OUTCOME OF DRUG MANAGEMENT OF PATIENTS WITH AIDS-RELATED KAPOSI'S SARCOMA IN A REFERRAL HOSPITAL.

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DECLARATION

This thesis is my original work and has not been presented for a degree in any other University .

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This thesis has been submitted for examination with our approval as university supervisors.

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DEDICATION

I wish to dedicate this study to all health care workers who manage the cancer patients.

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ABREVIATIONS

A	Adriamycin
ACTG	AIDS Clinical Trials Group
AIDS	Acquired Immune-Deficiency Syndrome
ALP	Aspartate Amino Transferase
ALT	Alanine Amino Transferase
AP	Attending Physician
ART	Anti- Retroviral Therapy
ARV 's	Anti- Retro-Virals
AST	Aspartate Transaminase
CL	Chloride
CNS	Central nervous system
CVS	Cardio-vascular system
Creat.	Creatinine
ESR	Erythrocyte sedimentation rate
GIT	Gastro- Intestinal Tract
HAART	Highly Active Anti- Retroviral Therapy
Hb	Haemoglobin
HIV	Human Immuno- Deficiency Virus
K	Potassium

K.N.H	Kenyatta National Hospital
KS	Kaposi's sarcoma
KSHV	Kaposi's Sarcoma Herpes Virus
LDH	Lactate Dehydrogenase
LFT's	Liver Function Tests
LN	Lymph Nodes
Na	Sodium
OC	Oral Cavity
O.K	Sufficient
PI	Principal Investigator
PNS	Peripheral Nervous System
RT	Radiotherapy
S	Skin
TBC	Total Blood Count
U/E	Urea and Electrolyte
V	Viscera
V.B	Vincristine and Bleomycin
Vin	Vincristine
WBC	White Blood Cells

ABSTRACT

Kaposi's sarcoma (KS) is the most common malignant complication in patients suffering from human immune deficiency virus (HIV) infection. It was recognized in 1994, that the tumour was caused by infection with a human *gamma herpes virus* -8(HHV-8). HIV seropositive patients have a 73,000 fold greater chance of developing KS than HIV seronegative individuals. The tumour in HIV seropostive patients is more aggressive compared to HIV seronegative patients .The tumour involves the lymphoreticular system, often with visceral dissemination, poor prognosis and shortened survival, where as in non HIV setting ,the tumour is indolent and slow growing and patients live over 10 years even without treatment .

Management of AIDS-related KS is palliative and is aimed at controlling the progression of the disease, improving the patients quality of life and reducing disease relapse. However there is no standard management protocol available for the management of AIDS related KS .Therefore ,there was need to conduct this research to assess the outcome of drug management of patients with AIDS- related KS at Kenyatta National Hospital in order to compare the clinical outcome of the cytotoxic drug schedules and identify a suitable cost effective protocol among the drugs used at the hospital for the management of patients with AIDS -related KS.

The study was conducted between September and December of 2005 at the Hospital's Haematology and Radiotherapy Clinics and the Medical wards.

Approval of the study was granted by the ethics and research committee at Kenyatta National Hospital before the investigations were commenced.

Patients were enrolled into the study on the basis of the inclusion criteria and after undergoing a comprehensive consenting process.

During the study period a total of 95 patients with KS were on management at K.N.H. Out of these 74 patients were enrolled in the study .The sex distribution of the study population was 57% males and 43% females. Age ranged between 13 years to 55 years. The median age was 35.5 years and the mean age was 36.5 years. The following were the drugs/therapies used for the management of the patients ; Vincristine(Vin) , Bleomycin(B) , Doxorubicin(A) , Actinomycin –D (ACT-D) and Radiotherapy(RT).

The pattern of protocol distribution among the patients was as follows; Vin/B,44, Vin./B/A. 2 , Vin./A. 3, Vin.3, RT. 12,Vin./RT. 1, Vin./A./Actinimycin- D.(ACT.D) 2. Seven (7) patients were not on any specific treatment for KS .

The outcome of management was as follows; 54 patients were lost to follow up,29 males and 25 females, 15 patients survived,10 males and five (5) females and five(5) patients died , three(3)males and two (2)females.

The relationship between outcome and therapy administered was as follows :

Vin./B. 35 were lost to follow up, two (2) died and seven(7) survived, Vin./B./A. the only two(2) patients were lost to follow up, Vin./A all the three (3)were lost to follow up, Vin. One (1) was lost to follow up and two (2) survived ,RT. six(6) were lost to follow up , two(2) died and four(4)survived,Vin./RT the only one (1) patient was lost to follow ,Vin./A./ACT-D,one(1) died and the other one(1) was lost to follow up. Those patients not on KS treatment five (5) were lost to follow up and two(2) survived.

Test for association showed that there was no significant association between drug schedule($p=0.347$) and the outcome.

However comparing the cost and adverse effect profile of the therapeutic regimens , Vincristine was the cheapest and most tolerated by the patients Therefore Vincristine only regimen is suitable for the management of patients with AIDS- related KS in Kenyatta National Hospital.

CHAPTER ONE

1.0 INTRODUCTION

Kaposi's sarcoma(KS) is a multifocal proliferative neoplasm of the vascular and lymphatic endothelium. It is characterized by the development of morphological changes in the endothelium leading to the formation of spindle shaped cells, creation of vascular spaces between the endothelial cells and development of new blood vessel .Through the vascular spaces, blood leaks out of the capillaries and pools in the extracellular spaces . The pooled blood is noticed as a purple or pink lesion which is characteristic of Kaposi's sarcoma (Aboulafina , 1998).

There are four sub types of Kaposi's sarcoma with distinct characteristics.

The sub types are ;

Classic Kaposi's sarcoma : This type is found in elderly men over 70 years of Central Europe or Mediterranean descent . The tumour is slow growing usually confined to the skin of the feet . Patients survive between 15-20 years.

African endemic Kaposi's sarcoma : This type is found in Equatorial Africa .The tumour involves the lypmhoreticullar system with a predilection for young boys .It is more aggressive compared to the classic type and patients live up to eight (8) years with the disease .

Iatrogenic Kaposi's sarcoma: This type is found in patients on immunosuppressive treatment following solid organ transplant. It has been found that the tunour regresses on reduction of the immunosuppressive therapy (Mwanda *et al.* , 2002).

AIDS-related KS :In 1981, KS was one of the first conditions recognized as an opportunistic sequela of HIV infection and this type was named AIDS –related KS. This

type of KS is the most frequent type of KS compared to the other types KS and is the most common AIDS- related neoplasm .AIDS- related KS occurs frequently in all HIV transmission groups, in both male and female ,compared to the general population but at a high rate in homosexual men .

AIDS- related KS is more aggressive compared to the other types of KS. It involves the lymphoreticular system, the viscera, the oral cavity and the skin. The tumour in HIV infection is associated with poor prognosis and shortened survival (Mitsuyasu *et al* ., 1986).

The search for the factor responsible for the transmission or development of KS led, in 1994, to the discovery of Kaposi's sarcoma – associated herpes virus (KSHV) (Chang *et al.*, 1994). This virus is found in all forms of KS and infection with the virus appears necessary for KS to develop.

1.1.0 MANAGEMENT OF AIDS- RELATED KAPOSIS'S SARCOMA

Chemotherapy and radiotherapy have been used in the treatment of AIDS – related KS. Clinical outcome, is however dependent on ; the clinical condition of the patient at the institution of therapy, immune status, whether the patient is on antiretroviral therapy and the presence of other opportunistic infections such as tuberculosis (TB) and pneumocystis carinii pneumonia (PCP) which are poor prognostic factors (Krown *et al.*, 1998).

Studies have found that patients with CD4+ cells count greater than 400cells/mm^3,without other opportunistic infections and on Highly Active Antiretroviral Therapy (HAART) do better than those patients with poor prognostic factors and CD4+ cells count less than 150cells/ mm^3 without HAART (Krown ., 2004 a)..

There is however no standard protocol for the management of patients with AIDS-related KS since access to suitable tolerable drug therapy and availability of (HAART) is limited .

Therefore appropriate strategic planning is required before the initiation of therapy, in order to ensure that, patients are able to withstand the treatment, are likely to benefit from the treatment patients have the potential to afford the drugs and most importantly are willing to get the treatment.

In our local setting various obstacles have made management goals difficult toachieve. These obstacles include; lack of standard management protocol, inadequate medical services due to economic constrains, insufficient infrastructure and late diagnosis due to lack of early diagnosis at the primary health care facility .

There is need therefore to continue with research, to document ,analyze and rank therapies which are in current use and formulate suitable management protocol for patients managed at Kenyatta National Hospital

1.2.0 . OBJECTIVES

1.2.1. GENERAL OBJECTIVE

To assess the clinical outcome of Drug Management of patients with AIDS -related KS at Kenyatta National Hospital over 10-week period.

1.2.2. SPECIFIC OBJECTIVES

i) To assess and compare the cytotoxic schedules in use at Kenyatta National Hospital for treatment of patients with AIDS- related KS .

ii) To identify the drug schedule which yields the best clinical outcome so as to recommended it for use at Kenyatta National Hospital.

iii) To select a drug schedule that is tolerable and affordable to the patients

CHAPTER TWO

2.0. LITERATURE REVIEW

2.1.0 EPIDEMIOLOGY OF KAPOSI'S SARCOMA

Initially Kaposi's sarcoma as described by Moritz Kaposi in 1872, had a restricted epidemiological pattern. Most cases were elderly men of Mediterranean, Ashkenazi Jewish or central European descent. The tumor was mainly confined to the skin, especially on the lower extremities, and the disease pursued an indolent course, with cases typically surviving 15-20 years (Mwanda *et al* ., 2002).

By the 1960's, endemic KS was recognized in some parts of equatorial Africa and took four distinct forms; the nodular, akin to the classical form; florid ; exophytic and 'lymphadenopathic. The lympadenopathic form was particularly alarming since it had a predilection for children and was characterized by both extensive involvement of the lymphoreticular system, often with visceral dissemination, poor prognosis and relatively short survival. There was no evidence that the endemic disease was associated with immune deficiency of any sort, although for many years a transmissible agent was suspected to be involved in the pathogenesis of the tumour.

The emergence of KS in homosexual men in U.S.A, in 1981, signalled the beginning of the AIDS epidemic. The tumor in the HIV setting, commonly referred to as epidemic KS, resembled the lymphadenopathic form previously seen in Africa and is a frequent cause of morbidity and mortality (Ronald ., 1999).

2.1.1 ETIOLOGY OF KAPOSI'S SARCOMA

It was recognized by 1994 that infection with a gamma herpes virus which was named Kaposi's sarcoma herpes virus (KSHV) or human herpes virus- 8 caused the tumour (Chang *et al.*, 1994). It is now known that patients with underlying HIV-1 infection have a 73,000-fold greater estimated relative risk of developing KS than HIV-seronegative individuals, a difference which is strongly related to immune deficiency (Mwanda *et al.*, 2002).Detection of KSHV-8 DNA in the blood of homosexual men is predictive of subsequent KS development and the risk increases as the immune function declines as measured by CD4 cells counts and the duration of HIV infection (Krown *et a*l., 1989).

Other factors believed to be involved in the development of AIDS- related KS include altered expression and response of growth factors and cytokines, and modulation of KS growth by an HIV gene product, the Tat protein (Mwanda *et al* ., 2002). AIDS- related KS varies in its presentation from an indolent process with minimal clinical consequences to a disseminated, aggressive disease (Krown., 2004b).

2.1.2 NATURAL HISTORY OF AIDS- RELATED KS.

All forms of Kaposi's sarcoma are more common in men than women and are characterized by purple to pink lesions involving the skin or oral cavity. Visceral and nodal KS may precede cutaneous involvement and a definitive diagnosis is recommended to distinguish KS from other pigmented skin conditions.

Progression of KS usually follows an orderly fashion from a few localized lesions to generalized disseminated disease (Chang *et al.*, 1994).

With advances in the therapy of HIV infection and its neoplastic complications, the natural history of HIV infection is modified and overall patient survival is prolonged.

Although these advances have clearly been associated with a decreased incidence of KS and a better prognosis for patients with this tumour, it has also been shown that .Anti-Retroviral Therapy(ART) may enable some patients with KS to live longer and develop late KS-related complications, whereas others with HIV-infection may survive long enough to develop KS later in the course of their HIV- infection (Mwanda *et al* ., 2005). Studies show that in regions of the world where Highly Active Antiretroviral Therapy (HAART) is available, the incidence of KS is on the decline, suggesting, that , drug management has a positive impact on the management of patients with HIV and related opportunistic conditions (Gill *et al* ., 2002)

More recently, an analysis of data from a Multi-center AIDS Cohort study showed an 81% reduced risk of death in KS patients who receive effective HAART (Tam *et al* ., 2002). . Nevertheless, there is no known cure for HIV infection and no standard protocol available to guide physicians in the management of HIV-related neoplastic complications including KS. Therefore, the management HIV neoplastic complications such as KS is palliative and aims at improving the patients' quality of life and prolonging survival (Miles *et al*., 1994).

2.2.0 STAGING OF KAPOSI'S SARCOMA

Kaposi's sarcoma comprises of new blood vessels hence the pink or purplish colour, and presents with multiple irregular shaped lesions, of varying nodularity, which makes it difficult to accurately assess the size of the tumour. Since there is no clear primary lesion conventional oncology staging system cannot be applied effectively to KS (Khanlou *et al* ., 2000).

Various clinical and laboratory features of HIV- related KS are indicators of prognosis and have been used to develop KS staging systems (Ronald .,1999). A particular difficulty in evaluating prognosis is that, KS in HIV- infected individuals is a "disease within a disease", and it is not possible to identify and isolate tumour related complications, since some of the complications are common among the two diseases.

A four-stage classification system proposed by (Krigel *et al* .,1983) was based entirely on tumour extent and was designed to include AIDS –related KS as well as the non-HIV epidemic forms of the disease. A subsequent classification by (Krown *et al* .,1997) designed specifically for AIDS-related KS, categorized patients by extent of tumor and the presence or absence of systemic "B"- like symptoms and history of opportunistic infection(OI). Shaw and McLean , (1999), later proposed a classification that included the presence or absence of 'B'- like symptoms and opportunistic infections and the CD4+ cells count, but KS extent was not included as a staging variable.

Currently, the most widely used staging system is that proposed in 1988, by the Oncology Committee of the AIDS Clinical Trials Group (ACTG), (Krown *et al* ., 1997) This system takes tumour distribution, CD4+ cells count, HIV-related symptoms, and opportunistic complications into account, and separates patients into good and poor risk groups for each of these three variables. Subjecting this classification to prospective validation revealed that each of the three variables is significantly associated with survival. In multivariate analysis, however, and subsequent analysis suggests that a lower CD4+ cells count less than 150 cells/mm^3 is a better prognostic discriminant for survival than the originally proposed 200 cell/mm^3 cut off level. This analysis was

performed on patients treated prior to the introduction of effective ART, and its current relevance has not been tested (Mitsuyasu *et al.*, 1986).

2.3.0 COMPLICATIONS ASSOCIATED WITH AIDS-RELATED KAPOSI'S SARCOMA

AIDS- related Kaposi's sarcoma is associated with complications which contribute to high morbidity and mortality. Management of these complications is a great challenge since they are a contribution from two life threatening diseases. The complications include ; neurological derangements with accompanying psychotrauma, retinitis leading to blindness ,gastrointestinal disturbances such as loss of appetite ,nausea and vomiting, ulcerations, infections ,bleeding, anaemia, and oedema.

Management of the complications require use of multiple drugs which are costly and have associated toxicities which make patient adherence to treatment poor (Krown ,2004b).

2.4.0 MANAGEMENT OF CANCER

2.4.1 CHARACTERISTICS OF CANCER CELLS

Cancer cells arise from normal tissue-renewal stem cells and they have the following general characteristics :-

1. Proliferate in a dis-regulated manner and fail to differentiate normally.
2. Occupy space and crowd out normal cells.
3. Invade surrounding tissues and may cause hemorrhage
4. Metastasize or spread to secondary sites throughout the body.
5. Show alterations of cell surface components such as antigens, enzymes and

oncogenes. Some of these may be shed into the blood and are detectable by immunological techniques as tumor markers.

6. They have high metabolic rate and cause nutritional deficits and weight loss .

7. Cancer cells also decrease host defense mechanisms against infection.

2.4.2 THE CELL CYCLE

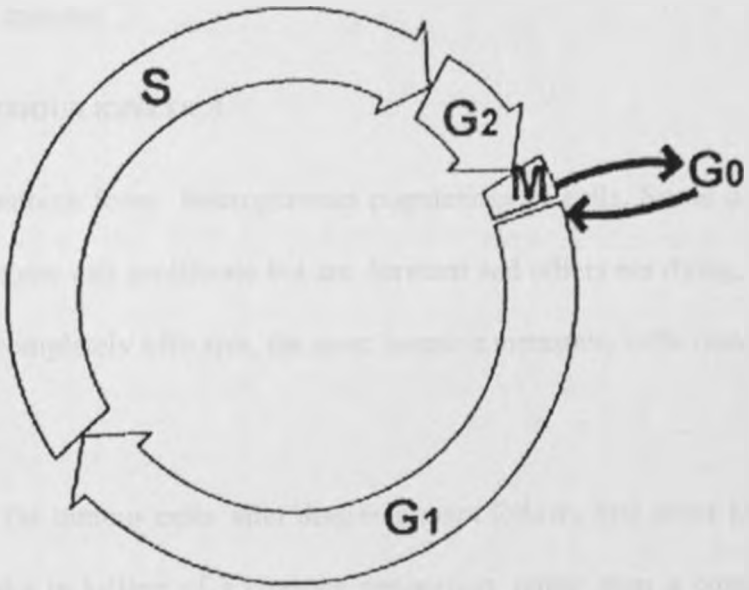
The cell cycle has five phases designated by letters and numbers as shown below.

G_0 = Resting stage

G_1 = RNA and protein synthesis

S = DNA synthesis

G_2 = Construction of mitotic apparatus



M = **Mitosis**

G_0 phase is a resting stage and the cells spend much of their lives in this phase. Depending on the type of cell, the phase can last for a few hours to a few years. When the

cell is signaled to reproduce by the cell's specific intrinsic characteristics, it moves into the G1 phase.

G_1 phase: in this phase, the cell makes proteins in preparation for cell division and the phase may last between 18 to 30 hours.

S phase: during the S phase ,the chromosomes containing the genetic code Deoxyreboneucleic acid (DNA) are copied so that both of the new cells formed will have the right amount of DNA. This phase lasts about 18 to 20 hours.

G_2 phase: The G2 phase is the phase just before the start of cell division and the phase lasts from 2 to 10 hours.

M phase is the mitosis phase and the cell splits into two daughter cells and the process lasts 30 to 60 minutes.

2.4.3 ANTI -TUMOUR KINETICS

Malignant tumours form heterogeneous populations of cells. Some of these cells are proliferating, some can proliferate but are dormant and others are dying. For any tumor therapy to be completely effective, the most invasive metastatic cells must be killed(Gale *et al*., 1991).

The killing of the tumour cells after drug treatment follows first order kinetics and each treatment results in killing of a constant proportion, rather than a constant number of tumour cells. After initial treatment, the rate of cell kill may change because the growth fraction and mass doubling time change as the tumour mass decreases from a large, bulky tumor to a smaller tumour .

Since the residual cells are likely to be less sensitive to the drug or are present in sites where the drug does not penetrate so well, treatment should continue even in the face of clinical remission until the tumor is totally eradicated. Cure is considered achieved when the disease-free survival plateau is reached and remission is continued for over12months

2.4.4 METHODS OF CANCER MANAGEMENT

The common methods applied in cancer management include ; Surgery ,Radiotherapy and Chemotherapy. Other methods include , immunotherapy, bone marrow transplant and gene therapy . Surgery and radiotherapy are mainly used in localized cancers while chemotherapy is used in both localized and disseminated cancers. Chemotherapy is the commonest method applied in the management of AIDS- related Kaposi's sarcoma and is often used in combination with other types of therapy(Crist *et al.*,1988) .The aim of cancer management is to remove all the abnormal cells from the body and restoring normal processes of cellular differentiation and growth (Gale *et a*l., 1991).

2.4.5. DETERMINANTS OF DRUG RESPONSE

1. **Growth fraction:-** this is the proportion of dividing cells in a tumor or normal tissue. It is the fraction of cells which are actively dividing with respect to the entire population of viable cells, the proportion of cells which are likely to suffer injury from chemotherapy and radiotherapy .

2. **Mass doubling:-** the time taken for the tumor to double in size.

As the tumour gets larger, the mass doubling time increases and the growth fraction decreases. Tumours with a high growth fraction are more susceptible to the cytotoxic effects of anticancer drugs unlike those with a high percentage of dormant cells. Unfortunately, normal tissues with high growth fractions such as the bone marrow, oral

and intestinal mucosa and hair follicles are also damaged by the anticancer drugs. Treatment with most of these drugs produces bone marrow depression leading to leukocytopenia and infection, thrombocytopenia and bleeding. In the gastrointestinal mucosa they cause stomatitis and gastrointestinal tract ulceration, while on the skin they cause reversible loss of hair.

3. **Total tumor burden** :- bulky tumours are perfused poorly and drug delivery to the tumour is limited. However the drug may reach the tumour but in insufficient amounts to kill the cells. Bulky tumours have dormant non-proliferative cells which are not responsive to treatment and can survive and re-establish the tumor mass after treatment period is over.

4. **Host factors:**-treatment outcome has been shown to differ among patients of the same age and with the same stage of the disease under similar management approach due to intrinsic differences within the hosts .

2.4.6 MECHANISMS OF ACTION OF ANTI- CANCER DRUGS

The main classes of anticancer drugs are as follows .

i) Alkylating agents(e.g) Cyclophosphamide

ii) Anti-metabolites (e.g) Methotrexate

iii) Plant -derived agents (eg) Vincristine

iv) Platinols (e.g) Cisplatinum

v) Glucocorticoids (e.g) Predinsone

vi) Cytotoxic Antibiotics (e.g) Doxorubicin

vii) Hormone antagonists (eg) Tamoxifen

viii) Biological products (eg) Monoclonal antibodies and Interferons

Anticancer drugs are either cytotoxic or cytostatic and exhibit maximum activity on actively dividing cells, both malignant and normal . The drugs display little or no activity at all on cells in the resting phase,(Ronald., 1999).Due to lack of selectivity, the drugs cause adverse effects on normal tissues in areas of high cellular turnover such as the bone marrow, the gastrointestinal tract, the skin and gonads.

Further, the drugs can be divided into Cell Cycle Specific (CCS) and Cell Cycle Non Specific(CCNS).Cell cycle specific drugs target the dividing cells in specific phases of cell division, while cell cycle nonspecific target cells at several phases of cell division.

The Alkylating agents such as Cyclophosphamide are non-specific in action while the Platinols , Anthracyclines, Vinca alkaloids and Anti-metabolites are cell cycle specific.

In order to ensure that all phases of the malignant cell cycle are inhibited by the drugs, combination chemotherapy is used. However ,the combined treatment is often associated with increased toxicities.

2.4.7 COMBINATION CHEMOTHERAPY AND DRUG RESISTANCE

Use of combinations of drugs in cancer chemotherapy has been one of the major advances made in cancer management. Combination chemotherapy has several important advantages such as decreased incidence of resistance, decreased overall toxicity or at least decreased toxicity to any one organ system and increased efficacy.

There are three accepted guidelines for choosing drugs for combination chemotherapy. The guidelines include :- selection of drugs which , are active against the tumor when used alone, have different mechanisms of action to avoid combined resistance, and have minimally overlapping toxicities (Gale et al., 1991).

2.4.8 MECHANISMS OF DRUG RESISTANCE

Drug resistance is one of the most important problems in cancer chemotherapy. As many as 40-45% of cancers may have intrinsic resistance or may develop resistance to anticancer drugs during treatment (Xiu et al.,1999). There are several different biochemical mechanisms by which tumor cells develop resistance to anticancer drugs.

These include:

1. Decreased intracellular drug levels. This could result from increased drug efflux or decreased inward transport. Among the drugs which become resistant by this mechanism are the anthracyclines, dactinomycin, vinca alkaloids, and epidopodophyllotoxins.
2. Increased drug inactivation. Included in this group are the alkylating agents, anti-metabolites and Bleomycin.
3. Decreased conversion of drug to an active form. This mechanism is most common among the anti- metabolites which must be converted to the nucleotide before they are active.
4. Altered amount of target enzyme or receptor .
5. Decreased affinity of target enzyme or receptor for drug.

6. Enhanced repair of the drug-induced defect.

7. Decreased activity of an enzyme required for the killing effect (e.g.)

(topoisomerase II) . This is a newly recognized target but decreased activity is important for resistance to doxorubicin.

8. Presence of Multi-drug Resistance (MDR) gene . This is a phenomenon whereby tumours become resistant to several, often unrelated drugs, simultaneously. The multi-drug Resistance gene encodes an ATP-dependent efflux pump, called p-glycoprotein, that may become amplified in drug-resistant tumors. MDR activity may be reversed by drugs such as cyclosporin, tamoxifen and calcium channel blockers like verapamil.

Multidrug resistance occurs between several different structurally unrelated antitumor agents which apparently have different mechanisms of action. This resistance is obtained through stepwise selection and it reflects the amplification of a gene that encodes a trans-membrane protein that pumps the drugs out of the cell. Thus the resistant cell maintains a lower intracellular drug level than the drug-sensitive parental cells . Xiu et al., 1999 discovered that cell lines with a high level of resistance produced large amounts of a 170,000 dalton glycoprotein which they called P170 or P-glycoprotein. It is now clear that P170 is overproduced as a result of gene amplification. The degree of P-glycoprotein overproduction correlates well with the degree of drug resistance as seen in vinca alkaloids.

2.4.9 .ADVERSE EFFECTS OF ANTICANCER DRUGS

Most of the anticancer drugs act by inhibiting DNA synthesis with some exceptions of L-asparaginase which affect protein synthesis .

Anticancer agents exhibit a greater toxicity for tissues with high growth fractions such as the bone marrow, gastrointestinal epithelium, hair follicles, and the gonads. These adverse effects may manifest as , pancytopenia, nausea and vomiting, and alopecia depending on the tissues affected .

The adverse effects interfere with patient's adherence to treatment, their quality of life and can lead to faster patient deterioration and death.

2.5.0 MANAGEMENT OF AIDS- RELATED KAPOSI'S SARCOMA

The use of chemotherapy is the main method employed in the management of Kaposi's sarcoma in HIV infection. Radiotherapy is used occasionally for management of localized skin lesion, while the use of surgery is limited and is used to improve cosmesis and general patient out- look, especially, where the tumours hang outside the body.

Management requires an individualized approach based on the extent and location of lesions, the presence of tumour- related symptoms, the degree of immunosuppression ,the patients ability to adhere to treatment, and the goal of the treatment.

Patients with wide spread disease with visceral involvement require prompt cytoreductive treatment ,usually with one or more chemotherapeutic agents. Aggressive treatment is not mandatory for patients with asymptomatic indolent lesions. Such patients would benefit from investigational therapies that are directed towards interrupting the pathogenesis of Kaposi's sarcoma or restoring immune competence (Ronald .,1999).

Local treatment for KS is appropriate for the patients with indolent mucocutaneous disease without visceral involvement , but recurrence of lesions mandates systemic therapy. The use of highly active antiretroviral therapy has been shown to cause spontaneous regression of KS lesions but the regression is usually incomplete and temporary (Krown,2004b). Thus, it is important to combine specific treatment for Kaposi's sarcoma with the antiretroviral therapy for maximum therapeutic benefit.

2.5.1 ANTI- CANCER AGENTS USED IN THE MANAGEMENT OF AIDS –RELATED KS .

The main anticancer agents used for the management of AIDS-related KS include :- Actinomycin-D, Bleomycin, Doxorubicin and Vincristine.

2.5.2 . ACTINOMYCIN –D

Actinomycin -D is a peptide antibiotic with anti-tumour properties and is produced by the fungus *Streptomyces parvulus* which produces over 95% of Actinomycin - D. The other *Streptomyces* species produce a mixture of related compounds.

Actinomycin- D has a chemical structure similar to anthracyclines, and consists of a planar ,multiring, phenoxazone moiety with two substituents. The planar nature of Actinomycin- D allows it to intercalate between DNA base pairs while the poly-peptide arms lie within the minor complementary strands of DNA, preventing the synthesis of the corresponding RNA molecules.

Actinomycin-D inhibits mainly DNA-directed RNA synthesis at low concentrations ,whereas at high concentrations, both RNA transcription and DNA replication are affected (McGarvey, *et al* ,1998) .

The drug is used in the management of various sarcomas, such as Kaposi's sarcoma, Wilms tumour and Choriocarcinoma.

Actinomycin- D is given intravenously and in combination with other cytotoxic drugs. Dosages vary with the clinical condition of the patient and the type of cancer .

In Kaposi's sarcoma, the dose is 15 mg/kg body weight for 5 days every 3 weeks.

Actinomycin- D diffuses freely into the cells and distributes rapidly into the peripheral tissues on administration. The drug has an elimination half life of 36 hours ,mainly due to slow release from tissues and DNA -binding sites. Actinomycin- D is not significantly metabolized and is excreted in unchanged form into the bile and urine.

The dose limiting toxicity of Actinomycin-D is primarily myelosuppression, although, nausea, vomiting, mucositis and diarrhoea are common. A dose reduction is recommended in patients with liver diseases. Actinomycin-D causes radiation recall due to inhibition of the DNA repair mechanism and care should be taken when administering the drug to patients on radiotherapy or to those who have been exposed recently to radiation.The skin and the gastrointestinal tract are the systems prone to this effect and patients get skin rash with hyper- pigmentation and mucositis (Bosl *et al* ., 1988).

2.5.3. BLEOMYCIN

Bleomycim is a mixture of fungal polypeptides isolated from *Streptomyces verticullus.* Like the anthracyclines, Bleomycin chelates iron and forms an activated complex, which then binds the guanine bases in the DNA .The DNA –bleomycin –iron complex then catalyzes the reduction of molecular oxygen to form highly active free radical species, that cause DNA strand scission in the linker regions between nucleosomes. Thus bleomycin causes DNA strand cleavage and the actual chromosomal breakage which can be visualized microscopically (Verwiij *et al.*, 1991).

Bleomycin is a phase- specific agent, which is most active in mitosis and G2 phases of the cell cycle and is used in the management of Hodgkin's disease, head and neck cancers and a variety of sarcomas including Kaposis's sarcoma.

Bleomycin is mainly administered by the intravenous route and it is also administered by intracavitary instillation for sclerosis of the pleural and peritoneal cavities.

A sensitivity test dose of 1-2 units of bleomycin is recommended two to four hours before the actual therapy and the necessary equipment and medication should always be available at each administration in case of an anaphylactic reaction. Some clinicians recommend pre-medication with acetaminophen ,steroids, and diphenhydramine to reduce fever and risk of anaphylaxis.

The dose varies with the condition being treated, but a dose of 15U/ m^2 is given as a continuous infusion or as a bolus .In Kaposi's sarcoma, the dose is 15U/ m^2 every two weeks in combination with other cytotoxic drugs such as vincristine. Cumulative dose of 250-450 U should not be exceeded and lower doses are recommended for patients with renal impairment (Waid –Johns and Coursin., 1991).

Up to 45% of the drug is absorbed into systemic circulation following intracavitary administration and protein binding is less than 1%.

The drug is metabolized through degradative pathways by aminohydrolases which are abundant in the liver and the enzyme activity is also high .The aminohydrolase activity in the bone marrow ,lymph nodes,lungs and skin is low and lung fibrosis is the dose limiting toxicity. The patients on Bleomycin are advised not to smoke.

Upto 70% of the administered drug is excreted through the kidneys. Excretion decreases with decrease in creatinine clearance and dose reduction is recommended in patients with renal malfunction. (Smith *et al.*, 1991).

2.5.4. DOXORUBICIN

Doxorubicin belongs to anthracycline group of compounds which comprise of a series of large multiring structures attached to a daunosamine sugar. The planar semiquinone ring facilitates intercalation into DNA which is a key reaction because incorporation of the anthracycline creates local conditions critical to its cytotoxicity.

Doxorubicin is used against non-haematologic tumours and interferes with DNA topoisomerase- 11 leading to stabilization of topoisomerase- DNA complex in the cleaved configuration. This leads to breakage of single stands , creates further breakage of DNA double strands (Smith, *et al.*, 1991).

The doxorubicin, in the body creates free radicals, which are cytotoxic to both normal and malignant cells. The drug is also very reactive against heavy metal ions like iron in the body and forms chelates and complexes. The drug-ion complex binds on cell membranes and causes oxidative cell damage. Most systems in the body are capable of protecting themselves against these oxidative insults, except the cardiac muscle ,which is deficient in this defense mechanism. It is therefore very vulnerable to doxorubicin and other anthracycline injuries (Conant , *et al* ,1997).

Doxorubicin is used in the management of various sarcomas like Kaposi's sarcoma , Osteogenic sarcoma and Ewing's sarcoma.

The drug is usually given intravenously as an infusion or bolus and the dose varies with the type of tumour. The dose used in most cancers and Kaposi's sarcoma is 60-75

mg/m^2 every 21 days. However , in patients with previous chest radiation a maximum accumulated dose of 550 mg / m^2 should not be exceeded.

Following intravenous injection, the drug is distributed rapidly in the peripheral tissues depending on the content of DNA in the peripheral tissues.

The drug is concentrated and metabolized in the liver and excreted in the bile. The dose of doxorubicin should be reduced in abnormal liver function especially in elevated bilirubin levels.

Toxicity of the drug varies with the route of administration and the dose given. When the drug is given as a bolus ,cardiac toxicity characterized by acute pericarditis-myocarditis and chronic heart failure predominates, but when the drug is given as a continuous infusion over several days, myelosuppression ,mucositis and alopecia predominates (Shapiro *et al* .,1990).

2.5.5. VINCRISTINE

Vincristine is an alkaloid extracted from *Vinca rosea lynn.* Vincristine and the related compound vinblastine are the most widely used plant- derived chemotherapeutic agents. These alkaloids were initially tested for their hypoglycemic potential, but were found to cause bone marrow suppression in rats. This finding led to the systematic extraction of vincristine and vinblastine for use as anticancer agents (Schiff *et al.*, 1997).

The drugs are highly hydrophobic and they bind lipid molecules at the cell membranes leading to cellular disruption. The two drugs also arrest mitosis in the metaphase by reversibly binding to tubulin ,the structural proteins which are an integral part of eukaryotic cells and are the major components of mitotic spindle, thus interfering with microtubule assembly.

Vincristine is used in the management of various cancers including Kaposi's sarcoma, renal cell carcinoma, lymphomas and testicular cancer. The dose varies with the type of tumour being managed.

In Kaposis's sarcoma, vincristine is given as a single agent ,at a dose of $2mg/m^2$ weekly for six weeks or in combination with other cytototoxic drugs such as bleomycin at a dose of vincristine 2 mg/ m^2 and bleomycin 15 IU every two weeks for six courses. Sensory motor neuropathy is the dose limiting toxicity , manifesting as neuropathy and paresthesias in the toes, fingers and loss of ankle jerk reflexes .Most of these toxicities are reversible and they clear within a few days or weeks after administration is discontinued .

However, foot and wrist drop are late manifestations of toxicity and are not reversible. The other adverse effects which are common and reversible include loss of hair, endocrine and hematological changes. (Kirkwood *et al.*, 2004).

The pharmacokinetics of the vinca alkaloids depends on the route of administration. When the agents are given intravenously as a bolus, the agents exhibit tri-phasic pattern of plasma clearance, with a terminal half- life of approximately 24 hours.

Vincristine administered is distributed rapidly in the tissues and platelets which leads to initial rapid clearance from circulation. The drug is then released slowly from these sites ,leading to the prolonged terminal phase.

The drug is metabolized actively in the liver ,and is excreted through the bile. Meaning that a dose reduction of 50% is recommended in patients with liver failure . Administration of vincristine by continuous intravenous infusion leads to higher steady state concentrations than those achieved by bolus therapy.

Prolonged usage of vinca alkaloids has been shown to lead to resistance to other related products (Kirkwood *et al.*, 2004). The membrane protein , p-glycoprotein, is thought to be responsible for the mechanism of resistance. P-glycoprotein is found in high concentrations in the drug resistant cells and is thought to function as a membrane pump that actively extrudes chemotherapeutic drugs from the interior of the cell by energy ATP- dependent mechanism, leading to decreased intracellular drug concentrations (Cabral, *et al,* 1986*).*

2.5.6 OTHER THERAPEUTIC MEASURES

Patients with minimal indolent disease are better managed using other therapeutic measures such as Cryotherapy, topical 9-cis- retinoic acid, Paclitaxel, Vinblstine , intra lesional cytotoxics and radiotherapy. Liposomal formulation of the conventional cytotoxic drugs like doxorubicin have been found to have better pharmacokinetic profile and to yield better results ,but they are too costly for use in third world countries like Kenya The approximate cost of these drugs in Kenya according to the international market would be as follows: Liposomal Doxorubicin Ksh.1,100,000.00 ,Intralesional Vinblastine Ksh.300,000.00,Paclitaxel Ksh.109,200.00 , Interferon alpha Ksh 500,000.00(Ronald, 1999).

2.6 .0 ADVERSE EFFECTS ASSOCIATED WITH KAPOSI'S SARCOMA THERAPY

Multiple organ toxicities occur frequently following the use of chemotherapy and radiotherapy . Some of the adverse effects are given below.

Product/therapy	Common adverse effects
Doxorubicin	Bone marrow suppression
	Alopecia

Bleomycin	Lung fibrosis
Vincristine	Peripheral neuropathy
Actinomycin- D	Bone marrow suppression
Thalidomide	Fetal malformation
Radiotherapy	Bone marrow suppression, skin rash, local pain and ulceration

These adverse effects have similar symptoms like those presented by the HIV infection and Kaposi's sarcoma and this makes it difficult to differentiate the origin of the symptoms and can easily mask the disease progression. Therefore, care should be taken when choosing the drugs and the physician should aim at maximizing the treatment benefit for the patient and minimizing the level of toxicity .

2.7.0 IMPLICATIONS FOR THE DESIGN OF THERAPEUTIC TRIALS IN PATIENTS WITH ADVANCED SYMPTOMATIC KAPOSI'S SARCOMA.

The incidence of AIDS –related KS has declined sharply since the introduction of highly active antiretroviral therapy. The HAART has been associated with lengthening of time to treatment failure and longer survival among patients with pulmonary KS who have received chemotherapy (Bower *et al.*, 1999).

The responsible mechanisms are not well understood but restored immunity to the KS associated herpes virus, decreased levels of angiogenic factors which stimulate KS proliferation, and direct anti-angiogenesis inhibitory effects of HIV– 1 protease inhibitors could all be involved (Murphy *et al* .,1997).A study to demonstrate the clinical benefit of pegylated liposomal doxorubicin in patients with advanced AIDS – related KS and one

or more specific tumour – related symptoms, indicated that , 48 patients out of 60 showed clinical benefit (Dupin *et al* .,1999).

In 11 prospective studies, where 156 patients with AIDS-related KS were on HAART therapy, 102 (65%) had good risk [TO] and 54 (35%) had poor risk. Time to response was given with median times ranging from 3 to 9 months .One study by Tavio showed that the median time to response was significantly shorter (p=0.003) for patients not receiving chemotherapy at baseline (123 days) than those with more advanced KS receiving chemotherapy (314.5 days) (Tavio *et al*., 1998)

In one of the studies , the authors remarked that, patients whose KS responded, "tended to have less severe disease at baseline than did those who had progressive disease" and documented only one partial response among eight patients who received concomitant KS therapy. One of the eight patients who received concomitant radiation therapy to cutaneous KS lesions, died from rapidly progressive pulmonary KS (before chemotherapy could be instituted) (Miles *et al* ., 1994).

Although the eventual response rate was high, responses occurred slowly among patients who had KS of sufficient severity to warrant systemic chemotherapy and up to date there is insufficient data on which to base conclusions about the activity of HAART in patients with advanced. symptomatic disease. In most prospective studies, patients with advanced KS received chemotherapy either from the outset of HAART or had it added after KS failed to respond to HAART alone, the lesions of such patients regressed less often, and more slowly, than the lesions of patients with severe KS who received only HAART. Once KS regression was achieved with a combination of HAART and

systemic KS therapy, however, chemotherapy could often be withdrawn (Paparizos *et al* ., 2002).

Vaccher *et al* ., 1999, described a stage I KS which progressed during initial HAART therapy despite suppression of HIV viraemia and increasing CD4+ cells counts. Chemotherapy was then added and the patient achieved partial response. On discontinuation of chemotherapy, residual KS lesions regressed completely when the patient received HAART alone during the next 5 months. Thus, although HAART is an important component of treatment for all patients with KS, there is no sufficient evidence to indicate that HAART induces regression of advanced symptomatic KS without concomitant KS therapy, and neither any of the studies addressed clinical benefit nor provided enough data to guide clinical practice or study designs in which KS therapy is withheld from symptomatic patients while awaiting response to HAART.

This presents a challenge in designing clinical studies to assess the benefits of chemotherapy and concurrent initiation of HAART and KS therapy may make it more difficult to determine the individual contribution of HAART to KS – response.

CHAPTER THREE

3.0. MATERIALS AND METHODS

3.1.0. . STUDY AREA AND SITE

The study was conducted at Kenyatta National Hospital in the Haematology and Radiotherapy clinics for the out-patients and the Medical Wards for the in-patients.

3.2. 0 STUDY DESIGN

This was a prospective, observational , cross-sectional period prevalence study on patients with Kaposi's sarcoma. The subjects were both male and female patients of any age with histologically proven Kaposi's sarcoma on treatment at KN.H

3.3. 0. STUDY POPULATION

The study population consisted of 74 patients with histologically proven Kaposi's Sarcoma, on management at K.N.H.who agreed to participate in this study .

3.4.0 . SUBJECT SELECTION

3.4. 1. INCLUSION CRITERIA

Male and female subjects of any age with biopsy proven Kaposi's sarcoma who consented to be in the study were enrolled .

3.4.2. EXCLUSION CRITERIA

Patients excluded were those who did not give consent to participate in the study

3.5.0. SAMPLE SIZE

The sample size was determined based on the number of patients seen weekly in the clinics and wards. This was because there was no observational time prevalence study on AIDS- related Kaposi's sarcoma that had been done at K.N.H. before . On average, five to six patients were seen in the out-patient clinic per week and about one patient was admitted every month .

A total of 95 patients with AIDS-Related KS were followed up at Kenyatta National Hospital between September and December 2005 and 74(78%) patients were enrolled in the study. Those enrolled were 42 (57%) males and 32 (43%) females .The patients' age ranged from 13 years to 55 years. The median age was 35.5 years and the mean was 36.5years. The patients recruited were, from Haematology clinic, 55(74.0%) , Radiotherapy clinic 13(18.0%) and Medical wards 6 (8.0%).

3.6.0. SUBJECT RECRUITMENT

The attending physician (AP) diagnosed and decided on the treatment for each patient as patients attended the clinics and when they were admitted in the wards.

The management protocols used during the period of study were as follows;

i) Single drug protocol -Vincristine only.

ii) Two drug protocol -Vincristine/Bleomycin

iii) Multiple drug protocol -Vincristine/Doxorubicin/ Bleomycin.

or

- Vincristine/Actinomycin–D./ Doxorubicin

iv) Radiotherapy + Vincristine

v) No specific KS therapy administered

vi) Radiotherapy only

Patients with Kaposi's sarcoma were thereafter identified with help of the nursing staff. After the attending physician finished attending to the patient, the researcher introduced herself and invited the patient to a side room for an interview. In the side room , the researcher introduced the purpose of the study to the patient, which was to assess the outcome of drug management of patients with AIDS-related Kaposi's sarcoma

in Kenyatta National Hospital over a 10 –week period, with the aim of defining suitable management protocol which would be effective ,affordable and manageable at Kenyatta National Hospital . After the introduction, the researcher described the study requirements to the patient guided by Forms A and B in Appendix I and II respectively. The researcher then gave the patient the informed consent form to read in the waiting area while she talked to the other patients with Kaposi's sarcoma. For those patients in the wards, the researcher introduced herself after the ward round at the patient's bed side .

Those patients who agreed to be in the study, signed the informed consent form and returned a copy to the researcher. Those who could not sign the form, gave verbal consent in the presence of their guardians and the word 'verbal consent' was entered in the consent form in the place of the signature. Patients were allowed to seek clarification on anything which was not clear about the study, and they were further informed that their participation in the study was entirely voluntary and that they were free to withdraw from the study any time they needed to. Those who did not agree to be in the study, returned their forms and were assured that, they will continue to get their treatment as scheduled.

3.7.0 SUBJECT ENROLLMENT

Each consenting subject was enrolled in the study and was given study serial number . The serial number, the patients hospital number and their initials were entered in the data collection sheet, in Form A.

For ease of identification, the patients medical file was marked with a plus(+) sign at the left- bottom corner. Eligible participants continued to be selected consecutively for the period between September and December 2005.

The subjects were followed up for a period of 10 weeks from the time they enrolled. The patients met the researcher when they came to the clinic or when in the wards after a major ward round.

The attending physician decided on the choice of the management protocol, the clinic appointments, and the investigations to be done on each patient. The study did not require any extra consultation or tests from the patient but relied upon the findings and recommendations from the attending physician. This meant that, patients took care of their bills as required by the hospital.

Participation in the study was voluntary and failure to participate did not interfere with the patient's management in the hospital .

3.8.0. DATA COLLECTION AND DOCUMENTATION

The baseline observations were noted and documented in the investigations check list in Forms A and B before the first treatment was administered. Documentation continued for a period of 10 weeks for each patient during their attendance to the clinics or during their stay in the wards.

The following information was documented for each patient according to the format in the Forms A and B (Appendix I and II)

i) Name, age, and continuous residence in the last six months.

ii) Past surgical history, part of the body, reason for the operation when the

operation was done and outcome of surgery .

iii) Past medical history, diagnosis, drugs given, when they were given, duration of treatment, and outcome of treatment.

iv) Past hospital admission, the reason for the admission, duration of admission ,

v) clinical management offered and outcome of management.

vi) Presenting chief complaint, and for how long had the problem persisted.

The patients were further informed that, the following information would be documented from their medical files every time they came to the clinic and after every ward round for those in the wards during the study.

i) Treatment protocol prescribed .

ii) The site of the site

iii) Date of first treatment and date of last treatment according to protocol or date of last treatment in the 10- weeks ,whichever came first.

iv) Changes noted at the tumour site such as - color size ,ulceration and any other sign.

v) The effects of treatment on the lesion and on the main body systems gastro-intestinal tract(GIT),cardiovascular system(CVS), central nervous system(CNS),respiratory and musculoskeletal systems, eyes, face, oral cavity, weight changes, night sweats, oedema, and any other presenting symptom during the study period.

vi) The total number of protocol drugs administered during the 10 weeks, any other drugs administered, and protocol drugs missed.

vii) Hospital admission(s) during the study period ,reason for admission, drugs administered and outcome.

viii) Presence of paleness, jaundice, oedema, weight-loss, pain ,state of lymph nodes.

ix) Temperature, pulse rate, respiration rate, blood pressure.

x) The clinical impression drawn by the attending physician from the investigations.

Patients were also informed that, the following information would be solicited from them when in the clinics or in the wards .

i) If the subject slept well, had headaches, confusion or was irritable.

ii) If patient coughed, or had difficulties in breathing or chest pain.

iii) If patient had any problems while eating ,any pain in the stomach, the state of his appetite.

iv) If patient had had any bleeding episodes, if yes, from which part of the body, how frequent and for how long,

v) If patient had any swelling in any part of the body .

vi) Result of laboratory investigations such .

a) Liver function tests : Aspertate transaminase (AST), Lactate dehydrogenase (LDH), Alanine transaminase(ALP), Total and free Bilirubin .

b) Total blood counts (TBC) and their differentials,

c) Platelet counts

d) Erythrocyte sedimentation rate(ESR)

e) Urea and electrolyte(U/E),(K+, Na+, CL-, Urea, Creatinine)

f) Uric acid levels

g) Blood in stool

h) Chest X-Ray and abdominal Ultra- sound,

vii) Any other test result relevant to the study and clinical outcome over the 10 weeks, if known.

3.9.0. VARIABLES DOCUMENTED

Independent variable such age, sex and residence were documented for each patient when they enrolled in the study and tumour dependent variables such as anatomic site, stage of the disease complications, infections at the tumour site , cytotoxic treatment schedules, other drugs administered and hospital admission were also documented.

3.9.1 OUTCOME AFTER 10 WEEKS OF FOLLOW -UP

i) Stage of disease

ii) Remission status

a) Complete remission with complete disappearance of lesions

b) Partial remission with 50 % reduction in size of lesions

c) Stable disease with no noticeable change in size

d) Progressive disease with 50 % increase in size

iii) Protocol drugs administered

iv) Protocol drugs missed

v) Other drugs administered

vi) Hospital admissions

vii) Survived ,Died or got Lost to follow -up .

3.10.0 DATA COLLECTING INSTRUMENTS

The patient's information was recorded by indelible ink directly in the Forms A and B during the patient's visit to the clinic and after ward round .This information was screened and transferred into a computer, where ,the data was protected by a pass word to ensure confidentiality. The collection of data for each patient continued from the time of recruitment up to 10 weeks or until the patient got lost to follow- up or died , which ever happened first.

3.10.1. DATA ANALYSIS AND PRESENTATION

Data was analyzed using the Instat Biostatistics Programme which was available from the Department of Public Health Pharmacology and Toxicology ,University of Nairobi.

The study outcome was compared against the following dependent and independent variables.

i)sex

ii)age

ii)Site of the tumour

iii)Stage of the tumour

iv)Complications associated with the tumour

v)Infections associated with the tumour

vi)Hospital admissions

vii)Remission status in 3 weeks

viii)Cytotoxic drugs given

ix)Other drugs given

x)Remission status in 10 weeks

The results are presented inform of tables as shown in the results section 4.0

The response measures included :

1) Remission status

   (i) Complete remission with complete disappearance of lesions .

   (ii) Partial remission, characterized by, 50% reduction in size of lesion.

   (iii) Stable disease, where by , no noticeable change in the lesions.

   (iv) Progressive disease, with a 50% increase in size of lesion and spread to other organs.

2) Use of other supportive measures such as antibiotics, analgesics , anti-emetics and blood transfusion, etc.

3) Hospital admissions and duration of stay

4) Effect of treatment on the other body systems

5) Quality of life

6) Survival

7) Death

8) Got lost to follow-up

CHAPTER FOUR

4.0 RESULTS

Seventy four (74) patients were followed up during the study period. Forty two(42)males and 32 females ,age range between 13years to 55years .Fifty four (54) patients were lost to follow up , five (5) died before the study period was over, and 15 survived to the end of the 10 week follow up period .

Forty nine (49) patients came from Nairobi province (urban) and the rest 25 came from the other provinces in the country .However ,there were no cases from North eastern and Coast provinces or outside the country.

4.1.0 PATIENT CHARACTERISTICS

4.1.1 ANATOMIC SITE OF KAPOSI'S SARCOMA LESIONS

The study subjects had multiple lesions in various parts of the body (Table 1).

Table 1: Distribution of Kaposi's sarcoma lesions among the study subjects and outcome of management within 10 weeks .

Tumour site	Outcome of management			
	Died	Survived	Lost to follow up/withdrawal	Number of cases
Lymph nodes (LN)	0	2	11	13
Lymph nodes/skin (LN/S)	2	7	10	19
Oral cavity (OC)	1	2	8	11
Oral cavity/skin(OC/S)	1	0	2	3
OC, S /Viscera (V)	0	0	2	2
Oral cavity / Viscera(OC/V)	0	0	2	2
Skin (S)	0	1	13	14
Viscera(V)	1	2	5	8
Viscera / Skin(V/S)	0	1	1	2
Total	5	15	54	74

The p-value (0.628) suggests that there was no association between the anatomic site of the tumour and the outcome of management over 10weeks

4.1.2 ASSOCIATED ILLNESSES

A total of 69 patients had advanced disease with various complications which were also due to the HIV infection. These complications included bleeding, ulceration, oedema, pain , skin discoloration, and gastrointestinal tract symptoms such as diarrhoea and vomiting. Five (5) patients had previously sought specific treatment for the tumour, 40 patients had waited for the symptoms to disappear on their own, while 15 patients associated the symptoms with the other drugs they took .Ten patients had tried herbal medicines which did not help them and four (4) patients had had surgical excision of the tumours on the feet and toes.

4.1.3 LABORATORY FINDINGS

Twenty (20) patients, did total blood count test, of whom 15 patients had low total blood counts and five(5) patients had counts within the normal range. Eighteen patients did only one test during the study period and two patients did serial tests of whom one did three tests, whose parameters remained within the normal range while the other one did four tests and the parameters were decreased with time (Appendix IV).

Among the 20 patients who did their total blood counts, nine had their liver function tests determined , six of them had elevated enzyme levels and three had normal enzyme levels. Four patients out of the 20 patients had their urea and electrolyte parameters determined, three of them had normal parameters while one had abnormal parameters (Appendix IV).

4.2.0 INTERVENTION MEASURES

Chemotherapy was the main therapeutic intervention used for Kaposi's sarcoma, followed by radiotherapy **(Table 2).** Surgery had no role in the management of the tumour except for diagnostic biopsy and to facilitate movement in two patients whose

tumours hang on the toes and feet . Cytotoxic drugs were used in 54 of the patients and radiotherapy in 12 patients .

One(1) patient was on radiotherapy and vincristine ,while seven (7) patients were not on any specific treatment for Kaposi's sarcoma.

Additional non-cytotoxic drugs were given to patients with other illnesses such as tuberculosis ,anaemia , gastritis, and therapy related adverse effects like local pain , nausea and vomiting .

Table 2 Specific anti- tumour therapy and the outcome of treatment within 10 weeks

Drugs/Intervention	Outcome of drug management			
	Died	Survived	Lost to follow up /withdrawal	Number of patients
NONE	0	2	5	7
RT	2	4	6	12
RT/Vin	0	0	1	1
Vin	0	2	1	3
Vin.A	0	0	3	3
Vin.A ACT.D	1	0	1	2
Vin.B	2	7	35	44
Vin.B.A	0	0	2	2
Total	**5**	**15**	**54**	**74**

Key: A- Doxorubicin ; Acti.D- Actinomycin-D; B- Bleomycin;

RT –Radiotherapy; Vin.- Vincristine

The P-value (0.245) suggests that, there was no association between the drug administered and the outcome.

4.3.0 HOSPITAL ADMISSIONS AND NON-SCHEDULED DRUGS

Six patients were admitted in the hospital and 68 were treated as out patients. Five of the admitted patients died and one was discharged and was lost to follow-up.

The duration of stay in the hospital for those admitted ranged between two and seven days . Two patients died within 48 hours of admission, and one patient was discharged after seven days of admission and was lost to follow- up. The other three patients died within seven days of admission. The admitted patients were too sick to get chemotherapy during their stay in the hospital, but were managed on non- cytotoxic drugs including re-hydration fluids.

Out of the 74 study subjects , 64 patients were given other non-cytotoxic drugs to manage, either , the disease complications, infections or to counter the adverse effects of the cytotoxic drugs. Patients on radiotherapy had the highest pill burden with an average of five drugs per patient. The drugs included opioid analgesics, non-steroidal anti-inflammatory drugs , anti-emetic, antibiotics and laxatives, while patients on chemotherapy were on at least three non-scheduled drugs mainly analgesics, anti-emetics and antibiotics. Patients continued taking the drugs they had been taking or drugs which were prescribed by other physicians outside the cancer management team.

4.4.0 ADVERSE EFFECTS ASSOCIATED WITH THERAPY

Nausea , vomiting and abdominal discomfort were the most common adverse effects associated with therapy, while coughing and fatigue were common even before

treatment was started. It was therefore difficult to differentiate between therapy- induced cough and fatigue from that caused by the disease condition(s).

Patients on vincristine- based regimen complained of numbness and tingling on toes and finger tips, while those on radiotherapy, complained of excruciating pain on lesions after treatment and were treated with opioid analgesics.

Patients on non- steroidal anti- inflammatory drugs complained of epigastric pain and were treated with antacid while those on opioid analgesics developed constipation and were treated with laxatives.

Identification of adverse effects from bleomycin and doxorubicin was not feasible since the symptoms are common in HIV infection and Kaposi's sarcoma.

4.5.0 OUTCOME OF MANAGEMENT WITHIN THE STUDY DURATION OF 10 WEEKS

Fifteen patients survived by the end of the 10 weeks study period , 10 males and five females. Fifty four(54) patients were lost to follow- up, 29 were males and 25 were females. Five(5) patients died, three were males and two females(**Table 3**)

Of the fifteen (15) patients who survived, four(4) had partial remission within three weeks after treatment was started and the male: female ratio was 1:1. Seven (47%) patients had progressive disease and only 4 had stable disease. All the patients who died, had progressive disease. The remission status of the patients who were lost to follow up could not be ascertained.

Table 3 Outcome of drug management of patients within 10 weeks period .

	OUTCOME			
Sex	**Died**	**Survived**	**withdrawal**	**Total**
Female	2	5	25	32
Male	3	10	29	42
Total	**5**	**15**	**54**	**74**

4.6.0 FACTORS ASSOCIATED WITH OUTCOME

4.6.1 SEX

The test for association between sex and outcome (P - 0.661) suggested no significant association between sex and outcome.

4.6.2 HOSPITAL ADMISSION

Table 4. Association between hospital admission and the outcome within 10 weeks

	Outcome of drug management within 10 weeks			
Admission	Died	Survived	Withdrawal	**Total**
NO	0	15	53	68
YES	5	0	1	6
Total	**5**	**15**	**54**	**74**

The p-value (0.001) was significant, suggesting that , there was an association between hospital admission and outcome.

4.6.3 TUMOUR RELATED COMPLICATIONS

Table 5. The relationship between tumour related complications and the outcome within 10 weeks

Complications	Outcome of drug management within 10 weeks			
	Died	Survived	Withdrawal	Total
NO	0	1	3	4
Yes	5	14	51	70
Total	**5**	**15**	**54**	**74**

The P- value(0.554) implies that , there was no association between the complications and the outcome .

4.6.4 INFECTIONS

Table 6. Relationship between infection and the outcome within 10 weeks.

Infection	Outcome			
	Died	Survived	Withdrawal	Total
NO	0	3	15	18
YES	5	12	39	56
Total	**5**	**15**	**54**	**74**

The p-value (0.345) suggests that, no association between infection and the outcome of drug management within 10 weeks.

4.7.0 OTHER FACTORS ASSOCIATED WITH MANAGEMENT

4.7.1 COST OF THERAPY

Table 7. Cost of Drug and Radiotherapy management at K.N.H

	Average Cost Per Patient in Kenya shilling		
DRUGS /RT	**Cost per vial**	**cost per patient/dose**	**cost of treatment Minimum of six courses**
NONE	0	0	0
RT	-	300.00	9,000.00
RT/Vin	500.00	700.00	11,400.00
Vin.	200.00	400.00	2,400.00
Vin.A	700.00	900.00	5,400.00
Vin.A.ACT.D	1200.00	1400.00	8,400.00
Vin.B	1700.00	1900.00	11,400.00
Vin.B.A	2200.00	2400.00	14,000.00

Key : A- doxorubicin ; Acti.D- Actinomycin-D; B- Bleomycin;

RT –Radiotherapy; Vin.- Vincristine,

The cost of the non- cytotoxic drugs ranged from Ksh 5000.00 to 20,000.00 for the full course of treatment excluding the ARVs and Anti-Tuberculosis drugs which were given for long periods and patients had varying sources.Some patients bought the drugs outside the hospital while others were given for free.

CHAPTER FIVE

5.0. DISCUSSION

5.1.0 EPIDEMIOLOGY OF KAPOSI'S SARCOMA

Kaposi's sarcoma had a very restricted epidemiological pattern prior to the AIDS epidemic. In 1981 the male to female ratio in Kenya was 8.5:1 according to a study done by Kungu and Gatei .In the present study ,there was a decline in age of patients with the disease and the majority of the patients were between 31 to 40 years of age compared with the age observed during the pre- AIDS era in Kenya (Kungu and Gatei ,1981).There was also marked decrease in male predominance of KS cases and the male to female ratio was 1.3:1.This pattern reflects the heterosexual transmission of HIV infection and poor control of the disease in Kenya (Mwanda *et al.*,2005).

The lymphadenopathic form of the disease was common in both male and female patients and there appeared to be a trend towards oral mucosal involvement to more cutaneous ,with or without lymph nodes involvement **(Table 1)**

5.1.1.OUTCOME OF MANAGEMENT

The management of AIDS -related Kaposi's sarcoma is palliative and is aimed at prolonging survival of the patients by controlling symptoms , prolonging disease free period and improving the quality of life (Krown *et al.*, 2004b). In this study, most patients 54 patients were lost to follow up ,15 survived and five (5) died.

The outcome of drug management was independent of the drug schedule used (P-0.245) meaning there was no association between the treatment given and the outcome. Fifty eight percent of the patients got only one dose of chemotherapy ,7% got two doses, 1% three doses, another 1% got four doses .Only two(3%) patients got full treatment within the 10 weeks of follow-up.

Complications(P-0.554) and the stage of disease(P-0.280) did not influence the management outcome .Hospital admission was however associated with poor treatment outcome (P- 0.001). 83% of those who got admitted died and only 17% were discharged but got lost to follow up.

The median survival could not be ascertained since most of the patients withdrew from the study through loss to follow- up and could not be assumed dead or alive. However ,the median survival observed in the U.S.A, for patients treated for AIDS -related KS was found to be eight times higher(795 *v* 104 days) than that observed in a study done at the same study period in East Africa (Mwanda *et al.*, 2005).The disparity in therapeutic outcome was probably not attributed to differences in the cytotoxic chemotherapy administered, but due to the availability ,in the USA., of more potent and effective antiretroviral regimens which inhibit viral replication and restore immune function, better supportive care including broad spectrum antibiotic and blood products. In Kenya, where resources are limited, most of the patient cannot afford a balanced diet and supportive care is limited.

The number of survivors was small for any fair judgment to be made on the effect of each specific regimen on the outcome. Nevertheless, vincristine /bleomycin regimen featured in all the remission status bearing the majority of the patients. It was more expensive than the vincristine only and had more toxic effects. It was more prescribed but it did not have any advantage over the single agent vincristine. The results showed that only 3% of the total number of enrolled patients got their full treatment in 10 weeks and 1.5%of those who got full therapy had progressive disease, the rest of the patients got partial treatment due to random clinic attendance.

Loss to follow up of patients was the most common observation in the study and it occurred among all patient groups, irrespective of age, sex ,residence ,stage of disease, location of lesions and drug schedule administered. Treatment failure and death at home or in other health care facilities could be one of the main reasons why patients did not continue with their follow up. Economic constrains (Table 7)and therapy related adverse events could not be overlooked .

Cytotoxic drugs and radiotherapy are associated with varying degrees of toxicity ,which include, nausea and vomiting, bone marrow suppression leading to infections, bleeding and anemia, local ulceration and psychological derangements such as anxiety and depression.

Management of the adverse effects require use of more drugs and sometimes withdrawal or suspension of therapy. When the toxic events are not managed well, they can lead to death (Von Roenn *et al.*, 1998) and may explain why most of the patients were lost to follow up. Either the patients felt sick after the first or the subsequent treatments ,or they suffered adverse effects which made them to avoid going back to hospital.

Some patients could have developed treatment associated complications and died or they could have died of ailments associated with HIV- infection or the Kaposi's sarcoma; while other patients may have improved on treatment and felt there was no need to continue with clinic attendance.

5.2.0 OTHER FACTORS AFFECTING PATIENT MANAGEMENT

5.2.1 PATIENT FACTORS

Most of the patients were newly diagnosed with HIV infection, which was secondary to the diagnosis of Kaposi's sarcoma. As such, patient were in denial and this could have accounted to their loss to follow up . Other patients may have felt that there was no

need to get treatment for KS when they knew HIV infection had no cure. 56(76%) had advanced disease with complications and infections at diagnosis .The late diagnosis was as a result of ,lack of diagnostic services at the primary health care , culture , economic constraints and ignorance .The patients came to the hospital in the company of one or more relatives and it was possible that some patients could not get someone to accompany them in the subsequent visits.

5.2.2 THERAPY RELATED FACTORS

Chemotherapy and radiotherapy are associated with immuno- suppressive effects, which, if not well managed can lead to patient deterioration especially in HIV infection (Mitsuyasu , *et al*; 1997). One of the most serious toxicity in both chemotherapy and radiotherapy is myelosuppression which can lead to leucopenia, neutropenia, thrombocytopenia and anaemia. The amount of bone marrow damaged depends on the ability of the marrow to tolerate the therapy , the exposure time to the assaulting agent, age of the patient, cancer in the bone marrow , patient's nutritional status, patient's ability to metabolize drugs normally, type of therapy used, dose, schedule and the method of administration used (Beck .,1990).

The anticancer agents used for the management of patients with AIDS-related KS in Kenyatta National Hospital during the study period included Actinomycin- D, Bleomycin, Doxorubicin, Vincristine and Radiotherapy. These agents have varying degrees of toxicity and due to the large withdrawal of patients from follow up, it was difficult to assess the toxic effects of the drugs among the patients. However , patients on the vincristine only regimen, did better and more survived. They were also among the 3% who got full treatment in 10 weeks. This could be explained by the fact that, vincristine, was better tolerated , within the doses administered -2mg/m^2 in every two

weeks at K.N.H. Peripheral neuropathy is the limiting toxicity in vincristine, and does not have bone marrow suppression and GIT disturbances common in the other regimens(Rowinsky and Donehower 1987). The cost of vincristine, compared to the other schedules was minimal (Table 7).This means that, most patients on vincristine alone were able to afford the treatment and the burden of extra drugs to counter therapy associated toxicity was minimal. The regimen vincristine,bleomycin and adriamycin was a very aggressive treatment in patients with immune suppression and especially in a set up where supportive care was limited (Mwanda *et al* 2005), as such, the patients on this regimen died and the others were lost to follow up.

Conventional doxorubicin is commonly used in a variety of sarcomas but it is highly myelosuppressive and exposes the patient to infections and bleeding disorders Liposomal doxorubicin has better pharmacokinetic profile with modified toxicity and is used with other drugs for AIDS -related KS (Ronald 1999).It is very costly and is not available in Kenya .The patients on doxorubicin regimen were among those patients who withdrew from the study and it is possible that they suffered immununosuppression with accompanying complications and died later .

Belomycin is used in combination with vincristine for the management of AIDS-related KS, and is associated with lung toxicity and cough. Unfortunately, most patients had a cough or chest infections at diagnosis ,so, it was difficult to differentiate therapy induced cough from that cough due to the other diseases. Local pain and ulceration were most common adverse effects experienced by patients on radiotherapy.

Drug resistance is common in cytotoxic therapy and is responsible for treatment failure (Ronald, 1999).In this study it was difficult to identify patients who had drug resistance due to the large loss to follow up .

5.2.3 INSTITUTIONAL FACTORS

Kenyatta National Hospital is a referral hospital catering for referral cases from all over the country including East and Central Africa .The overall patient turn- over is therefore very high and this high turn over accounts for delays in disease diagnosis and management . In this study most (55%) of the patients came from Nairobi province. Others came from Western province(16%) , Eastern province (15%) ,Central province(7%) , Rift Valley province (4%) and Nyanza province (3%) . There were no patients from North eastern , Coast provinces or the neighboring countries who were enrolled in the study or were among those patients who declined .

It was observed that patients were not consistent in their clinic attendance and determination of their laboratory tests. These inconsistencies led to poor management outcome.

Among those who died ,the cause of death was difficult to define, since AIDS- related KS is a disease within a disease and the two conditions , HIV infection and KS lead to fatal illnesses.

Due to economic constraints, most patients probably could not afford balanced diet and this combined with the adverse effects of chemotherapy could have led to rapid patient deterioration.

In the month of December 2005, there were three public holidays which fell on clinic days and patients missed their appointments and treatment on these days .

The study site was at a tertiary level and most of the patients were referral cases with advanced disease. This accounted for uneven distribution of patients among the various stages of the disease.

CHAPTER SIX

6.0. CONCLUSIONS AND RECOMMENDATIONS

6.1.0 CONCLUSIONS

AIDS- related KS remains a major cause of morbidity and mortality among HIV – infected patients in Kenya ,and the burden of the disease is clearly increasing in the country. The most notable observation in this study was, loss of patients to follow up, decline in mean age of patients and decline in the predominance in males . Patients are developing KS at an early stage of their HIV infection compared to patients in other regions of the world where HAART is available. It is hoped that, with the emergence of ARVs in Kenya , prospects for prolonged survival and late development of HIV- related complications in patients with HIV infection will be enhanced. It is therefore necessary for all patients with HIV infection to be started on ARVs .It is also important, to encourage and educate people in the general population to know their HIV status in order to initiate ARV therapy early and possibly delay the development of AIDS and its malignant complications.

In this study, patient turnover was higher than that seen in the previous studies done on patients with AIDS- related KS by Mwanda *et al.*, 2005 in K.N.H. This means that , there are either, increasing numbers of patients with AIDS- related KS or there is increased awareness and more patients are seeking treatment.

The outcome of drug management of patients with AIDS - related KS in K.N.H over the 10 week follow up was very poor. Most (73%) of the cases were lost to follow up and only 20% survived most of whom had progressive disease and 7% died.

Among the treatment regimen used ,vincristine only regimen yielded better results compared to the other regimen. Vincristine was more affordable and its adverse effects tolerable within the prescribed doses. The other drug combinations were more expensive and most of the patients could not afford them. These drug combinations were also very aggressive for the immune suppressed patients, especially, in Kenya ,where supportive care is limited due to economic constraints .

It is difficult to predict what happened to the patients who were lost to follow up, but, it is possible that, some patients died of further immune suppression and accompanying infections, or of therapy associated effects such as drug resistance and treatment failure.

Test for association between variables showed that sex (P-0.661) , tumour- related complications(P-0.846), infections(P-0.348) ,site of tumour (P-0.628) ,stage of the disease (P-0.602) and other drugs (P-0.347) were not associated with the management out come. Where as hospital admission (P-0.001) was however associated with poor management outcome.

Other factors that may have contributed to loss to follow up were, inadequate knowledge about the disease, the requirements of disease management and economic constraints .

Based on these findings, vincristine only regimen was better tolerated than the other regimens .It was also more affordable and the toxic effects were manageable within the prescribed doses. Thus vincristine only regimen would be a suitable regimen for use in Kenyatta National Hospital for the management of patients with AIDS-related Kaposi's sarcoma.

6.2.0 RECOMMENDATIONS

- Most of the patients had advanced stage IV disease at diagnosis . This is attributed to lack of diagnostic services at the primary health care facilities. There is therefore a need to provide diagnostic services within the primary health care facilities .
- It is important to create a national public awareness for people to know about HIV infection and AIDS- related KS and the need to seek medical attention.
- There is need to develop and provide free of charge management protocols in the primary and secondary health care facilities and encourage early institution of therapy at the referral hospital.
- Loss to follow up was common among the patients and further studies will be necessary to establish the causes of loss to follow up among the patient with AIDS- related Kaposi's sarcoma.
- The number of patients who reached the study end point was very small .This makes it difficult to assess the impact of chemotherapy on patients being treated for AIDS- related KS in K.N.H .This aspect will need to be assessed in a long term study to enable recruitment of a large number of patients and facilitate the development of appropriate therapeutic strategies. It is also equally important to determine the incidence of the AIDS – related KS in Kenya, because the majority of large collaborative epidemiological studies have not included cohorts of patients from Kenya and may have under estimated the burden of AIDS –related KS in Kenya.

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APPENDICES

APPENDIX. 1 : QUESTIONARE FOR DEMOGRAPHIC AND CLINICAL INFORMATION

FORM A

PART I

a)Demographic Data

Serial ..... Initials.....

Hospital No..... Site of Study: Ward..... Clinic .....

Age..... Sex..... Residence in the past six months .....

b) Past surgical history (Yes/No)

Reason for surgery.....Site of surgery.....

Date (if known)..... Results of surgery.....

c) Past medical history(Yes/No)

Type of drugs given.....,.....,.....,.....,.....

Date when given .....

Duration of treatment..... Outcome of treatment .....

d) Past Hospital admissions (Yes/No)

Reason for admission ..... Date of admission.....

Duration of admission..... Date of discharge.....

e) Previous hospital visits (Yes/No)

Reason for visit.....Date .....

f) Other Clinical management

State..... Outcome .....

Presenting chief complaint.....

PART II

a) Treatment and follow up

Treatment Protocol .....,.....,.....,.....,

Tumour Site: ..... Stage..... Size : .....cm^2

Date of 1st treatment:.....Date of Last treatment: .....

Evaluable parameters	**Visit/Date**								
Drugs taken									
Effects observed at lesion Tenderness									
Change in -Color									
-Size									
Ulceration									
Other									
Effects observed at the other Systems									
G I T									
C V S									
C N S									

Respiratory system									
Musculoskeletal system									
Eyes and face									
Oral cavity									
Lymph nodes									
Other symptoms Nausea /Vomiting Loss of appetite Night sweats Diarrhoea Weight loss									

Total number of doses received within 10 weeks:..... Number of doses missed at week 10.....Other drugs given:.....,.....

Hospital admissions.....Date..... Reason .....

b) SYSTEMIC PATIENT ENQUIRY **Date /Visit**

Do you get sleep?					
Do you get headache?					
Do you feel dizzy?					
Do you get confused, irritable or loose memory?					
Do you have any difficulty breathing?					
Do you cough ?					
Do you feel pain in the chest ?					
Do you have any difficult while eating ?					
Do you feel pain in the abdomen ? If so where					
Do you bleed ? State where and when.....					
Do you have any difficult in your vision?					
Do you have any swelling in the body ? If so ,where...					
How else do you feel ?					

APPENDIX .11:QUESTIONARE FOR PHYSICAL EXAMINATION AND LABORATORY INVESTIGATIONS

FORM B.

Part 1

a) Physical Examination findings

Evaluable parameters	**Visit/Date/Remarks**						
Pallor							
Jaundice							
Oedema							
Wasting							
Lymph nodes site.....							
Others Pain Diarrhoea							

Guide to remarks: Mild+ Moderate ++ Severe +++ Absent -

b) Vital Signs Findings

Vital signs	**Visit/Date**					
Temperature						
Pulse rate						
Respiration rate						
Blood pressure						

c) Systemic Examination **Visit/date**

Mucocutaneous system					
Musculoskeletal					
Cardiovascular system					
Gastro intestinal system					
Respiratory					
Other systems					

Normal(N) ..... Abnormal (AN)..... Clinical impression.....

PART I I LABORATORY INVESTIGATION

Test	Date/results			
Liver function tests (LFT's) Enzymes- LDH AST ALT ALP Billirubin - Total - Free				
Total blood count (TBC) Hb WBC Neutrophils Monocytes Lymphocytes				
Platelet count				
ESR				
Urea & Electrolytes K+ Na+ CL- Urea Creatinine				
Uric acid				

Urinalysis -Urobilinogen -Ketones -Glucose -Protein -Nitrite -PH -Leucocytes				
Stool for occult blood				
Chest X-Ray				
Any other investigation				

APPPENDIX III SUMMARY OF STUDY

ID	Age	Sex	site	stage	complications	infection	drugs	admission	other drugs	Remission 3 wks	outcome
1	50	F	LN/S	IV	Yes	Yes	V.B	withdrawa	YES	withdrawal	Lost
2	30	M	LN/S	IV	Yes	Yes	V.B	NO	YES	Progressed	Survived
3	30	F	OC	II	Yes	NO	V.B	withdrawa	YES	withdrawal	withdrawal
4	26	M	S	II	Yes	NO	V.B.A	NO	YES	Progressed	withdrawal
5	44	M	LN/S	IV	Yes	Yes	V	NO	YES	Partial	Survived
6	30	M	LN/S	IV	Yes	Yes	V.B	withdrawa	YES	withdrawal	withdrawal
7	23	F	OC	IV	Yes	Yes	V.B	withdrawa	YES	withdrawal	withdrawal
8	29	F	OC/S	IV	Yes	Yes	V.B	YES	NO	Progressed	Died
9	35	F	LN	IV	Yes	Yes	V.B	withdrawa	YES	withdrawal	withdrawal
10	20	F	LN	IV	Yes	Yes	V.B	NO	YES	Progressed	withdrawal
11	35	F	LN/S	IV	Yes	Yes	V.B	NO	YES	Progressed	Survived
12	45	F	LN	IV	Yes	Yes	V.B	withdrawa	YES	withdrawal	withdrawal
13	35	F	V/S	IV	Yes	Yes	NONE	NO	NO	stable	Survived
14	32	M	V	IV	Yes	Yes	V.B	withdrawa	YES	withdrawal	withdrawal
15	32	F	LN	IV	Yes	Yes	V.B	withdrawa	NO	withdrawal	withdrawal
16	39	M	V	IV	Yes	Yes	V.B	withdrawa	YES	withdrawal	withdrawal
17	40	M	OC	IV	Yes	Yes	V.B	YES	YES	Progressed	Died
18	36	M	LN/S	IV	Yes	NO	V.B	NO	YES	Stable	Survived
19	40	M	S	I	Yes	NO	V.B	withdrawa	YES	withdrawal	withdrawal

20	34	F	LN/S	IV	Yes	Yes	V.A	withdrawa	YES	withdrawal	withdrawal
21	30	F	S	I	NO	NO	NONE	withdrawa	-	withdrawal	withdrawal
22	35	M	V	IV	Yes	Yes	V.B	withdrawa	YES	withdrawal	withdrawal
23	13	M	S	II	NO	NO	V.A ACT.D	withdrawa	YES	withdrawal	withdrawal
24	14	M	V	IV	Yes	Yes	V.A ACT.D	YES	YES	Progressed	Died
25	52	M	LN	IV	Yes	NO	V.B	withdrawa	YES	withdrawal	withdrawal
26	30	M	S	II	NO	NO	NONE	withdrawa	NO	withdrawal	withdrawal
27	40	F	LN/S	IV	Yes	NO	V.B	withdrawa	YES	withdrawal	withdrawal
28	50	M	S	II	Yes	Yes	V.B	withdrawa	YES	withdrawal	withdrawal
29	32	F	V	IV	Yes	Yes	V.B	NO	YES	stable	Survived
30	55	M	OC	II	Yes	NO	V.B	NO	YES	Partial	Survived
31	36	M	OC/S/V	IV	Yes	Yes	V.B	withdrawa	YES	withdrawal	withdrawal
32	30	F	OC/S/V	IV	Yes	Yes	NONE	NO	YES	withdrawal	withdrawal
33	54	M	S	IV	Yes	Yes	V.B	withdrawa	YES	withdrawal	withdrawal
34	39	M	LN/S	IV	Yes	Yes	R.T	NO	YES	Progressed	Survived
35	25	F	S	I	Yes	Yes	R.T	NO	YES	Partial	withdrawal
36	43	M	LN	IV	Yes	Yes	V.B	withdrawa	YES	withdrawal	withdrawal
37	32	M	V	IV	Yes	Yes	V.B	withdrawa	YES	withdrawal	withdrawal
38	45	F	OC	II	Yes	Yes	V.B	withdrawa	YES	withdrawal	withdrawal
39	43	F	OC	II	Yes	Yes	V.B	NO	YES	Partial	Survived
40	40	M	V	IV	Yes	Yes	V	NO	YES	Progressed	Survived
41	37	F	OC/V	IV	Yes	Yes	V.B	NO	YES	withdrawal	withdrawal
42	55	M	OC/S	IV	Yes	Yes	V.B	withdrawa	NO	withdrawal	withdrawal
43	50	M	LN	IV	Yes	NO	V.B	withdrawa	YES	withdrawal	withdrawal
44	37	M	S	II	Yes	NO	V.B	withdrawa	YES	withdrawal	withdrawal
45	45	M	LN	IV	Yes	Yes	V.B	NO	YES	Partial	Survived
46	33	F	V/S	IV	Yes	Yes	V.B	withdrawa	YES	withdrawal	withdrawal
47	50	M	V	IV	Yes	Yes	V	withdrawa	YES	withdrawal	withdrawal
48	38	M	LN/S	IV	Yes	Yes	R.T	YES	NO	Progressed	Died

49	28	M	OC/V	IV	Yes	Yes	NONE	withdrawal	YES	withdrawal	withdrawal
50	43	M	LN/S	IV	Yes	NO	V.B	withdrawal	NO	withdrawal	withdrawal
51	32	M	OC	II	Yes	NO	V.B	withdrawal	YES	withdrawal	withdrawal
52	29	F	S	II	Yes	NO	RT	withdrawal	NO	withdrawal	withdrawal
53	32	F	LN	IV	Yes	Yes	V.B	withdrawal	YES	withdrawal	withdrawal
54	55	M	OC	II	Yes	Yes	V.B	withdrawal	YES	withdrawal	withdrawal
55	38	M	LN/S	IV	Yes	NO	V.B	withdrawal	YES	Progressed	withdrawal
56	38	F	LN/S	IV	Yes	Yes	V.B	withdrawal	YES	withdrawal	withdrawal
57	28	M	LN	IV	Yes	Yes	V.B	withdrawal	YES	withdrawal	withdrawal
58	47	F	LN	IV	Yes	Yes	V.B	withdrawal	YES	withdrawal	withdrawal
59	37	F	L	IV	Yes	Yes	V.B	withdrawal	NO	withdrawal	withdrawal
60	28	F	LN/S	IV	Yes	Yes	V.A	withdrawal	YES	withdrawal	withdrawal
61	21	F	OC/S	IV	Yes	Yes	V.B	withdrawal	YES	withdrawal	withdrawal
62	40	F	OC	II	Yes	NO	V.B.A	withdrawal	YES	withdrawal	withdrawal
63	50	F	S	IV	Yes	Yes	V.A	withdrawal	YES	withdrawal	withdrawal
64	25	F	OC	IV	Yes	Yes	RT	withdrawal	YES	withdrawal	withdrawal
65	45	M	LN	II	NO	NO	RT	NO	YES	Progressed	Survived
66	35	F	LN/S	IV	Yes	Yes	RT	NO	YES	stable	Survived
67	28	M	S	II	Yes	Yes	RT	YES	YES	Progressed	withdrawal
68	41	M	LN/S	IV	Yes	Yes	RT	NO	YES	Progressed	Survived
69	28	M	OC	IV	Yes	Yes	RT	withdrawal	YES	withdrawal	withdrawal
70	30	F	LN/S	IV	Yes	Yes	RT	YES	YES	Progressed	Died
71	45	M	LN/S	IV	Yes	Yes	RT/V	withdrawal	YES	Progressed	withdrawal
72	30	M	S	IV	Yes	Yes	NONE	withdrawal	YES	withdrawal	withdrawal
73	45	M	LN/S	IV	Yes	Yes	RT	NO	YES	withdrawal	withdrawal
74	35	M	S	IV	Yes	Yes	NONE	NO	YES	Progressed	Survived

APPENDIX IV : SUMMARY OF LABORATORY RESULTS:

Patient	sex	TOTAL BLOOD COUNT						Therapy	Other Tests
		HB	WBC	Monocytes	Lymphocytes	Neutrophils	Platelets		
1	F	9.35	2.83	13.1	1.35	1.2	333	RT	U/E Urea 3.2 K 4.4 Na 143 CL 110 Creat. 74
2	M	9.7	3.99	0.4	1.0	-	-	RT	
3	M	12.4	4.4	-	-	-	410	RT	
4	M	11.8	6.3	0.55	3.15	1.82	367	V.B	
5	F	13.1	3.7	-	-	-	259	V	AST 32 Billirubin Total 3.0 Free 1.0 U/E Urea 7.2 K 5.3 Na 147 CL- 114.9 Creat. 110

6	M	12.6	3.63	0.76	0.951	1.33	415	V.B	
7	M	13.2	8.1	-	-	-	O.K	A.B.V	Creat. 85.9
8	M	7.1	2.9	-	-	-	515	V	ESR 59
9	M	13.3	6.7	0.19	2.71	3.8	-	V.B	U/E Urea 3.7 K 3.8 Na 84 CL 98 Creat. 79.9
10	M	16.0 16.8 15.2 14.7	8.1 7.2 8.8 7.2	0.70 0.34 - -	1.42 1.42 - -	6.33 4.78	414 224 -	NONE	LFT AST 21 ALT 20 ALP 107 ESR 22
11	M	10.2	5.32	0.302	2.16	2.62	328	NONE	AST 49 ALT 130 Billirubin Total 5.3 Free 1.2 U/E Urea 8.8 K 4.3 Na 138 CL 107

									Creat. 82
12	F	10.5	4.74	0.269	1.74	1.97	345	V.B	
13	M	8.75	4.33	0.282	1.62	2.27	234	V	AST 47 ALP 18 ESR 33 Creat.108
14	M	8.6	4.1	-	-	-	22	RT	Urea 14.2 Creat. 206 AST 79 Billirubin Total 213 Free 159
15	F	5.79	2.9	0.437	1.01	1.41	246	V.B	U/E Urea 3.8 K 3.3 Na 127 CL 97.2 Creat. 66
16	F	11.8 13.3	6.3 7.3	0.55 0.04	3.15 0.13	1.82 0.82	367 197	V.B	Urea 5.1
17	F	12.6	4.6	-	-	-	434	RT	-
18	M	12.3	9.01	0.64	2.47	5.6	341	RT	U/E Urea 3.9

									K 4.7 Na 142 CL 107 Creat.109
19	M	8.3	3.9	-	-	-	349	VB	**LFT** **AST 44** **ALT 16** **Billirubin** Total 6.3 Free 1.5 **Creat.** 117
20	F	5.49 7.36. 7.50 6.20	6.99 5.05 2.37 4.35	- - - -	-	-3.3	834 760 721 766	V.B	U/E Urea 2.2 K 5.4 Na 142 CL 102

KEY: Units of measurement

HB gm/dl
WBC x 10^9 /litre
Monocyte x 10^9 /litre
Lymphocytes x 10^9 /litre,
Neutrophils x 10^9 /litre
Urea millimoles /litre
Na millimoles/ litre
K millimoles/litre

Creat. Micromoles /litre
Billirubin Micromoles/litre
Cl Millimoles/litre
AST International units/litre
ALT International units /litre