenia. It also recommends filgrastim support where dose-dense or dose-intense chemotherapy have survival. If reductions in chemotherapy intensity are known to be associated with poor prognosis primary filgrastim prophylaxis may be used to maintain chemotherapy(79). NCCN guidelines evaluate risk for FN on the basis of disease, patient risk factors, and chemotherapy regimen and treatment intent. Filgrastim prophylaxis is recommended for 20% or higher risk. It is given consideration when it is 10-20% but not recommended when risk is low at less than 10% (80).EORTC, ASCO, and NCCN all recommend prophylactic use of filgrastim in high-risk regimens (27). Katy L Cooper et al carried out a systematic review and meta-analysis where twenty studies compared primary prophylaxis with filgrastim compared with no prophylaxis. It observed that filgrastim prophylaxis minimizes the occurrence of neutropenia and its complications so that the treatment schedule is adhered to resulting in favorable outcomes (81). Hartenbach EM et al reported no treatment delay with use of filgrastim on days 3-6 and 9-14 of each cycle in high-risk GTN patients on EMACO (82). Kuderer et al carried out a comprehensive systematic review and meta-analysis of RCTs comparing primary prophylactic filgrastim to placebo or no treatment found that in addition to reducing the risk of FN and early deaths primary filgrastim prophylaxis increased relative dose-intensity (RDI) (83). Primary prophylactic filgrastim use has been demonstrated to have an economic advantage over a wide range of settings as seen in analyses carried out by G.H Lyman (84). Perhaps the relatively high cost of filgrastim limits its use in many settings. Lyman et al described risk models to identify patients at risk for neutropenia so that filgrastim prophylaxis can be used with guidance (34). This maximizes the benefits and minimizes costs in the management of these patients (85).

CHAPTER THREE: METHODOLOGY

3.1 Introduction

This chapter outlines the methods that were used to carry out the study. They included the research design, study location, target population, sample size calculation, methods of sampling, data collection techniques, data management, ethical considerations of the study, work plan and the budget.

3.2 Research design

A retrospective longitudinal study design was used where the effectiveness of EMACO, the prevalence of adverse effects, risk factors of adverse effects and prevalence of filgrastim prophylaxis were evaluated. The longitudinal study design was suitable because this study aimed to observe the effect of various variables in the same sample over a period of time.

3.3 Location of the study

The study was carried out in Kenyatta National Hospital, the largest public hospital in the country. It receives patients on referral from other hospitals or institutions within or outside Kenya and provides them with specialized health care services. The hospital facilitates medical training and research as it is the teaching hospital of the University of Nairobi, College of Health Sciences. It also provides facilities for training in nursing and other health and allied professions. The hospital is located in the area to the immediate west of Upper Hill in Nairobi, the capital and largest city of Kenya. It is about 3.5 kilometers to the west of the city's central business district. The hospital is administered by a 10-person board of directors and employs over 6000 staff. The hospital receives patients through various clinics and wards. Majority of the patients, at least 60% suffer from common illnesses. It has a bed capacity of 1,800 but due to congestion patient numbers can rise as high as 3000. The specialized services provided by the hospital include cancer treatment, radiotherapy, heart surgery, neurosurgery, renal dialysis, and kidney transplant operations, plastic and reconstructive surgery, orthopedic surgery and burns management among others. Data was collected in the health information department and gynecological oncology wards 1B and 1D.

3.4 Target population

Female patients aged 13 years and above diagnosed with GTN who received EMACO regimen in KNH between March 2013 and April 2018.

3.5 Eligibility criteria

3.5.1 Inclusion criteria

Participants who were included were:

1. 13 years and above
2. had a diagnosis of GTN
3. on treatment with EMACO regimen
4. had complete medical records

3.5.2 Exclusion criteria

Study subjects were excluded if they sought treatment outside KNH, patients whose records were missing or suffered from leukemia and other conditions that affected the bone marrow.

3. 6 Sampling

3.6.1 Sample size determination

The sampling frame was drawn from the list of all GTN patients who received treatment at Kenyatta National Hospital in the period extending March 2013 and April 2018.GTN patients treated with chemotherapy throughout the research period were searched through a query of data at the KNH master electronic registry, at the health information department. The records were maintained after coding using the ICD10 classification codes. A search using the code D39 yielded a total of 77 patients. Among these patients, those that were managed with EMACO regimen were included in the study. Wards 1B and 1D treatment registers were also checked to ensure all patients managed with EMACO regimen were included in the study.

Table 4 - Cases of Gestational Trophoblastic Neoplasia (GTN) from March 2013 to April 2018

Source: Health Information Department

Year	Alive	Dead	Total
2013	7	0	7
2014	11	2	13
2015	13	3	16
2016	25	2	27
2017	3	0	3
2018	11	0	11
Total	70	7	77

The formula for sample size estimation was as follows (77);

$n = z^2pq/e^2$

Where;

n = desired sample size,

e = margin of error to be set at 5%,

z = the standard normal variate at 95 % confidence interval (1.96),

p = proportion of patient with neutropenia according to the previous studies. In this study, the prevalence of neutropenia was 52% (55). Thus p = 0.52. Neutropenia was considered because it is a major adverse effect of EMACO.

q = 1 – p, thus q = 1- 0.52 q = 0.48

n = 1.96^2 x 0.48 x 0.52/ 05^2 = 383

Therefore, the estimated sample size should be 383. The total number of patients treated for GTN is 77 for the period under consideration. Because the population was finite, the calculated sample size required adjustment using the formula

n= N x n /N + n, where N is the total number of patients with GTN.

Thus n = 383X77 / 383+77 = 64

Therefore, the sample size was 64

3.6.2 Sampling technique

Universal sampling was used since GTN is a rare condition. Data was obtained from the patient files in the health information department and treatment registers in wards 1B and 1D. Patient files were obtained from the nursing desk. The nursing officer in charge and the health information officer were informed of the study at least one week prior to the study to allow access to the patient records. Patient characteristics were checked to see if the patients were eligible for the study. The number of patients who met the criteria were included in the study. Data abstraction was done at the health records department and the ward stations.

3.7 Data collection

Data was collected using a data extraction form (Appendix 1). The tool was used to abstract information from patient files. It was designed to obtain information on patient demographics, diagnosis, baseline ANC and HCG levels. The exposure of interest was risk factors for adverse effects while the outcome of interest was the reduction of HCG levels and prevalence of adverse effects. Additional information on nutritional status, co-morbidities and concomitant therapy were obtained from patient records. The information was noted on the data extraction form.

3.8 Quality assurance

Data were extracted from patient medical records/files and treatment register. The data extraction forms were pretested in KNH. Patient files were counter checked for accuracy. All data obtained from patient files were double checked by the investigator during data entry. All data extraction case reports were checked for completeness.

3.9 Data management

Records were coded using unique patient numbers to ensure confidentiality. The patient medical records were handled at health information department and within wards 1B and 1D. Any document linking collected data to patient files including raw data were put under lock and key and only accessed by the principal investigator or on request by regulator teams like the ethics committee. All collected data was entered into Microsoft Excel Spreadsheet (2016) software and a database created. Data was stored on a compact disk and flash disk. Data entry was done accurately and analysis carried out.

3.10 Variables

The study was mainly descriptive with an aim to study the effectiveness, adverse effects of EMACO and associated risk factors and prevalence of filgrastim prophylaxis. The independent variable of interest was EMACO regimen while extraneous independent variables were age, nutritional status, co-morbidities, and concomitant therapy. The dependent variable was adverse effects.

3.11 Data analysis

Age of the participants was summarized in form of means, while adverse effects were summarized as proportions and percentages. The bivariate analysis was done to show the outcome variable of interest across different arms of predictor variables. The outcome variable, adverse effects were regressed against potential predictor variables; age, nutritional status, co-morbidities, and concomitant therapy.

3.12 Ethical considerations

Approval to carry out research was sought from KNH/UoN Ethics and Research Committee. Information was provided about the purpose and nature of the research. Privacy and confidentiality were maintained throughout the study by ensuring that identifiable information was replaced by a serial number. Information was protected by a password and only accessed by the principal investigator.

3.13 Study limitations

The small number of study subjects may have made it difficult to apply the results to a larger population. Time constraints limited the scope of the study.

CHAPTER FOUR: RESULTS

4.1 Introduction

This chapter describes the results of the study. It covers the prevalence of adverse effects, the risk factors of adverse effects, the trend of beta HCG levels and the prevalence of filgrastim prophylaxis

4.2 Sociodemographic data

The majority (52, 76.5%) of the participants in this study were between 20 – 39 years of age (Table 5). Most (44, 64.71%) of them were married and 31 (45.59%) had a primary level of education. Many (35, 46.8%) of the patients were overweight or obese.

Table 5 - Sociodemographic characteristics

Characteristic	**Category**	**Participants**	**Percentage**
Age	13-19	2	2.94
	20-29	29	42.65
	30-39	23	33.82
	40-49	14	20.59
Marital status	Single	24	35.29
	Married	44	64.71
Education level	Primary	31	45.59
	Secondary	25	36.67
	Tertiary	12	17.65
Employment	Permanent	4	5.88
	Casual	8	11.76
	Self-employment	22	32.35
	None	34	50.00
BMI	Underweight	6	9.68
	Normal	27	43.55
	Overweight	25	30.65
	Obese	10	16.13

4.3 Prognostic factors

The hydatidiform mole was the most frequent (30, 44.1%) antecedent pregnancy (Table 6). Abortions (28, 41.2%) were also frequent before a diagnosis of GTN while participants with term pregnancy were 9 (13.2%). Thirty-three (48.5%) participants had GTN less than four

Table 6 - Prognostic Factors

Characteristic	Category	Frequency	Percentage
Antecedent pregnancy	Term pregnancy	9	13.24
	Hydatidiform mole	30	44.12
	Ectopic pregnancy	1	1.47
	Abortion	28	41.18
Period of antecedent pregnancy	<4	33	48.53
	4-6	6	8.82
	7-12	10	14.71
	>12	19	27.94
Pre-treatment serum β-HCG (IU/liter)	<1000	8	11.76%
	<10000	23	33.82%
	<100000	16	23.53%
	>100000	21	30.88%
Metastasis	None	47	69.12
	Vaginal/Uterus	8	11.76
	Lung	9	13.24
	Liver	1	1.47%
	Spleen	1	1.47%
	Brain	2	2.94%
Previous chemotherapy	None	51	75
	Single-agent	16	23.53
	Multiple agents	1	1.47
Method of contraception	Oral hormonal	29	42.65
	Non-oral hormonal	20	29.41
	None	19	27.94
Parity	Primipara	9	13.24
	Para 1-Para 5	54	79.41
	Para >5	5	7.35

months after the previous pregnancy; of these participants (8, 11.7%) had low-risk GTN while (25,36.7%) had high-risk GTN. Pre-treatment serum β-HCG levels greater than 100,000 were seen in (21, 30.8%) of the participants.

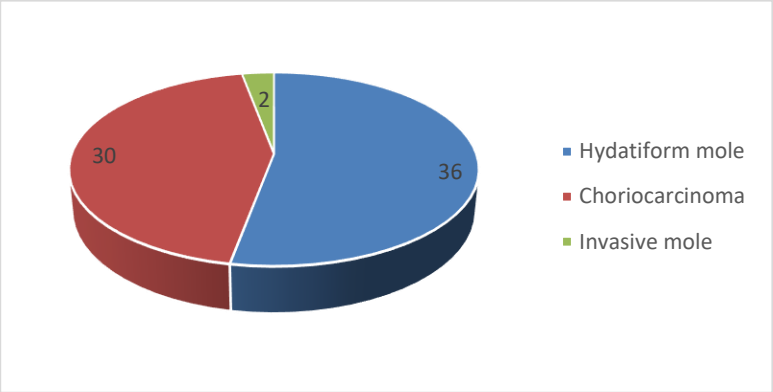
There was no metastasis among 47(69.1%) participants while the rest had vaginal, lung, liver or brain metastases. Fifty-one (75%) participants had no history of chemotherapy use while

16(23.5%) had been managed with single-agent chemotherapy and 1(1.47) with multi-agent chemotherapy. Fifty-nine (86.76%) participants were multiparous while 9 (13.2%) were nulliparous. The majority (49, 72.05%) of the participants were on contraception while the remaining 19 (28%) did not use any form of contraception.

Types of tumor

The majority (36, 52.9%) of the participants were diagnosed with hydatidiform mole while

Figure 2 - Types of tumors

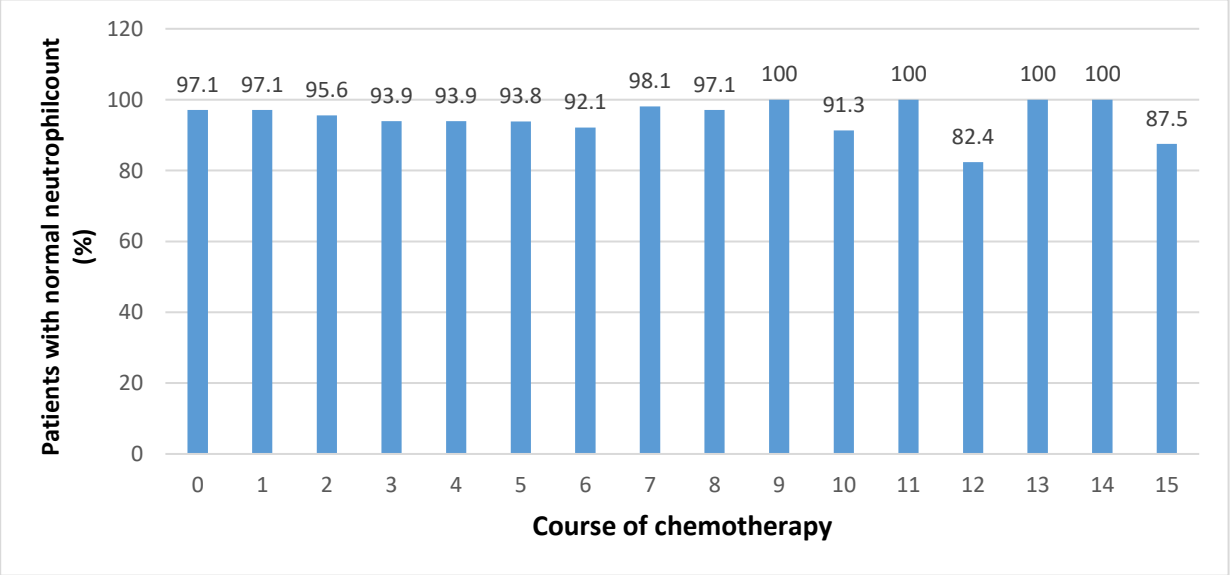


30(44.1%) were diagnosed with choriocarcinoma and only 2(2.9%) had an invasive mole.

4.4 Patient investigations

Ninety-seven percent (97.1%) of patients had a normal neutrophil count at pretreatment levels and after the first course of chemotherapy (Figure 3). With each course of chemotherapy there

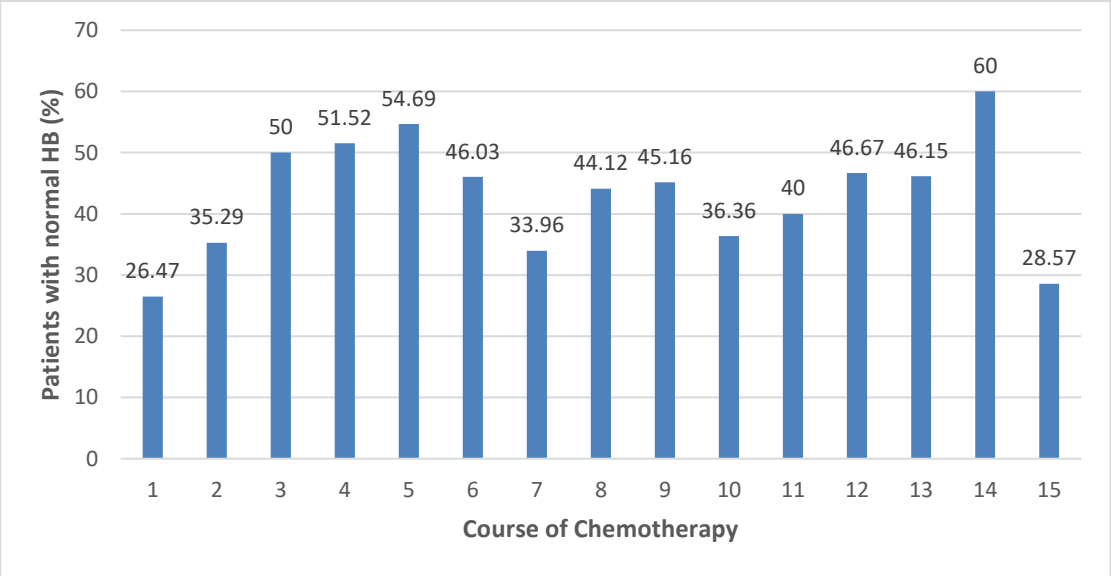
Figure 3 - Patients with normal neutrophil count during chemotherapy



was a decline in the number of patients with normal neutrophil count up to 92.1% of the participants. Granulocyte colony-stimulating factors support was administered to enable the neutrophil count to rise to normal levels.

When treatment was started, a few patients (26.5%) had hemoglobin levels within normal range (Figure 4). Blood transfusion was done to raise hemoglobin levels to the recommended count before treatment could be started. Hematinics were prescribed for these patients throughout treatment due to the risk of developing anemia during treatment. With each course of chemotherapy, there was a gradual increase in the proportion of patients with normal

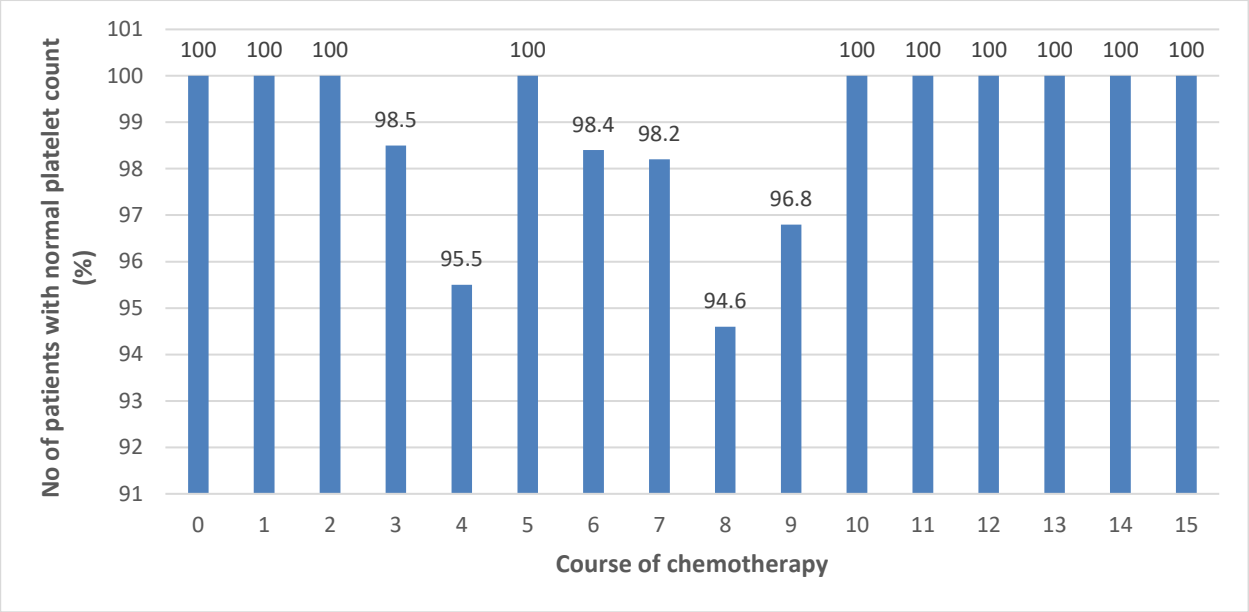
Figure 4 - Patients with normal hemoglobin levels during chemotherapy



hemoglobin levels up to 54.7%.

At the start of chemotherapy, all participants had platelet counts that were within normal range (Figure 5). After the 3rd course of treatment, there was a decline in a number of patients with normal platelet count up to 95.5%. The affected patients were transfused with platelets resulting

Figure 5 - Patients with normal platelet count during chemotherapy



in the increase in the proportion of patients with normal platelet count seen after the 4th course of treatment. Generally, the majority of the patients had normal platelet count throughout the course of treatment with only a few cases of declining platelet count.

4.5 Adverse effects of EMACO regimen

A wide range of adverse effects was seen in this study (Table 7). The most common (62,91.18%) was myelosuppression followed by extravasation at the site of injection, nausea, and vomiting, alopecia, diarrhea, mucositis and loss of appetite.

Table 7 - Adverse effects of EMACO

Adverse event	**Frequency**	**Percent**
Myelosuppression	62	91.18
Extravasation	61	89.71
Nausea and vomiting	59	86.76
Alopecia	57	83.82
Diarrhea	47	69.12
Mucositis	43	63.24
Loss of appetite	38	55.88
CNS disturbances	21	30.88
Allergic reactions	17	25
Peripheral neuropathy	8	11.76
Genital irritation	6	8.82
Bladder irritation/hematuria	3	4.41
Liver derangement	3	4.41
Acute tubular necrosis	1	1.47
Temporary paralysis	1	1.47
Taste perversion	1	1.47

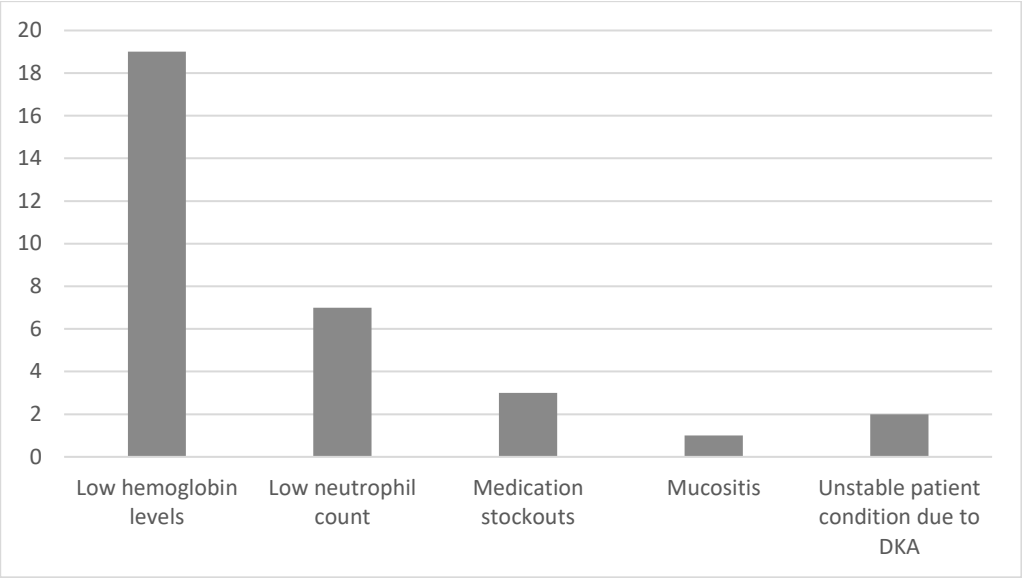
Most (20,29.4%) participants had seven adverse effects per participant. The average number of adverse effects was 6.

Table 8 - Frequency of adverse effects per patient

Number of adverse effects	1	2	3	4	5	6	7	8	9	10	11
Frequency (n=68)	1	3	4	5	3	15	20	10	4	1	2

Treatment delay was seen in (32,47%) of the participants . The majority (19,27.9%) of cases of treatment delay were due to low hemoglobin counts that resulted in patients having to wait for

Figure 6- Causes of treatment delay among GTN patients on EMACO regimen



blood transfusion. Low neutrophil count caused treatment delay in (7, 10.3%) of the participants. Unavailability of chemotherapy drugs caused treatment delay in (2,2.9%). Two participants who had diabetes mellitus developed symptoms of diabetic ketoacidosis (DKA) during treatment and treatment was interrupted to allow the patient to be stable. Mucositis was the cause in (1,1.47%) of the participants.

4.6 Comorbidities

More than half (37,54.4%) of the participants had comorbidities (Table 9). These comorbidities included anemia, hypertension, human immunodeficiency virus, tuberculosis, rheumatoid arthritis.

Table 9 - Comorbidities

Comorbidity	**Frequency**	**Percent**
Anemia	9	13.23
Hypertension	8	11.76
HIV	5	7.35
Rheumatoid arthritis	3	4.41
Tuberculosis	3	4.41
Bacterial sepsis	2	2.94
Diabetes mellitus	2	2.94
Congestive cardiac failure	2	2.94
Chronic autoimmune hepatitis, viral hepatitis	1	1.47
Malaria	1	1.47
Acute kidney injury	1	1.47

4.7 Concomitant therapy

NSAIDS (33, 48.5%), penicillins (30, 44.1%), cephalosporins (23, 33.8%) and other medications like ART, tuberculosis drugs, ACEIs, hematinics, and radiotherapy were among the drugs among participants beside EMACO regimen.

Table 10 - Concomitant therapy

Drug	**Frequency**	**Percent**
Ibuprofen	33	48.53
Penicillin	30	44.12
Hematinics	25	36.76
Cephalosporins	23	33.82
Metronidazole	18	26.47
Antidepressants	3	4.41
Sulfonamides	3	4.41
Macrolides	3	4.41
Radiotherapy	3	4.41
Antipsychotics(phenothiazines)	2	2.94
Antithyroid medication (propylthiouracil)	2	2.94
ACEIs	2	2.94
Antiretroviral Therapy	2	2.94
Tuberculosis drugs	2	2.94
Hydralazine	1	1.47

4.8 Diet

Table 11- Diet

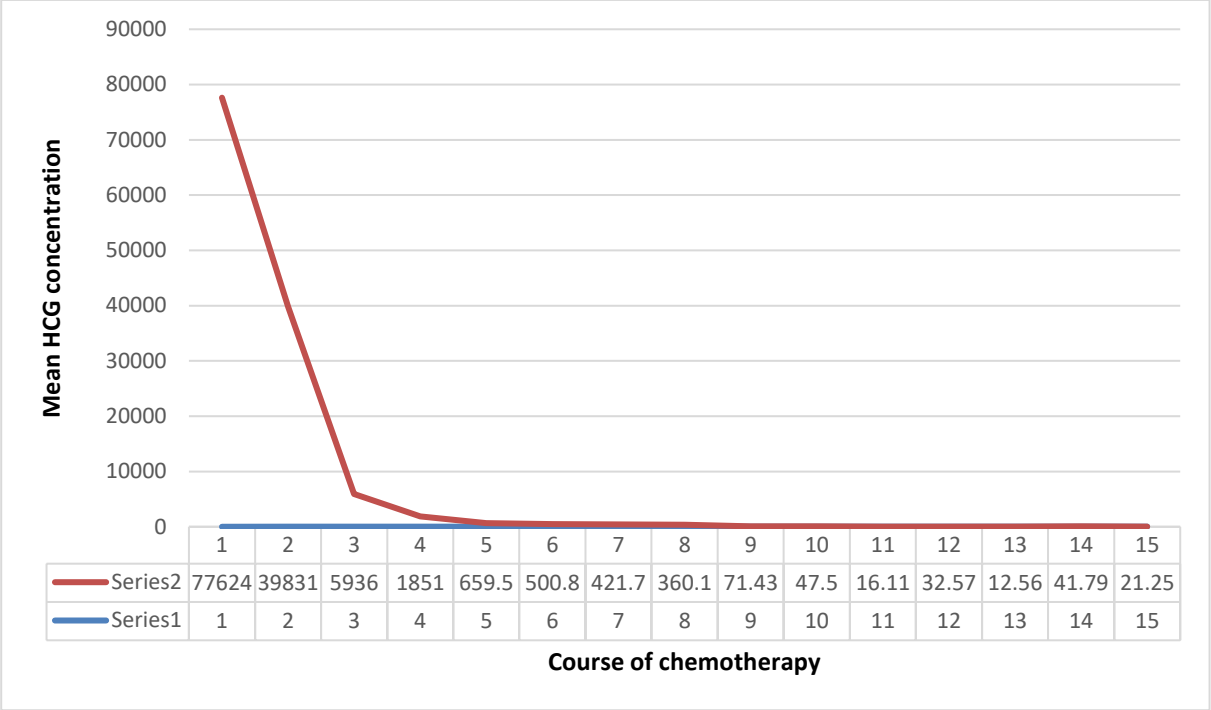
Diet deficient of;	Present (0)	Absent (1)
Vitamin B12	0	68
Folate	0	68
Copper	0	68
Iron	2	66

All participants had a diet that was sufficient with vitamin B12, folate and copper (Table 11). Only two participants had iron deficiency in their diet.

4.9 HCG levels

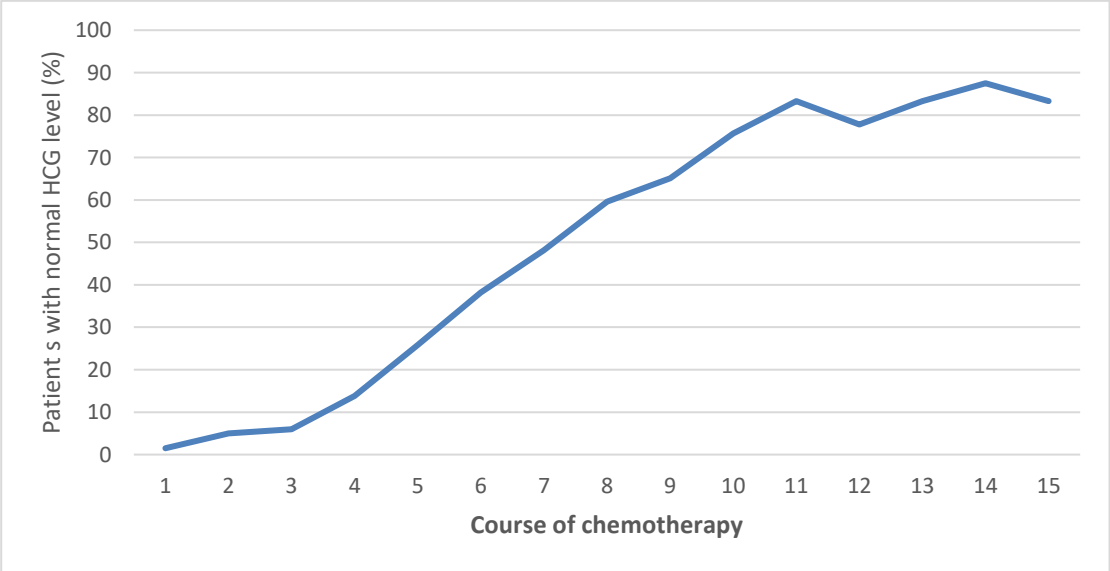
Figure 6 shows the decline in the concentration of beta HCG with the administration of EMACO regimen. Initially, there was a steady decline in HCG levels in response to treatment.

Figure 6 - The trend of HCG levels during treatment with EMACO



After the third course of treatment, the rate of decline was slower with a plateau after the eleventh course of chemotherapy. Figure 8 shows the proportion of patients who attained

Figure 7 - Patients with normal HCG levels during chemotherapy



normal HCG levels with each course of chemotherapy. There was a gradual increase in the number of patients with each course of treatment. After the fifteenth course of treatment, about 88% of the patients achieved normal HCG levels.

Out of the 68 participants, 59 achieved at least three consecutive readings of weekly HCG levels that were within normal range. Each of these participants received two courses of EMACO regimen and a follow-up period of one year was done, during which serum β-HCG levels were obtained monthly. Seventeen (25%) participants completed the follow-up period. During follow up period participants were advised to be on contraception. One participant became pregnant during the follow-up period and she was registered at the antenatal clinic. The outcome of the pregnancy was not documented.

4.10 Filgrastim use

Filgrastim use was observed in (29, 42.6%) participants. In all cases, it was prescribed when the neutrophil count was below 1000 cells per microliter so that treatment could continue once neutrophil count rose to the recommended levels. Only one participant required filgrastim support before treatment was started. In most (22,32.4%) participants required it was administered after cycle 8 of chemotherapy while a few (6, 8.8%) participants received filgrastim prophylaxis after cycle 6 of chemotherapy.

4.11 Bivariate analysis

The associations between adverse effects with age are shown in Table 12. The lowest age category (13-19) had two participants and showed the least incidence of adverse effects per

Table 12 - Association between age and adverse effects

Adverse effect	Age categories (%)				P-value
	13-19 (0) N=2	20-29 (1) N=29	30-39 (2) N=23	40-49 (3) N=14	
Myelosuppression	2 (100)	26 (89.7)	20 (86.9)	14(100)	0.565
Stomatitis	1 (50)	21 (72.4)	14 (60.9)	7 (50)	0.447
Diarrhea	2 (100)	22 (75.9)	13 (56.5)	10 (71.4)	0.423
Alopecia	1 (50)	26 (89.7)	18 (78.3)	12 (85.7)	0.327
Allergic reaction	0 (0)	10 (34.5)	6 (26.1)	1 (7.1)	0.240
Peripheral neuropathy	0 (0)	3 (10.3)	1 (4.3)	4 (28.6)	0.173
Hematuria	0 (0)	2 (6.9)	1 (4.3)	0 (0)	1.000
Acute tubular necrosis	0 (0)	1 (3.4)	0 (0)	0 (0)	1.000
Liver derangement	0 (0)	1 (3.4)	1 (4.3)	1 (7.1)	1.000
CNS disturbances	0 (0)	10 (34.5)	7 (30.4)	4 (28.6)	1.000
Hemiparesis	0 (0)	0 (0)	0 (0)	1 (7.1)	0.235
Genital irritation	0 (0)	3 (10.3)	2 (8.7)	1 (7.1)	1.000
Taste perversion	0 (0)	0 (0)	1 (4.3)	0 (0)	0.574
Loss of appetite	0 (0)	17 (58.6)	12 (52.2)	9 (64.3)	0.465
Nausea and vomiting	2 (100)	26 (89.6)	19 (82.6)	12 (85.7)	0.922
Extravasation	2 (100)	27 (93.1)	19 (82.6)	13 (92.8)	0.665

Participant, compared to the other age categories. Both participants had myelosuppression, diarrhea, extravasation, nausea, and vomiting while alopecia and stomatitis affected one participant in this age group. In the 20-29 age group, (27,93.1%) participants had extravasation. Myelosuppression, alopecia, nausea, and vomiting were each seen in (26,89.6%) of the participants. Diarrhea affected (22,75.9%), stomatitis (21,72.4%), loss of appetite (17, 58.6%), CNS disturbances and allergic reactions each affected (10,34.5%), genital irritation and peripheral neuropathy each affected (3,10.3%) while (2,6.9%) had hematuria and (1,3.4%) had

liver and kidney derangements. Myelosuppression affected (20,86.9%) of participants in the 30-39 age category. Extravasation, nausea and vomiting each affected (19,82.6%) participants while alopecia affected (18,78.3%). Stomatitis and diarrhea affected (14,60.9%) and (13,56.5%) respectively. Loss of appetite was seen in (12,52.2%) participants while CNS disturbances were seen in (7,30.4%) and allergic reactions in (6,26.1%). Two (8.7%) participants experienced genital irritation while taste perversion, liver derangement, hematuria, and peripheral neuropathy were seen in (1,4.3%) participants. All participants in the 40-49 age category had myelosuppression. Extravasation affected (13,92.8%) participants while alopecia, nausea and vomiting each affected (12,85.7%). Diarrhea was seen in (10,71.4%), loss of appetite in (9,64.3) stomatitis in (7,50%). CNS disturbances and peripheral neuropathy each affected (4,28.6%) while genital irritation, hemiparesis, liver derangement, and allergic reaction each affected (1,7.1%) participant.

Table 13 shows the association between the occurrence of adverse effects and previous use of chemotherapy. Diarrhea and alopecia showed statistically significant results. A statistically significant association was also seen between previous use of multi-agent chemotherapy (MAC-methotrexate, actinomycin-D, cyclophosphamide) and genital irritation.

Table 13 - Relationship between previous chemotherapy and adverse effects

Adverse effect	**Previous chemotherapy**			**P-value**
	None	**Methotrexate**	**Multiple agents**	
Myelosuppression	46 (67.6)	15 (22.1)	1 (1.5)	1.000
Stomatitis	35 (51.5)	8 (11.8)	0	0.173
Diarrhea	40 (58.8)	7 (10.3)	0	**0.007***
Alopecia	45 (66.2)	12 (17.6)	0	**0.052***
Allergic reaction	15 (22.1)	2 (2.9)	0	0.492
Peripheral neuropathy	5 (7.4)	3 (4.4)	0	0.457
Hematuria	2 (2.9)	1 (1.5)	0	0.584
Acute tubular necrosis	0 (0)	1 (1.5)	0	0.250
Liver derangement	1 (1.5)	2 (2.9)	0	0.177
CNS disturbances	18 (26.5)	3 (4.4)	0	0.554
Hemiparesis	1 (1.5)	0	0	1.000
Genital irritation	5 (7.3)	0	1 (1.5)	**0.052***
Taste perversion	1 (1.5)	0	0	1.000
Loss of appetite	30 (44.1)	8 (11.8)	0	0.471
Nausea and vomiting	46 (67.6)	13 (19.1)	0	0.077
Extravasation	47 (69.1)	13 (19.1)	1	0.412

The associations between the occurrence of adverse drug events and metastases are shown in **Table 14.** Only the association between metastases and CNS disturbances was statistically significant.

Table 14 - Relationship between metastasis and adverse effects

Adverse effect	**Metastasis**				**P-value**
	None	**Vagina/uterus**	**Lung**	**Other**	
Myelosuppression	41 (60.3)	8 (11.8)	9 (13.2)	4 (5.9)	0.644
Stomatitis	30 (44.1)	6 (8.8)	5 (7.3)	2 (2.9)	0.787
Diarrhea	33 (48.5)	5 (7.3)	6 (8.8)	3 (4.4)	0.962
Alopecia	40 (58.8)	6 (8.8)	7 (10.3)	4 (5.9)	0.719
Allergic reaction	10 (14.7)	3 (4.4)	4 (5.9)	0	0.262
Peripheral neuropathy	4 (5.9)	2 (2.9)	2 (2.9)	0	0.253
CNS disturbances	12 (17.6)	1 (1.5)	6 (8.8)	2 (2.9)	**0.043***
Genital irritation	4 (5.9)	1 (1.5)	1 (1.5)	0	0.874
Loss of appetite	27 (39.7)	6 (8.8)	3 (4.4)	2 (2.9)	0.392
Nausea and vomiting	42 (61.8)	6 (8.8)	7 (10.3)	4 (5.9)	0.415
Extravasation	43 (63.2)	8 (11.8)	6 (8.8)	4 (5.9)	0.127

*-*Statistically significant p-value*

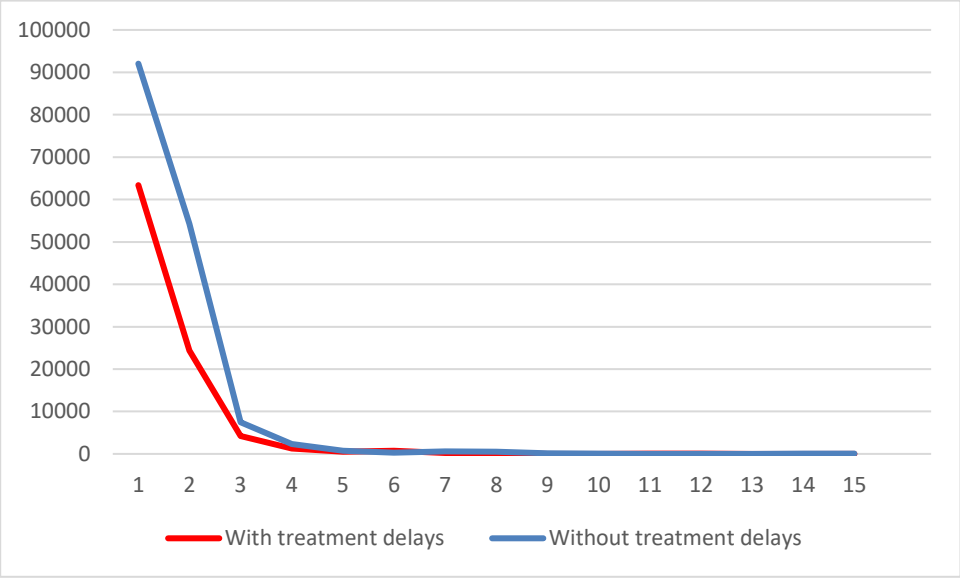
Table 15 - Relationship between filgrastim prophylaxis and treatment delay

Filgrastim prophylaxis	Treatment delay			P-value
	Yes	No		
Yes	16	13	29	0.327
No	16	23	39	
	32	36		

The prevalence of treatment delay among participants exposed to filgrastim prophylaxis was 0.5517 while among unexposed participants was 0.4102 (Table 15). The prevalence rate was 1.345 implying that participants receiving filgrastim prophylaxis are 1.345 times likely to have treatment delay.

Figure 9 shows rate of decline of HCG levels among participants with treatment delay and those who did not experience delay. The rate of decline is slower among patients with treatment delay.

Figure 8- β-HCG trends in participants with treatment delay and without delay



CHAPTER FIVE: DISCUSSION, SUMMARY, CONCLUSION AND RECOMMENDATIONS

5.1 Introduction

This chapter discusses key findings of the study within the context of existing literature. Conclusions and recommendations for policy, practice and further research have been highlighted based on key findings from the research study.

5.2 Discussion

Maternal age is a well-established risk factor for gestational trophoblastic neoplasia. Women who are older than 35 years and those younger than 20 years are at high risk. In this study, the mean age of the participants was 31.7 years, with the youngest and oldest participants being 16 and 49 years old respectively. These findings were similar to those of other studies carried out in the same setting and in different parts of the world (3) (4) (5) (86) (87). However, A few studies have reported a lower mean age (31) (88) and others a higher one (59).
Most of the participants were multiparous, an observation that is in tandem with other studies (5) (4) (31). Hydatidiform mole most frequently preceded the diagnosis of GTN, followed by abortions while term pregnancies were the least frequent. These findings are similar to those of previous studies at KNH and in other parts of the world (5) (2) (3).In Asia, abortions most often preceded GTN followed by term pregnancy and molar pregnancy (41) and similar findings were observed in Nigeria (86).

In this study, myelosuppression occurred in the majority of the participants. Anemia was a common complication of treatment. Anemia in these types of patients arises from suppression of erythropoiesis and bleeding associated with GTN and has been reported in several studies (12) (15) (79) (84) (85). Research in the same setting found that 68.97% of patients on EMACO developed anemia (5). Houwen et al found anemia is the most common complication of treatment, with 16.7% grade III anemia that necessitated blood transfusion in patients (40). Chronic diseases such as HIV, tuberculosis and autoimmune conditions like rheumatoid arthritis may have contributed to the occurrence of anemia among the participants, as seen in other studies. Iron deficiency contributes to the development of anemia as in other studies (89).

Neutropenia was the second most common myelosuppressive effect of EMACO. This arises due to the effect of these drugs on the proliferation of myeloid progenitors and it is a common observation these types of patients (57)(58) (62). Susceptibility to infections which is characterized by high fever is associated with neutropenia (86) (87) (88). The infections can be life-threatening depending on the grade of leukopenia (12). In this study, no complications of neutropenia occurred among the study participants. Thrombocytopenia was the least common hematological adverse effect as has been observed in other studies (9) (12) (15).

Treatment delay affected 47% of our participants. The main cause of treatment delay was low hemoglobin levels. Blood transfusion to improve hemoglobin levels was done and in addition, patients were put on hematinics. Similar findings were reported by Houwen et al and Shrivastava et al (40)(29). Neutropenia was the second most common cause of treatment delay among the participants and Granulocyte colony stimulating factors was administered to alleviate the situation. Treatment delay is essential in situations where the patient is debilitated and the body immune system weakened in order to allow the body to recover. This scenario has been observed in several studies (58) (59) (88) 89). Incorporating granulocyte colony stimulating factor during treatment with EMACO reduces the incidence of treatment delay (73). Occasionally there were stock-outs of chemotherapeutic agents and this contributed to treatment delay. Similar challenges were seen in studies in other resource-limited settings like Dakar (88). In Rwanda, poor procurement procedures of chemotherapy drugs negatively impacted treatment (3). Other challenges encountered include advanced disease, poor compliance with the management plan due to ignorance, poverty, myths, and superstitions associated with malignancies (86).

Extravasation affected about 90% of the participants. This may be attributed to the improper placement of cannulas resulting in leakage of the medicine. Nausea and vomiting are common among these types of patients on cytotoxic therapy and may also due to high blood levels of HCG (29)(15) (90). Alopecia, which is common in chemotherapy treatment due to the destruction of the rapidly dividing hair follicles was seen in many participants in this study. Alopecia, nausea, and myelosuppression occur early in the majority of patients on EMACO regimen (29). Diarrhea developed in over half of our participants as has been observed by Pritchett et al (86) and Schink et al (90).

Mucositis affected 63% of our participants as was seen in other studies(17)(30). Mucositis is associated with a number of chemotherapy agents in the regimen notably methotrexate. It results

in poor food and fluid intake, reduced ability to absorb nutrients and increased susceptibility to infections(3). It may also reduce the ability of the patient to tolerate treatment, and often results in discontinued treatment, as was seen in one participant in this study (29)(67). CNS disturbances such as a headache, dizziness, confusion and psychotic episodes were seen in 31% of the participants. These effects were largely reversible. Inadequate pre-hydration may have exacerbated these symptoms which could be alleviated by increased intake of water and use of NSAIDs. Participants with brain metastases may have also experienced these symptoms. Allergic reactions that presented as itching in the eyes and the skin were seen in 25% of the participants, as reported by L S Dobson et al (61) Peripheral neuropathy affected 12% of our participants and improved symptoms are seen when the dose of vincristine is reduced or discontinued in severe cases (40)(90) (30). Genital irritation and hematuria occurred in 9% and 4% of our participants respectively. Two participants developed liver derangements as seen in other studies which reported more cases (17)(30). Transfusion was done to those with low hemoglobin level and is a risk for hepatitis B virus infection which can worsen drug-induced liver derangements (15). Both acute tubular necrosis and temporary paralysis were seen in 1.47% of our participants. Generalized symptoms such as pain, and weakness have been reported (3). Secondary malignancies were not seen in this study. A number of studies reported cases of acute myeloid leukemia (40)(30)(32).

Majority of the participants had not received chemotherapy before treatment with EMACO regimen. A significant number of patients managed with the single agent were unresponsive to treatment and were put on EMACO regimen. Similar results were reported by McGrath et al who found that low-risk patients managed with single-agent chemotherapy were treated successfully and more required additional multi-agent chemotherapy to achieve complete remission (81). Single agents have been observed not to be effective and lead to a high rate of recurrence in some malignancies (91)(92). In contrast, however, this approach has been very effective in the treatment of stage II and III low-risk GTN to the extent of achieving complete remission occasionally (93).

The prevalence of side effects was similar among the participants regardless of HIV status as reported elsewhere (94). However, El-Lamie et al observe that HIV-infected patients are more predisposed to treatment-related adverse effects since chemotherapy may further compromise immunity (70).

An increase in the incidence of adverse effects was seen in participants in the older age categories compared to the younger age categories. This is consistent with reports that age-

associated physiologic changes involving the hematologic system resulting in changes in the bone marrow microenvironment. There may be increased incidence of mucositis, and diarrhea due to age-related changes in the gastrointestinal system (35)(56)(95). There is also a high tendency to develop peripheral neuropathy and CNS disturbances among older participants due to physiologic changes. Older participants are likely to have comorbidities which may exacerbate some adverse effects of chemotherapy.

There was an association between alopecia, diarrhea and genital irritation and previous use of chemotherapy. Hair follicles and cells of the smooth muscle lining the gastrointestinal system and the genital tract are sensitive to chemotherapy which act by interfering with proliferation of rapidly dividing cells. Prolonged exposure to chemotherapy leads to an increased incidence in the occurrence of these adverse effects. Methotrexate has been associated with mucositis and liver dysfunction when used as single agent chemotherapy (96). Actinomycin D has been associated with myelosuppression, alopecia and nausea and vesicant effects (60)(47)(93). History of use of multiagent chemotherapy has been shown to have increased adverse effects (97).

Metastases and adverse effects of chemotherapy also showed a statistically significant association as reported elsewhere (98)(99). The widespread disease requires additional management strategies such as surgical intervention, irradiation resulting in an increased incidence of adverse effects (97). Metastatic disease is characterized by a wide range of symptoms depending on the degree and location of tumor spread. Adverse effects of chemotherapy may exacerbate these symptoms resulting in increased incidence of concerns among these patients.

HCG levels declined with each course of chemotherapy as seen in different studies (3)(5). This is due to the destruction of tumor cells that secrete the hormone in large quantities. However, in a number of participants, the levels remained higher than normal despite several courses of treatment. The mean number of cycles to the achievement of remission was 9.9. HCG titers dropped to normal levels in 88% the participants (8)(7)(100)(90) and lower remission rates were seen in advanced disease (15)(17)(88)(101). Participants who were unresponsive to EMACO regimen were managed with the cisplatin-based regimen, EMAEP, and showed regressing HCG levels as observed in similar studies (6)(101)(17). After HCG decreases to normal and chemotherapy is completed, serum HCG levels should be obtained at 1-month intervals for 12 months, in order to detect relapse during the first year after completion of therapy. Follow up was done for 25% of the participants for up to one year contrary to other

studies where 90% was achieved (29). Gestational trophoblastic neoplasia has been associated with a 1-2% risk of a second gestational trophoblastic disease event in subsequent pregnancies. Patients are therefore advised to delay conception for one year after cessation of chemotherapy to allow for uninterrupted monitoring of HCG levels and to permit the elimination of mature ova that may have been damaged by exposure chemotherapy. One participant became pregnant during the follow-up period but the outcome of the pregnancy was not documented. Priyanka et al reported uneventful pregnancies with no recurrent molar pregnancy (15).

In this study, filgrastim was administered to correct chemotherapy-induced neutropenia. Similar findings have been observed in our setting and in other resource-limited areas (5)(41)(29)(30). Use of filgrastim prophylaxis in patients managed with EMACO regimen resulted in adherence to treatment schedules and no incidence of neutropenia(82). Despite the overall increased cost of treatment, use of filgrastim prophylaxis improves efficiency in the management of these patients as it reduces the overall length of hospital admissions (48) (84).

5.3 Conclusion

EMACO regimen is highly effective for early gestational trophoblastic neoplasia. The regimen is associated with a wide range of adverse effects which are seen frequently among patients with a history of chemotherapy use and those with the advanced/metastatic disease. Comorbidities, concomitant therapy, and diet did not influence the frequency of adverse effects of EMACO. Filgrastim was used to treat neutropenia enabling maintenance of the treatment schedule.

5.4 Recommendations

5.4.1 Recommendations for policy and practice

1. Adverse effects should be actively identified and managed to improve adherence to the treatment schedule and quality of life of the patient.
2. Patients who have previously been exposed to chemotherapy, those with any advanced comorbidities and those with metastatic disease are at a higher risk of developing adverse effects and should be monitored closely.
3. Health workers administering chemotherapy should be given adequate training to minimize adverse effects such as extravasation.
4. Patient follow up should be done for at least one year after normal HCG levels are achieved and treatment is completed, this will enable timely management in case of recurrence.

5.4.2 Recommendations for research

More work should be done to determine measures taken to manage adverse effects of EMACO regimen in our setting and the effects on patient outcomes and quality of life.

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APPENDICES

Appendix 1 - Data extraction form

FORM CODE

PATIENT INITIALS

ADMISSION NUMBER

DATE OF STARTING EMACO

PATIENT CHARACTERISTICS

1. Age (years) _____

2. Age category

13-19 (0) … 20-29 (1) … 30-39 (2) … 40-49 (3) … 50-59 (4) … 60-69 (5) … >69 (6) …

3. Marital status

Single (0) ……. Married (1) …….

4. Education level

Primary (0) ……. Secondary (1) ……. College (2) ……. University (3) ……

5. Employment

Permanent (0) ……. Casual (1) ……. Self-employment (2) ……. None (3) ……

6. Weight……. Height…….

BMI

≤18.5 Underweight (0) 18.5-24.5 Normal (1) 25-29.5 Overweight (2) ≥30 Obese (3)

7. History of smoking of cigarettes

Yes (0) …… No (1) ……

8. Method of contraception

Oral hormonal (0) … Non-oral hormonal (1) … Barrier methods (2) … Sterilization (3) …

9. Parity

Primipara (0) ……. Para 2-Para5 (1) …… >Para 5 (2) ……

10. Antecedent pregnancy

Term pregnancy (0) …… Hydatidiform mole (1) ……

Ectopic pregnancy (2) …… Abortion (3) …….

11. Period of antecedent pregnancy to start of chemotherapy in months

<4 (0) …… 4-6 (1) ……. 7-12 (2) …… >12 (3) ……

12. Previous chemotherapy

None (0) ……. Single-agent (1) …… Multiple agents (2) …….

13. Metastasis

None (0) ……. Vagina/Uterus (1) …… Lung (2) …… Other sites (3) ……

PATIENT INVESTIGATIONS

14. Diagnosis/Tumor histology

Choriocarcinoma (0) ……. Invasive mole (1) …… PSTT/ETT (2) ……

15. Urea, electrolytes and creatinine

Within normal range (0) ……. High (1) ……. Low (2) …….

16. Liver Function Tests

Within normal range (0) ……. High (1) ……. Low (2) …….

PATIENT MANAGEMENT

17. Adjuvant prophylaxis with filgrastim

Yes (0) …… No (1) ……

18. Treatment delay

Yes (0) ……. No (1) …….

3. HCG regression

19. Pre-treatment HCG levels

<1000 (0) …… 1000-10000(1) …… 10000-100000 (2) …… >100000 (3) ……

20.

	Course	Date	Beta HCG (IU/l)
a)	1		
b)	2		
c)	3		
d)	4		
e)	5		
f)	6		
g)	7		
h)	8		
i)	9		
j)	10		
k)	11		
l)	12		
m)	13		
n)	14		
o)	15		

4. Hematological profile

	Course	21.Neutrophil count <1000 cells/µl (0) >1000 cells/µl (1)	22.Heamoglobin <12 g/dl (0) >12 g/dl (1)	23. Platelet count <100,000 cells/l (0) >100,000 cells/l (1)
a)	**Pre-treatment levels**			
b)	**1**			
c)	2			
d)	3			
e)	4			
f)	5			
g)	6			
h)	7			
i)	8			
j)	9			
k)	10			
l)	11			
m)	12			
n)	13			
o)	14			
p)	15			

5. Adverse effects of EMACO

	Adverse effect	Present (0)	Absent (1)
24	Myelosuppression		
25	Stomatitis		
26	Diarrhea		
27	Alopecia/hair loss		
28	Allergic reaction		
29	Peripheral neuropathy		
30	Bladder irritation/Hematuria		
31	Acute tubular necrosis		
32	Liver derangement		
33	Meningeal irritation/Encephalopathy		
34	Temporary paralysis/Hemiparesis		
35	Genital irritation		
36	Taste perversion		
37	Loss of appetite		
38	Nausea and vomiting		
39	Others (specify)		

6. Risk factors

i. Co-morbidities

	Co-morbidities	**Present (0)**	**Absent (1)**
40	Rheumatoid arthritis		
41	Chronic autoimmune hepatitis, viral hepatitis		
42	Systemic lupus erythematosus		
43	HIV		
44	Brucellosis		
45	Typhoid		
46	Tuberculosis		
47	Malaria		
48	Toxoplasmosis		
49	Bacterial sepsis		
50	Others (specify)		

ii. Concomitant therapy

	Concomitant therapy	**Present (0)**	**Absent (1)**
51	Antithyroid medications-propylthiouracil		
52	Macrolides		
53	Procainamide		
54	Antipsychotics-phenothiazines		
55	Chloramphenicol		
56	Gold		
57	Aminopyrine		
58	Quinidine		
59	Sulfonamides		
60	Hydralazine		
61	Ibuprofen		
62	Penicillins		
63	Cephalosporins		
64	Antidepressants		
65	Others (specify)		

iii. Diet

	Diet deficient of;	**Present (0)**	**Absent (1)**
66	Vitamin B12		
67	Folate		
68	Copper		
69	Others (specify)		

Appendix 2 - Permission to collect data

My name is Dr. Rose Jerono Keter.

I am pursuing a Masters of Pharmacy degree in the department of pharmaceutics and pharmacy practice at the University of Nairobi.

I am doing a research study on matters related to the effectiveness and adverse effects of etoposide, methotrexate, actinomycin D, cyclophosphamide and vincristine regimen among gestational trophoblastic neoplasia patients at Kenyatta National Hospital.

I am requesting to use your data and findings for the purposes of optimizing chemotherapy among GTN patients.

No name is required and your information will be treated as confidential. Your laboratory results and information obtained in interviews shall be utilized only for the purposes of research.

All information obtained in this study will be treated with utmost confidentiality and shall not be divulged to any unauthorized person.

Please note that your participation is voluntary and you have the right to decline or withdraw from the study.

Participant's signature……. Date ……

I certify that the patient has understood and consented to participate in this study.

Dr. Rose Jerono Keter

Signature…….. Date ……

Appendix 3 - Dummy tables

Table 16 - Prevalence of adverse effects

Adverse effect	N	%
Neutropenia		
Anemia		
Thrombocytopenia		
Stomatitis		
Diarrhea		
Alopecia/hair loss		
Allergic reactions		
Peripheral neuropathy		
Bladder irritation/ Hematuria		
Acute tubular necrosis		
Liver derangement		
Meningeal irritation/Encephalopathy		
Temporary paralysis		
Genital irritation		
Taste perversion		
Loss of appetite		
Nausea and vomiting		

Table 17 - Influence of risk factors on adverse effects

Adverse effects	**Risk factor**							
	Age		**Co-morbidities**		**Concomitant therapy**		**Diet**	
Neutropenia	**0**	**1**	**0**	**1**	**0**	**1**	**0**	**1**
Anemia								
Thrombocytopenia								
Stomatitis								
Diarrhea								
Alopecia								
Allergic reactions								
Peripheral neuropathy								
Bladder irritation / haematuria								
Acute tubular necrosis								
Liver derangements								
Meningeal irritation/Encephalopathy								
Temporary paralysis								
Genital irritation								
Taste perversion								
Loss of appetite								
Nausea and vomiting								

Table 18 - Relationship between filgrastim prophylaxis and treatment delay

Filgrastim prophylaxis		Treatment delay		
		Yes (0)	No (1)	
	Yes (0)			
	No (1)			

Appendix 4 – Permission to collect data from KNH

KENYATTA NATIONAL HOSPITAL,
P. O. BOX 20723-00202,NAIROBI
Tel: 2726300-9/2726450/2726550
Fax:2725272
Email: knhadmin@knh.or.ke

KNH/OBS & GYN/16/VOL.1

DATE: 30th August, 2018

To

Rose Jerono Keter
Reg.No.H56/86850/2016
Department of Pharmacy
School of Pharmacy
College of Health Sciences
University of Nairobi

RE: **RESEARCH PROPOSAL: "EFFECTIVENESS AND ADVERSE EFFECTS OF ETOPOSIDE, METHOTREXAXE, ACTINOMYCIN D, CYCLOPHOSPHAMIDE AND VINCRISTINE REGIMEN AMONG GESTATIONAL TROPHOBLASTIC NEOPLASIA PATIENTS AT KENYATTA NATIONAL HOSPITAL (P290/04/2018**

This is to inform you that the department has given you permission to conduct the above study which has been approved by ERC.

Liaise with the Senior Assistant Chief Nurse and Senior Nursing Officer in charge ward 1B to facilitate your study.

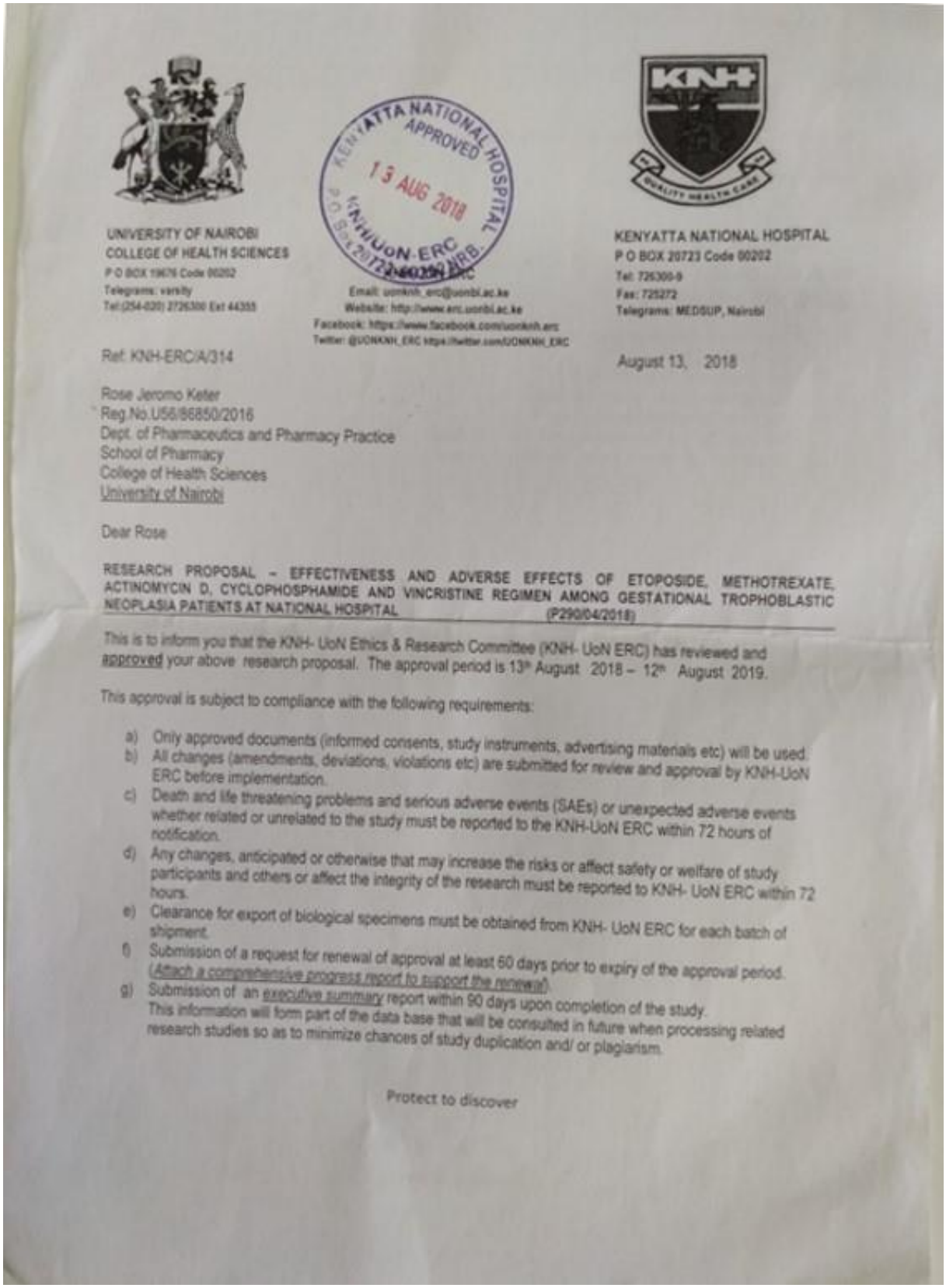
You will be expected to disseminate your results to the department upon completion of your study.

HEAD OF DEPARTMENT
31 AUG 2018
OBSTETRICS & GYNAECOLOGY

Dr. I.S.O. MARANGA
HEAD OF DEPARTMENT
OBSTETRICS & GYNAECOLOGY

CC: **SACN -RH**
Incharge Ward 1B
CC: Health Information Officer (Obs&Gyn)

Appendix 5 – Approval by KNH-UON ERC



UNIVERSITY OF NAIROBI
COLLEGE OF HEALTH SCIENCES
P O BOX 19676 Code 00202
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Tel:(254-020) 2726300 Ext 44355

KENYATTA NATIONAL HOSPITAL
APPROVED
13 AUG 2018
KNH/UON-ERC
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Twitter: @UONKNH_ERC https://twitter.com/UONKNH_ERC

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Ref: KNH-ERC/A/314

August 13, 2018

Rose Jeromo Keter
Reg.No.U56/86850/2016
Dept. of Pharmaceutics and Pharmacy Practice
School of Pharmacy
College of Health Sciences
University of Nairobi

Dear Rose

RESEARCH PROPOSAL – EFFECTIVENESS AND ADVERSE EFFECTS OF ETOPOSIDE, METHOTREXATE, ACTINOMYCIN D, CYCLOPHOSPHAMIDE AND VINCRISTINE REGIMEN AMONG GESTATIONAL TROPHOBLASTIC NEOPLASIA PATIENTS AT NATIONAL HOSPITAL (P290/04/2018)

This is to inform you that the KNH- UoN Ethics & Research Committee (KNH- UoN ERC) has reviewed and approved your above research proposal. The approval period is 13th August 2018 – 12th August 2019.

This approval is subject to compliance with the following requirements:

a) Only approved documents (informed consents, study instruments, advertising materials etc) will be used.
b) All changes (amendments, deviations, violations etc) are submitted for review and approval by KNH-UoN ERC before implementation.
c) Death and life threatening problems and serious adverse events (SAEs) or unexpected adverse events whether related or unrelated to the study must be reported to the KNH-UoN ERC within 72 hours of notification.
d) Any changes, anticipated or otherwise that may increase the risks or affect safety or welfare of study participants and others or affect the integrity of the research must be reported to KNH- UoN ERC within 72 hours.
e) Clearance for export of biological specimens must be obtained from KNH- UoN ERC for each batch of shipment.
f) Submission of a request for renewal of approval at least 60 days prior to expiry of the approval period. (Attach a comprehensive progress report to support the renewal)
g) Submission of an executive summary report within 90 days upon completion of the study. This information will form part of the data base that will be consulted in future when processing related research studies so as to minimize chances of study duplication and/ or plagiarism.

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For more details consult the KNH- UoN ERC website http://www.erc.uonbi.ac.ke

Yours sincerely,

PROF. M. L. CHINDIA
SECRETARY, KNH-UoN ERC

c.c. The Principal, College of Health Sciences, UoN
The Director, CS, KNH
The Chairperson, KNH-UON ERC
The Assistant Director, Health Information, KNH
The Dean, School of Pharmacy, UON
The Chair, Dept. of Pharmaceutics and Pharmacy Practice, UON
Supervisors: Dr. Peter N. Karimi, Dr. Nancy G. Nkonge

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