THERAPEUTIC OUTCOMES IN AIDS-ASSOCIATED KAPOSI'S SARCOMA PATIENTS ON ANTIRETROVIRAL THERAPY TREATED WITH CHEMOTHERAPY AT UNIVERSITY TEACHING HOSPITAL AND CANCER DISEASES HOSPITAL IN LUSAKA, ZAMBIA

By

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A dissertation submitted to the University of Zambia in partial fulfillment of the requirements for the award of a Master of Clinical Pharmacy in Dermatology

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DECLARATION

I Mtonga Watson do hereby declare that this dissertation, being presented for Master of Clinical Pharmacy in Dermatology is my original work and that to the best of my knowledge it has never been previously submitted to any other university or learning institution for the award of any degree or academic credentials.

Signed ……..……..

Date ……..……

APPROVAL

This dissertation of Mtonga Watson is approved, fulfilling part of the requirements for the award of the degree of Master of Clinical Pharmacy in Dermatology by the University of Zambia.

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ABSTRACT

The incidence of HIV-associated Kaposi's sarcoma remains high in Zambia in the antiretroviral therapy era. The most efficacious treatment regimen for KS has yet to be established. In both developed and developing countries, treatment regimens have had limited efficacy. Late presentation in Africa affects therapeutic outcomes. The aim of this study was to determine the therapeutic outcomes of epidemic KS patients after completion of six cycles of Adriamycin, Bleomycin, and Vincristine (ABV) chemotherapy. This was a descriptive cross-sectional study. Study participants were drawn from a study database of confirmed incident KS patients seen at the Skin Clinic of the University Teaching Hospitals (UTH) during the period between August, 2015 and September, 2016. Of the 38 successfully recruited study participants, a complete response was documented in 18 (47.4%) after 6 cycles of ABV whereas 20 (52.6%) experienced a partial response. KS recurrence was observed in 8 (44.4%) of individuals that experienced an initial complete response. At the time of the study, clinical assessment revealed that KS lesions had completely regressed in 21 (55.3%) of all the patients. ABV chemotherapy appears ineffective in long-term resolution of epidemic KS patients on ART. Recurrence rates are high after chemotherapy in patients that experience initially favorable responses to treatment. There is a need to diagnose KS earlier, and to develop more efficacious treatment options in order to reduce recurrence rates for epidemic KS.

Key words: Kaposi's Sarcoma, HIV-associated, treatment, chemotherapy, outcomes, recurrence.

DEDICATION

I dedicate this work to my mother Costina Mhango Mtonga, sthis work is owed to you for your hard work, prayers and encouragement. May our Almighty God bless you abundantly.

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LIST OF ABBREVIATIONS AND ACRONYMS

ABV	Adriamycin (Doxorubicin), Bleomycin, Vincristine
ACTG	AIDS Clinical Trial Group
AIDS	Acquired Immunodeficiency Syndrome
ART	Anti – retrovirotherapy
BV	Bleomycin, Vincristine
CDH	Cancer Diseases Hospital
EBV	Epstein - Barr Vir0us
EKS	Epidemic Kaposi's sarcoma
HAART	Highly Active Anti retrovirotherapy
HHV-8	Human Herpes Virus 8
HIV	Human immunodeficiency Virus
KS	Kaposi's sarcoma
KSHV	Kaposi's sarcoma Herpes Virus
QoL	Quality of Life
UNZABREC	University of Zambia Biomedical Research Ethics Committee
UTH	University Teaching Hospital

CHAPTER ONE: INTRODUCTION

1.1 Background

Kaposi's sarcoma (KS) is a tumor of endothelial cell origin, and is regarded as an AIDS – defining illness caused by the human herpesvirus-8 (HHV-8) and its lesions are characterized by abnormal angiogenesis, inflammation and proliferation of spindled tumor cells infected with HHV-8 (International Agency for Research on Cancer, 2012). KS remains the most common malignancy in people living with HIV, especially in Sub-Saharan Africa (SSA) (Mosam *et al.*, 2010). And mortality among AIDS patients with KS is substantially higher than that among AIDS patients without KS (Makombe *et al.*, 2008). In 2012, it was estimated that there were 44,247 new KS cases of which 85% (37,509) of them occurred in Africa and 26,974 deaths worldwide (about 25,000 of these deaths occurred in SSA) (GLOBOCAN, 2012).

The optimal approach to management of HIV/AIDS-associated KS also known as Epidemic KS (EKS) is unknown (Mosam *et al.*, 2012). Treatment usually is based on the extent of disease and the patient's immune status. The challenge is to treat EKS effectively without immunocompromising the patient further (Schwartz, 2008).

The introduction of multi-drug antiretroviral therapy (ART) regimens in developed countries has been associated with a significant decrease in the incidence of EKS as well as improved patient survival in developed countries (Engels *et al.*, 2006). However, developing countries, especially in SSA, continue to experience significantly high incidence rates of EKS despite the introduction of ART, possibly due to high prevalence of human herpesvirus-8 (HHV-8) and HIV co-infection. Overburdening already frail health care systems with EKS leads to substantial morbidity and mortality, which may be improved by chemotherapy (Mosam *et al.*, 2012).

Doxorubicin, Bleomycin and Vincristine (ABV) combination is one of the widely used treatment regimens for KS in resource-limited countries, including Zambia. Administration of at least six (6) cycles of ABV given 21 days apart in addition to ART is considered one of the standards of care for advanced EKS. According to Gbabe *et al*, after a review of chemotherapy clinical trials concluded that there was a

significant reduction in disease progression in patients that received both ART and ABV chemotherapy (Gbabe *et al.,* 2014).

In 2012, Mosam *et al* reported that chemotherapy has a beneficial role in some EKS patients, and the addition of chemotherapy to ART results in improved overall response rate, time to response and progression free survival (Mosam *et al.,* 2012).
Studies from North American and European cohorts have demonstrated significant tumor regression and 5-year EKS survival rates near 90% after initiation of ART in early-stage disease (Zachariah *et al.,* 2006). However, similar outcome data for EKS patients from SSA populations, where EKS remains a significant cause of morbidity and mortality resulting in 10–14% of deaths in ART programs are lacking (Zachariah *et al.,* 2006).
Researchers in a randomized phase III clinical trial that compared pegylated liposomal doxorubicin and ABV in the treatment of EKS concluded that pegylated liposomal doxorubicin is better tolerated and more effective than ABV because ABV has a high rate of adverse drug reactions compared to pegylated liposomal doxorubicin (Northfelt *et al.,* 1998). However, liposomal preparations are expensive, not widely available, remain under patent, and require cold storage (Rudek *et al.,* 2011). This poses a challenge in resource limited countries like Zambia to have pegylated liposomal anthracyclines as first line treatment for EKS, therefore, further studies of KS specific therapies combined with ART are warranted for African patients with advanced EKS.
It is against this background that a study to determine therapeutic outcomes of recommended chemotherapeutic regimens was undertaken so as to generate local and enhance the evidence – based recommendations in the provision of pharmaceutical care to EKS patients in Zambia.

1.2 Statement of the problem

There is an increase in the number of EKS patients seen at the adult hospital of UTH; however, it is not well-known how these patients respond to ABV chemotherapy which is the first line treatment for EKS in Zambia. This paucity of knowledge on the therapeutic outcomes of EKS patients in Zambia and the increase in the disease burden poses a great challenge to the effective management of the disease**.**

This is a problem because morbidity and mortality among EKS patients is on the rise in SSA and a solution is needed to reduce morbidity and mortality among EKS patients.

Furthermore, there seems to lack an established follow-up system for EKS patients at the dermatology clinic after completion of chemotherapy from either CDH or other UTH wings, this makes aggregation of therapeutic information difficult.

Even though it is well understood that the treatment of EKS remains under debate and that no therapy has been shown to be curative (Uldrick *et al.,* 2011), there should be some measurable evidence of the benefits of currently recommended regimen which are anecdotally unavailable.

1.3 Study justification

This study was very important because KS is the most common malignancy among AIDS patients in Africa, affecting a high proportion of these individuals (Mosam *et al.,* 2010). It is considered as an AIDS defining illness (Baffa and Shehu, 2016) and is a major cause of morbidity and mortality in SSA resulting in approximately 25,000 deaths each year (GLOBOCAN, 2012).

The study was conducted to highlight how EKS patients respond to at least six cycles of ABV chemotherapy. The study will help to enhance the evidence-based provision of pharmaceutical care to EKS patients because information on how EKS patients respond to the currently recommended therapeutic regimen in Zambia is paramount in helping manage the problem.

1.4 Objectives

1.4.1 Main objective

To determine the treatment outcomes of AIDS-associated Kaposi's sarcoma patients at UTH and CDH

1.4.2 Specific Objectives

1. To determine the change in number and size of KS skin lesions after at least 6 cycles of ABV chemotherapy
2. To assess the response of KS-associated lymphedema to at least 6 cycles of ABV chemotherapy
3. To determine the hemoglobin levels before and after at least 6 cycles of ABV chemotherapy
4. To determine the side effects experienced by EKS patients during and after at least 6 cycles of ABV chemotherapy

1.5 Research Question

What are the treatment outcomes of AIDS-associated Kaposi's sarcoma patients who have received at least 6 cycles of ABV chemotherapy at UTH and/or (CDH)?

CHAPTER TWO: LITERATURE REVIEW

2.1 Epidemiology of KS

KS, the most common neoplasm in patients with AIDS, is a significant clinical problem for which current therapies are frequently unsatisfactory (Northfelt et al, 1996). Kaposi's sarcoma herpes virus (KSHV) infection is very common in SSA with seropositivity rates of >50%; It is moderately prevalent in Mediterranean countries between 20–30% (Uldrick *et al*., 2011). In Zambia, there is a 44% seroprevalence rate of HHV-8 infection amongst the adult population (Ciro and David, 2008).

The incidence of KS increased exponentially with the HIV/AIDS pandemic, with a shift in trend demonstrating a dramatic increase in females and occurrence in younger individuals (Mosam *et al*., 2010). Chu et al, noted that even in the era of wider access to ART, KS remains a significant contributor to morbidity and mortality in sub-Saharan Africa (Chu *et al*., 2010).

In a related study in 2011, Minhas et al also noted that the epidemic of HIV in Zambia has led to a dramatic rise in the incidence of KS in both adults and children (Minhas *et al*., 2011).

Ngalamika et al, reported that between 2008 and 2013**,** the Dermatology and Venereology Division of UTH in Zambia recorded at least 726 pathologist-confirmed KS cases. Of these, 460 (63.4%) cases were diagnosed in HIV infected patients (epidemic KS) and 266 (36.6%) cases in HIV negative patients (endemic KS) (Ngalamika *et al*., 2015).

2.2 Drug therapy of KS and associated treatment outcomes

Treatment of EKS remains under debate and curative therapy has not yet been determined. Debilitating cutaneous or visceral lesions are currently treated with cytotoxic drugs, either alone or in combination, although no clear benefit on survival has been demonstrated with either regimen (Lilenbaum *et al*., 1994). There are several chemotherapy regimens that are used in treating EKS patients. These range from single agent to triple agent chemotherapy. A few examples of these regimens are described below.

2.2.1 Vincristine and Vinblastine

Alternating vincristine and vinblastine weekly achieves a response rate of 33%. Toxicity includes vincristine-induced neurotoxicity (which limits its usefulness as a single agent) and vinblastine-induced myelosuppression (Volberding *et al.*, 1985).

2.2.2 Doxorubicin

Weekly treatment with doxorubicin at 25mg/m² in patients with EKS achieved a partial response rate of only 10%. The primary toxicity of weekly doxorubicin was myelosuppression, even with the relatively low doses and cardiomyopathy is the most significant long term toxicity (Fischl *et al.*, 193).

2.2.3 Vinorelbine

Jamie in 2003 reported that thirty-five evaluable patients were treated with vinorelbine 30mg/m² every 2 weeks. Clinical complete and partial remissions were achieved in 43% of patients, with a median progression-free survival of 151 days. The agent was well tolerated with neutropenia as the most frequent dose-limiting toxicity (Jamie, 2003).

2.2.4 Liposomal Agents

Two liposomal agents are currently approved for the treatment of KS: liposome-encapsulated daunorubicin (DaunoXome) and liposome-encapsulated doxorubicin (Doxil). Both agents are highly active against KS and have less toxicity than the non-liposomal anthracyclines. Myelosuppression, however, remains the dose-limiting toxicity (Northfelt *et al.*, 1996).

2.2.5 Bleomycin

The recommended dose of Bleomycin is 10 – 30 U/m^2 given weekly by the intravenous, intramuscular or subcutaneous route. The most serious adverse reaction to Bleomycin is pulmonary fibrosis which usually begins with a dry cough (Stewart *et al.*, 1996).

2.2.6 Combination Chemotherapy Regimens

Combination chemotherapy regimens have been evaluated in hopes of improving both the overall response rate and duration of response to chemotherapy for patients with advanced EKS. Response rates for the combination regimens vary from 28% to 88% (Jamie, 2003). Differences in response rates are largely attributable to differences in the patient populations evaluated, the lack of strictly defined response

criteria, and variations in the dosing schedules used. The combination regimen studied and used most widely is the Doxorubicin (Adriamycin), Bleomycin and Vincristine (ABV) regimen given every 2-3 weeks. The initial report of ABV therapy in 30 patients described a response rate of 88%, whereas in other randomized trials, response rates were as low as 28% (Jamie, 2003). The toxicity profile of this regimen includes myelosuppression, mild nausea, moderate alopecia, and peripheral neuropathy (Jamie 2003).

An alternative regimen, which is associated with less myelosuppression and alopecia, is Bleomycin and Vincristine (BV). A single-institution phase II study of BV in 18 patients reported a response rate of 72%. This result is in marked contrast to the response rate of 23.3% reported in the phase III trial of BV versus liposomal doxorubicin (Gill *et al*., 1996).

Liposomal anthracyclines are effective against KS and may be less toxic than non-liposomal anthracyclines. Liposomal daunorubicin given intravenously every two weeks produced response rates of 25 to 62% (Gill *et al*., 1996). However, these liposomal formulations are quite expensive and are not readily available on the Zambian market, as a result, despite their low toxicity profile they are not widely used at UTH.

Therefore, the Dermatology and Venereology Division at UTH has adopted the use of triple agent combination chemotherapy regimen of ABV in addition to ART as a first line treatment for advanced EKS.

A study by Ayoro in 2014 in Kenya found that there were poor short-term outcomes of patients with EKS receiving chemotherapy at a national referral hospital (Ayoro, 2014). In a similar study in Malawi conducted by Michael et al in 2013, it was concluded that their chemotherapy program for EKS was a success, though their study included all patients who had received any form of chemotherapy (Michael *et al*., 2015). The fact that the study done by Michael et al did not evaluate a specific chemotherapy regimen makes it difficult to make inference to their findings.

Another Malawian study described a successful EKS treatment program characterized by excellent one-year Overall Survival of 88% following at least a cycle of BV (Makombe *et al*., 2008). In the Makombe led study only patients that had received BV were evaluated however, they included patients that had received at

least one cycle of BV and their main outcome was survival regardless of the actual response to BV chemotherapy as regards KS lesion regression and lymphedema.

A more recent KS study by Baffa and Shehu in Nigeria found and concluded that; i) Patients with KS visceral involvement (especially the lungs) have poor outcomes; ii) Treatment of KS does not improve CD4 counts in patients with HIV; iii) There is need to clinically identify patients with KS in ART centres early in order to improve their outcomes by initiating ARVs early; iv) Combination chemotherapy of ABV should be used as first line treatment while Liposomal Daunorubicin and Paclitaxel can be employed as second-line (Baffa and Shehu, 2016).

Several studies have shown that ART plus chemotherapy may be beneficial in reducing KS disease progression compared to ART alone in patients with severe or progressive EKS (Gbabe *et al*., 2013).

From the reviewed literature, it is not clear how EKS patients respond to at least 6 cycles of ABV chemotherapy as most studies did not categorically state the minimum number of cycles each patient received and in Zambia, anecdotal data shows paucity of information on the subject. Therefore, it was important to undertake a study of this nature so as to provide a clear standpoint of the therapeutic outcomes of ABV chemotherapy in EKS patients.

CHAPTER THREE: RESEARCH METHODOLOGY

3.1 Research Methods

In this part of the dissertation detailed descriptions of methods used in the study are presented. Cardinal aspects include data collection techniques, study type, sampling methods and procedures, data collection and analysis, ethical considerations.

3.1.1 Study Design

The study was a descriptive cross-sectional study involving human participants. It involved the review of the patient's clinical records and physical review of the patients by a consultant Dermatologist to determine the treatment outcomes in accordance with the modified protocols of the AIDS Clinical Trial Group (ACTG) after completing at least 6 cycles of ABV. Those that were found to have poor response or KS recurrence were recommended for commencement of second line chemotherapy.

3.1.2 Study Definition of Treatment Outcomes

The classification of treatment outcomes was adapted and modified from the ACTG classification. This classification was grouped in four (4) categories as follows;

Outcome 1: Failure

Upon the patient being reviewed by the Dermatologist, patients who presented with disease progression or worsening of the condition such as appearance of new KS lesions after completion of at least 6 cycles of ABV chemotherapy were classified as having failed to respond to treatment.

Outcome 2: Stable

Patients who presented with no disease progression for a minimum of 4 consecutive weeks after having completed at least 6 cycles of ABV chemotherapy were classified as stable.

Outcome 3: Partial Response

Patients who did not develop new KS lesions, had regression of some of the KS lesions for a minimum of 4 consecutive weeks after having completed at

least 6 cycles of ABV chemotherapy were classified as having partially responded to treatment.

Outcome 4: Complete Response

Patients who did not have active KS lesions and lymphedema for a minimum of 4 consecutive weeks after having completed at least 6 cycles of ABV chemotherapy were classified as having had a complete response to treatment.

3.1.3 Study Population

The study considered all HIV-positive patients with KS, who were enrolled for treatment at UTH and/or CDH between **August, 2015 and September, 2016.** These patients had been entered into an **Access© database** at the Dermatology and Venereology Section at UTH. This is a hospital database and there were a total of 160 KS patients with confirmed histology results for this period. These patients had been initially recruited for a different study and had been initiated on ABV chemotherapy upon confirmation of their KS diagnosis.

3.2 Sampling Methods

Out of the 160 KS patients in the database for the period under review, only 61 patients had complete follow up information thus, study employed purposive sampling method. Therefore, all the patients that met the inclusion criteria for the period the period under review were part of the study and the study succeeded to review 38 patients.

3.3 Inclusion Criteria

1. All HIV-positive patients who had a confirmed histology report of Kaposi's sarcoma
2. Patients who were 18 years of age and above at the time of KS diagnosis
3. Patients who had received at least 6 cycles of ABV chemotherapy prior to this study.
4. Patients who had complete initial and follow-up information

5. Patients who were reachable by phone and consented to participate in the study.

3.4 Exclusion Criteria

1. Patients residing outside Lusaka were excluded due to logistic challenges
2. Patients on other forms of chemotherapy
3. Patients who were bed-ridden and not admitted at UTH or CDH at the time of the study

3.5 Data Management

3.5.1Data Collection

Data was collected using a patient review form which is attached in the appendices. The review form was adapted and modified from the World Health Organization Quality of Life Assessment tool (WHOQOL-100). The review form was tailored to how the consultant dermatologist would review the participants in as far as their response to the ABV chemotherapy was concerned.

Firstly, the patient clinical record was retrieved from the database then secondly, the patient was interviewed as per review form, and then a physical examination was done by a Consultant Dermatologist. On examination the following were the emphasis points:

1. Presence of KS lesions was assessed in affected areas, this included identifying active KS lesions and/or post-inflammatory changes.
2. Presence or absence or KS-induced lymphedema
3. Ability to walk, flex or extend limbs that were severely affected by lymphedema, if any
4. Ability to perform daily chores relating to participants' routine activities prior to the KS development and after KS treatment

The independent variable in this study was the ABV treatment regimen and the dependent variables were the treatment outcomes.

Table 1: Variables and the Scale of Measurement

VARIABLE	DEFINITION	SCALE OF MEASUREMENT
Age	18 years and above	Continuous
Gender	Male or female	Categorical
Treatment outcome	Failure, stable, partial response and complete response	Categorical
Hemoglobin (Hb)		Continuous
CD4 Cell count		Continuous

3.5.2 Data Analysis

Data was entered into the Microsoft excel sheets and analyzed using **Statistical Package for Social Scientists (IBM SPSS Statistics 20)** and **GraphPad Prism Version 5.0**

Continuous variables such as CD4 cell count and hemoglobin were subjected to D'Agostino and Pearson omnibus normality test. Hemoglobin was normally distributed and so unpaired t-test was used and for CD4 cell count Mann-Whitney was used to analyze the data because the data was not normally distributed.

3.6 Ethical Consideration and Permissions

Ethical approval was sought from the University of Zambia Biomedical Research Ethics Committee (UNZABREC) before commencement of the study. The patient review form did not capture any patient names or identity numbers that could lead to the actual identification of individual patients. The patient details that were obtained from the database and patient's clinical records were treated with utmost confidentiality.

Participants were called by phone to come for a review visit at the skin clinic of UTH and their transport logistics were taken care of by the researcher. Participants

were given transport refund equivalent to the government rate at the time of the study.

Permission was sought from the managements of UTH and CDH to conduct this study at their institutions. Further permission was sought from the **Access© database** rights holders to use some of their primary information contained in their database to conduct this study.

CHAPTER FOUR: RESULTS

4.1 Enrollment

The study enrolled a total of 38 participants (62% response rate) comprising of 7 females and 31 males making a ratio of 1:4. The age range of the participants was from 19 years to 63 years and the median age was 35.5 years. Table 4.1, summarizes all baseline and clinical characteristics of the participants.

Table 2: Baseline and Clinical characteristics of the study participants

Characteristic	Frequency	Percentage
Demographic characteristics		
Sex		
Female	7	18.4
Male	31	81.6
Age (Years)		
19-29	5	13.1
30-39	21	55.3
Above 40	12	31.6
Marital Status		
Divorced	5	13.2
Married	26	68.4
Single	6	15.8
Widowed	1	2.6
Clinical characteristics		
Primary site of lesion		
Face	1	2.6
Upper limbs	2	5.3
Upper/lower limbs	3	7.9
Lower limbs	32	84.2
Edema resolution		
No	15	39.5
Yes	23	60.5
KS lesion regression		
Completely regressed	21	55.3
Partially regressed	17	44.7
Therapeutic outcome		
Complete response	18	47.4
Partial response	20	52.6
KS lesion recurrence		
No	10	55.6
Yes	8	44.4

Side effects during chemotherapy		
Nausea	31	81.6
Loss of appetite	34	89.5
Diarrhoea	25	65.8
Alopecia	28	73.7
Side effects after chemotherapy		
Numbness	18	47.4
Joint pains	29	76.3
Skin hyperpigmentation	31	81.6
Quality of life		
Daily activities before chemotherapy		
Yes	16	42.1
No	22	57.9
Daily activities after chemotherapy		
Yes	38	100
No	0	0
Bed ridden before chemotherapy		
Yes	26	68.4
No	12	31.6
Bed ridden after chemotherapy		
Yes	0	0
No	38	100

4.2 Determination of the change in number and size of KS skin lesions after at least 6 cycles of ABV chemotherapy

Majority of the patients had complete regression of KS skin lesions. This is evidenced by the fact that 55.3% (n=18) of the patients had complete regression compare to 44.7% of the patients who had partial KS skin lesion regression as can be seen in figure 1 below. In this study, there was no record of failure or stable disease.

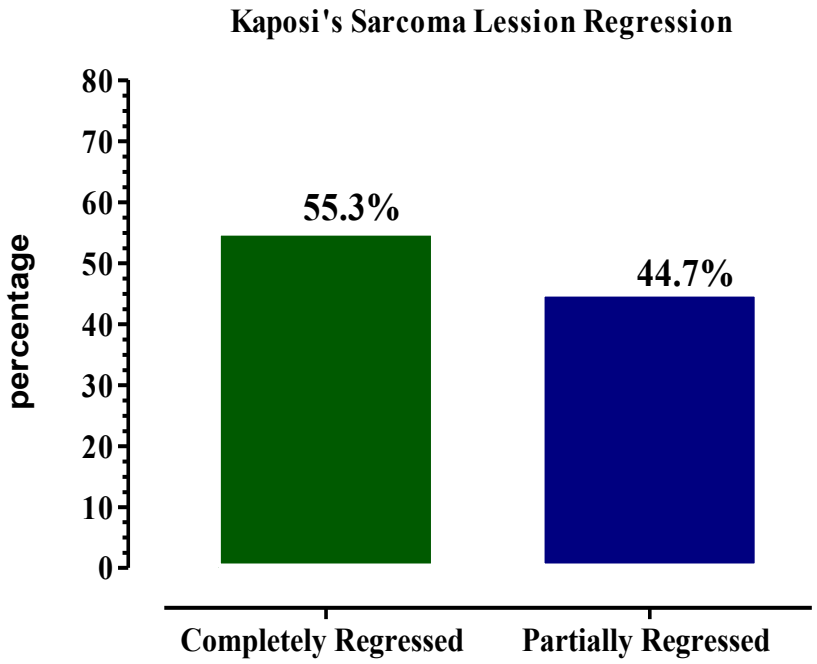

Figure 1: Presentation of Kaposi's sarcoma lesion regression, showing 55.3% complete regression and 44.7% patrial regression of after at least 6 cycles of ABV chemotherapy.

4.3 Assessment of the response of KS-associated lymphedema to at least 6 cycles of ABV chemotherapy

About two-thirds of the patients had their lymphedema resolved. Of the 38 patients, 23 (60.5%) had edema resolution while 15 (39.5%) of the patients had their edema unresolved after at least 6 cycles of ABV chemotherapy.

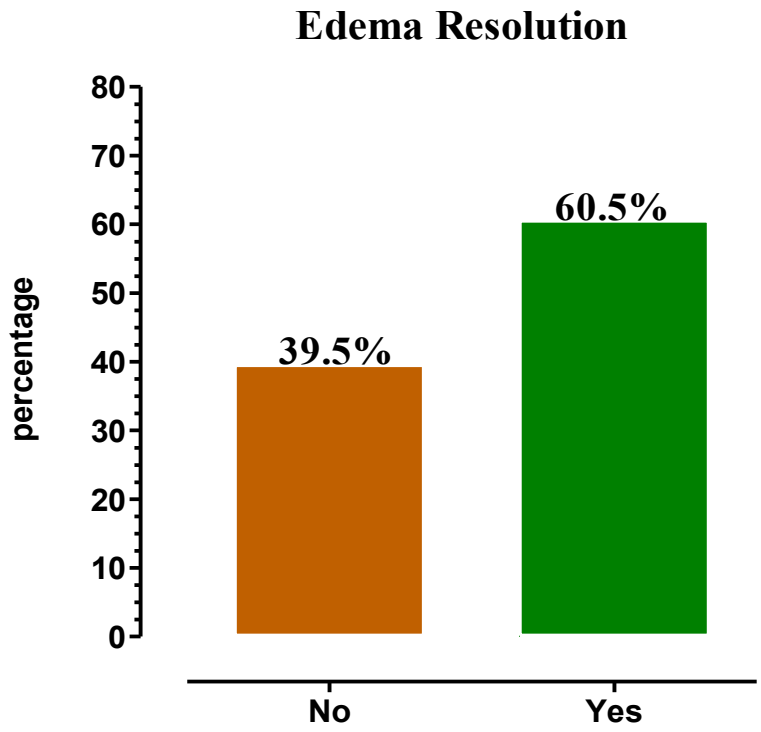

Figure 2: Showing 60.5% edema resolution of the patients and 39.5% unresolved KS-associated lymphedema to at least 6 cycles of ABV chemotherapy.

4.4 Determination of the hemoglobin levels before and after at least 6 cycles of ABV chemotherapy

There was a slight raise in hemoglobin levels after 6 cycles of ABV chemotherapy though it was statistically insignificant as can be seen from the p-value in figure 3 below

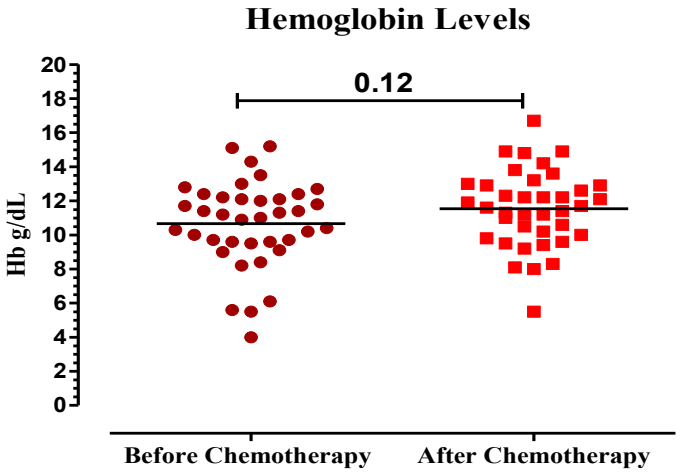

Figure 3: Shows the difference in hemoglobin levels before and after chemotherapy (p=0.12)

4.5 Determination of the hemoglobin levels before and after at least 6 cycles of ABV chemotherapy

There was a statistically significant improvement in the CD4 Cell count post ABV chemotherapy. This improvement in CD4 Cell count could be attributed to ART

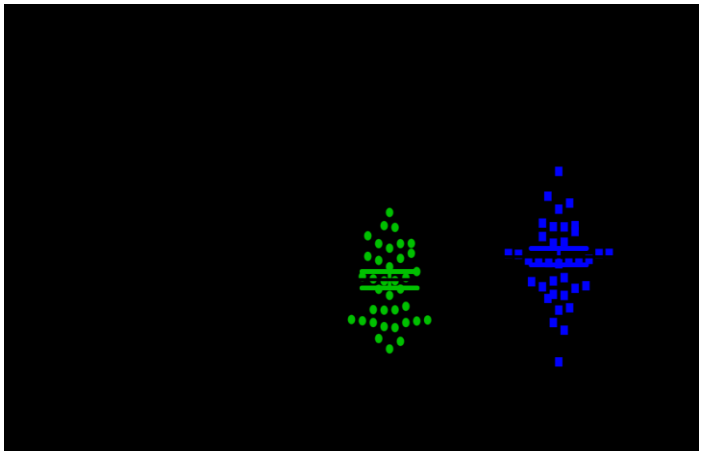

Figure 4: Shows the difference in hemoglobin levels before and after chemotherapy (p=0.0001)

4.6 Determination of the side effects experienced by EKS patients during and after at least 6 cycles of ABV chemotherapy

During the ABV chemotherapy, patients experienced a number of side effects the most pronounced ones were lack of appetite experienced by 89.5%, nausea and vomiting by 81.6% of the patients and reversible alopecia by 73.3%. After chemotherapy, some side effects had persisted such as hyperpigmentation of the skin and nails experienced by 81.6% of the patients and joint pains by 76.3%. On the other hand, 26 patients (68.4%) were bed ridden at the time of KS diagnosis, but no patient was bed ridden after at least 6 cycles of ABV chemotherapy.

Figure 4.5 below is a bar graph showing the proportions of the most suffered side effects during chemotherapy. Out of the 38 participants, only 16 (42.1%) were able to perform their daily chores at the time of KS diagnosis and initiation of ABV chemotherapy, however, after at least 6 cycles of ABV, all the patients were able to perform their daily chores. On the other hand, 26 patients (68.4%) were bed ridden at the time of KS diagnosis, but no patient was bed ridden after at least 6 cycles of ABV chemotherapy.

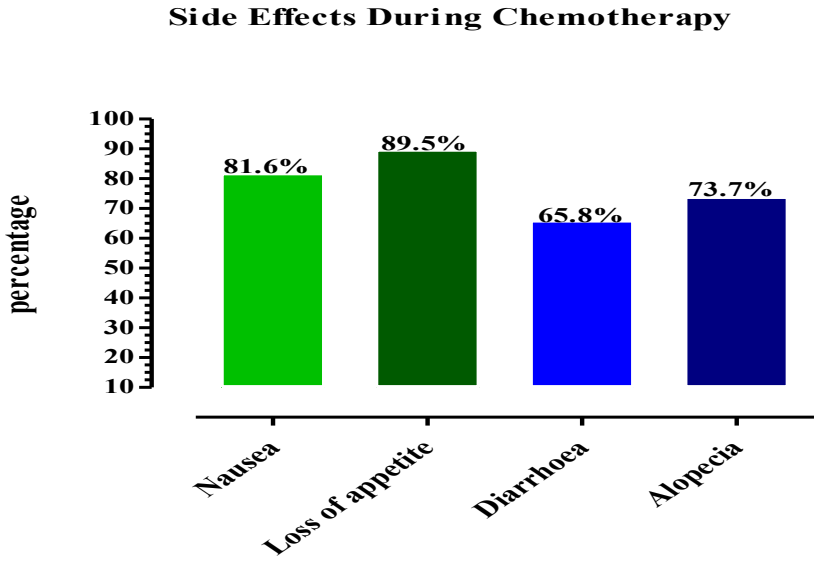

Figure 5: shows the most common side effects during chemotherapy with the highest being that of loss of appetite at 89.5% and the least was diarrhoea at 65.8%.

4.7 Determination of the therapeutic outcome of EKS patients after at least 6 cycles of ABV chemotherapy

A total of 18 patients (47.4%) had complete response sustained for at least 90 days and rest of the patients had partial response. Figure 4.6 below is bar chat presentation of this outcome.

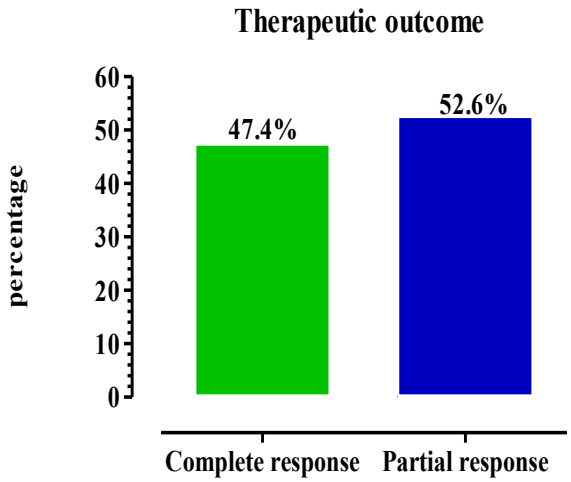

Figure 6: shows the 47.4% of the participants having achieved complete therapeutic response after at least 6 cycles of ABV chemotherapy.

4.8 Recurrence of KS lesions

Of the 18 patients who had reported complete response, 44.4% had recurrence of the KS lesions at least 90 days after the last cycle of ABV chemotherapy. This is shown in figure 4.7 below.

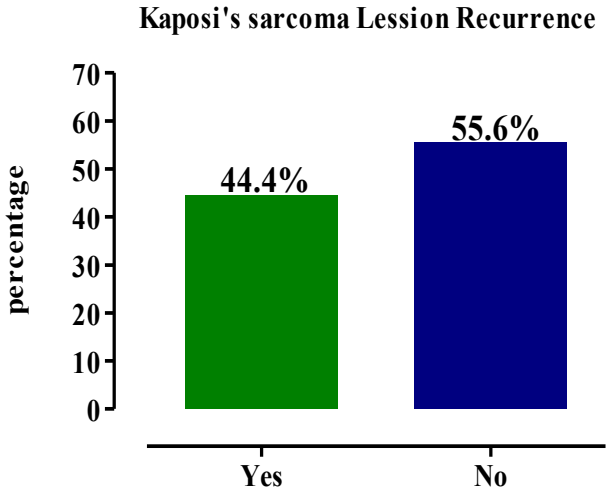

Figure 7: shows that more than half (55.6%) of that the participants that had achieved complete response had recurrence of the KS lesions at least 90 days after ABV chemotherapy.

CHAPTER FIVE: DISCUSSION

It is believed that this is the first study to assess therapeutic outcomes of EKS patients on any form of therapy in Zambia. There were more males than females in this study. This is consistent with the findings of Ngalamika *et al* who reported that more males than females present with EKS at UTH (Ngalamika *et al*., 2014). The exact reasons as to why more males are affected by KS compared to females are not known, however, the poor health seeking behavior among men which often times leads to late diagnosis of HIV and KS can be a contributing factor. Furthermore, the increased risk of KS in men is most likely to be related to differences in exposure, the sex-related differences in presentation and course may be due in part to delay in diagnosis (Cooley *et al*., 1996).

This study shows that lower limbs were the most common primary site for the KS lesions (84% of all patients) while the face was the least common. This is in conformity with a study done by Phipps and colleagues in 2010 where they found that more than 70% of KS lesions occurred in the legs (Phipps *et al.,* 2010).

In this study, more than half of the patients were aged between 30 and 39 years and the mean age was 35.5years. This is similar to the findings of Olweny et al who conducted a study on comparative treatment of EKS in Zimbabwe where the mean age was 36 years (Olweny *et al.,* 2005).

More than half of the patients had regression of KS lesions after at least 6 cycles of ABV chemotherapy in this study. Partial regression of KS lesions could be attributed to inconsistencies in receiving cycles of ABV probably due to hematological toxicities. And about two-thirds of the participants had resolved lymphedema.

In this study there was a rise in mean hemoglobin levels post chemotherapy though statistically insignificant. The reason for the observed rise in hemoglobin levels could be attributed to the prescribed hematinics the patients were taking daily during the entire duration of treatment. On the other hand, there was a statistically significant improvement in the CD4 Cell count post ABV chemotherapy. This improvement in CD4 Cell count could be attributed to ART. This finding contradicts the findings of Baffa and Shehu who concluded that treatment of EKS is not associated with an improvement in CD4 count (Baffa and Shehu, 2016). The

statistically significant CD4 count improvement observed in this study could be attributed to ART-induced viral suppression and immune reconstitution.

Most patients experienced lack of appetite, nausea and vomiting and reversible alopecia during the time they were receiving ABV chemotherapy. On the other hand, hyperpigmentation of the skin and nails, numbness and joint pains had persisted for several months in most patients after their last cycle of ABV chemotherapy. Side effects such as lack of appetite and nausea and vomiting could have contributed to patients missing their scheduled appointments for chemotherapy thereby affecting therapeutic response.

Of the 38 patients, 18 (47%) had a complete response and 53% had a partial response to at least 6 ABV chemotherapy cycles. This finding is similar to the findings of Gbabe *et al* in their Cochrane review of the treatment of severe EKS where they concluded that there was a significant reduction in KS disease progression after ABV chemotherapy (Gbabe *et al.*, 2013). In a study by Núñez *et al* in 2015 which evaluated the treatment of liposomal doxorubicin for EKS patients in the era of ART, there was a 40% complete response (Núñez *et al.,* 2015) which is a very comparable result to the findings of this study.

Of the evaluated patients, all of them showed a positive response to at least 6 cycles of ABV chemotherapy as there was no progressive disease noted in any of the patients except that most of them disease recurrence several months later. The 100% response rate could be owed to the fact that all the patients were on ART and that could also possibly explain the noted CD4 Cell count improvement noted in this particular study.

Despite the observed complete response in 18 patients, about half of these patients developed KS lesion recurrence within 90 days of completing chemotherapy. This is of particular concern because the therapeutic goal of EKS has shifted from palliative care to long-term durable complete remission (Núñez *et al.,* 2015). Nguyen *et al* in 2008 reported that HAART and chemotherapy are important in clinical KS response, however despite widespread availability of HAART and chemotherapy in the developed countries, KS continues to be a clinical problem; only half the patients achieved complete resolution of disease in their study (Nguyen *et al.,* 2008).

More than half of the patients were unable to perform their daily chores including self-care prior to ABV chemotherapy. However, all the patients were able to perform their daily chores and self-care after ABV chemotherapy. Furthermore, all the patients who were bed-ridden prior to ABV chemotherapy were no longer bed-ridden after receiving at least 6 cycles of ABV chemotherapy. This indicates that there was an improvement in the QoL after at least 6 cycles of ABV chemotherapy plus ART in EKS patients.

5.1 Limitations

The study had some limitations. Firstly, certain information was subjective as the patients had to recall how they felt or what happened months earlier prior to the study. Secondly, incomplete patient details such as phone number led to the exclusion of a lot of participants because contacting them was a challenge. This limited the number of patients evaluated. Thirdly, the study did not take into account the dosing modalities of the drugs used, so as to tell whether the response or adverse reactions were dose dependent or not.

CHAPTER SIX: CONCLUSIONS AND RECOMMENDATIONS

6.1 Conclusions

It can be concluded that more than half of the patients had a complete regression of KS skin lesions (55.3%) while about two-thirds of the patients had their lymphedema resolved. Further, there was a slight rise in the mean hemoglobin levels after 6 cycles of ABV chemotherapy although insignificant statistically ($p = 0.12$). It can be further concluded that the most experienced side effects during ABV chemotherapy were lack of appetite, nausea and vomiting and reversible alopecia whereas skin and nail hyperpigmentation persisted for several months after ABV chemotherapy in most of the patients. Overly, less than half of the patients achieved complete response (44.7%) to at least 6 cycles of ABV chemotherapy and of these patients only about half (55.6%) did not have a recurrence of KS lesions within 90 days.

6.2 Recommendations

1. The search for better therapeutic options is warranted so as to achieve durable complete remission as opposed to palliation.
2. There is need for clinicians in ART centers to intensify on early detection of EKS
3. The management of UTH need to equip the histopathology laboratory so as to respond to the urgent need of quick histopathology results for EKS patients to enable them receive treatment early.

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APPENDICES

APPENDIX 1: PARTICIPANT CONSENT FORM

Dear Participant,

My name is Watson Mtonga, a Master of Clinical Pharmacy student in Dermatoogy at the University of Zambia, school of medicine. I am conducting a research on "***Assessment of Therapeutic outcomes in AIDS Associated Kaposi's Sarcoma Patients at University Teaching Hospital and Cancer Diseases Hospital – Lusaka, Zambia."***

I am requesting for your participation in this very important study. Your participation in this study will not disrupt nor divulge your private life. The information you will provide in this study will be treated with utmost confidentiality, you are not required to provide any personal information that may lead to the identification of your true identity. The study will require that you be reviewed physically by the Consultant Dermatologist in order to assess your response to the treatment you received.

You are free to withdraw your participation from this study at any time and you will not suffer any form of penalty in the event that you choose to withdraw from the study.

Thank you for your time.

Yours faithfully,

Watson Mtonga (+260 979 255 436)

I agree to participate in this study: **Signature/Thumb print**

……

I do not agree to participate in this study: **Signature/Thumb print**

…….

Witness: **Signature/Thumbprint**

…….

APPENDIX 2: DATA COLLECTION TOOL: STUDY TREATMENT OUTCOME REVIEW FORM

ASSESSMENT OF TREATMENT OUTCOMES OF AIDS – ASSOCIATED KAPOSI'S SARCOMA PATIENTS WHO HAVE RECEIVED COMPLETE CHEMOTHERAPY CYCLES OF ABV AT UTH AND CDH

Questionnaire Number……

Part 1: Demographic parameters

1. Age of the patient at the time of KS diagnosis……
2. Sex:
   a) Male
   b) Female
3. Marital status:
   a) Single
   b) Married
   c) Divorced
   d) Widowed
   e) Separated

Part 2: Clinical parameters

4. How long the patient has known their HIV status prior to KS diagnosis
   a) Knew HIV status at the time of KS diagnosis
   b) Less than 1 year
   c) 1-5 years
   d) 6-10 years
   e) More than 10 years
5. Which body location did the KS lesions start from (primary site)?
   a) Lower limbs
   b) Upper limbs
   c) Mouth
   d) Chest/Abdomen
   e) Face

6. Was the patient on HAART at the time of KS diagnosis?
   a) Yes
   b) No
7. If the answer is No to question 6 above, was the patient initiated on HAART prior to chemotherapy?
   a) Yes
   b) No
8. What was the Hb level prior to chemotherapy? .....
9. What was the latest Hb level prior to the study? .....
10. How many cycles of ABV chemotherapy did the patient receive? ……..
11. How long ago did the patient complete ABV chemotherapy prior to the study? ……
12. After how many chemotherapy cycles did the patient start to note improvement if there was any improvement? .....
13. If the patient initially presented with woody edema, did the edema resolve after 6 cycles of ABV chemotherapy?
   a) Yes
   b) No
14. Did the KS skin lesions completely regress after completion of 6 cycles of ABV chemotherapy?
   a) Yes
   b) No
15. Did the KS skin lesions partially regress after completion of 6 cycles of ABV chemotherapy?
   c) Yes
   d) No
16. Did the KS skin lesions remain the same after completion of 6 cycles of ABV chemotherapy?
   a) Yes

b) No

17. Did the KS skin lesions worsen after completion of 6 cycles of ABV chemotherapy?
    a) Yes
    b) No
18. If the answer to question 17 above is yes, was the patient put on second line treatment?
    a) Yes
    b) No
19. Taking a 10cm X 10cm measurement on any part that had/has KS lesions, how many active lesions are there?.....
20. Taking a 10cm X 10cm measurement on any part that had/has KS lesions, how many post-inflammatory lesions are there?.....
21. NOTES on Examination:
    1.
    2.
    3.

Part 3: Quality of Life

22. Was the patient able to do normal daily activities such as cooking, bathing, or eating without help **before** starting the ABV chemotherapy?
    a) Yes
    b) No
23. Was the patient able to do normal daily activities such as cooking, bathing, or eating without help **after** completion of 6 cycles of ABV chemotherapy?
    a) Yes
    b) No
24. Was the patient bed ridden **before** starting the ABV chemotherapy?
    a) Yes

b) No

25. Was the patient bed ridden **after** completion of 6 cycles of ABV chemotherapy?

    a) Yes

    b) No

4.

26. Was the patient experiencing nausea and or vomiting **before** starting the ABV chemotherapy?

    a) Yes

    b) No

27. Was the patient experiencing nausea and or vomiting **after** chemotherapy sessions?

    a) Yes

    b) No

28. Was the patient experiencing nausea and or vomiting **after** completion of 6 cycles of ABV chemotherapy?

    a) Yes

    b) No

29. Was the patient's appetite good **before** starting the ABV chemotherapy?

    a) Yes

    b) No

30. Was the patient's appetite good **during** the time of receiving chemotherapy?

    a) Yes

    b) No

31. Was the patient's appetite good **after** completion of 6 cycles of ABV chemotherapy?

    a) Yes

    b) No

32. Was the patient normally emptying the bowels **before** starting the ABV chemotherapy?

    a) Yes

b) No

33. Was the patient normally emptying **during** the time of receiving chemotherapy?

    a) Yes

    b) No

34. Was the patient normally emptying the bowels **after** completing the ABV chemotherapy?

    a) Yes

    b) No

35. Was the patient experiencing muscle or joint pains **before** starting the ABV chemotherapy?

    a) Yes

    b) No

36. Was the patient experiencing muscle or joint pains **during** the time of receiving chemotherapy?

    a) Yes

    b) No

37. Was the patient experiencing muscle or joint pains **after** completion of 6 cycles of ABV chemotherapy?

    a) Yes

    b) No

38. Side effects experienced:

Side effect	Reversible Hair loss	Darkening of skin, nails, palms and soles	Loss of sexual drive	Diarrhoea	Other
Yes					
No					

39. What was the treatment outcome of the patient?

    a) Failure

b) Stable

c) Partial response

d) Complete response

APPENDIX 3: GRADUATE PROPOSAL PRESENTATION FORUM CLEARANCE LETTER

UNIVERSITY OF ZAMBIA

SCHOOL OF MEDICINE

Telephone : +260211252641
Telegram: UNZA, Lusaka
Telex: UNZALU ZA 44370

P.O Box 50110
Lusaka, Zambia

Email: assistantdeanpgmedicine@unza.zm

24 January 2017

Mr. Watson Mtonga
School of Medicine
Department of Pharmacy
UNZA
LUSAKA

Dear Mr. Mtonga,

RE: GRADUATE PROPOSAL PRESENTATION FORUM

Following the presentation of your dissertation entitled **"Assessment of the Treatment Outcomes of AIDS Associated KS Patients Treated with Triple Combination Chemotherapy at UTH and CDH, Lusaka, Zambia"** your supervisor has confirmed that the necessary corrections to your research proposal have been done.

You can proceed and present to the Research Ethics.

Yours faithfully,

Dr. L. Prashar
ASSISTANT DEAN, POSTGRADUATE

UNIVERSITY OF ZAMBIA
SCHOOL OF MEDICINE
24 JAN 2017
ASSISTANT DEAN (PG)
P.O. BOX 50110, LUSAKA.

cc: Assistant Dean (PG) - School of Health Sciences

APPENDIX 4: UTH PERMISSION LETTER

Mtonga Watson
University of Zambia
Pharmacy department
Lusaka

10th March, 2017

The Senior Medical Superintendent
University Teaching Hospital
Lusaka

Dear Sir,

Ref: Application for permission to conduct my research at Skin Clinic entitled "***Assessment Of Treatment Outcomes in AIDS Associated Kaposi's Sarcoma Patients Treated With Triple Combination Chemotherapy at The University Teaching Hospital And Cancer Diseases Hospital – Lusaka, Zambia***"

Reference is made to the above captioned subject.

I am a Master of clinical pharmacy student at the University of Zambia, school of medicine. I wish to conduct part of the above stated study at the University Teaching Hospital's Dermatology and Venereology section (Skin Clinic). I am anticipating your kindest action towards my application.

Yours faithfully,

Mtonga Watson

0979 255 436 (mtongawatson@ymail.com , dpdmtonga@gmail.com)

APPENDIX 5: CDH PERMISSION LETTER

All Correspondence should be addressed to the
Executive Director
Tel/Fax: +260 211 257706

In reply please quote:

No.:.....

REPUBLIC OF ZAMBIA
MINISTRY OF HEALTH
CANCER DISEASES HOSPITAL

MH/CDH/101/18/1

P. O. Box Rw 51337
LUSAKA

27th March, 2017

Mr. Mtonga Waston
University of Zambia
Department of Pharmacy
Box 50110
LUSAKA

RE: APPROVAL TO CONDUCT PART OF YOUR RESEARCH AT CANCER DISEASES HOSPITAL – MTONGA WATSON. STUDENT NUMBER: 514702070

Refer to the above.

I wish to inform you that CDH has no objection to your request for you t to conduct part of your research **at Cancer Diseases Hospital entitled *'Assessment of Therapeutic outcomes in AIDS Associated Kaposi's Sarcoma Patients at University Teaching Hospital and Cancer Diseases Hospital, Lusaka, Zambia.***

You should come with a copy of this letter during your data collection.

Dr. Lewis Banda
SENIOR MEDICAL SUPERINTENDENT

- Nurse in charge - OPD assist/guide student in collecting data fra KS patients in F/U clinic on thurs
- Head medical records assist i patient files KS, previously Kaposi's AIDS

10/05/17

APPENDIX 6: ETHICS CLEARANCE LETTER

THE UNIVERSITY OF ZAMBIA

BIOMEDICAL RESEARCH ETHICS COMMITTEE

Telephone: 260-1-256067
Telegrams: UNZA, LUSAKA
Telex: UNZALU ZA 44370
Fax: + 260-1-250753
E-mail: unzarec@unza.zm
Assurance No. FWA00000338
IRB00001131 of IORG0000774

Ridgeway Campus
P.O. Box 50110
Lusaka, Zambia

21st April, 2017.

Your Ref: 001-02-17.

Mr. Watson Mtonga,
University of Zambia,
School of Medicine,
Department of Pharmacy,
P.O Box 50110,
Lusaka.

Dear Mr. Mtonga,

RE: RESUBMITTED RESEARCH PROPOSAL: "ASSESSMENT OF THERAPEUTIC OUTCOMES IN AIDS ASSOCIATED KAPOSI'S SARCOMA PATIENTS AT UNIVERSITY TEACHING HOSPITAL AND CANCER DISEASES HOSPITAL, LUSAKA, ZAMBIA" (REF. 001-02-17)

The above-mentioned research proposal was presented to the Biomedical Research Ethics Committee on 13th April, 2017. The proposal is approved.

CONDITIONS:

- This approval is based strictly on your submitted proposal. Should there be need for you to modify or change the study design or methodology, you will need to seek clearance from the Research Ethics Committee.
- If you have need for further clarification please consult this office. Please note that it is mandatory that you submit a detailed progress report of your study to this Committee every six months and a final copy of your report at the end of the study.
- Any serious adverse events must be reported at once to this Committee.
- Please note that when your approval expires you may need to request for renewal. The request should be accompanied by a Progress Report (Progress Report Forms can be obtained from the Secretariat).
- **Ensure that a final copy of the results is submitted to this Committee.**

Yours sincerely,

M.C Maimbolwa PhD
CHAIRPERSON

Date of approval: 21st April, 2017. **Date of expiry**: 20th April, 2018.