Predictors of Gestational Trophoblastic Neoplasms Chemotherapy Outcomes at Kenyatta National Hospital

A Retrospective Cohort Design Study

Period: 1st January 2010 to 31st December 2015

University of Nairobi
College of Health Sciences
School of Medicine
Department of Obstetrics & Gynaecology

Principal Investigator:
Dr Gitau S. M.
H58/69023/2013

Supervisors:
Prof Zahida Qureshi
Prof James Kiarie
Dr Frank Kagema

A Thesis Dissertation Submitted in Part Fulfilment for the Award of the Degree in Master of Medicine in Obstetrics & Gynaecology of the University of Nairobi

DECLARATION

This is to certify that the work presented herein is my original work, has not been presented for a degree course in any other university and was supervised by senior members of the Department of Obstetrics and Gynecology, University of Nairobi, School of Health Sciences, Faculty of Medicine, Kenyatta National Hospital, Nairobi, Kenya.

…….
Signature

…….
Date

Dr Gitau S. M.
Department of Obstetrics & Gynaecology
University of Nairobi

CERTIFICATION OF SUPERVISION

This is to certify that this proposal by Dr. Gitau Simon M was researched upon under my supervision and that this dissertation is submitted with my approval.

PROF ZAHIDA QURESHI
ASSOCIATE PROFESSOR OF OBSTETRICS & GYNAECOLOGY
CONSULTANT OBSTETRICIAN & GYNAECOLOGIST,
DEPARTMENT OF OBSTETRICS AND GYNAECOLOGY,
UNIVERSITY OF NAIROBI

…… ……..

Signature Date

DR F. KAGEMA
MEDICAL SPECIALIST
CONSULTANT OBSTETRICIAN & GYNAECOLOGIST,
DEPARTMENT OF REPRODUCTIVE HEALTH,
KENYATTA NATIONAL HOSPITAL

…… ……..

Signature Date

CERTIFICATE OF AUTHENTICITY

This is to certify that this research study was undertaken and written by **DR GITAU SIMON M** and supervised by faculty in the department of Obstetrics and Gynaecology of the University of Nairobi.

PROF OMONDI OGUTU, MB.Ch.B, M.Med (OBS & GYN), PGDRM
Professor and Consultant.
Chairperson,
Department of Obstetrics and Gynaecology
University of Nairobi

..... **.....**

Signature **Date**

ACKNOWLEDGEMENT

This work would not have been to this level of success without the concerted effort of my dedicated supervisors, faculties at department of obstetrics & gynaecology of University of Nairobi, postgraduate student colleagues and the Kenyatta National Hospital staff. I sincerely appreciate your support in all the facets it came; technical, encouragement and financial.

DEDICATION

This work is dedicated to every patient who bears the scars of chemotherapy and have the courage to look back and say “thank you” to the care givers.

LIST OF ABBREVIATION

AAV---------- Adeno-associated Virus
Act-D ---------- Actinomycin-D/Actinomycin-D
BiCHM ---------- Biparental Complete Hydatiform Moles
CC ---------- Choriocarcinoma
CHAMOCA ----- Cyclophosphamide, Hydroxycarbamide, Doxorubicin, Actinomycin-D, Methotrexate, Melphalan, and Vincristine
CHM---------- Complete Hydatidiform Mole
CXR ---------- Chest X-ray
DNA ---------- Deoxyribonucleic acid
EMACO --------- Etoposide, Methotrexate, Actinomycin-D, Cyclophosphamide, Vincristine
EMA-EP --------- Etoposide, Methotrexate, Actinomycin-D - Etoposide, Cisplatin
ERC ---------- Ethics and Research Committee
ETT---------- Epithelial Trophoblastic Tumour
FA---------- Folinic Acid
FRHM---------- Familial Recurrent Hydatidiform Mole
FIGO ---------- International Federation of Gynaecology and Obstetrics
GCSF ---------- Granulocyte Colony Stimulating Factor
GTN ---------- Gestational Trophoblastic Neoplasm
GTD ---------- Gestational Trophoblastic Disease
hCG ---------- Human Chorionic Gonadotropin
HM---------- Hydatidiform Mole
HPV ---------- Human Papilloma Virus
IUCD ---------- Intrauterine Contraceptive Device
KNH ---------- Kenyatta National Hospital
MAC---------- Methotrexate, Actinomycin-D, and Cyclophosphamide
MCAR---------- Missing Completely at Random
MFA ---------- Methotrexate, Folinic acid, Actinomycin-D
MTX ---------- Methotrexate
OC ---------- Oral Contraceptive
pGTD---------- Persistent Gestational Trophoblastic Disease
PHM---------- Partial Hydatidiform Mole
PSTT---------- Placenta-site Trophoblastic Tumour
RNA ---------- Ribonucleic Acid
SCGE---------- Single Cell Gel Electrophoresis
WHO ---------- World Health Organisation

LIST OF FIGURES

LIST OF TABLES

Table of Contents

ABSTRACT

Background: Gestational trophoblastic neoplasms (GTN) span a spectrum of abnormal neoplastic trophoblastic proliferation that include choriocarcinoma, persistent Hydatidiform mole, invasive mole, placenta site trophoblastic tumour and epithelioid trophoblastic tumour. Except for the latter two, the tumours are highly curable with chemotherapy with remission rates reaching over 90%. The neoplasms are classified as low or high risk to single agent chemotherapy resistance depending on the WHO/FIGO scoring system. Treatment with single agent actinomycin-D or methotrexate for low risk and EMACO for high risk GTN are widely accepted standards of care.

Justification: This study purposes to evaluate the GTN management and treatment outcomes at KNH in order to strengthen existing treatment guidelines and optimise patient treatment outcomes. No similar study has been carried out in comparable settings in sub-Saharan Africa.

Broad Objective: To describe the management of gestational trophoblastic neoplasm at Kenyatta National Hospital and determine the predictors of chemotherapy treatment outcomes between 1st January 2010 and 31st December 2015.

Methods: This is a retrospective cohort study with a calculated sample size of 156 using Kasiulevičius et al method with Fleiss continuity correction. All 158 patients treated at KNH between 1st January 2010 and 31st December 2015 whose records were accessed were analysed. Data was abstracted from the patients' clinical records and entered in Epi Info version 7.1.2.0 for analysis. Univariate and bivariate analysis were used to calculate descriptive statistics and relative risks (RR) at 95% confidence interval. Chi square was used to determine statistical significance of various exposures on treatment outcomes. p values of less than 0.05 were considered statistically significant.

Results: One hundred and fifty eight patient records were analysed that included 96 low risk and 62 high risk GTN patients. 42% of low risk GTN were treated with EMACO while as all but one of high risk patients were treated either with EMACO or EMA-EP. In addition, 14% and 7 % of patients required radiotherapy or surgery respectively. The overall remission rate was 65.2%. Methotrexate had a median of 5 courses and EMACO 4 courses to remission. Patients with WHO/FIGO score of 6 had

chemoresistance of 75% while on methotrexate while EMACO achieved 87.5% remission. Factors associated with treatment failure included use of single agent chemotherapy with RR 5.6 (95% CI 2.17 – 14.52 p<0.001), choriocarcinoma histopathology RR 2.9 (95% CI 1.37 – 6.30 p=0.015), term antecedent pregnancy RR 3.52 (95% CI 1.66 – 7.48 p=0.001), metastatic disease RR 1.98 (95% CI 1.56 – 2.48 P<0.001) and WHO/FIGO score of 6 or initial hCG >100,000 IU/L treated with methotrexate single agent RR 2.67 (95% CI 1.35 – 5.28 p=0.041). An hCG decline rate less than 10% between second and third courses of chemotherapy was predictive of treatment failure (p=0.03) with sensitivity of 60% and specificity of 72%. The median time lost from treatment initiation to outcome was significantly longer (p=0.015) for patients with treatment failure (45 days, IQR 16 - 52) compared to those with remission (22 days, IQR 12 - 37). Brain metastasis (100%) and choriocarcinoma histopathology RR 7.2 (95% CI 1.0 – 55.6) were invariably associated with death.

Conclusion: The management of GTN at KNH does not strictly conform to WHO/FIGO guidelines. The treatment remission rate in the institution is significantly below that of comparable reference facilities. The identifiable predictors of treatment failure include high risk disease by WHO/FIGO score classification, choriocarcinoma histopathology, presence of metastasis, the rate of hCG decline between second and third course of chemotherapy less than 10%, and noncompliance with treatment protocol.

Recommendations. The findings of this study validate an urgent need to standardize GTN care at KNH through a written guideline based on WHO/FIGO recommendations with regular monitoring of adherence to its protocols. Patients with histological diagnosis of choriocarcinoma and/or initial hCG >100,000 IU/L should be treated with EMACO irrespective of their WHO/FIGO score.

CHAPTER I

INTRODUCTION AND LITERATURE REVIEW

INTRODUCTION

Gestational Trophoblastic Diseases (GTD) span a spectrum of abnormal trophoblastic proliferation ranging from the benign hydatiform mole to malignant choriocarcinoma with an intermediate entities. The diagnosis is based on clinical rather than histological diagnostic criteria. These heterogeneous tumours arise from trophoblastic epithelium following a normal or abnormal pregnancy. Hydatiform moles are benign tumours with malignant transformation potential. According to current International Federation of Gynaecology and Obstetrics (FIGO) classification, hydatiform moles are considered to have undergone malignant transformation and therefore meet the definition of gestational trophoblastic neoplasm (GTN) if after evacuation there are four values or more indicating an hCG plateau during a period of at least 3 weeks; a rise of hCG of 10% or greater for three values or more during a period of at least 2 weeks; or persistence of hCG six months after molar pregnancy evacuation(1). The hydatidiform moles that meet this criteria (commonly referred to as persistent H. mole), invasive mole, choriocarcinoma (CC), placenta-site trophoblastic tumour (PSTT) and epithelioid trophoblastic tumour (ETT) are collectively referred to as GTNs (2).

The GTNs are staged and risk scoring assessment done using the Modified WHO prognostic scoring system as adapted by FIGO. Using this staging system, the GTNs are categorised as low risk or high risk for developing resistance to single agent chemotherapy. The standard of care for patients with GTN depends on this classification(3).

Tumour chemoresistance is recognised as the primary cause of tumour chemotherapy treatment failure. Though there is no internationally agreed definition of GTN

chemoresistance, this study adopts the widely used definition of an increase or stagnation or decline by less than 10% of hCG levels over 3 weeks period or evidence of new metastasis in a patient on chemotherapy. Treatment failure is often a multifactorial phenomenon involving complex independent or interrelated mechanisms. In this study, treatment failure is defined as occurrence of chemoresistance, death related to disease process, complication or treatment, loss to follow-up or pregnancy in the course of chemotherapy treatment.

Extrinsic factors that may contribute to treatment failure include inadequate dosages, failure to adhere to recommended drug administration schedules, concomitant comorbidities, failure to use standardised regimes and severe drug toxicities necessitating treatment interruption, dose reduction/change in frequency of administration/change in regimen/withdrawal of drugs(s) or delayed administration of sequential dosages.

At Kenyatta National Hospital (KNH) there are no official guidelines for management of GTNs. The WHO/FIGO guidelines are presumably followed. No study has been conducted nor any analysis found in either grey or published literature on treatment outcomes or potential factors impacting on treatment outcomes at the institution.

Purpose of the Study

This study evaluates gestational trophoblastic neoplasms (GTN) patient management practices at KNH between 1st January 2010 and 31st December 2015. It also analyses the patient treatment outcomes and identifies factors associated with chemotherapy treatment failure. In addition it does establish the number of chemotherapy courses need to achieve remission. For the first time in the history of GTN treatment at KNH, it establishes the institutional GTN chemotherapy-hCG response normogram for low and high risk neoplasms.

LITERATURE REVIEW

INCIDENCE AND EPIDEMIOLOGY

The true estimate of the incidence and prevalence of GTNs has been difficult to establish due to inconsistencies in case definition, inability to adequately characterise the population at risk thus making equally difficult to identify control groups, use of hospital-based data, lack of universal agreed denominator and the general rarity of the neoplasms.

Literature on incidence and prevalence of GTNs in Africa is dearth. The Altieri et al cancer registry analysis showed a choriocarcinoma generalised incidence of 0.38 per 100,000 women of reproductive age in Africa. A review of hospital based data in Lagos Teaching Hospital in Nigeria showed an estimated incidence of 543 and 335 per 100,000 deliveries for hydatidiform mole and choriocarcinoma respectively (4). A retrospective study in Ghana using referral hospital based data found choriocarcinoma to be the commonest gynaecological malignancy below the age of 30 years and to contribute 6.83% of all gynaecological cancers (5)

Indonesia is reported to have the highest incidence of GTDs of 1,299/100,000 deliveries while as a study in Paraguay reported the lowest incidence of 23 cases per 100,000 deliveries(6). In the United States where specific data on choriocarcinoma is available the incidence of this aggressive malignant tumour is 0.18 per 100,000 women of reproductive age(6). It has been estimated that in that country 1 in 40 moles, 1 in 5000 ectopic pregnancies, 1 in 15,000 abortions and 1 in 150,000 normal pregnancies result in choriocarcinoma. Using pooled data from cancer registries, Altieri et al have shown the incidence of choriocarcinoma to vary significantly across continents and countries(6). High incidences are found in Asian countries especially Vietnam where

the incidence is about 1.68/100,000 compared with Japan where rates is 0.09/100,000women age 15-49 years.

HISTOPATHOLOGY AND CYTOGENETICS

All GTNs arise from embryonic trophoblastic tissue. Trophoblasts are specialised cells that originate from early embryonic differentiation of outermost blastocyst layer. The trophoblasts are classified into three distinct classes based on morphology, immunohistochemical characteristics and functions; cytotrophoblasts, synciotrophoblasts and intermediate trophoblasts. The intermediate trophoblasts invade the decidua, the myometrium, spiral arteries during the second wave of trophoblastic proliferation and establish the foetal-maternal circulation. The trophoblasts covering the chorionic villi differentiate into multinucleated synciotrophoblast with no proliferative potential.

Hydatidiform mole (HM) is characterised by a trophoblastic proliferation and vacuolar (hydropic) swelling of chorionic villi. Complete Hydatidiform Mole (CHM) features hyperplasia of all three trophoblastic cell linages on the chorionic villi. Most CHM is diploid with 46XX karyotype with paternal chromosomes. It arises from monospermic fertilisation of anuclear ovum by a haploid (23X) sperm followed by duplication of the genome. A minority of CHM, 4-15%, may arise from dispermic fertilization of anuclear ovum and thus may have 46XX or 46XY karyotype. However, the mitochondrial DNA in both cases remain maternal. In rare cases, CHM may arise as diploid biparental due to autosomal recessive mutation of *NLRP7* and *KHDC3L* genes which presents as familial recurrent Hydatidiform mole (FRHM). Patients with FRHM can only achieve normal pregnancy through ovum donation(7). Partial Hydatidiform moles (PHM) are inherently triploid as they arise from dispermic fertilization of a normal haploid ovum.

The resultant biparental zygote has 69XXY, 69XXX or more rarely 69XYY chromosomal configuration.

Malignant transformation of GTD to GTN involves activation of oncogenes and inactivation of tumour suppressor genes. Currently, there is no test that can reliably predict molar pregnancy that will undergo neoplastic transformation. Furthermore, normal trophoblast are rapidly proliferating cells and invasive and thus may show increased expression of oncogenes and tumour suppressor genes for their normal cell function. As such all molar pregnancies require hCG surveillance and all products of conception should undergo histopathological examination.

Both invasive mole and Choriocarcinoma (CC) are derived from villous trophoblast. Invasive mole is HM characterised by hyperplastic molar villi penetrating into the myometrium. It may produce secondary metastatic lesions in the vagina and lungs. Choriocarcinoma is histopathologically avillous with invasive proliferation of cytotrophoblast and syncytiotrophoblast surrounded by necrosis and haemorrhage. This aggressive tumour is largely aneuploid.

PSTT and ETT are derived from extravillous intermediate trophoblast cells. The two tumours can be differentiated by expression pattern of p63, a p53 gene transcription factor with several isoforms. ETT cells express the TAp63 isoform while as PSTT does not express p63. PSTT arises from neoplastic transformation of intermediate trophoblastic cells and thus shows minimal expression of hCG though there is increased expression of Human Placental Lactogen (hPL) in both plasma and histological sections(8).

MECHANISMS OF CHEMORESISTANCE AND TREATMENT FAILURE

The most commonly used chemotherapeutic agents in GTN treatment includes antimetabolites (methotrexate and 5-fluorouracil), purine analogs (6-mercaptopurine),

cytotoxic antibiotics (Actinomycin-D), plant alkaloids podophyllotoxins (Etoposide), taxanes (paclitaxel), platinums (cisplatin and carboplatin), Nitrogen mastards (melphalan and cyclophosphamides), and anthracyclines (adriamycin). The antimetabolite methotrexate inhibit folic acid reductase (tetrahydrofolate reductase) leading to thymidylate synthesis inhibition and consequently deoxyribonucleic acid (DNA) synthesis inhibition. The antibiotic Actinomycin-D intercalates in DNA minor groove between adjacent guanine-cytosine (G-C) base pairs inducing DNA strand breaks and interferes with ribonucleic acid (RNA) polymerase movement thus inhibiting transcription. It is also postulated to inhibit topoisomerase II in a similar manner to etoposide which inhibits DNA synthesis by forming complexes with the enzyme and DNA. The Vinca alkaloid vincristine (Oncovin), like the taxanes, interfere with microtubule and spindle assembly thus arresting mitosis. Exposure of tumour cells to these agents lead to activation of tumour cell apoptosis pathways. This works preferentially in actively proliferating cells. The GTNs are generally rapidly proliferating thus usually highly chemosensitive.

Tumour chemoresistance is largely ascribable to mechanisms that mediate drug resistance at the cellular level or factors intrinsic to the tumour microenvironment and the host. This includes intracellular mechanisms that increase drug efflux like overexpression of plasma membrane efflux proteins like P-glycoprotein-170 (9) or decrease intracellular transportation and activation of the drugs as is the case in methotrexate resistance. Other mechanism include increased drug detoxification by up-regulation of phase II detoxifying enzymes for example glutathione S-transferase, enhanced DNA repair counteracting drug induced DNA damage and mutations in drug target-encoding genes thus reducing drug affinity at the active site. In the latter mechanism, tubulin and topoisomerase gene mutation lead to taxanes tumour

resistance. Cell lines with mutated p53, a tumour suppressor gene, develop capacity to proliferate even in the presence of adequate methotrexate inhibitory concentrations.

It is evident that the incomplete and immature vasculature within the tumours and low haemoglobin (Hb) levels plays a fundamental role in drug resistance. The immature vasculature and low Hb lead to reduced oxygenation and nourishment of cancer cells, and cancer cells adapt to grow in these critical conditions. The adaptation leads to changes in gene expression and metabolic pathways, which contributes to diminishing pH values in the tumour until an acidic pH is achieved and maintained. In these conditions, drug resistance phenomena may begin to occur because many drugs become ionized. Weak basic drugs, such as anthracyclines and vinca alkaloids, diffuse poorly in an acidic extracellular milieu because their ionized status obstructs their passage through cell membranes. In similar mechanism, hypoxia leads to drug resistance (10).

Chemotherapeutic agents toxic side effects lead to delayed in administration of sequential courses of therapy, reduced agent bioavailability or change of treatment regime. In most cases, the second line agent(s) adopted have lower effectiveness in achieving remission. It is estimated that between 9% and 33% of GTN resistance may be ascribed to severe side effects of the chemotherapy agents(11). Similarly, skipped courses, increasing dosing intervals and administration of sub-therapeutic doses of the chemotherapeutic agents allow growth of the tumour especially tumour cell sub-populations with potential resistance to the agents.

Delayed initiation of prescribed treatment due to any cause allows further progression of the tumour. GTN growth is exponential and relative short time may lead to rapid growth of the tumour to warrant reclassification as evidenced by rapid rise in serum hCG.

MANAGEMENT OF GTN

Staging & Risk Assessment

In 1982, FIGO introduced anatomical GTN staging. In this staging the tumour in Stage I is confined to the uterus; Stage II is spread to pelvis and vagina; Stage III is spread to lung and Stage IV to other distant metastatic sites. However, this classification is inadequate as it fails to capture other factors that are important for prognostication.

The prognostic scoring factors were first devised by Bagshawe in 1976 who identified ten risk factors in a retrospective cohort of 317 patients treated for trophoblastic tumours(12). In 1983, a WHO working group adopted nine of the Bagshawe's prognostic factors. In 1992, the FIGO Gynaecologic Oncology Committee summarised the risk factors to two (hCG higher than 100,000 IU/L and duration from termination of antecedent pregnancy to diagnosis more than 6 months) as the revised FIGO staging system, but was later expanded to include eight factors in the modified WHO/FIGO staging system. The modified WHO/FIGO classification differs from the original WHO classification in that it disregards the ABO blood group as a factor, risk associated with hepatic metastasis is score 4 rather than 2 (1,13) and has two risk groups; low and high risk, with elimination of medium-risk group. With the modified WHO/FIGO system, fewer patients fall into the high risk group, but in terms of chemotherapy resistance treatment outcome is not compromised.

Despite the wide acceptance of the modified WHO/FIGO prognostic scoring system, the system fails to capture several issues relating to GTNs. The system fails to capture Hydatidiform Mole (HM) especially CHM which is a well-known premalignant condition. The inclusion of molar pregnancy is only when there is progression to gestational neoplasia. Both PSTT and ETT are not included in the scoring system though the two tumours originate from gestational trophoblastic tissues just like the other GTNs.

Currently, the KNH utilises the modified WHO/FIGO classification for GTN staging, prognostic scoring and defining management (Annex 2). The score values for the risk factors are 1, 2, and 4. The cut-off scores for low risk and high risk neoplasia were ratified by the FIGO Committee on Gynaecologic Oncology in June 2002 as part of FIGO staging and scoring system. In order to stage and allot a risk factor score a patient's diagnosis is allocated to a stage as represented by a Roman numeral I, II, III, and IV. This is then separated by a colon from the sum of all the actual risk factor scores expressed in Arabic numerals. A score of 6 or less is low risk disease treatable by single agent chemotherapy. A score of 7 or greater is high risk disease that requires combination chemotherapy.

The FIGO anatomical staging is not useful in determining therapy but assists in communicating disease severity and outcomes for comparison.

Investigations for Staging and Treatment Stratification

Appropriate staging and prognostic scoring of GTN requires thorough clinical evaluation, radiological and laboratory investigations. Patient developing GTN following molar pregnancies are usually detected early through hCG monitoring. The pre-treatment hCG level is an independent marker of both metastasis and risk for single agent (MTX) resistance (14). The amount of hCG the tumour produces directly correlate with the amount of viable trophoblastic tissue present. Based on exponential growth of tumours, it has been estimated that one gram of trophoblastic neoplasm containing 10^9 tumour cells produces about 10^5 IU of hCG per day. Current experience in United Kingdom (UK) has shown post molar disease with hCG higher than 20,000 IU/L a month after evacuation is unlikely to regress and needs chemotherapy(3). Further, patients with pre-treatment levels exceeding 100,000 IU/L are likely to develop resistant to single-agent chemotherapy with a 99% specificity and 52% sensitivity(14).

The currently recommended method for estimation of hCG is radioimmunoassay (RIA) which detects both free ß sub-unit, c-terminal peptide, nicked hCG, hyperglycosylated and intact hCG. The RIA hCG test is specific and can detect hCG concentrations less than 2 IU/L in serum. Serum levels less than 5 IU/ML are considered negative.

A pelvic Doppler ultrasound is useful in confirming absence of pregnancy, estimate uterine size, tumour spread within the pelvis and degree of vascularity. It has been suggested that Doppler pulsatility index is an independent prognostic factor for methotrexate monotherapy resistance(15).

Patients suspected to have brain metastatic lesions benefit from lumber puncture to assess the cerebrospinal fluid to serum ration of hCG. A ratio greater than 1:60 is suggestive of occult brain lesions. This is critical as patients with brain lesions required adjustment of treatment regimen to include intrathecal methotrexate, radiotherapy and or surgery.

A chest radiograph is essential given that pulmonary metastases are common. A normal chest X-ray (CXR) excludes the need for computed tomography (CT) scan or Magnetic Resonance Imaging (MRI) of the chest though approximately 40% of normal CXR will have micrometastases on the latter two imaging modalities(3). The micrometastases do not influence treatment, prognosis or outcome. Patients with lesions on CXR should undergo further evaluation with CT or MRI scans to exclude disease involving other sites like brain and liver which have significant impact on prognosis and management.

Genetic studies are useful in differentiating between gestational and non-gestational hCG producing tumours such as lung and gastric neoplasms. In non-gestational tumours, the tumour genotype resemble that of the patient(16). Though non-

gestational tumours show initial response to GTN-based chemotherapy, their prognosis and outcome are invariably poor.

Chemotherapeutic Management

Indication for Chemotherapy

All gestational trophoblastic neoplasm, as defined by FIGO, should be treated with chemotherapy.

The onset of malignant change after HM evacuation as indicated by plateaued or rising hCG(17) is an indication for chemotherapy. Plateau is defined as four or more equivalent values of hCG over at least three weeks (days 1, 7, 14 and 21) while as rising is defined as two consecutive increase in hCG of 10% or more over at two weeks (days 1, 7 and 14). Patients with high levels of hCG (>20,000 IU/L) four weeks after molar evacuation should be treated with chemotherapy as experience has shown such disease is unlikely to remit spontaneously (18).

Heavy vaginal bleeding or evidence of gastrointestinal or intraperitoneal haemorrhage warrant initiation of chemotherapy. Patients with histological diagnosis of choriocarcinoma, any evidence of brain, liver, gastrointestinal or CXR opacities > 2cm should be treated with chemotherapy(17).

Low risk GTN

Low risk gestational trophoblastic neoplasm constitutes non-metastatic (except lung metastases) disease that scores 0-6 on the modified WHO/FIGO scoring criteria and FIGO stage I-III. About 95% of HM who develop GTN are in this group. For all patients with low risk GTN, single agent chemotherapy with MTX or actinomycin-D (Act-D) is treatment of choice(19). Several protocols based on the two agents have been developed with relatively comparable results.

The original protocol, still widely used in the United States, uses MTX 0.4mg/kg IM for 5 days repeated every 2 weeks. This protocol is associated with primary treatment failure rate of about 11-15% for non-metastatic and 27-33% for metastatic disease(13). Alternative to this protocol is Act-D 12ug/kg IV daily for five days, repeated every 2 weeks. This protocol carries an 8% primary failure rate. It is also the preferred protocol in patients with liver dysfunction.

In the UK, MTX with Leucovorin rescue protocol is widely used. MTX 1.0mg/kg IM is given alternate days for 4 doses with Leucovorin 0.4mg/kg 24-30 hours after every MTX dose. This protocol has a higher primary failure rate of 20-25%. The alternative regimen of MTX 50mg/M^2 IM weekly has even higher primary failure rate of 30%. Act-D 1.25mg/M2 every fortnight protocol with 20% primary failure rate is an alternative to the pulsed weekly MTX regimen.

A 2013 Cochrane review comparing MTX to Act-D concluded that Act-D is superior to MTX in achieving primary cure in patients with low risk GTN. The side-effect profile for the two agents were at least comparable. However, MTX with folinic acid rescues (MTX/FA) is well tolerated and does not induce hair loss as compared to the Act-D protocols. Furthermore, patients developing resistance to MTX protocols can be switched to Act-D regimen if hCG is less than 300 IU/L with near 100% cure (20).

The chosen protocol is continued until hCG normalises (hCG <5 IU/L) and then for further 2 or 3 courses to eliminate residue tumour cells and reduce the risk of relapse. Though the number of consolidation courses largely depend on centre guidelines, reducing to one course doubles the risk of relapse. Three courses are also preferred for patients with slow hCG regression.

With above protocols, only about 30% of patients with WHO/FIGO score of 5 or 6 achieve cure. Moreover, patients with such score and hCG >400 000 IU/L are unlikely to be cured by the single agent chemotherapy and therefore combination chemotherapy is preferred (18). Identification of patient likely to develop resistant to single agent chemotherapy can also be inferred from hCG regression normograms and hCG kinetic analysis (11,21).

High Risk GTN

A high risk GTN includes disease that scores seven or more on the modified WHO/FIGO scoring criteria and FIGO stage III or IV. High risk GTN has increased resistance to single agent chemotherapeutics, increased risk of recurrence, and generally requires combination chemotherapy to achieve remission. Without multi-agent chemotherapy, only about 30% of high risk GTN achieve remission with single agent chemotherapy (22).

Several chemotherapy combination regimes have been developed to treat high risk GTN. The combination that includes Etoposide, Methotrexate, Actinomycin-D, Cyclophosphamide and Vincristine, EMACO, developed at Charing Cross Hospital in the United Kingdom has been widely used and is now considered the standard of care. This regime has been found to have the highest effectiveness-to-toxicity ratio (23). EMACO induces remission in 76% to 97% of patients with high risk disease. This regimen is administered every 14 days as etoposide 100 mg/m^2 days 1 and 2, methotrexate 300 mg/m^2 day 1 and actinomycin D 0.5 mg IV bolus day 1 and 2. Four doses of folinic acid 15mg 12 hourly are also administered from day 2 starting from 24 hours after commencement of methotrexate. The EMA alternates with cyclophosphamide 600 mg/m^2 and vincristine 1 mg/m^2 on day 8. The second cycle is thus begun on 15th day(13).Chemotherapy is initiated when white cell count is greater

than 3000 per mL, granulocytes are greater than 1500 per mL, platelets are greater than 100 000 per mL, and a Grade 3 gastrointestinal infection and mucositis morbidity have cleared. Subsequent doses are administered if granulocyte count is greater than 1000 per mL and platelets above 75 000 per mL. If toxicity necessitates a delay in cyclophosphamide and vincristine administration for longer than 6 days, day 1 and 2 treatment with EMA is repeated (that is cycle is restarted).

Other regiment that have been described include MFA (MTX, folinic acid, ACT-D), MAC (MTX, ACT-D, and Cyclophosphamide) and CHAMOCA (cyclophosphamide, hydroxycarbamide, doxorubicin, ACT-D, MTX, melphalan, and vincristine). A retrospective review of these regimen effectiveness demonstrated remission rates of 63%, 68%, 71%, and 91%, respectively(24). In that review EMACO was reported to have remission rate of 90.6%. A Cochrane review in 2012 showed no statistical difference in effectiveness of MAC and CHAMOCA. However, the latter regimen is associated with severe toxicities and is rarely used (25). Two controlled trials have compared MAC to EMACO and shown the two regimen to be equipotent in achieving remission. However, retrospective studies have shown EMACO to have a higher remission rate but with an increased risk of secondary tumours. Retrospective review of 1337 women with total of 15,279 person-years of observation showed that patients treated with more than 2 g/m^2 of etoposide, had a relative risk of 16.6 for developing leukemia, 5.8 for breast cancer, 4.6 for colon cancer, and 3.4 for melanoma (26).

A regimen including cisplatin, EMACP (etoposide, methotrexate, cyclophosphamide, actinomycin D and cisplatin) has been shown to be effective treatment for GTN with remission rates higher than EMACO and a shorter period of treatment. However, the regimen is associated with more toxicities that includes fever, renal toxicity, nausea and diarrhoea, anaemia, neuropathies and hepatotoxicity (27).

Management of PSTT and ETT

Where histologically diagnosed PSTT and ETT are treated with hysterectomy as first line mode of treatment as the two tumours are highly chemoresistant. In addition, patients with metastatic disease are treated with intensive chemotherapy. Recent studies have shown mitotic index to be a good indicator of the tumours response to chemotherapy (28).

Treatment Follow-up

Patients with GTN should have follow-up serum hCG titres once per week until 4 normal values are obtained and then obtained once per month for 1 year. The hCG assay must measure all portions of the hCG molecule, particularly the free beta subunit, hyperglycosylated hCG (hCG-H), nicked hCG, and hCG missing the terminal carboxyl segment which are common products in patients with GTN.

The patients should be put on reliable contraceptive method. The contraception avoids pregnancy in the course of follow-up which can be confused with tumour relapse and avoids potential foetal malformation associated with chemotherapy. Contraception should be continued for at least six months after hCG normalization.

CHEMOTHERAPY AND HCG REGRESSION

Measured by radioimmunoassay (RIA), serum hCG is the standard tumour marker for monitoring GTN response to chemotherapy. The rate of serum clearance of hCG can be used to predict likelihood of resistance or remission. Using routine patient data, You et al identified low risk GTN patients with hCG clearance ≤0.37 l/day to have 35.5% risk of biochemical MTX resistance(21). The risk of resistance in patients with higher hCG clearance was only 6%. In addition, Kerkmeijer et al has shown patients with hCG concentration greater than 737 IU L^{-1} before the fourth MTX course had a 52% risk of developing chemoresistance with a 97.5% specificity(14).

TREATMENT OUTCOMES

Though there are no longitudinal studies comparing EMACO to other combination chemotherapy regimens it is widely accepted as standard of care for management of high risk GTN. This regimen achieves remission in 76% to 97%(29). Other regimens are less effective or have greater side effects profile thus less tolerated. In a retrospective study with median of 4.5 years of follow-up and 272 subjects, EMACO achieved a cumulative 86.2% (95% CI 81.9% to 90.5%) 5 year survival rate. In this study, death attributable to GTN occurred in 11.4% and while as 17% of the patients developed chemoresistance(25). EMACO is reported to be well tolerated with the regimen having the lowest side effects of all regimens in use for high risk GTN. Haematological toxicity is often the commonest and severest and deaths have been reported. Though beyond the scope of this study, in the long-term, EMACO has been associated with secondary tumours especially leukaemia with poor prognosis(23).

Low risk GTN treated with MTX with folinic acid or low dose Act-D achieves near 100% cure rates. In a Cochrane review that included five randomised clinical trials (RCTs) in 2014, Act-D was associated with higher primary cure rate than MTX, and conversely MTX with higher treatment failure (513 participants; RR 3.81, 95% CI 1.64 to 8.86, P = 0.002)(19). Both agents had statistically comparable side effects profiles (nausea, vomiting, alopecia, diarrhoea and anaemia) with none being associated with severe side effects leading to treatment discontinuation. Low cure rates, 9% and 43% with MTX and Act-D respectively, has been reported for patients with WHO/FIGO scores of five or six. Patients whose initial prechemotherapy hCG is greater than 100,000IU l^{-1} are unlikely to be cured with MTX or Act-D monotherapy(21,30). Similarly, patients with histologically confirmed choriocarcinoma are less likely to achieve remission with a single agent chemotherapy.

Chemoresistance and Treatment Failure

Initial and hCG levels in the first few courses of MTX treatment can identify 50% of patients whose treatment with single-agent chemotherapy will be ineffective. Patients with hCG pre-treatment levels exceeding 100,000IU/L are likely to develop resistant to single-agent chemotherapy with a 99% specificity and 52% sensitivity(11). This is related to the finding that hCG levels correlates with tumour size and high levels may therefore be a sign of metastatic disease. Independent of individual scoring factors, only about 30% of patients with WHO/FIGO score of 5 or 6 achieve cure on single agent chemotherapy(11).

You et al has shown the rate of hCG clearance can predict risk of single agent treatment failure. Patients with hCG clearance <0.37l/day have 35.5% risk of developing MTX resistance. Patients with hCG greater than 737 IU/L by 4^{th} MTX course have a 52% risk of developing chemoresistance(21). If before the fourth course of single-agent chemotherapy the serum hCG concentration exceeds the P97.5 of a normal regression curve, it can be concluded with 50% sensitivity that combination chemotherapy is essential to achieve cure(11).

Patient with metastatic disease (FIGO stage IV) are unlikely to achieve remission without adjuvant radiation, surgery or chemotherapy. Without irradiation or intrathecal MTX, patient with brain metastasis have up to 44% mortality rate.

Remission is also dependent on agent(s) and/or schedule of administration of the chemotherapy. Low risk disease with weekly MTX and biweekly Act-D achieve 58% and 73% remission respectively. The 5 day or 8 day MTX regimen has remission rates comparable to the biweekly Act-D regimen. For high risk disease, EMACO achieves up to over 90% remission rates. MFA (MTX, folinic acid, ACT-D), MAC, CHAMOCA (cyclophosphamide, hydroxycarbamide, doxorubicin, ACT-D, MTX, melphalan, and

vincristine) have remission rates of 63%, 68%, and 71% respectively(23,31). Only about 30% of patients with WHO/FIGO high risk risk disease treated with single agent chemotherapy achieve remission(22).

Tumour histopathology influences mode of treatment and treatment outcome. PSTT and ETT are considered primarily resistant to chemotherapy. Surgery and radiotherapy are considered first line mode of treatment for the two tumours. Irrespective of the WHO/FIGO score choriocarcinoma histopathology is independently associated MTX chemoresistance (21).

Side Effects Related to GTN Chemotherapy

EMACO used for management of high risk GTN is associated with DNA damage that has been linked to several side effects. Using single cell gel electrophoresis assay (SCGE) of peripheral lymphocytes, Akylol D et al showed the severity of DNA damage to correlate with severity of the toxic effects of the chemotherapy. However, all the side effects were noted to be predictable and reversible and did not necessitate change or abandonment of treatment. The side effects and frequency as reported were fever (71.4%), leukopenia (57%), elevated liver enzymes (57%), thrombocytopenia (57%), and anaemia (57%)(32).

Methotrexate is metabolised and eliminated by the liver. It associated with elevated liver enzymes. Where the serum bilirubin levels exceed double the upper limit of the reference values, methotrexate therapy should be stopped.

Methotrexate, etoposide and cyclophosphamide are associated with bone marrow toxicity. This is reflected as thrombocytopenia, leukopenia or anaemia. There is increased risk of febrile neutropenia. Administration of subsequent courses should be withheld where the neutrophils are less than 1000/ul. Granulocyte colony stimulating factor G-CSF (Neupogen) can be administered to boost granulocyte recovery.

Vincristine is associated with peripheral neuropathy. Methotrexate is associated with meningeal irritation, temporary or permanent paralysis or encephalopathy.

Methotrexate monotherapy is also associated with acute renal tubular necrosis and deranged renal function. Sodium bicarbonate and adequate hydration may be necessary to reverse the toxicity.

Cyclophosphamide has been associated with mucositis especially of the urinary bladder. This may present with haematuria. Adequate rehydration to increase urine flow or administration of mesna is indicated if the side effect is encountered.

Alopecia, hair loss, is a common side effect of chemotherapy. It may be complete or partial but is largely reversible.

CHAPTER II

JUSTIFICATION, RESEARCH QUESTION AND OBJECTIVES

JUSTIFICATION

The gestational trophoblastic neoplasms are the only disseminated solid tumours that are curable with chemotherapy. In addition, fertility is preserved. As such effort should not be spared in ensuring optimal patient outcomes.

This is study evaluates the management of GTNs at Kenyatta National Hospital. By evaluating the management decisions and patient care, practices that lead to suboptimal outcomes are identified. This is essential in informing care givers and health system of gaps and areas that need strengthening. Strengths identified are also highlighted for sharing with other GTN treatment centres and may potentially inform changes in standards of care.

This study also evaluates the chemotherapy treatment outcomes. This is essential in comparing institutional performance with other GTN treatment centres and appraising patient management decisions. Since Kenyatta National Hospital is the main public GTN treatment centre, the performance of the centre provides a proxy indicator of the national GTN treatment outcomes. Such an evaluation has not been carried out at KNH and therefore the findings of this study provides a baseline for future reviews and comparison. Such information is therefore critical in appraisal of adapted guideline protocols on GTN management at the institution.

By identifying factors associated with unfavourable treatment outcomes KNH will be able to adapt international standards of care guidelines with emphasis in areas that will enhance improvement in treatment remission locally. This domestication of the international standards with regard to local factors that may be unique to our setting is essential in ensuring adherence to treatment protocols and optimising patient care.

The identification of factors also appraises the current management practices at KNH and highlights the need to adhere to established international standards.

In recent studies, hCG titres thresholds have been found to be important predictors of GTN chemoresistance. Van Trommel et al(11) and Savage et al(33) have proposed a cut off 520.24 mIU/ml and 500 Miu/ml respectively at 7th week of chemotherapy as predictive of single agent Methotrexate resistance. An hCG clearance of less than or equal to 0.37 l/day has also been shown to be predictive of chemoresistance. This study has imperatively developed local GTN treatment hCG clearance normograms contributing to this growing body of knowledge in identifying potential chemoresistant GTNs early.

RESEARCH QUESTION

What are the predictors of gestational trophoblastic neoplasms chemotherapy treatment outcomes for patients initiated on chemotherapy at Kenyatta National Hospital between 1st January 2010 and 31st December 2015?

NULL HYPOTHESIS

There are no differences between characteristics of gestational trophoblastic neoplasms patients with chemotherapy treatment failure and those with remission treated at Kenyatta National Hospital between 1st January 2010 and 31st December 2015.

BROAD OBJECTIVE

To determine the predictors of gestational trophoblastic neoplasms chemotherapy treatment outcomes at Kenyatta National Hospital between 1st January 2010 and 31st December 2015.

SPECIFIC OBJECTIVES

i. To determine Gestational Trophoblastic Neoplasm (GTN) management practices at Kenyatta National Hospital

ii. To determine the Gestational Trophoblastic Neoplasm treatment outcomes at KNH between 1st January 2010 and 31st December 2014

iii. To determine factors associated with GTN chemotherapy treatment failure at Kenyatta National Hospital

CHAPTER III

METHODS

CONCEPTUAL FRAMEWORK

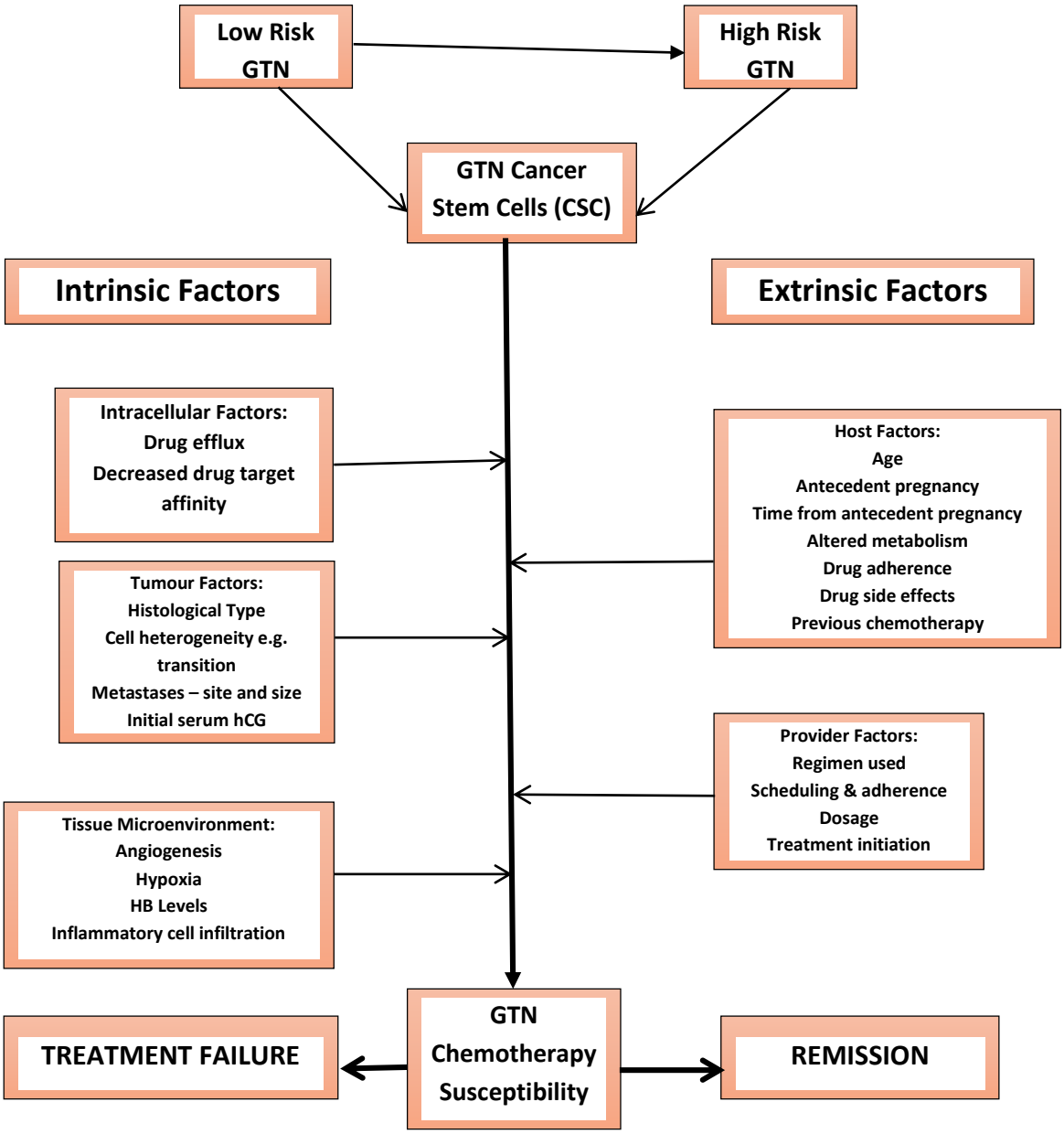


Figure 1 Conceptual Framework

Representative important determinants and concepts implicated in Gestational Trophoblastic Neoplasm (GTN) chemotherapy treatment outcomes. Adopted from Recurrent oral cancer: current and emerging therapeutic approaches(34)

This study concentrates on distal factors impacting on GTN treatment outcomes – remission and treatment failure. The molecular basis and pathogenesis of the chemoresistance is beyond the scope of this study.

The factors that determine tumour cells susceptibility to chemotherapy can largely classified as intrinsic or extrinsic to the tumours. The intrinsic factors are innate to the tumours cells or are acquired after exposure to chemotherapeutic agents. Intracellular factors affect drug target affinity or intracellular drug concentration. Tumour factors include the histological type and heterogeneity of tumour cells. The location of metastases affects response to chemotherapeutic agents. Blood brain barrier makes it difficult to achieve therapeutic concentration to treat brain metastases. Relative hypoxia at the core of large tumours reduces chemosensitivity of the tumour cells.

Extrinsic factors are either host or healthcare provider related. Failure to use the established standard of care regimen and hence use of inferior treatment is likely to lead to higher treatment failure rates. Patients who are misclassified due to inept scoring may be over treated with likely resultant higher side effects. This places the patient at risk of treatment discontinuation and attendant risk of secondary tumours associated multiagent chemotherapy. Conversely, only about 20-30% of high risk GTN patients treated with single agent chemotherapy achieve remission(31). In addition to high treatment failure rate, the patients are exposed to long periods of chemotherapy and may lead to anxiety that can affect treatment adherence.

Maranga et al has shown treatment delay is a major contributor to low survival of cervical cancer patient (35). Significant delays between chemotherapy treatment courses may leads to sub-therapeutic drug concentrations and tumour progression. Lead time to this effect is not known for GTN chemotherapy treatment.

Chemotherapy side effects may affect drug dosages, scheduling of courses, drug plasma concentration and even necessitate change of regimen or lead to unfavourable outcome.

STUDY DESIGN

The study employs a retrospective cohort design. This design was preferred because it relatively fast with readily accessible data, less costly, has minimal ethical concerns, and robust to answer the research question. The retrospective aspect suits investigations on the rare cancers. The exposures of interest include treatment regimen, adherence to treatment schedules, side effects, time to treatment initiation, initial hCG levels, rate of hCG decline with treatment, chemotherapy regimen used, tumour histopathology, WHO/FIGO score and the factors used in the scoring. The outcome of interest are treatment failure and remission as defined.

STUDY SETTING

The study was conducted at Kenyatta National Hospital, a national teaching and referral hospital located in the capital city of Nairobi. The institution was selected as it admits patients from all over the country thus providing external validity to the findings of the study. It has the largest number of patients on chemotherapy thus possible to meet the required sample size for the rare neoplasms. In addition, it is also a teaching hospital for almost all health cadres and therefore any changes occasioned by the findings and recommendations will potentially influence changes in the whole country. KNH admits on average two to four patients per month to ward 1B for GTN management. The diagnosis and prognostic classification of GTN in KNH is made using the modified WHO/FIGO prognostic scoring system. Patients are admitted the day before date of chemotherapy administration with baseline investigation results that includes renal function tests, liver function test, complete blood count and hCG levels. Where single agent chemotherapy is indicated, methotrexate alternating with folinic

acid are administered for one week followed by a break of 7 days before starting the next course. EMACO and EMA-EP are administered as per protocol on day one, two and eight with the next course starting on day 15. Patients are followed with hCG levels done before course initiation to monitor response to treatment.

STUDY POPULATION

Patients GTNs managed with chemotherapy between 1st January 2010 and 31st December 2015 provided an open retrospective cohort for this study. The patients are drawn from the KNH catchment population and referrals from peripheral health facilities countrywide. Due to the later and given that KNH is the only established public GTN treatment referral centre, the study population may be said to be drawn from the entire country.

SELECTION CRITERIA

Inclusion Criteria

All patients admitted to Kenyatta National Hospital with diagnosis of Gestational Trophoblastic Neoplasm between 1st January 2010 and 31st December 2015 and initiated on chemotherapy treatment within that time period were included in the study cohort.

Exclusion criteria

Patients whose chemotherapy was initiated elsewhere and patients with other co-existing malignancies were excluded from the study.

SAMPLE SIZE DETERMINATION

For the analytic section of the study, the formulae below, published by Kasiulevičius et al (36) and widely used for calculating the sample size in independent cohort study for two-sided equality hypothesis testing for retrospective cohort studies was employed to determine the sample size.

$$n = \frac{\left[Z_\alpha \sqrt{(1+1/m)\bar{p}(1-\bar{p})} + Z_\beta \sqrt{p_0(1-p_0)/m + p_1(1-p_1)}\right]^2}{(p_0 - p_1)^2} \qquad n_c = \frac{n}{4}\left\{1 + \sqrt{1 + \frac{2(m+1)}{n\,m\,|p_0 - p_1|}}\right\}^2$$

Where:

- Power (ß): probability of detecting a real effect.
- Alpha (α): probability of detecting a false effect for a two sided type 1 error probability
- P_0: probability of event in controls / general population.
- *: input either P1 or RR, where RR=P_1/P_0.
- P_1: probability of event in experimental subjects.
- RR: relative risk of events between experimental subjects and controls.
- Z_α: standard normal variate for level of significance (Z_α=1.96)
- $Z_ß$ =Standard normal variate for power (power = 80% then $Z_ß$=0.84)
- m: Number of control subjects per exposure subject

$$\bar{p} = \frac{p_1 + m\,p_0}{m+1}$$

- n: Sample size (exposed cases) = 44
- n_c: Continuity corrected sample size = 52

Review of literature reveals EMACO (the most used combination chemotherapy in KNH for high risk GTN) achieves remission in about 90% of high risk GTN (2, 5) under standard conditions of patient care and follow up (thus probability of treatment failure is 10%). This study will use a ratio of one exposed for every two control subjects. A pre-study assumption is that the remission rate decreases to 70% (probability of treatment failure in the exposed groups is 30% i.e. RR is 3) due to delay in initiating treatment, poor adherence and/or use of nonstandard regimens and other exposures. When this data is substituted in the Kasiulevičius et al formulae with a 95% two-sided confidence level and power of 80% it yields sample size of 44 exposed subjects. Fleiss continuity correction yields sample size of 52 exposed cases and using a ratio of unity the calculated sample size sums up to 104 subjects.

However, all patients meeting the inclusion and not excluded were considered with a total of 158 patients considered for analysis. This is acknowledged to have improved

the precision and power of the study above the anticipated when calculating the sample size.

SAMPLING METHOD, RECRUITMENT AND DATA SEARCHES

The sampling frame was drawn from the list of all GTN patients diagnosed and admitted chemotherapy treatment at Kenyatta National Hospital in the period extending from 1st January 2010 to 31st December 2015. Gestational trophoblastic neoplasm patients treated with chemotherapy throughout the research period were searched through a query of data at Kenyatta National Hospital master electronic registry. The records are maintained after coding using the ICD10 classification codes. Using the codes O01.0 (Classical hydatidiform mole), O01.9 (hydatidiform mole unclassified), D39.0 (Neoplasm of uncertain or unknown behavior), D39.2 (Neoplasm of uncertain or unknown behavior, placenta), D39.7 (Neoplasm of uncertain or unknown behavior, other female genital organs), and C58 (Malignant neoplasm of placenta) yielded a total of 562 patients. These were further filtered using code Z51.1 (Chemotherapy) to identify GTN that were managed with chemotherapy. The list of the filtered patients was the compared with ward 1 B (ward that administers chemotherapy for all gynaecological malignancies) treatment register. The extra patients realised from the ward register were added to the list from the electronic register.

MEASUREMENT OF EXPOSURES AND OUTCOMES

Measurement of exposure

Chemotherapy treatment initiation delay: Was measured in days as from recorded date of clinical/histological GTN diagnosis or referral receipt at KNH to the date of treatment initiation. Chemotherapy treatment non-adherence was measured as cumulative days chemotherapy is delayed between the courses till a defined outcome was determined to have occurred. In this study, delays along the course of chemotherapy was treated to have the same impact on treatment outcome irrespective of number of courses

already administered. The exposure induction time (chemotherapy delay needed to initiate chemoresistance) for GTN is not yet described in literature and thus any delay was treated as having effect on the outcome. Reasons for such delays not was not investigated in this study.

The hCG levels considered as likely predictor of treatment outcome are the levels taken within two weeks before initiation of chemotherapy. The rate of decline of hCG in response to chemotherapy was measured as an intermediate predictor of outcomes of treatment. The rate between the first and third chemotherapy course was considered in addition to though best fit chemotherapy-hCG response curve for all treatment outcome categories was developed.

All side effects recorded in patients clinical records were categorised and analysed.

Patient GTN score was determined using the modified WHO/FIGO scoring systems or recorded in patients clinical records.

Other variables considered as exposures included the age of the patient, the histological diagnosis where available, previous exposure to chemotherapy, antecedent pregnancy and time from antecedent pregnancy and chemotherapy regimen used as first line for treatment under review.

Measurement of Outcomes

The primary outcomes were chemotherapy treatment remission or treatment failure. Complete remission was deemed to have been achieved when the patient has at least two consecutive hCG values less than 5IU/L while under chemotherapy.

Treatment failure was deemed to have occurred when patient died in the course of GTN treatment due to non-incidental causes, rate of decline of hCG was less that 10% between 3 consecutive courses of chemotherapy (chemoresistance), chemotherapy regime was changed due to any reason or patient became pregnant in the course of

chemotherapy treatment. Patient with complete loss to follow-up were categorised as treatment failure.

Other outcome of interest were the median number of chemotherapy courses required to achieve complete remission and rate of hCG decline per chemotherapy course predictive of complete remission or chemoresistance.

DATA QUALITY ASSURANCE PROCEDURES

The data was extracted from patient medical records/files, charts, histopathological reports and outpatient clinic follow-up notes. The data extraction case report forms (annex-1) was pretested at Kenyatta National Hospital with GTN patients treated in the year 2008 and 2009.

The study engaged clinical officers who were working in gynaecology oncology ward at a Thika Level Five Hospital at the time as research assistants. The research assistance were therefore deemed knowledge on subject matter.

The patients' files were traced by the records officer at KNH and data extracted by the two trained research assistants. Fifty per cent of the qualifying patients' records were counterchecked for accuracy by the principle investigator within a day of completing entries by comparing the research assistants' data extraction case report with the original patients' records. Where discrepancies arose, reference to the original record was final. All the data extraction case reports were checked for completeness by the principle investigator within a day of extraction and missing data crosschecked by the alternate research assistant.

VARIABLES

General Patient Characteristics/Potential Confounders

i. Age
ii. Parity
iii. Period from antecedent pregnancy to start of chemotherapy
iv. Method of family planning in course of chemotherapy
v. Laboratory where hCG was done

vi. Year of treatment
vii. Patient source – KNH or referral

Below is a summary of predictor and outcome variables. Data from these variables was used for inference statistics.

Independent variables	Intermediate Variables	Dependent Variables
Treatment delay	Rate of hCG decline	Remission
Treatment regimen		Treatment Failure:
Initial HCG levels	Number of chemotherapy courses to treatment outcome	• Pregnancy in the course of treatment
Non-adherence		• Chemoresistance
Histological diagnosis		• Loss to follow-up
WHO/FIGO score		• Death
Major side effects	Adherence with treatment protocol schedule	
Previous chemotherapy		
Site of metastases		
Antecedent pregnancy		

STUDY INSTRUMENTS

A structured case data extraction form (annex 1) was used to summarise relevant case data from patient clinical records.

DATA MANAGEMENT AND ANALYSIS

The data was transferred from the case data extraction form to EpiInfo Version 7.1.2.0 data entry form by two independent data entry clerks. The two entries were compared for accuracy and consistency. Any discrepancies between the two data sets was referred to the case data extraction form and corrected appropriately. The original data extraction questionnaires will be stored safely for a period of 5 years with digital data back-up of entered data and secured with access codes.

The data was analysed using Epi Info version 7.1.2.0. Univariate analysis and bivariate analysis were used to calculate descriptive statistics and relative risks (RR) to satisfy objectives 1 and 2. Chi square was used to determine statistical significance of various exposures on treatment outcomes. The RR and the 95% confidence intervals was

computed for each of the exposures and p values of less than 0.05 were considered statistically significant. Comparison of initial serum hCG before chemotherapy between remission and treatment failure patients were done using the Mann-Whitney *U* test. Multivariate analysis was used to compute the adjusted relative risks (ARR). The hCG measurements for patients reaching remission was used to construct the hCG regression normograms for low risk and high risk GTN chemotherapy treatment.

DEALING WITH MISSING DATA

Data missing in each of the variables under consideration in this study was assumed to occur through the missing completely at random (MCAR) mechanism and hence complete-case analysis was applicable. However, the remaining number of cases with variable values met the calculated minimum sample size so as to be considered as a potential exposures.

ETHICAL CONSIDERATION

The study was dependent on historical data in patients' medical records. To this end, individual consent from patients/subjects was not sought. However, the data extraction was anonymised. Ethical approval was sought from the department of Obstetrics & Gynaecology, University of Nairobi and the Ethics & Research Committee (ERC) of Kenyatta National Hospital (annex 3). Written consent and approval was sought from Kenyatta National Hospital, the custodians of the patient data utilised in this study.

STUDY LIMITATIONS

This study employed a retrospective approach with secondary data which is prone to missing data problem. As highlighted above majority of the missing data were treated as to have occurred through the ignorable (MCAR) mechanism and complete-case analysis (analyses of cases with available data for each variable) was utilised. Though missing data was minimal, where it occurred it may have compromised the precision of the calculated variable estimates.

The data used in this study was derived from routine data and not obtained from specifically designed study that would have measured predictive factors with greater accuracy and precision. However, this data represents real life patient care records and thus admissible for study analysis.

Study Budget and Funding

The study is estimated to cost three hundred and ninety three thousands five hundred Kenya shillings. The bulk of the budget was spent on data collection. Funding was provided by Kenyatta National Hospital research grant office supplemented with personal resources. The details of the expenditure and funding sources summarized in annex 3.

Study Time Line

The study was conducted over period of 24 months from concept initiation to publication of the results. A detailed Ghant chart showing schedule of activities is attached as annex 4.

CHAPTER IV

RESULTS

Gestational trophoblastic neoplasm patients treated with chemotherapy throughout the study period were searched through a query of data at Kenyatta National Hospital master electronic registry. The data search described in the methodology section yielded a total of GTD 562 patients. These were further filtered using code Z51.1 (Chemotherapy) to identify GTN that were managed with chemotherapy yielding 197 patients. A further 6 patients were identified from the ward chemotherapy register. Out of the 203 patients, files for 158 patients were traced from the records department and hospital archives and data extracted for analysis. This is illustrated in study profile figure 2 below.

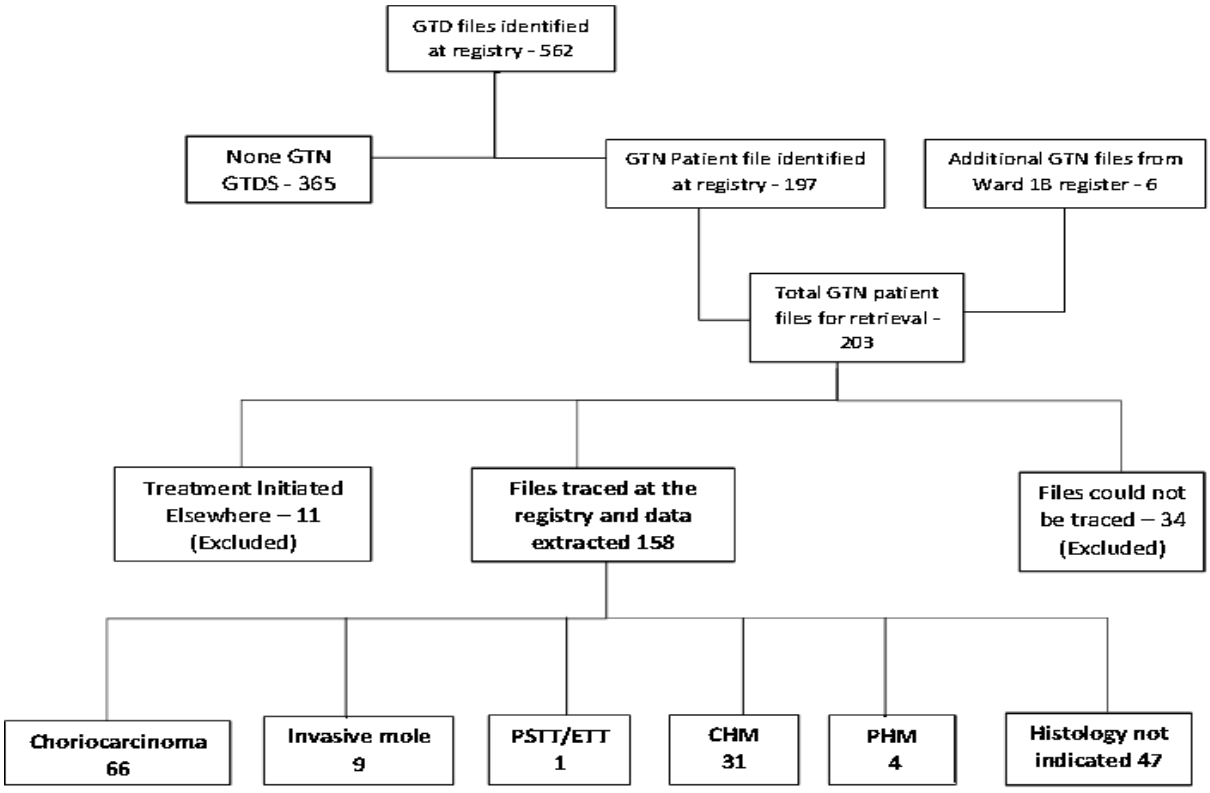


Figure 2 Study Flow Profile
GTD - gestational trophoblastic disease, GTN – gestational trophoblastic neoplasm. PSTT – placenta site trophoblastic tumour. ETT – epithelioid trophoblastic tumour. CHM – complete hydatidiform mole. PHM – partial hydatidiform mole.

General Characteristics

The general characteristics of GTN patient treated at KNH during the study period and whose clinical records could be traced is summarized in table 1 below. Patients referred from peripheral health facilities were near as many as those seen primarily at the hospital with no association between referral status and WHO/FIGO score classification/disease severity. There was no association between age as stratified by WHO/FIGO risk assessment guideline and WHO/FIGO score classification. The median age of diagnosis was 29 years (IQR=24 – 34). Though no association was found between parity and disease severity, GTN was very rare in primiparas with only one case in record. Slightly over two thirds of GTN (67.09%) followed a molar pregnancy. The median time from antecedent pregnancy to diagnosis of GTN was statistically different depending on antecedent pregnancy.

Term pregnancy had the longest latency period with median time of 9 months (IQR=5 – 9). Molar pregnancy had the shortest time of about three months. Twenty patients had received previous chemotherapy with single agent while eight had received combination chemotherapy. Approximately half (51.27%) of patients had no metastasis, or if they had, such information was not recorded. Vagina and uterus (28.48%) were the commonest sites of metastasis followed by lungs (24.05%).

Choriocarcinoma was the commonest histological diagnosis (41.03%). There was only one case of histologically confirmed PSTT/ETT that followed a molar pregnancy. Nearly a third (30.13%) of patients had no histological diagnosis recorded in their clinical records.

Table 2 General patient characteristics of all patients (N=158)

Characteristic			n (%)	p value
Patient source	Referral	High risk	37 (44.58%)	p=0.19
		Low risk	46 (55.42%)	
	KNH	High risk	25 (33.33%)	
		Low risk	50 (66.67%)	
Age in years	<40	Low risk	79(50%)	p=0.54
		High risk	48(30.38%)	
	= or >40	Low risk	17(10.76%)	
		High risk	14(8.86%)	
Parity	Primipara		1 (0.63%)	p=0.63
	Para 2 - para 5	Low risk	47 (29.75%)	
		High risk	28 (17.72%)	
	>para 5	Low risk	48 (30.38%)	
		High risk	34 (21.52%)	
Antecedent pregnancy	Term Pregnancy		21 (13.29%)	
	H Mole		106 (67.1%)	
	Ectopic		8 (5.06%)	
	Miscarriage/Abortion		23 (14.56%)	
Median time (months) from antecedent pregnancy to GTN diagnosis (25-75 percentile)	Term Pregnancy	7 (5-8)		p<0.001
	H Mole	3 (2-7)		
	Ectopic Pregnancy	5.5 (4-6.5)		
	Miscarriage/Abortion	7 (5-9)		
Previous chemotherapy	None	124		
	Single Agent	20		
	Multiple Agent	8		
Initial b-hCG levels	$<10^3$		28 (17.72%)	
	10^3-10^4		29 (18.35%)	
	10^4-10^5		28 (17.72%)	
	$>10^5$		73 (46.20%)	
Metastasis	None		81 (51.27%)	
	Vagina/Uterus		45 (28.48%)	
	Lung		38 (24.05%)	
	Not Indicated		19 (12.03%)	
	Other Sites		15 (9.49%)	
	Brain/CNS		4 (2.53%)	
Histological tumour type	Choriocarcinoma		64 (41.03%)	
	Invasive Mole		9 (5.77%)	
	PSTT/ETT		1 (0.64%)	
	Complete Mole		31 (19.87%)	
	Partial Mole		4 (2.56%)	
	Not Indicated		49 (30.13%)	
WHO/FIGO score	0-6 (Low Risk)		96 (60.76%)	
	>6 (High Risk)		62 (39.24%)	p<0.001

Management of Gestational Trophoblastic Neoplasm

As illustrated in Table 2 here below, nearly all patients had baseline hematological and biochemical investigations done prior to starting chemotherapy. However, only about two thirds (68.92%) had record of having taken a chest radiograph for purposes of identifying chest metastatic lesions and WHO/FIGO scoring. Biometric information that is utilized in chemotherapeutic agent dosage determination was available in 87.25%, 85.91% and 77.24% for weight, height and total body surface area (TBSA) respectively.

Table 3 GTN patients with minimum investigations and prechemotherapy *clinical evaluation*

	Investigation	Number	Percentage
Minimum baseline investigations	CBC	148	99.33%
	UECr	148	99.33%
	PELVIC Ultrasound	146	97.99%
	LFT	133	93.01%
	CXR	102	68.92%
	CTMRISCAN	12	8.16%
Prechemotherapy clinical evaluation	Weight	130	87.25%
	Height	128	85.91%
	TBSA	112	77.24%

CBC = Total Blood Count, UECR = Urea, Electrolytes & Creatinine, LFT = Liver Function Test, CXR = Chest Xray, CT= Computerized Tomography Scan, MRI = Magnetic Resonance Imaging, TBSA = Total Body Surface Area

All patients had WHO/FIGO scoring done. Methotrexate was used for monotherapy protocol while those requiring combination chemotherapy were treated with either EMACO or EMA-EP. Treatment was initiated within median time of 11 days (IQR=1 – 20) for high risk and 25 days (IQR=10.5 – 49) for low risk disease. There was no significance difference in treatment initiation delay between the referred and the non-referral patients.

Table 3 below summarizes patient treatment. Patients with low risk disease (WHO/FIGO score of equal to or less than 6) were treated with either the recommended single agent chemotherapy (58.95%) or combination chemotherapy (41.05%). Rationale for the latter indication in patients with low risk neoplasm was not

in record. Incidentally, only one patient with high risk GTN was treated with single agent chemotherapy. About 61% of all patients were put on modern methods of family planning. Eleven patients (7.19%) required adjuvant radiotherapy and twenty one (13.64%) patients had surgery (hysterectomy) in addition to chemotherapy. Slight above half of patients (56.74%) received blood transfusion at least once in the course of treatment. A further 45 (31.47%) patients received neupogen, a synthetic granulocyte colony stimulating factor (G-CSF) analog, to correct chemotherapy induced neutropenia. Majority (88.89%) of those requiring neupogen were on EMACO chemotherapy. Those treated with combination chemotherapy had a relative risk (RR) of 4.6 (95% CI 2.27 – 9.49 p<0.001) of developing severe neutropenia requiring treatment with neupogen.

Table 4 GTN Chemotherapy administered and adjuvant Treatments

			n (%)
Chemotherapy	WHO score <6 (Low Risk)	Single agent	56 (58.95%)
		Combined chemotherapy	39 (41.05%)
	WHO score >6 (High Risk)	Single Agent	1 (1.69%)
		Combined chemotherapy	58 (98.31%)
Adjuvant treatment	Surgery		21 (13.64%)
	Radiotherapy		11 (7.19%)
	Family planning		94 (61.04%)
	Blood transfusion		80 (56.74%)
	Neupogen		45 (31.47%)

Treatment Outcomes

During the period under review, Kenyatta National Hospital had an overall remission rate of 65.15% for all GTN as tabularized in table 4 below. There was no significant difference between the low and high risk disease remission rates. Low risk GTN had higher rates of Chemoresistance at 26.04% and total treatment failure of 34.38%. Mortality was significant higher among patients with high risk disease with RR of 8.51

(95% CI 1.95 – 37.13 p=0.001) with risk difference of 15.66 (95% CI 5.73 – 25.59 p=0.001) compared to low risk disease.

Table 5 Treatment outcomes by WHO/FIGO Risk Category

		Treatment Outcomes					
			Treatment Failure				TOTAL
		Remission	Change of regimen - other reasons	Chemore sistance	Loss to Follow-up	Death	
WHO/FIGO Risk Category	Low Risk	63 (65.63%)	2 (2.08%)	25 (26.04%)	4 (4.17%)	2 (2.08%)	**96**
	High Risk	40 (64.52%)	0	9 (14.52%)	2 (1.27%)	11 (17.74%)	**62**
	TOTAL	**103 (65.19%)**	**2 (1.27%)**	**34 (21.52%)**	**6 (3.80%)**	**13 (8.23%)**	**158**

The issue of high resistance among patient with WHO/FIGO score of 6 (previously classified as intermediate risk under WHO risk classification) treated with single agent has been raised. The findings at KNH regarding this group of patients are highlighted in table 5 below, showing high level of chemoresistance when treated with methotrexate monotherapy. Three quarters of the patient treated with methotrexate only developed chemoresistance compared to 87.50% remission with EMACO. The relative risk of treatment failure with methotrexate monotherapy was 7.88 (95% CI 1.23 – 50.44 p<0.001). The low precision of the RR estimate could be explained by the low numbers of patients (22 out of 158) in this category.

Table 6 Patients with WHO/FIGO score of 6: Treatment outcomes categorized by chemotherapy regimen administered

		Remission	Chemoresi stance	Death	TOTAL
Chemotherapy	MTX	2 (12.50%)	12 (75.00%)	2 (12.50%)	**16**
	EMACO	7 (87.50%)	1 (12.50%)	0	**8**
	TOTAL	**7 (31.82%)**	**13 (59.09%)**	**2 (9.09%)**	**22**

MTX= Methotrexate, EMACO = Etoposide, Methotrexate, Actinomycin-D, Cyclophosphamide & Vincristine

As demonstrated in table 6 below, patient on methotrexate monotherapy had low remission rate of 48.28% (95% CI 34.66 – 61.97%). When patient with WHO/FIGO score of 6 are excluded (16 patients), methotrexate monotherapy achieves a remission rate of 62.50% (95% C1 45.80% - 77.27%) with no mortality. Patients treated with methotrexate single agent had a high chemoresistance and treatment failure of 39.29% and 51.79% respectively. The greater contribution of this treatment failure was by low risk patients scoring 6 as illustrated in table 6 above (12 out of the 25 with chemoresistance had WHO/FIGO score of 6). The single patient with high risk disease treated with single agent methotrexate developed chemoresistance. Mortality was low at 3.54% (95% CI 0.43- 12.11%) amongst patient on methotrexate monotherapy. Table 6 below summarizes the treatment outcomes with methotrexate single agent chemotherapy.

Table 7 Treatment outcomes for GTN patients treated with Methotrexate monotherapy

		Frequency	Percent	95% confidence interval
TREATMENT OUTCOME	Remission	27	48.21%	34.66 - 61.97%
	Change of chemotherapy - other reasons	2	3.57%	0.44 - 12.31%
	Chemoresistance	22	39.29%	26.50 - 53.25%
	Loss to follow-up in course of treatment	3	5.36%	1.12 - 14.87%
	Death	2	3.57%	0.44-12.31%
	TOTAL	**57**	**100.00%**	

As illustrated in table 7 and 8 below, EMACO achieved remission rate of 77.53% (95% CI 67.45 – 85.70%), irrespective of WHO/FIGO scoring classification. However, mortality in the group treated with EMACO was significantly higher at 7.87% (95% CI 3.22 – 15.54 p=0.03). High risk GTN when treated with standard of care regimen (EMACO) had a remission rate of 69.23%. Even with this indication, death was significantly higher at 13.46%. However, no deaths were recorded among low risk

patients treated with EMACO. This implies that death was likely associated with disease severity and not regimen administered.

Table 8 Treatment Outcomes for GTN patients treated with EMACO *combination chemotherapy*

		Frequency	Percent	95% confidence interval
Treatment Outcome	Remission	69	77.53%	67.45 - 85.70%
	Chemoresistance	10	11.24%	5.52 -1 9.69%
	Loss to follow-up	3	3.37%	0.70 - 9.54%
	Death	7	7.87%	3.22 - 15.54%
	TOTAL	**89**	**100.00%**	

Table 9 Treatment Outcomes for GTN patients treated with EMACO stratified by *WHO/FIGO Risk Classification*

		Treatment Outcome				n (%)
		Remission	**Chemoresistance**	**Loss To Follow-up**	**Death**	
WHO/FIGO Category	Low Risk	33 (89.19%)	3 (8.11%)	1 (2.70%)	0	**37 (41.57%)**
	High Risk	36 (69.23%)	7 (13.46%)	2 (3.85%)	7 (13.46%)	**52 (58.43%)**
	n (%)	**69 (77.53%)**	**10 (11.24%)**	**3 (3.37%)**	**7 (7.87%)**	**89**

EMA-EP was administered to 7 patients. All the patients were previously treated with EMACO unsuccessfully. The regimen achieved a remission rate of 71.43% (95% CI 29.04 – 96.33%). The numbers treated with this chemotherapy regimen were too low for further statistical analysis.

Table 9 below summarizes treatment outcome for patient who had histopathological diagnosis recorded in their files. The presence or absence of histopathological diagnosis did not influence treatment outcome (RR 0.94 95% CI 0.74 – 1.19 p=0.753). Patients with histological diagnosis of choriocarcinoma had the highest level of chemoresistance contributing 38.24% of all the patients with this unfavourable

outcome. This was statistically significant with RR of 4.80 (95% CI 1.38 – 16.77 p=0.014). Mortality was also highest among these patients contributing 76.92% of deaths recorded. The single patient with PSTT/ETT achieved remission with hysterectomy followed by EMA-EP combination chemotherapy.

Table 10 GTN treatment outcome stratified by tumour histology (N=158)

		Treatment Outcome					
			Treatment failure				
		Remission	Change of regimen	Chemore sistance	Loss to Follow-up	Death	TOTAL
Histology	Choriocarcinoma	38	2	13	3	10	66
	Invasive Mole	7	0	2	0	0	**9**
	PSTT/ETT	1	0	0	0	0	**1**
	CHM	22	0	5	3	1	**31**
	PHM	3	0	1	0	0	**4**
	Not Indicated	32	0	13	0	2	**47**
	TOTAL	103 (65.19%)	2 (1.27%)	34 (21.52%)	6 (3.80%)	13 (8.23%)	158

Table 10 below summarizes chemotherapy courses needed to achieve remission. The median courses to remission for patient on methotrexate monotherapy was 5 courses (IQR= 3 – 6) and that of patients with EMACO was 4 courses (IQR= 3-6). EMA-EP seems to be relatively efficacious where indicated with a median of 2 courses to remission irrespective of WHO/FIGO score classification. However, patients on EMA-EP had already received EMACO thus likely to require significantly lesser courses to remission. There was no significant difference in median courses to remission for high risk and low risk disease patients treated with EMACO.

Amongst the low risk patients treated with methotrexate, the number of courses to remission was not dependent on antecedent pregnancy, histological diagnosis, parity or actual WHO/FIGO score. However, it was associated with initial hCG levels on linear regression with p=0.018. This was the same with high risk disease treated with EMACO, p=0.012. The median time to remission from the initiation of chemotherapy

was 72 days (IQR=43 – 114), 81 days (IQR=59 – 122) and 43 days (IQR= 43 – 62) for methotrexate monotherapy, EMACO and EMA-EP regimen respectively. Given the regimen are administered every fourteen days, the difference in days between actual time taken to administer the number of courses leading to remission and the calculated expected time (product of courses administered and inter-course time of fourteen days) measures the cumulative regimen protocol noncompliance time. There was no statistical difference in time taken to remission in different chemotherapy regimen and WHO/FIGO score classification strata. On linear regression, the treatment time to remission in days was only dependent on initial hCG levels (antecedent pregnancy p=0.55, chemotherapy regimen administered p=0.85 and initial hCG levels p=0.029).

Table 11 Number of chemotherapy courses administered to achieve remission

	Chemotherapy regimen	Number of patients (n)	Median number of courses	interquartile range
High Risk	EMACO	36	4.5	3 - 6
	EMA-EP	3	2	1 - 4
Low Risk	MTX	26	4.5	3 - 6
	EMACO	33	5	3 - 6
	EMA-EP	2	2.5	2 - 3

Table 11 below summarizes side effects related to chemotherapy treatment. The institutional does not have special tool for capturing or reporting the side effects and data was derived from clinical notes. Most side effects are therefore potentially under reported. Anaemia was the commonest side effect reported in 62.50% of patients. The occurrence of anaemia was statistically related to chemotherapy regimen with patients on EMACO having RR of 1.38 (95% CI 1.02 – 1.86 p=0.036) of developing the haematological side effect. Severe neutropenia (neutrophils less than 1.5 x 10^9/L) comparatively affected patient on EMACO more with RR of 4.6 (95% CI 2.25 - 9.41 p<0.001) with a risk difference of 44.97 (95% CI 31.44 – 58.50). Thrombocytopenia was the rarest of haematological side effects with no statistical association with

chemotherapy administered, RR of 1.81 (95% CI 0.51 – 6.41 p=0.526). Stomatitis was the commonest side effect reported amongst patients treated with methotrexate single agent affecting 29.82% of the patients. The only patient reported to have deranged renal function was on EMA-EP combination chemotherapy. Where severe side effects occurred (anaemia with HB < 10gm/dl or neutrophils <1.5 x 109/L or WCC less than 2.0 x 109/L) chemotherapy was withheld till corrective measures were instituted that included blood transfusion or administration of GM-CSF (neupogen). These two interventions were administered to 43.15% and 69.18% of all patients respectively.

Table 12 Frequency of some of the side effects reported

Side Effect Reported by chemotherapy regimen		**Frequency n (%)**	**p value**
Anaemia	MTX	28 (50%)	0.17
	EMACO	60 (68.97%)	
	EMA-EP	4 (66.67%)	
Alopecia		78 (49.37%)	
Neutropenia	MTX	7 (12.50%)	<0.001
	EMACO	51 (58.62%)	
	EMA-EP	4 (50%)	
Thrombocytopenia	MTX	3 (5.43%)	0.12
	EMACO	7 (8.24%)	
	EMA-EP	2 (33.33)	
Cystitis (Bladder mucositis)		7 (4.43%)	
Renal (High Urea/Creatine)	EMA-EP	1 (0.63%)	

MTX= Methotrexate, EMACO = Etoposide, Methotrexate, Actinomyci-D, Cyclophosphamide & Vincristine, EMA-EP = Etoposide, Methotrexate, Actinomycin-D, Etoposide & Cisplatin

hCG Regression Curves

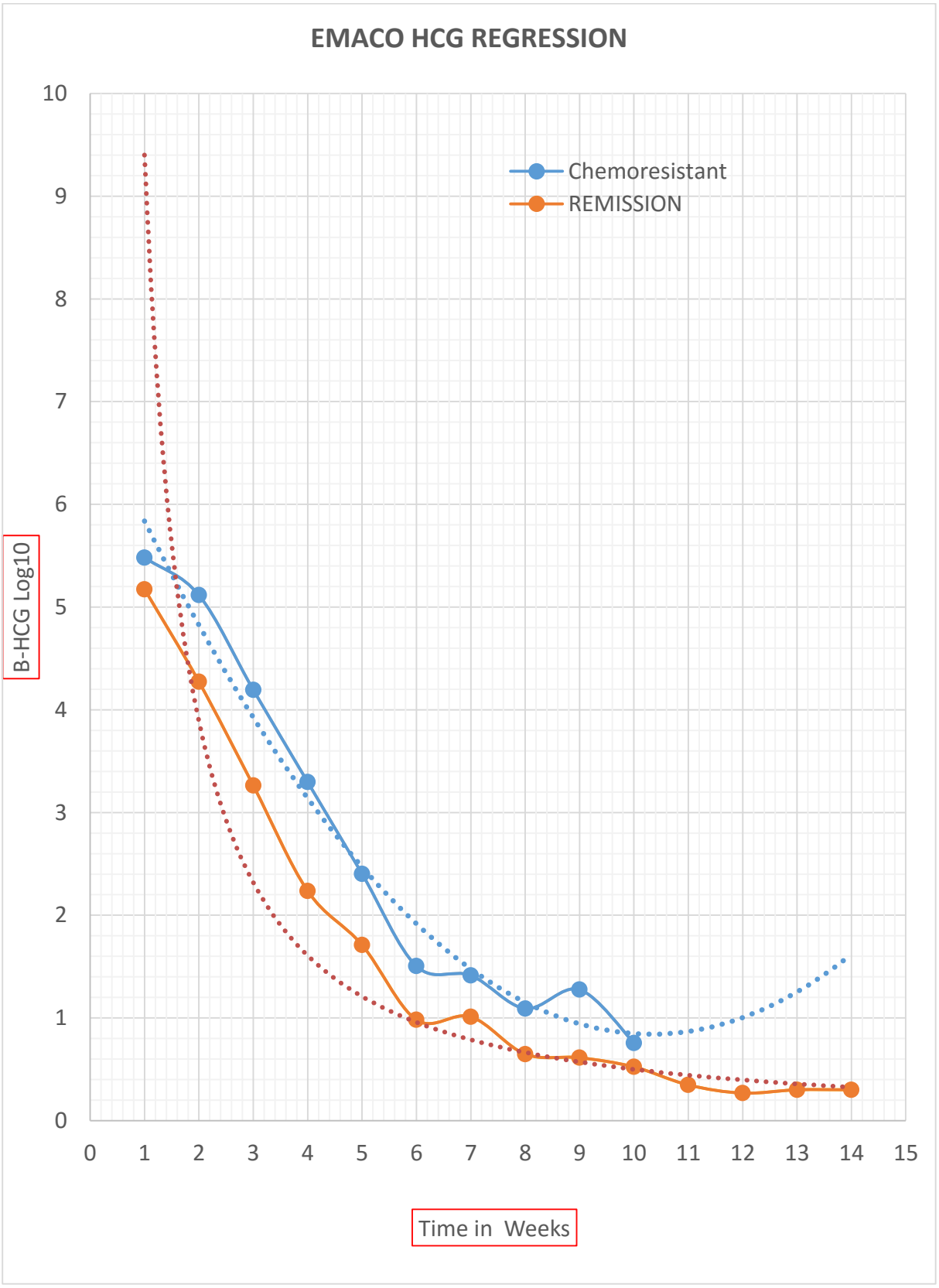


Figure 3 hCG response curve for GTN patients treated with EMACO combination chemotherapy

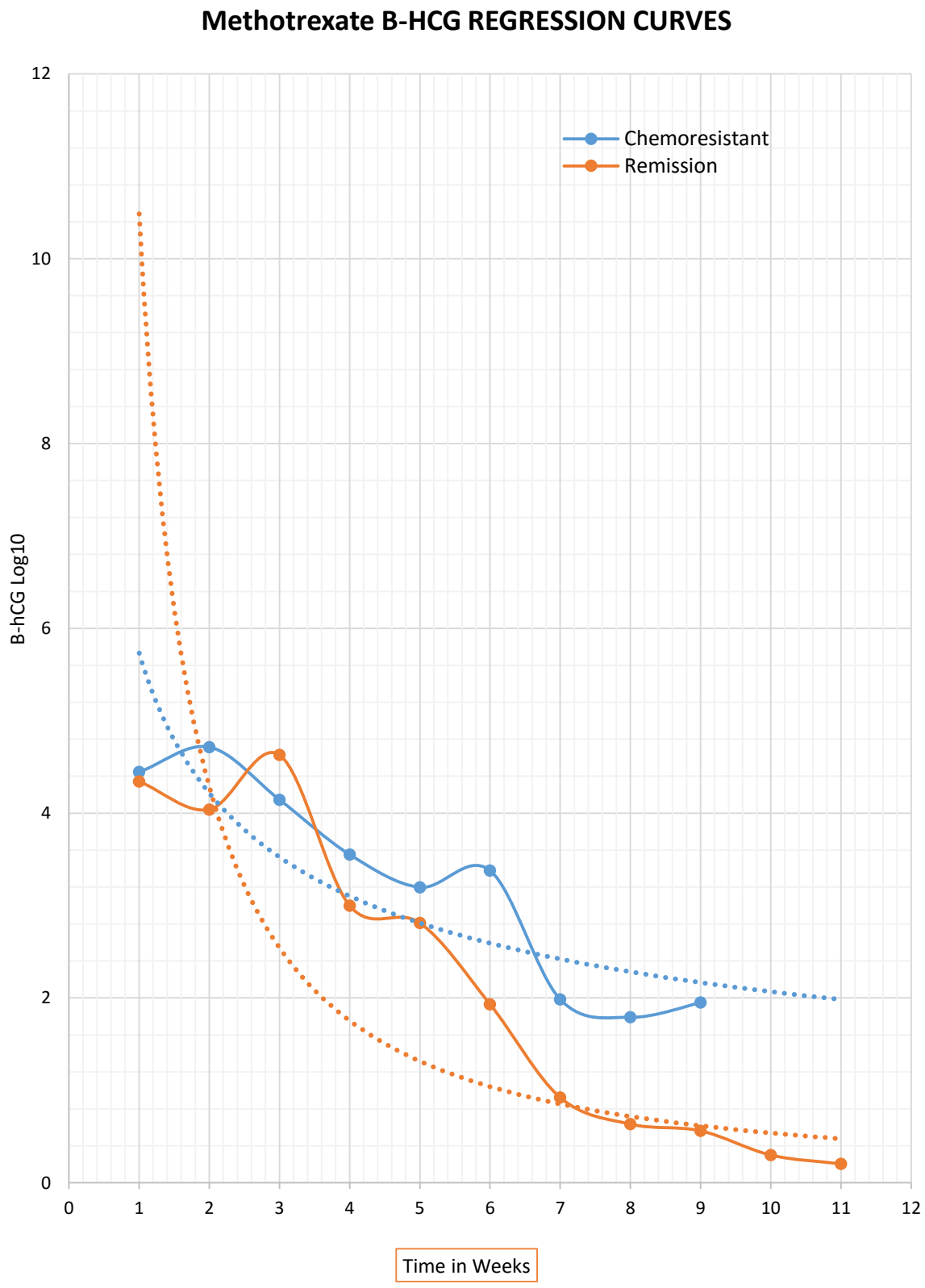


Figure 4 hCG Regression curve for GTN patients treated with methotrexate monotherapy

Bivariate and Multivariate Analysis

Table 12 below summarizes factors found to predict treatment failure. Term antecedent pregnancy was associated with treatment failure with RR 3.52 (95% CI 1.66-7.48 p=0.002) when high risk disease treated with combination chemotherapy. Central nervous system (CNS) metastases were associated with treatment failure RR 3.02 (95% CI 2.41 – 3.78 p=0.025). All four patients with documented brain metastasis died. These patients did not receive surgical, intrathecal methotrexate, CNS methotrexate dosing or irradiation as adjuvant treatment as is to be found WHO/FIGO and other leading authorities GTN treatment recommendations. Liver metastasis was also associated with treatment failure with RR 2.38 (95% CI 1.61 – 3.53 p=0.0026). Patient with lung metastasis had treatment failure with RR 1.80 (95% CI 1.20 – 2.72 p=0.014). Vagina and uterus metastases were the commonest and were associated with treatment failure with RR 1.80 (95% CI 1.20 – 2.72 = 0.011). The adjusted metastasis treatment failure relative risk was 1.98 (95% CI 1.56 – 2.48 p<0.001)

Gestational trophoblastic neoplasm with initial hCG >100,000 IU/L had treatment failure with RR 2.67 (95% CI 1.35 – 5.28 p=0.041) when treated with methotrexate single agent. Two out of the eight patients (25%) with hCG >100,000 IU/L treated with methotrexate died in the course of treatment compared to four out of thirty two (12.5%) patients treated with EMACO. Chemoresistance was also high amongst the methotrexate single agent treated patients with RR 6.22 (95% CI 1.86 – 20.86 p=0.012) irrespective of WHO/FIGO score classification.

Low risk GTN treated with methotrexate single agent had treatment failure of 51.79% with 39.29% developing chemoresistance. This yielded a treatment failure RR of 5.6 (95% CI 2.17 – 14.52 p<0.001) when compared to similar patients treated with EMACO. Patients without previous exposure to chemotherapy developed

chemoresistance with RR 2.01 (95% CI 1.25 – 3.26 p=0.005) when treated with methotrexate only. Amongst these patients, those with choriocarcinoma histological diagnosis, treatment with single agent (methotrexate) was associated with treatment failure with RR 2.90 (95% CI 1.37 – 6.30 p=0.015).

Table 13 Multivariate analysis of factors influencing treatment failure

FACTOR	ARR	95% CI	P
Antecedent Pregnancy	3.52	1.66 - 7.48	0.0017
Brain Metastases	3.02	2.41 – 3.78	0.025
Liver Metastases	2.38	1.61 – 3.53	0.0026
Lung Metastasis	1.80	1.20 – 2.70	0.014
Vagina & Uterus Metastasis	1.80	1.20 – 2.72	0.011
Adjusted Metastasis	1.98	1.56 – 2.48	<0.001
B-HCG >100,000 treated with MTX	2.67	1.35 – 5.28	0.041
Single agent (MTX) treatment	6.22	1.86 – 20.86	0.012
WHO/FIGO Score=6 treated with MTX	7.9	1.2 – 50.4	0.001
Choriocarcinoma histology	2.9	1.37 – 6.30	0.015
Low Risk GTN	5.6	2.17 – 14.52	<0.001
Choriocarcinoma (death)	7.2	1.0 – 55.6	0.029

Among patient treated with EMACO, choriocarcinoma histology was important predictor of treatment failure with RR of 2.3 (95% CI 1.0 – 5.4 p=0.042). Histology also negatively impacted risk of death with choriocarcinoma histopathological diagnosis being associated with death with RR 7.2 (95% CI 1.0 – 55.65 p=0.029). The other factor associated with death amongst patient with high risk neoplasms was term antecedent pregnancy with RR 4.5 (95% CI 1.3 - 15.5 p=0.031) compared to CHM.

Failure to adhere to standard treatment schedule as per hospital protocol was significantly associated with treatment failure. Tables 13 below summarizes treatment schedule compliance. This was calculated by subtracting the product of the number of chemotherapy courses given and the inter-course interval of 14 days (both methotrexate and combined chemotherapy are given every 14 days at KNH) from time in days from treatment initiation to treatment outcome. Patients with treatment failure had a median of 27.5 days (IQR=6 – 58). This was significantly longer (p=0.005) than patients with remission who had a median time of 15 days (IQR=2 – 37).

Table 14 Chemotherapy regimen and Noncompliance with Treatment Schedule in Days stratified by outcome status

		Cumulative days chemotherapy missed							
		Remission (N=103)				Treatment failure (N=52)			
		n	Mean	Median	Interquartile range	n	Mean	Median	Interquartile range
Chemotherapy regimen	Mtx	27	21.22	10	2 - 37	30	36.37	35.0	7 – 48
	EMACO	69	22.30	15	3 - 32	20	49.15	15.0	6 - 51.5
	EMA-EP	5	19.6	15	15 - 20	2	35.50	35.5	6 – 65
	All	101	22.20	15	2 - 37	52	45.24	27.5	6 – 58

CHAPTER V
DISCUSSION

Gestational trophoblastic diseases are disease of ovulation and fertilization defect (37). This study has shown, in parallel with this principle pathologic process, the prevalence of GTN at KNH increases with advancing age and parity. Only one patient in the study setting was a primipara compared to 51% of patient being para five and above.

GTNS are highly metastatic tumours. About 63% of the patients had metastatic lesions. Haematogenous tumour cell embolization is the commonest mode of spread and thus most vascular tissues are the earliest sites of metastasis. The lungs, with 28% of patients affected, were the commonest organ affected outside the reproductive system. At KNH patients with metastatic disease were almost two times likely not to achieve remission (RR 1.98 95% CI 1.56 – 2.48 P<0.001). Brain metastasis is often an ominous finding as shown by May et al. Without adjuvant therapy brain metastasis had 100% case fatality.

You B et al has shown patients with choriocarcinoma have low remission rates with single agent (38). The findings of this study are in keeping with the You B et al with choriocarcinoma patients treated with methotrexate single agent chemotherapy achieving low remission rates of 35.7%.

Patient with low risk disease treated with methotrexate single agent had remission rates of 48.21% compared to 90% achieved at comparable institutions like Charing Cross Hospital in UK (39). Further, low risk disease with WHO/FIGO score of six had chemoresistance rate of 75% with single agent treatment compared to 87.5% remission when treated with EMACO. This latter finding is supported by findings by Nienke et al who showed that patients with WHO/FIGO score of 5 or 6 had remission rates of 30% when treated with single agent chemotherapy (40). In addition, Seckl et al has demonstrated that patients with pre-treatment hCG > 400,000 IU/L are unlikely

to be cured with single agent chemotherapy (41). In an effort to identify patient likely to develop methotrexate chemoresistance, von Tromel showed patients with pre-treatment hCG>100,000 IU/L were likely to develop chemoresistance with 99% specificity and 52% sensitivity (40). It is well established that the hCG levels correlates with tumour size with that 1gm of tumour approximately equivalent to 10^9 tumour cells produces 10^5 IU of hCG per day. It is thus deducible that the high level of hCG in these patients correlates with a more advanced disease with larger tumour masses that requires combination chemotherapy to achieve remission.

Liang X-J et al has shown the toxicity of current chemotherapeutic agents limits clinical drug combination protocols (42). EMACO and EMA-EP in this study had significant side effects comparable to those reported by Akylol et al in a Turkish GTN patients population treated with similar regimens. Methotrexate, etoposide and cyclophosphamide used in these combination regimes are associated with myelotoxicity (43). In KNH setting, severe haematological side effects including leukopenia, neutropenia and anaemia affected up to 63% of the patients on EMACO. This lead to delay in administration of sequential chemotherapy courses and additional treatment with blood transfusion, haematinic agents and GM-CSF. While analysing EMACO induced DNA damage of peripheral blood lymphocytes, Akylol et al showed 9% to 33% of high risk disease treatment failure (chemoresistance) was associated with toxic chemotherapeutic agents' side effects. At KNH, the side effects were not shown to be associated with treatment failure but were statistically associated with prolongation of time to remission. This could have been due to timely management of the side effects with withholding of chemotherapy till blood parameters met recommended thresholds.

In this study setting, Maranga et al has shown delay in initiation of treatment and administration of subsequent treatment courses of cervical cancer at KNH is associated with unfavourable outcomes (35). This study also demonstrates failure to adhere to the recommended course administration schedules is associated with treatment failure (p=0.005). Patients with treatment failure had a median of 27.5 days (IQR=6 – 58) lost in the course of treatment compared to 15 days (IQR=2 – 37) for patient on remission.

By constructing an hCG-time regression normogram, Van Tromel et al was able to demonstrate that when hCG concentration exceeds 97.5 percentile of normal regression curve then it can be concluded with 50% sensitivity that combination chemotherapy is essential to achieve cure (40). Kerkmeijer et al used regression normograms to show that patients with hCG greater than 737 IU/L before fourth chemotherapy course had a 52% risk of developing chemoresistance with a 97.5% specificity(44). The KNH hCG regression normogram equally predicted the likelihood of treatment failure with comparable precision. An hCG decline less than 10% between the second and third courses was predictive of treatment failure (p=0.03) with sensitivity of 60%, specificity of 92%, positive predictive value of 82% and negative predictive value of 87%. From the methotrexate hCG regression normogram patients with hCG greater than 737 IU/L before the fourth course had 70% risk of developing treatment failure with 70% sensitivity and negative predictive value of 89%. The hCG regression normogram can therefore be used to predict the probability of treatment failure for patient on methotrexate before administration of fourth chemotherapy course.

CHAPTER VI

CONCLUSION AND RECOMMENDATIONS

CONCLUSION

Adherence to established standard of care for patients with gestational trophoblastic diseases at Kenyatta National Hospital is suboptimal. About 37% of patients did not have histological diagnosis as recommended by WHO/FIGO. Patients with low risk neoplasms are treated with either single agent methotrexate or EMACO combination chemotherapy without clear documentation of reasons for this deviation from standards of care recommendations. There is wide variation in course scheduling even for patient with remission. The treatment of patients with central nervous system metastatic lesions is suboptimal with no patient receiving recommended adjuvant therapy.

Treatment outcomes for patient with low risk GTN are less favourable visa-a-vis comparable reference facilities globally. However, the remission rate for patient with high risk disease is comparable to that of Charing Cross Hospital in UK, a renown institution in treatment of GTNs.

Treatment failure at KNH is predicted by choriocarcinoma histology, WHO/FIGO score classification, presence of metastases, chemotherapy regimen used, the rate of hCG regression between second and third chemotherapy courses and noncompliance with treatment protocol schedules.

RECOMMENDATIONS

A written clinical guideline preferably adaption of the WHO/FIGO guidelines for management of GTNs should be developed at KNH. This would facilitate standardization of care and develop a mechanism for regular monitoring and evaluation of treatment.

To further optimise patient outcomes, particular emphasis should be paid to care and monitoring of patients with choriocarcinoma on histology, high risk GTN, patients with CNS and liver metastases, previous chemotherapy exposure, patients with hCG greater than 737 IU/L before fourth chemotherapy course who are likely to develop treatment failure.

Patients with histological diagnosis of choriocarcinoma, WHO/FIGO score of six or pre-chemotherapy hCG greater than 100,000 IU/L should be treated with EMACO combination chemotherapy irrespective of WHO/FIGO classification. This is due to the high treatment failure rates associated with methotrexate chemotherapy when used in these subpopulations.

FURTHER RESEARCH

In order to further improve treatment outcome it would be important to carry out further research to elucidate factors associated with nonadherence with treatment protocol schedules. This would inform strategies to reduce the cumulative days treatment is missed that this study has demonstrated is associated with treatment failure.

REFERENCES

1. Ngan H, Bender H, Benedet JL, Jones H, Montruccoli GC, Pecorelli S, et al. Gestational trophoblastic neoplasia, FIGO 2000 staging and classification. Int J Gynecol Obstet. 2003 Oct;83, Supplement 1:175–7.

2. Lurain JR. Gestational trophoblastic disease II: classification and management of gestational trophoblastic neoplasia. Am J Obstet Gynecol. 2011 Jan;204(1):11–8.

3. Seckl MJ, Sebire NJ, Fisher RA, Golfier F, Massuger L, Sessa C, et al. Gestational trophoblastic disease: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2013 Oct 1;24(suppl 6):vi39-vi50.

4. Agboola A, Abudu OO. Epidemiology of trophoblast disease in Africa--Lagos. Adv Exp Med Biol. 1984;176:187–95.

5. Nkyekyer K. Pattern of gynaecological cancers in Ghana. East Afr Med J. 2000 Oct;77(10):534–8.

6. Altieri A, Franceschi S, Ferlay J, Smith J, Vecchia CL. Epidemiology and aetiology of gestational trophoblastic diseases. Lancet Oncol. 2003 Nov;4(11):670–8.

7. Fisher RA, Lavery SA, Carby A, Abu-Hayyeh S, Swingler R, Sebire NJ, et al. What a difference an egg makes. Lancet. 2011 Dec 3;378(9807):1974.

8. Kim SJ. Placental site trophoblastic tumour. Best Pract Res Clin Obstet Gynaecol. 2003 Dec;17(6):969–84.

9. Trédan O, Galmarini CM, Patel K, Tannock IF. Drug resistance and the solid tumor microenvironment. J Natl Cancer Inst. 2007 Oct 3;99(19):1441–54.

10. Liang X-J, Chen C, Zhao Y, Wang PC. Circumventing Tumor Resistance to Chemotherapy by Nanotechnology. Methods Mol Biol Clifton NJ. 2010;596:467–88.

11. van Trommel NE, Massuger LF, Schijf CP, ten Kate-Booij MJ, Sweep FC, Thomas CM. Early identification of resistance to first-line single-agent methotrexate in patients with persistent trophoblastic disease. J Clin Oncol Off J Am Soc Clin Oncol. 2006 Jan 1;24(1):52–8.

12. Bagshawe KD. Risk and prognostic factors in trophoblastic neoplasia. Cancer. 1976 Sep;38(3):1373–85.

13. Denny L, Quinn M, Hacker N. FIGO Cancer Report 2012. Int J Gynecol Obstet. 2012 Oct 1;119:S89.

14. Kerkmeijer LG, Thomas CM, Harvey R, Sweep FC, Mitchell H, Massuger LF, et al. External validation of serum hCG cutoff levels for prediction of resistance to single-agent chemotherapy in patients with persistent trophoblastic disease. Br J Cancer. 2009 Mar 24;100(6):979–84.

15. Sita-Lumsden A, Medani H, Fisher R, Harvey R, Short D, Sebire N, et al. Uterine artery pulsatility index improves prediction of methotrexate resistance in women with gestational trophoblastic neoplasia with FIGO score 5-6. BJOG Int J Obstet Gynaecol. 2013 Jul;120(8):1012–5.

16. Fisher RA, Savage PM, MacDermott C, Hook J, Sebire NJ, Lindsay I, et al. The impact of molecular genetic diagnosis on the management of women with hCG-producing malignancies. Gynecol Oncol. 2007 Dec;107(3):413–9.

17. Kohorn EI. Negotiating a staging and risk factor scoring system for gestational trophoblastic neoplasia. A progress report. J Reprod Med. 2002 Jun;47(6):445–50.

18. Seckl MJ, Sebire NJ, Berkowitz RS. Gestational trophoblastic disease. Lancet. 2010 Aug 28;376(9742):717–29.

19. Alazzam M, Tidy J, Hancock BW, Osborne R, Lawrie TA. First-line chemotherapy in low-risk gestational trophoblastic neoplasia. Cochrane Database Syst Rev. 2012 Jul 11;7:CD007102.

20. Aghajanian C. Treatment of Low-Risk Gestational Trophoblastic Neoplasia. J Clin Oncol. 2011 Mar 1;29(7):786–8.

21. You B, Pollet-Villard M, Fronton L, Labrousse C, Schott A-M, Hajri T, et al. Predictive values of hCG clearance for risk of methotrexate resistance in low-risk gestational trophoblastic neoplasias. Ann Oncol Off J Eur Soc Med Oncol ESMO. 2010 Aug;21(8):1643–50.

22. Tocharoenvanich S, Chichareon S, Wootipoom V, Bu-ngachat R, Piyananjarassri K. Correlation of risk categorization in gestational trophoblastic tumor between old and new combined staging and scoring system. J Obstet Gynaecol Res. 2003 Feb 1;29(1):20–7.

23. May T, Goldstein DP, Berkowitz RS. Current Chemotherapeutic Management of Patients with Gestational Trophoblastic Neoplasia. Chemother Res Pract [Internet]. 2011 [cited 2015 Feb 9];2011. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3265241/

24. Kim SJ, Bae SN, Kim JH, Kim CT, Han KT, Lee JM, et al. Effects of multiagent chemotherapy and independent risk factors in the treatment of high-risk GTT--25 years experiences of KRI-TRD. Int J Gynaecol Obstet Off Organ Int Fed Gynaecol Obstet. 1998 Apr;60 Suppl 1:S85-96.

25. Deng L, Zhang J, Wu T, Lawrie TA. Combination chemotherapy for primary treatment of high-risk gestational trophoblastic tumour. Cochrane Database Syst Rev. 2013;1:CD005196.

26. Rustin GJ, Newlands ES, Lutz JM, Holden L, Bagshawe KD, Hiscox JG, et al. Combination but not single-agent methotrexate chemotherapy for gestational trophoblastic tumors increases the incidence of second tumors. J Clin Oncol. 1996 Oct 1;14(10):2769–73.

27. Lybol C, Thomas CMG, Blanken EA, Sweep FCGJ, Verheijen RH, Westermann AM, et al. Comparing cisplatin-based combination chemotherapy with EMA/CO chemotherapy for the treatment of high risk gestational trophoblastic neoplasia. Eur J Cancer. 2013 Mar;49(4):860–7.

28. Colleen M Feltmate DRG. Advances in the understanding of placental site trophoblastic tumor. J Reprod Med. 2002;47(5):337–41.

29. Deng L, Yan X, Zhang J, Wu T. Combination chemotherapy for high-risk gestational trophoblastic tumour. Cochrane Database Syst Rev. 2009;(2):CD005196.

30. McGrath S, Short D, Harvey R, Schmid P, Savage PM, Seckl MJ. The management and outcome of women with post-hydatidiform mole 'low-risk' gestational trophoblastic neoplasia, but hCG levels in excess of 100 000 IU l|[minus]|1. Br J Cancer. 2010 Feb 16;102(5):810–4.

31. Hoekstra AV, Lurain JR, Rademaker AW, Schink JC. Gestational trophoblastic neoplasia: treatment outcomes. Obstet Gynecol. 2008 Aug;112(2 Pt 1):251–8.

32. Akyol D, Mungan T, Baltaci V, Kozinoglu H, Oguz S, Oztekin O, et al. Clinical assessment of EMA/CO induced DNA damage in peripheral blood lymphocytes of high-risk gestational trophoblastic tumor patients. Eur J Gynaecol Oncol. 1999;20(2):150–5.

33. Savage P, Seckl M, Short D. Practical issues in the management of low-risk gestational trophoblast tumors. J Reprod Med. 2008 Oct;53(10):774–80.

34. da Silva SD, Hier M, Mlynarek A, Kowalski LP, Alaoui-Jamali MA. Recurrent Oral Cancer: Current and Emerging Therapeutic Approaches. Front Pharmacol [Internet]. 2012 [cited 2015 Jul 30];3. Available from: http://journal.frontiersin.org/article/10.3389/fphar.2012.00149/abstract

35. Maranga IO, Hampson L, Oliver AW, Gamal A, Gichangi P, Opiyo A, et al. Analysis of factors contributing to the low survival of cervical cancer patients undergoing radiotherapy in Kenya. PLoS ONE. 2013 Oct;8(10):1–9.

36. Kasiulevičius V, Šapoka V, Filipavičiūtė R. Sample size calculation in epidemiological studies. Gerontologija. 2006;7(4):225–231.

37. Altieri A, Franceschi S, Ferlay J, Smith J, La Vecchia C. Epidemiology and aetiology of gestational trophoblastic diseases. Lancet Oncol. 2003 Nov;4(11):670–8.

38. You B, Deng W, Hénin E, Oza A, Osborne R. Validation of the Predictive Value of Modeled Human Chorionic Gonadotrophin Residual Production in Low-Risk Gestational Trophoblastic Neoplasia Patients Treated in NRG Oncology/Gynecologic Oncology Group-174 Phase III Trial. Int J Gynecol Cancer Off J Int Gynecol Cancer Soc. 2016 Jan;26(1):208–15.

39. Lybol C, Thomas CMG, Blanken EA, Sweep FCGJ, Verheijen RH, Westermann AM, et al. Comparing cisplatin-based combination chemotherapy with EMA/CO chemotherapy for the treatment of high risk gestational trophoblastic neoplasia. Eur J Cancer Oxf Engl 1990. 2013 Mar;49(4):860–7.

40. van Trommel NE, Massuger LF, Schijf CP, ten Kate-Booij MJ, Sweep FC, Thomas CM. Early identification of resistance to first-line single-agent methotrexate in patients with persistent trophoblastic disease. J Clin Oncol Off J Am Soc Clin Oncol. 2006 Jan 1;24(1):52–8.

41. Seckl MJ, Fisher RA, Salerno G, Rees H, Paradinas FJ, Foskett M, et al. Choriocarcinoma and partial hydatidiform moles. Lancet Lond Engl. 2000 Jul 1;356(9223):36–9.

42. Liang X-J, Chen C, Zhao Y, Wang PC. Circumventing tumor resistance to chemotherapy by nanotechnology. Methods Mol Biol Clifton NJ. 2010;596:467–88.

43. Akyol D, Mungan T, Baltaci V, Kozinoglu H, Oguz S, Oztekin O, et al. Clinical assessment of EMA/CO induced DNA damage in peripheral blood lymphocytes of high-risk gestational trophoblastic tumor patients. Eur J Gynaecol Oncol. 1999;20(2):150–5.

44. Kerkmeijer LG, Thomas CM, Harvey R, Sweep FC, Mitchell H, Massuger LF, et al. External validation of serum hCG cutoff levels for prediction of resistance to single-agent chemotherapy in patients with persistent trophoblastic disease. Br J Cancer. 2009;100(6):979–84.

ANNEX 1: Case Summary/Data Extraction Form

FORM CODE

PATIENT INITIALS

ADMISSION NUMBER

DATE OF DIAGNOSIS

DATE CHEMOTHERAPY INITIA

PATIENT CHARACTERISTICS

a) PATIENT SOURCE

Referral	
KNH	

b) AGE AT DIAGNOSIS (YEARS)

Parity

c) Para ……+……..

d) ANTECEDENT PREGNANCY

Term Pregnancy		
Hydatidiform Mole		
Ectopic Pregnancy		
Miscarriage/Abortion		
Not indicated		

e) Time from index/antecedent pregnancy to start of chemotherapy (MONTHS)

f) Previous chemotherapy (Tick one as is appropriate)

None		
Monotherapy	Methotrexate	
	Actinomycin D	
	Other	
Combination Chemotherapy	EMACO	
	EMA-EP	
	MAC	
	MFA	
	CHOMOCA	
	OTHER	
NOT INDICATED		

g) Metastasis (Tick as many as recorded in patients clinical records

NONE	
Lung	
Vagina/Uterus	
Brain/CNS	
Other Sites	
Not Indicated	

h) PRETREATMENT/INITIAL hCG LEVELS

…….IU/L

i) Laboratory where hCG was done

KNH	
University of Nairobi	
Lancet Lobaratories	
Nairobi Hospital	
Aga Khan University Hospital	
Other	
Multiple Labs	

j) Tumour Histopathology:

Choriocarcinoma	
Invasive Mole	
PSTT/ETT	
Complete Mole	
Partial Mole	
Other (State)	
Not Indicated	

PATIENT MANAGEMENT

k) FIGO/WHO Score ……..

l) Pre-chemotherapy Evaluation

Investigation	Done	Not Done
Initial HCG		
CBC		
U/E/Cr		
LFT		
Pelvic US		
Chest Xray		
MRI/CT Scan		
Weight		
Height		
TBSA		

m) Chemotherapy administered

Methotrexate (MTX)/Folinic Acid	
Actinomycin D	
EMACO	
MAC	
EMA-EP	
MFA	
CHOMOCA	
Other (state)	

n) Other management/ Procedures

Surgery	
Radiotherapy	
Family Planning	
NONE	

o) HCG REGRESSION

Course	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
Date													
B hCG level (IU/L)													

p) Hematological and Renal profile

Course	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Date												
WBC												
Neutrophils												
Hb												
Platelets												
BUN/Urea												
Creatinine												
TRANSFUSION												
NEUPOGEN												

q) Reported Side effects

Neuropathy	
Hypersensitivity	
Bladder Mucositis (Haematuria)	
Stomatitis	
Diarrhoea	
Alopecia	
Other (State)	

TREATMENT OUTCOME

Treatment Outcome

Remission	
Treatment Failure:	
Change of regimen due to toxicity	
Change of regimen due to other reasons	
Chemoresistance	
Loss to follow-up	
Pregnancy in course of treatment	
Death	

Remission

a) Date of remission (date first hCG level <5 IU

b) Number of chemotherapy courses to remissi

c) Number of consolidation chemotherapy courses

(Courses after remission)

Treatment Failure

Date of treatment failure (date last chemotherapy administe

Number of chemotherapy courses to treatment failure

ANNEX 2: FIGO Anatomical GTN Staging and The Modified WHO Prognostic Scoring System as Adapted by FIGO

FIGO Anatomical Staging

Stage I	Disease confined to the uterus
Stage II	GTN extends outside of the uterus, but is limited to the genital structures (adnexa, vagina, broad ligament)
Stage III	GTN extends to the lungs, with or without known genital tract involvement
Stage IV	All other metastatic sites

Modified WHO Prognostic Scoring System as Adapted by FIGO

Scores	0	1	3	4
Age	<40	⩾40	–	–
Antecedent pregnancy	mole	abortion	term	–
Interval months from index pregnancy	<4	4 –<7	7– <13	⩾13
Pretreatment serum hCG (iu/l)	$<10^3$	10^3–$<10^4$	10^4–$<10^5$	⩾10^5
Largest tumor size (including uterus)	–	3–<5 cm	⩾5 cm	–
Site of metastases	lung	spleen, kidney	gastro-intestinal	liver, brain
Number of metastases	–	1–4	5–8	>8
Previous failed chemotherapy	–	–	single drug	2 or more drugs

Format for reporting to FIGO Annual Report. In order to stage and allot a risk factor score, a patient's diagnosis is allocated to a stage as represented by a Roman numeral I, II, III, and IV. This is then separated by a colon from the sum of all the actual risk factor scores expressed in Arabic numerals, e.g. Stage II:4, Stage IV:9. This stage and score will be allotted for each patient.

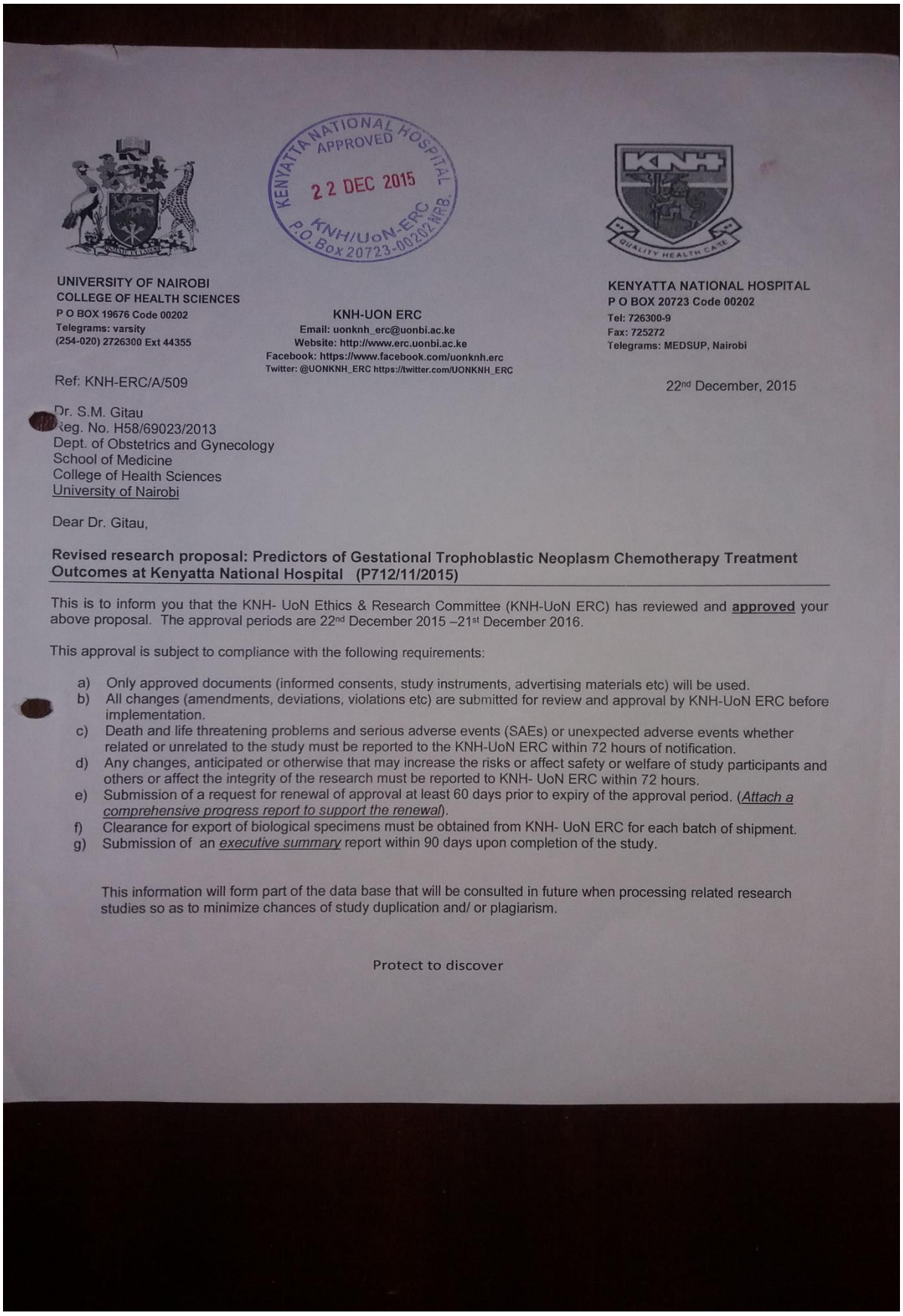
ANNEX 3: Budget and Source of Funding

				FUNDING SOURCE	
Item	RATE	UNITS	TOTAL	KNH	PERSONAL SOURCES
ERC fees	2,000.00	1	2,000.00	2,000.00	-
KNH Record access fee	1,500.00	1	1,500.00	1,500.00	-
Laptop	52,000.00	1	52,000.00	-	52,000.00
MS-Office software	10,000.00	1	10,000.00	-	10,000.00
Data extraction tool	30,000.00	1	30,000.00	3,320.00	26,680.00
Pretesting of study instruments	20,000.00	1	20,000.00	1,080.00	18,920.00
Data collection	100,000.00	1	100,000.00	100,000.00	-
Data entry	10,000.00	2	20,000.00	17,000.00	3,000.00
Data analysis – Statistician	30,000.00	1	30,000.00	30,000.00	-
Development of bound research book	1,000.00	5	5,000.00	4,500.00	500.00
Dissemination	5,000.00	3	15,000.00		15,000.00
Publication	40,000.00	2	80,000.00	-	80,000.00
Total			363,500.00	159,400.00	204,100.00

ANNEX 4: Study Timeline

	MONTH – 2015												MONTH - 2016											
Milestone/Months	1	2	3	4	5	6	7	8	9	10	11	12	1	2	3	4	5	6	7	8	9	10	11	12
Develop concept note	■																							
Literature review		■	■	■	■	■	■								■	■	■		■					
Methodology				■	■																			
Submit draft proposal to supervisors		■		■		■		■		■			■			■		■		■				
Proposal presentation to Department of OBGY-UoN		■							■															
Make necessary revisions			■		■					■	■	■				■		■		■				
Submit draft proposal to ERC											■													
Make necessary revisions as guided by ERC												■												
Data collection tools preparation												■	■											
Pretesting and revision of data collection tools													■	■										
Data collection														■	■	■								
Data entry														■	■	■								
Data analysis																■	■							
Write results, discussion and conclusion																	■	■						
Study finding presentation – Depart of OBGY UoN																		■						
Make final revisions																			■	■				
Publication																					■			
Dissemination – KNH and UoN symposiums																								

ANNEX 5: Study Approval Letter from KNH/UON ERC



KENYATTA NATIONAL HOSPITAL APPROVED 22 DEC 2015 KNH/UoN-ERC P.O. Box 20723-00202 NAIROBI

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

KNH-UON ERC
Email: uonknh_erc@uonbi.ac.ke
Website: http://www.erc.uonbi.ac.ke
Facebook: https://www.facebook.com/uonknh.erc
Twitter: @UONKNH_ERC https://twitter.com/UONKNH_ERC

KENYATTA NATIONAL HOSPITAL
P O BOX 20723 Code 00202
Tel: 726300-9
Fax: 725272
Telegrams: MEDSUP, Nairobi

Ref: KNH-ERC/A/509

22nd December, 2015

Dr. S.M. Gitau
Reg. No. H58/69023/2013
Dept. of Obstetrics and Gynecology
School of Medicine
College of Health Sciences
University of Nairobi

Dear Dr. Gitau,

Revised research proposal: Predictors of Gestational Trophoblastic Neoplasm Chemotherapy Treatment Outcomes at Kenyatta National Hospital (P712/11/2015)

This is to inform you that the KNH- UoN Ethics & Research Committee (KNH-UoN ERC) has reviewed and **approved** your above proposal. The approval periods are 22nd December 2015 –21st December 2016.

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) 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*).
f) Clearance for export of biological specimens must be obtained from KNH- UoN ERC for each batch of shipment.
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.

Protect to discover

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 Deputy Director, CS, KNH
The Chair, KNH-UoN ERC
The Assistant Director, Health Information, KNH
The Dean, School of Medicine, UoN
The Chair, Dept. of Obstetrics and Gynecology, UoN
Supervisors: Prof. Z. Qureshi, Dr. Frank Kagema

Protect to discover