A TEN YEAR RETROSPECTIVE STUDY ON THERAPEUTIC MANAGEMENT AND CLINICAL OUTCOMES OF ACUTE LYMPHOBLASTIC LEUKEMIA AMONG CHILDREN AT KENYATTA NATIONAL HOSPITAL, KENYA

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DECLARATION

I hereby declare that this dissertation is my original work and has not been presented to any other academic institution for evaluation, examination and award of degree.

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DEDICATION

I dedicate this work to my two sons, Sir Ferdinand William Wilberforce Bob junior and Lloyd Rutherfold Von Rechenberg Bob II to be future intellectuals, prolific thinkers and academicians, my parents Mr. and Mr.Samson Agwata and Dorcas mwango for intensive inspiration.

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LIST OF ABBREVIATIONS

ACF: Africa Cancer Foundation

ADR: Adverse drug Reactions

AIDS: Acquired Immune Deficiency Syndrome

ALL :   Acute Lymphoblastic Leukemia

AML :   Acute Myeloblastic leukemia

BFM   :   Berlin-frankfurt-munster

BMA: Bone Marrow Aspirate

CI :   Confidence Interval

CLL: Chronic Lymphoblastic leukemia

CML: Chronic Myeloblastic leukemia

CNS: Central Nervous system

CR   :   Complete Remission

EFS :   Event free survival

FAB: French American British System

FBC: Full Blood Count

HIV   : Human Immune Deficiency Virus

IM :   Intramuscular

IT :   Intrathecal

IV :   Intravenous

KEMRI: Kenya Medical Research Institute

MDG: Millennium Development Goal

MRC: Medical Research Council

MRD: Minimal Residual Disease

NY   :   New York

OS   :   Overall survival

PH :   Philadelphia

PO   :   per oral

QOL: Quality of Life

RBC: Red Blood Cells

SD   :   Standard deviation

SE   :   Standard error

USA: United States of America

WBC: White Blood Cells

WHO: World Health Organization

ABSTRACT

Background

In the past three decades, leukemias were considered rare hematological cancers because cases were sporadic and in places like Africa, where data were lacking, were even considered non-existent. Of all types of Leukemia, acute lymphoblastic leukemia is the commonest. Its treatment outcome and survival rates improved gradually over decades from a mere 30% in the 60's and 70's to approximately 80% currently in most developed countries. This has been due to change in regimens to newer drugs and improved diagnostic technology, among others. There is limited data on treatment outcomes of acute lymphoblastic leukemia in the developing countries and hence the impetus for the present study.

Objectives

To describe the therapeutic management and evaluate the clinical outcomes of acute lymphoblastic leukemia among children at Kenyatta National Hospital.

Methodology

The study was a descriptive retrospective cohort that followed treatment outcomes from the time of diagnosis and initiation of treatment. All incident cases of pediatric acute lymphoblastic leukaemia seen at Kenyatta National Hospital from January 2001 to December 2010 were reviewed.

Data analysis

Data collected was collected and entered into a database and then exported to SPSS (Version 12.0) for analysis. All variables were subjected to descriptive data analysis. Student t-test and ANOVAs were used to compare differences between treatment regimens. Key prognostic factors and survival were identified using logistic regression modeling.

Eligibility Criteria

The patients included in this study met the following criteria: Aged between 0- 15 years, diagnosed with acute lymphoblastic leukemia with confirmatory laboratory tests, diagnosed between 2001 and 2010.

Results: One hundred and seventy one patient medical record files were reviewed. Out of the 171 cases, 100(58.5%) were males and 71(41.5%) were females. The mean age at diagnosis was 6.69 years (sd ±3.64). Median follow up time was 17.92 months.The most predominant subtype of ALL was found to be L2-T precursor cell occurring with 137 cases (80.1%) followed by L1 B precursor cells with 16 cases (9.4%) while 17 cases (9.9%) were uncharacterised. Mortality was the most commonly occurring treatment outcome with 110 deaths giving a case fatality rate of 64.3% among childhood cases of acute lymphoblastic leukemia in Kenya. Initial remission occurred in 105 cases (61.4%). Eighty (46.8%) patients had a relapse, and the commonest site of relapse was central nervous system with 60 cases (67.4%). Cure rate was 34 cases (22.7%). Twenty three cases (67.6%) of those that achieved cure were alive while 11 (32.4%) died due to other causes. Extravasations and treatment failure at the initial stages of therapy rarely occurred. Among the 171 children with acute lymphoblastic leukaemia, 150 (87.7%) were managed on KNH 1 regimen. Eight cases (4.7%) were managed using alternative regimens (either KNH 2, n =2 or "other regimen", n = 6) while 13 (7.6%) had no treatment instituted. The patient characteristics that showed significant association with mortality as a treatment outcome were: blood film (p = 0.011), failure to initiate a regimen (p = 0.005), absence of remission (p < 0.0010). Clinical features that showed statistically significant associations with the outcome of mortality were bleeding (p < 0.001) and splenomegaly (p = 0.032).

Conclusion: Overall outcome of chemotherapeutic management of acute lymphoblastic leukaemia was poor. Mortality being the highest, frequent relapse and overall poor cure and survival rates were noted. There is, therefore, an opportunity to review the management of patients with acute lymphoblastic leukemia at Kenyatta National Hospital with the aim of improving treatment outcomes and overall survival.

CHAPTER ONE

1.1 INTRODUCTION

Leukemias are heterogeneous hematologic malignancies characterized by unregulated proliferation of blood forming cells in the bone marrow. The term leukemia was coined by Virchow to describe the "white blood "of the patients that he saw under the microscope in 1845[1].

Historically leukemia has been classified as acute or chronic based on differences in the cell of origin and cell line maturation, clinical presentation rapidity of progression of the untreated disease and response to therapy [1].

Four major leukemias are: Acute Lymphoblastic leukemia(ALL), Acute Myeloblastic leukemia(AML), Chronic Lymphoblastic leukemia(CLL) and Chronic Myeloblastic Leukemia(CML).The difference between 'acute' and 'chronic' is that in acute leukemias undifferentiated immature cells proliferate autonomously while in chronic, although the cells proliferate autonomously, they are more differentiated and mature[1].

Acute Lymphoblastic leukemia (ALL) is a malignant (clonal) disease of the bone marrow in which early lymphoid precursors proliferate and replace the normal hematopoietic cells of the marrow. ALL may be distinguished from other malignant lymphoid disorders by the immune phenotype of the cells which is similar to B or T precursor cells. Immunochemistry, cytochemistry and cytogenetic markers may also aid in the categorizing the malignant lymphoid clone [1].

Acute refers to the fact that the disease appears suddenly, is fast developing and may quickly distribute to the other vital organs. In a healthy individual the T and B lymphocytes produce antibodies to fight infections. These lymphocytes are distributed in the blood, lymph nodes and

spleen. In patients with ALL the lymphocytes remain immature and are referred to as lymphoblasts. These immature cells rapidly proliferate and outnumber the blood cells in the blood, bone marrow and lymph tissue.

1.2   LITERATURE REVIEW

1.2.1 Pathophysiology of acute lymphoblastic leukemia

Generally in Leukemia, the normal process of heamatopoiesis is altered and transformation to malignancy appears to occur in a single cell, usually at the pluripotential stem cell level, but it may occur in a committed stem cell with capacity for more limited differentiation. Accumulation of malignant cells leads to progressive impairment of the normal bone marrow function and bone marrow failure (3).In acute leukemia the normal bone marrow is replaced by a malignant clone of immature blast cells derived from the lymphoid & myeloid series. Usually more than 30% of the cellular elements of the bone marrow are replaced with blasts.

In ALL the blasts may infiltrate lymph nodes and other tissues such as liver, spleen, testis and meninges in particular. In ALL a lymphoid progenitor cell becomes genetically altered and subsequently undergoes deregulated proliferation, survival and clonal expansion. In most cases the pathophysiology of the transformed lymphoid cells reflects the altered expression of genes whose products contribute to the normal development of B cell and T cells [3].

1.2.2 Etiology of acute lymphoblastic leukemia

Similar to other cancers, the etiology of leukemia is not fully understood .Leukemia is thought to arise from combination of factors that induce genetic mutations which allow mutated cells to

proliferate faster than normal cells and fail to die in response to normal apoptotic signals. Some epidemiological studies have identified a number of risk factors for development of leukemia, ALL included: genetic factors, environmental and polymorphism.

1.2.2.1   Genetic Factors

De keers Maeker et al (2005) in their investigation on the pathogenesis of a T – cell acute lymphoblastic leukemia identified recurrent chromosomal aberrations and more subtle genetic defects. They came up with four classes of mutations which are required for development of T – ALL [4].

Down's syndrome, constitutional trisomy of chromosome 21 is associated with increased risk or leukemia development .This alterations may permit the expression of oncogenes which promote malignant transformation.

Genetic predisposition has been suggested too by Greaves et al(2003) on close study of identical twins who following initiation of leukemia in one twin's fetus clonal progen spread to the co-twin via vascular anastosomes within a single monochorionic placenta hence giving an equivocal evidence that twin pairs of leukemia have a common clonal origin . This has been proofed too by molecular markers of clonality including unique genomic fusion gene sequences [5].

1.2.2.2   Environmental Factors

Ionizing radiation and benzene exposure are the only environmental risk factors strongly associated with ALL although a number of environmental factors are inconsistently linked to the disease like toxic chemicals, herbicides and pesticides, natural use of contraceptives, smoking, parental exposure to drugs, alcohol consumption before pregnancy and chemical contamination of ground water [6, 7].

1.2.2.3 Folate Metabolism Polymorphs

Low penetrance polymorphism and folate metabolizing enzymes have also been associated with development of ALL. First Polymorphic variants of methylenetetrahydrofolate reductase which catalyses the reduction of 5, 10, methylenetetrahydrofolate (the predominant circulating form of folate) have been linked to a decreased risk of adult and pediatric ALL. This protective effect may be due to the greater availability 5, 10 methylenetetrahydrofolate and thymidine pools and to an increased fidelity to DNA synthesis [8, 9].

1.2.3 Epidemiology of acute lymphoblastic leukemia

Fortunately cancer in children and adolescents are rare, although the overall incidences of childhood cancer has slowly been increasing since 1975 .In United states ALL is the most common cancer diagnosed in children and represents 23% of cancer diagnosed at an annual rate of approximately 30 to 40 per million[10].

There are approximately 2900 children and adolescents younger than 20 years diagnosed with ALL each year in the United States. A sharp peak in ALL incidence is observed among children aged 2-3 years (> 80 per million per year) with rates decreasing to 20 per million for ages 8-10 years. The incidence of ALL among children aged 2-3 years is approximately four fold greater than that for infants and is nearly tenfold greater than that for adolescents aged 16-21 years [11].

In Europe Childhood lymphoblastic leukemia incidence (including ALL) increased significantly by an average of 1.4 % per year during 1970 – 1999. In England and Wales, leukemia is the commonest cancer in children 0-14 years, representing a third of all malignances with incidence rates increasing up to a at a peak at around age 3-4 years and then declines. Some 400 children

are diagnosed in England and Wales each year and about 100 die of it. Four out of ten cases of leukemia in children are ALL and the remaining is almost all AML [12].

Studies have also indicated that there is a higher incidence of ALL in developed countries compared to developing ones. This difference though may be due to under reporting in most African countries (13). The incidence of ALL appears highest in Hispanic children; it is three fold higher for white children aged 2-3 years compared to black children of the same age [14].

The above statement has been reinforced by various studies one of which was that carried out by Swensen *et al* (1997) which found that white children indeed have a much higher incident rate of acute lymphoblastic leukemia than African American children. This discrepancy coupled with the geographical and temporal variations in the incidence of Childhood ALL have led to the speculation that factors associated with social economic status may play an important role in its etiology [15]. According to the study carried out by Kasili et al (1979) in Kenya, The overall national crude incidence of leukemia by 1979 was 0.5 cases per 100,000 with a maximum tribal specific incidences being 1.2 cases per 100,000 children below 15 years age group. Leukemia accounted for 28% of all types of leukemia giving an increase of 0.3 cases per 100,000 where as adult is 0.7 per 100,000 48% of all acute leukemia occurred in childhood as compared to 4.7 chronic type [16].

1.2.4   Classification of Acute Lymphoblastic Leukemia

The classification of acute Leukemia has evolved significantly over the past few decades. The FAB classification was based entirely on the morphological features of the blast cell population on Romanousky – stained bone marrow aspirate smears and the results of cytochemical studies.

While the FAB classification was modified overtime and eventually included immune phenotyping to distinguish minimally differentiated AML from ALL and as a means to identify acute megakaryoblast leukemia, it remained a primarily morphologic classification system. ALL is classified as follows: L1 or precursor B- Cells, L2 precursor T – Cells and L3 B – Cells.

1.2.5 Prognostic factors for acute lymphoblastic leukemia

Prognostic variables are important in predicting the general outcome of disease management and are of help in designing the therapy and management of any disease. Diseases with poor prognostic factors draw attention to a more aggressive management than those with good prognosis [17].

Risk based treatment assignment is utilized in children with ALL so that patients with favorable clinical and biological features who are likely to have a very good outcome are treated with modest therapy and can be spared more intensive and toxic treatment, while a more aggressive and potentially more toxic therapeutic approach can be provided for patients who have a lower probability of long term survival [18].

For children with ALL a number of clinical and laboratory features have demonstrated prognostic factors which include Patient characteristics at diagnosis, Leukemia cell characteristics at diagnosis and response to initial treatment. These prognostic factors have a sub set which will be discussed below and they are used for stratification of children with ALL for treatment assignment.

1.2.5.1   Patient Characteristics of Diagnosis

Age at diagnosis

Age at diagnosis has a strong prognostic significance, reflecting the different underlying biology of ALL in different age groups. Younger children aged 1-9 years have a better disease free survival (DFS) than older children, adolescents and infants. The better prognosis in younger children is partly explained by the more frequent occurrence   of favorable cytogenetic features in the leukemia blasts including hyperdiploid with 51 or more chromosomes and or favorable chromosome trisomies [19].

Infants with ALL have a particular high risk of treatment failure. Treatment failure is most common in infants younger than six months and in those with extremely high presenting leukocyte counts and or poor response to prednisone prophase [20]. This is because infants with ALL can be divided into two subgroups on the basis of the presence or absence of translocation that involve the MLL gene located at chromosome 11q 23[21].

Approximately 80% of infants with ALL have an MLL gene rearrangement. The rate of MLL gene translocation is extremely high in infants younger than six months. From 6 months to 1 year the incidences of MLL translocation decrease but remain higher than that observed in old children [22, 23].

WBC Count at Diagnosis

Patients with B- precursor ALL and high WBC counts at diagnosis have an increased risk of treatment failure compared with patients with low initial WBC count. A WBC count of

50,000cell/UL is generally used as an operational cut point between better and poor prognosis. [24].

CNS Involvement at Diagnosis

Usually the presence or absence of CNS leukemia has a significant prognostic value. Patients are classified into three classes depending on the Lumbar puncture tests and results that are CNS1, CNS2 and CNS3.

CNS1 is characterized by Cerebrospinal fluid (CSF) that is cytospin negative for blasts regardless of WBC count. In CNS2 the CSF has fewer than five WBC/UL and cytospin positive for blasts and finally in CNS 3(CNS Diseases): CSF has five or more WBC/UL and cytospin positive blasts. Depending on the classes above, children with ALL who present with CNS 3 or CNS disease at diagnosis are at high risk of treatment failure (both within the CNS and systemically [25].

An adverse prognostic significance with CNS 2 usually guarantees an application of more intensive intrathecal therapy especially during the induction phase [26].

Testicular Involvement at Diagnosis

This remains a controversial issue according to different groups. The Children's oncology group (COG) considers patients with testicular involvement to be at high risk regardless of other presenting features but most other large clinical trial groups in the United States and Europe do not consider testicular diseases to be high risk features [27].

Gender

The prognosis for girls with ALL appears to be slightly better than that for boys. One reason for poor prognosis for boys is due to the occurrence of testicular relapses among boys. Some studies indicate that boys appear also to be at increased risk for reasons not well understood [28].

Race

Although ALL is more common in white children and Hispanic children, sadly the story in treatment outcome and survival rates in black children and Hispanic children with ALL have been lower than in white children [29].

Asian Children with ALL fare slightly better than white children. This difference between Asian and white children doing better than black and Hispanic, has been explained to be partially due to different spectrum of ALL subtypes. Example most black children seem to have high incidences of T cell ALL and lower rates of favorable genetic subtypes of ALL [30].

1.2.5.2 Leukemia cell characteristics at diagnosis

Morphology

Using the FAB system of classification, ALL lymphoblasts were classified as L1, L2 and L3 Morphology but no independent prognostic significant has been found so far. The only significant thing is that the L3 morphology express surface immunoglobin (lg) and has a C-MTC gene translocation identical to that seen in Burkitt's lymphoma [31].

Cytogenetics

A number of recurrent chromosomal abnormalities have been shown to have prognostic significance especially in B- Precursor ALL. Some chromosomal abnormalities such as high

hyperdiploidy (51-56) chromosomes and the ETV6 –RUNXI Fusion are associated with more favorable outcomes while others including the Philadelphia chromosomes t (9, 22) rearrangements of the MLL gene (chromosome LLq23) and intrachromosomal amplication of the AMLI gene (IAMP21) are associated with poor prognosis [31].

A number of Polymorphisms of genes involved in the metabolism of chemotherapeutic agents have been reported to have prognostic significance in childhood ALL. Patients with mutant phenotypes of Thiopurine methyl transferase (a gene involved in metabolism of thiopurines such as 6-mercaptopurine) appear to have more favorable outcomes although such patients may also be at high risk of developing significant toxicity related to treatment including myelosuppression and infection[32,33].

1.2.5.3 Response to initial treatment

Treatment responses are usually influenced by the drug sensitivity of leukemia cells and host pharmacodynamics and pharmacogenomics. The rapidity with which Leukemia cells are eliminated following onset of treatment is usually associated with long term outcomes [34.]Some of the common ways of evaluating response includes the following.

Day 7 and 14 Bone marrow Response

A reduction of leukemia cells to less than 5% in the bone marrow with 7 to 14 days following initial induction therapy have a more favorable prognosis than do patients who have slower clearance [35.]

Peripheral Blood response to steroid prophase

Children with reduced peripheral blast count to less than 1000/UL after 7 day induction pro phase with prednisone and one dose intrathecal methotrexate have more favorable prognosis than those with blast counts above 1000/UL[36]. Patients with no circulating blasts on day 7 have a better outcome than those patients whose circulating blasts level II between 11 and 1000/UL [37,38].

Blood response to Multi agent induction therapy

The rate of clearance of peripheral blasts has been found to be of prognostic significance in both T-cell and B-lineage ALL. Children with persistent circulating Leukemia all at day 7 to 10 after initiation of multivalent chemotherapy are at increased risk of relapse compared to those who have no blasts with one week therapy [39].

Induction Failure

An induction failure which is characterized by a presence of greater than 5% Lymphoblast at the end of induction phase, and is a prognostic indicator of poor treatment outcomes [40].

Outcome factors

High expression of VLA -4 has been associated with adverse prognostic factors, poor molecular response to therapy and significantly worse probabilities of event free overall survival. This is an independent prognostic parameter which basically is a gene expression signaling pathway from the bone marrow after the start of the therapy [41].

1.2.6   Chemotherapeutic treatment of Acute Lymphoblastic Leukemia

1.2.6.1 Phases of treatment

There are different phases in treatment of ALL.

Induction Phase/ Remission

This is therapy given immediately at the time of diagnosis. It is aimed at killing as many cancer cells as possible to achieve a complete remission within four weeks. This phase is said to be successful if less than 5% blasts are in the bone marrow and blood count have returned to normal**.**

Consolidation and Intensification phase

Is the second phase of therapy, it begins when the leukemia is in remission. The purpose of consolidation/intensification therapy is to kill any remaining Leukemia cells that may not be active but could begin to grow and cause a relapse. Often the cancer treatments are given in lower doses than those used for induction and consolidation and intensification therapy .This is also called the continuation therapy costs.

Maintenance phase

This is the third and usually last phase of treatment. Its purpose is to kill any remaining leukemia that may regrow and cause a relapse. Often the cancer treatment in this phase are given in low doses than those used for induction and consolidation/intensification therapy .This is also called the continuation phase.

CNS Sanctuary Therapy

Usually given during each phase of therapy because chemotherapy that is given by mouth or injection into a vein may not reach Leukemia Cells in the CNS (brain and spinal code) the cells

are able to find a "sanctuary" (hide) in the CNS. This is done by intrathecal chemotherapy and radiation therapy is also called CNS prophylaxis [42].

1.2.6.2 Treatment protocols

Treatment of childhood Leukemia, especially acute Lymphoblastic leukemia (ALL) typically involves chemotherapy given for 2 to 3 years. Different protocols are used worldwide to treat ALL. For the purpose of our study we will highlight only 3 of these which are the British protocols [43], American protocol [45] and the Kasili protocol [46] that is used in KNH.

The British protocol [43]

Many protocols exist for the treatment of ALL in UK. But the one that is widely used is the one adopted from the UK medical research council protocol which is as below.

Induction Phase (four weeks)

Vinicristine	1.5mg/m2, IV Weekly for four weeks
Prednisolone	40mg/m2, PO daily for four weeks
L-asparaginase	6000u/m2 IM three times weekly for 3 weeks
Daunorubicin	45mg/m2, IV daily for two days

Intensification stage (one week)

Vinicristine	1.5 mg/m2 IV 1 dose
Paunorubicin	45mg/m2 IV daily for two days
Prednisolone	40mg/m2 orally daily for 5 days
Etoposide	100mg/m2 IV daily for 5 days
Cytarabine	100mg/m2 IV 2X daily for five days
Thioguanine	80 mg/m2 orally daily for five days

CNS prophylaxis (3 weeks)

Cranial irradiation   24GY

Methotrexate   1T weekly for 3 weeks also given during induction and intensification.

Maintenance therapy (2 years)

Methotrexate   20 mg/m2 orally weekly

C-Mercaptopurine   75 mg/m2 orally daily

Prednisolone   40 mg/m2 orally 5days /month

Vincristine   1.5 mg/m2 IV Monthly

The American protocol [44]

The American protocols are many, they are similar with British the only difference is that most therapies are tailored depending on the prognostic factors of individual patient but in general the drugs are used as follows:

Induction phase

Vincristine

Prednisone & Dexamethasone

L- Asparaginase

IT Therapy (Methotrexate & Cytarabine)

Daunorubicin (High risk factors)

Consolidation (Intensification Therapy)

High Dose Methotrexate (1-5 g/m2)

Leuclophosphamide

Cytarabine

Thiopurine

L- Asparaginase

Maintenance Therapy

Mercaptopurine PO Weekly

Methotrexate Parental

IT Chemotherapy

The Kenyan Protocol [45]

In Kenya the protocol used for treatment of ALL are contained in the Kasili synopsis of management of pediatric cancer in Kenya authored by Mwanda *et a*l at the University of Nairobi and are as follows:

Definitive chemotherapy

KNH1

Induction (4 weeks)

Vincristine	$1.5mg/m^2$ (max 2.0 mg), IV days 1, 8, 15, 22 (or weekly X 4)
Daunorubicin/Doxorubicin	$25mg/m^2$, IV days 1, 8, 15, 22 (or weekly X 4)
Prednisone	$40mg/m^2$/day for 28 days in 3 divided dose, then taper to zero over 7 days
Methotrexate intrathecal (MXT IT)	Once weekly for 5 doses age related doses (1-2 years 5.5mg; 3-5 years 7.5mg; 5-7 years 10mg; > 7 years 12.5mg)

Bone marrow aspirate is done at day 30: for assessment of remission - if not in remission, reassess with a view to prognosticating case. In the meantime, start consolidation and for those not in remissions consider giving at least three consolidations.

Consolidation

Starts 10-14 days after completing induction:

Cyclophosphamide   IV 1000 mg/m^2 in saline over 8 hrs on day 1 and 8

Vincristine   1.5mg/m^2 IV days 1 and 8, Give second course after 10-14 days as determined by level of blood counts.

Cytarabine   75mg/m^2 SC days 1-4, 22-25, 29-32

Cranial   Radiotherapy   given to patients starting 7-14 days after completing consolidation (DXT)

Methotrexate   25mg/m^2/week, PO weekly for 24 months. Rest period of two weeks in case of cytopenias for both 6MP and methotrexate

Vincristine   1.5mg/m^2 IV day 1 monthly for 24 months

IT MTX   Every 8 weeks for 1st year for those without CNS disease

Adriamycin   25mg/m^2 every three months for 24 months

Cyclophosphamide   300mg/m^2 every three months for 24 months

In disease free events (continuing remission) this maintenance is continued for 24 months.

Reinduction - (4 weeks)

Vincristine   1.5mg/m^2, IV days 1, 8, 15 and 22

Daunorubicin   25mg/m^2, IV days 1, 8, 15 and 22 (Echo cardiogram done before each dose)

Dexamethasone   4 mg/m^2/day, PO days 1-22, then taper to zero from day 22 to 29

        IT MTX   day 1 (dose for age) every week for 4 weeks

Reconsolidation

Cyclophosphamide   650 mg/m^2 (maximum 1000mg) IV starting on day 28 then every two

weeks times 3.

IT MTX   (dose for age) day 31, 38, 45 and 52 weekly for three weeks.

6-Mercaptopurine   60mg/m^2/day, PO days 29-57 starting on day 28 for 28 days.

Cytarabine   75mg/m^2, SC starting day 30 daily for four days and repeating every

week for 3 weeks.

Rest 2 weeks then proceed to maintenance as in (option A)

KNH2 ideal situation

Induction: Phase 1

Prednisone   60mg/m^2 orally on days 1 to 28

Vincristine   1.5mg/m^2 (max. 2.0mg) IV on days 1,8,15 and 22.

Daunorubicin   25mg/m^2 IV on days 1,8,15 and 22.

L-Asparaginase   5000 units/m^2 IV on days 1 to 14. (Dose may be adjusted downward at

3,000 unit/m^2 when given together with anthracycline).

Bone marrow on day 35 and if remission is achieved or not move to consolidation

Consolidation Phase II:

Cyclophosphamide   650 mg/m^2 (maximum 1000mg) IV starting on day 28 then every two

weeks times 3.

IT MTX   (dose for age) day 31, 38, 45 and 52 weekly for three weeks.

6-Mercaptopurine   60mg/m^2/day, PO days 29-57 starting on day 28 for 28 days.

Cytarabine   75mg/m^2, SC starting day 30 daily for four days and repeating every

week for 3 weeks.

If there is no remission or there is relapse consider re induction as follows.

Reinduction: Phase I

Dexamethasone   10mg/m^2 orally on days 1 to 28.

Vincristine   1.5mg/m^2 (max. 2.0mg) IV on days 1,8,15 and 22.

Doxorubicin   25mg/m^2 IV on days 1,8,15 and 22.

Cranial irradiation at 2,400 cGy is for 4 weeks instituted after remission is achieved.

Reconsolidation: Phase II

Cyclophosphamide   650 mg/m^2 (maximum 1000mg) IV starting on day 28 then every two

weeks times 3.

IT MTX   (dose for age) day 31, 38, 45 and 52 weekly for three weeks.

6-Mercaptopurine   60mg/m^2/day, PO days 29-57 starting on day 28 for 28 days.

Cytarabine   75mg/m^2, SC starting day 30 daily for four days and repeating every

week for 3 weeks.

Maintenance

6-Mercaptopurine   60mg/m^2 by mouth daily on weeks 10 to 18 and 29 to 130.

Methotrexate   20mg/m2 orally or IV weekly on weeks 10 to 18 and 29 to 130.

1.2.7   Treatment outcomes

The treatment outcomes in ALL can be:

Complete Remission (CR)

This is the complete killing of Leukemia cells to untraceable levels and this increases the chances of event free survival (EFS).

Relapses

This can be the CNS relapse, testicular relapse or even bone marrow relapse. This is basically the regrowing and reappearing of blasts and Leukemia cells in those areas. Children with relapse are said to be of poor prognosis and are often treated with more intensive and more toxic drugs.

Treatment Failure

This usually is when a patient is unresponsive to chemotherapy and is usually characterized by initial failure to achieve remission during induction phase. Treatment failure may spell a danger to the patient even death.

Different studies have reported different therapeutic outcomes for different countries and places. For instance, in the Netherlands, Veerman et al (1996) had reported EFS of 81% (SE=3%) Survival rate of 85% (SE=2.9%) and CNS replace of 1.1 %. [46]. In Greece Tzortazatou et al(2001) equally have reported a 5year overall and event free survival rates of 86% and 83% respectively. The 5 years overall survival rates for good risk and high risk groups were 94% and 81% respectively. The corresponding event free rates were 91% and 78% [47].

Another study carried out In India in by Aduan et al (1999), reported a CR in 91.3% patients and relapse in 29.9%. Going by risk groups those with WBC count < 60 000/m3 without lymphadenopathy had 77% EFS at 5years.   Those   with   WBC   <6000/mm3   with

lymphadenopathy had 53% EFS and those with WBC >60 000 and HB 6gm/al or above and 48% EFS while those with WBC > 60000 and HB below 6g/dl had only 16% EFS [48].

In the United States several studies have shown different outcomes one of them is that carried out by Steinheuz et al (1998) which reported CR of 97% at induction. The overall EFS +- standard deviation at 4% was 60% 6years after diagnosis in contrast to a historic group which reported 36% +- 6% SD. The EFS of the 371 T-cell Patients was 62% +-7 %SD. It was best in NY at 67% +- 7% and the BFM regimen at 67%+-6% arms. Testicular varied from (2-8 %) compared to 28% in historic group [49].

In conclusion Pui et al(2008) has summarized major international study groups and trials on treatment of childhood ALL and has found it to be between (70-80) % five year EFS with an overall cure rate of approximately 80% with a prospect of attaining a cure rate of 90% in the near future [50].

1.3   PROBLEM STATEMENT

Worldwide the therapeutic management and clinical outcomes of acute lymphoblastic Leukemia has shown a steady increase and improvement over time from 40% to almost 90% in most developed countries. However, there is minimal data reflecting the situation in developing countries. The data presented by the developed and high income countries with high social economic status may not be necessarily representative of the overall worldwide situation.

Anecdotal data in Kenya speculates that the incidence of relapse for ALL in children is high and the treatment outcomes are poor. Survival rate has been noted to be low. The use of newer regimens and the ideal one as highlighted in the Kasili's protocol has not been adopted due to limitations in availability of L- Asparaginase which is not only costly but also lacks a local

distributor. It is thought that for a season in 2005, when L-asparaginase was available in KNH, treatment outcomes improved, even though it was used in very few patients. However, this has not been supported with any designed study. In view of the above observations, it is important to have a study conducted to evaluate and describe in detail the reality of the situation.

1.4   JUSTIFICATION OF THE STUDY

Treatment of ALL in childhood has been one of the success stories for the last three decades. According to Pui *et al* (2005) over 80% of patients achieve a remission lasting more than 5 years in most developed countries. So this study endeavors to find if the success stories reported by other countries compare with our local setting specifically in KNH, the largest public hospital offering cancer treatment in the country.

There has been no recent work done on evaluating outcomes in treatment of Leukemia since 1978, when Kasili *et al* did a study in prevalence of Leukemia in Kenya. With recent introduction of new medicines and regimens, there is need for a local study to provide additional information to the data bank for the management of ALL in this country.

In the Kasili's protocol, which is mostly used as a guideline in treatment of most cancers in Kenya, there are two regimens given as option A and B (as described in our literature review). The one that is commonly used is the older one (option A), even though option B is more suitable .Therefore, there is need to evaluate the clinical outcomes of this regimen and give recommendations.

According to the 66th WHO general assembly paper, more emphasis has been put on communicable and infectious disease which has led to a significant neglect of non-communicable diseases including cancers like ALL. This study is aimed at giving attention to

non-communicable diseases (cancers) for the betterment of improved service delivery in their management.

This study will identify gaps and hence may help the policy makers and oncologists to revise the treatment guidelines.

1.5   OBJECTIVES

1.5.1   General Objective

To describe the chemotherapeutic management and to evaluate the clinical outcomes of ALL among children at KNH.

1.5.2   Specific Objectives

1.   To determine the prevalence of various subtypes of ALL based on morphological classification that is L1-B-precursor cells, L2-T-precursor cells and L3-B cells in children seen at KNH.

2.   To find out the clinical outcomes of ALL patients in relation to the therapeutic management instituted.

3.   To determine the frequency of use of various chemotherapeutic agents/regimens of ALL in KNH

4.   To identify factors correlated to the treatment outcomes of ALL in KNH

CHAPTER TWO: METHODOLOGY

2.1 Ethical Consideration

Permission to carry out research was sought from the KNH/UON Ethics and Research Committee before the research was conducted (Appendix 2).

There were no risks involved for the patients since the research involved retrospective review of patients files hence no direct patient involvement.

For confidentiality, the patients' files were only used within the confines of medical department of KNH and only the investigator, the assistants and the personnel of medical records department had access to the files for the purposes of the study. The patient names were not included in the data collection forms and instead, numbers were allocated to each patient files. All the filled data collection forms were filed and stored by the investigator in a locked drawer.

2.2 Study design

The study was a descriptive retrospective cohort that followed treatment outcomes from the time of diagnosis and initiation of treatment. All incident cases of pediatric ALL seen at KNH from January 2001 to December 2010 were reviewed. The design was described as retrospective since it entailed an evaluation of historical data. It was a cohort study since we were dealing with patients of similar condition. It was descriptive in nature since it did not involve comparison of two or more study arms.

2.3   Study Area

The study was conducted at KNH medical records department. KNH is the largest referral hospital in East Africa. The site was appropriate because it is the largest public hospital that provides cancer management and treatment services. It is also the facility with top oncology experts in the country hence justifying the large number of referrals to the hospital.

Most patients from all over the country are referred here because ALL is managed by specialists in an inpatient pediatric oncology clinic .The medical records department unit has a database and records which facilitated a retrospective study.

2.4   Study population

The study population was pediatric patients aged 0-15years who were diagnosed and treated for ALL at KNH between January 2001 and December 2010 covering a 10 year period. The time period was selected because KNH archives inactive patient medical records after every ten years therefore patient records for children seen before 2001 were not available and shorter period would not have given us a sufficient sample size since ALL is a rare disease. Those seen beyond December 2010 were excluded since they were not followed up for a sufficient time given that treatment of ALL takes 18-24months.

2.4.1   Eligibility/ Inclusion criteria

The patients included in this study met the following criteria

- Aged between 0- 15 years

- Diagnosed with ALL with confirmatory Laboratory tests

- Diagnosed between 2001 and 2010

2.4.2   Exclusion criteria

- Patients above 15 years of age

- Patients whose data on therapeutic management was missing.

- Patients diagnosed before 2001 or after 2010

2.5   Sample Size Determination

A sample of 384 patients was initially intended for study but only 171 files were available and eligible for study. The initial sample size was calculated in assumption of the anecdotal prevalence of 50% successful treatment outcomes and 5% level of significance. The Fischer *et al* formula for determining sample size was used;

$$n = \frac{Z^2 pq}{d^2}$$

Where;

n = Sample size

Z = 1.96   Standard normal deviation at required confidence level

p = 0.5   Assumed prevalence or proportion

q = 1 − 0.5 = 0.5

d = 0.05   Precision

$$n = \frac{1.96^2 \times 0.5 \times 0.5}{(0.05)^2} = \textbf{384 patients}$$

2.6 Sampling method

A list of all cases of ALL was provided but due to limited number of ALL coupled with mixing of files with different diagnoses; universal sampling was applied whereby all available and

eligible files were studied. A total of 450 files were provided but only 171 files were eligible for the study.

| A list of 450 files were provided as ALL cases from 2001 -2010 |

83 files contained different diagnoses and not ALL.

| 367 files were identified as ALL cases |

77 files could not be traced.

17 files were children above 15 years

56 files had no therapeutic management documented anywhere, volume 2, or had no documentation of either the disease or management

46 files were outside the study period

| 171 files were finally used for the study |

Figure 1: Sampling Frame

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2.7 Data collection

A pre-designed data collection tool (Appendix I) was pre-tested and used in collecting the relevant data. Patient demographics and characteristics at diagnosis, subtype of disease, chemotherapy regimens and other relevant history were recorded.

2.8 Data Quality Assurance procedures

A serialized data collection tool was used to avoid confusion and duplication of the data. The data collection tool was pre-tested before use. This was done by randomly sampling 10 patient files. Necessary modifications were done where inconsistencies or inadequacies were noted. After data collection, at least 10% of the total numbers of patients' files were reviewed by an independent m.med. (Pediatrics and child health) student who was not affiliated to the study who also filled a separate data collection form for comparison with the investigator's data and minor differences were noted in only one case. After complete information entry to form a database, data cleaning was done before analysis.

2.9   Data management

2.9.1   Data management

Data collection tools were serialized to minimize chances of data loss. Each participant's file was identified by a unique number to avoid confusion and duplication of the data. The unique identifier was used when transferring the file data into the data collection tool.

2.9.2   Data entry

Data collected was entered daily using statistical package for the social sciences (SPSS) software 9 version 12.0. At the end of every session of data entry, the data was examined for any

inconsistencies and rectified by verifying information as soon as possible from the data collection tool. Any missing variables were noted and rectified. Double data entry was used to check on discrepancies in data entry. The biostatistician set up a suitable database.

2.9.3 Data storage

For confidentiality and security, data was password protected and backed up at intervals of 2 weeks. A copy of the backed up and filled data collection tools was stored under lock and key where only the researcher and the biostatistician had access.

2.10 Statistical Analysis

Descriptive data analysis was carried out on all variables. For continuous variables the mean and standard deviation was reported. For all other variables the frequency distributions were reported. Inferential data analysis was conducted using as the Chi-test to compare for differences across regimens or patient groups. Associations were determined between treatment failure, outcomes and risk factors.

Key variables that determined prognosis were identified using logistic regression modeling.

In this, mortality was the independent variable. Covariates included patient demographics, treatment regimens and disease characteristics. A forward stepwise approach was used for model building. P-values of less than 0.05 were considered statistically significant.

2.11 Definition of cases

A diagnosis of ALL included an elaborate record in the patient's file with confirmed laboratory finding. The support data included any one of the following:-

- Full blood count film, differential WBC count (high) including thrombocytopenia with blasts of pancytopenia or without blasts.

- Bone marrow aspirate confirming morphology and cytochemistry

- Tissue infiltration i.e lymphadenopathy, Splenomegaly (common in ALL), hepatomegaly

- Severe anaemia and bleeding

- High urate and CNS involvement

- Testicle involvement

2.12 Variables, outcome of Interests and Confounders

The outcome of interest were treatment outcomes which included complete remission at induction phase, treatment failure, relapse of disease and mortality. The secondary outcomes were overall survival and event free survival by the end of 2 years. The covariates/independent variables included: treatment duration, age, gender, regimens used, and subtype of ALL.

CHAPTER THREE: RESULTS

3.1 Baseline Demographics Characteristics of the Study Population

Data were available for 171 children between the ages of 1 and 15 years treated for ALL at KNH from 2001 to 2010. The average age at ALL diagnosis was 6.69 years. The percentage age distribution in table 1 shows that most patients were aged below 5 years and specifically between 3 to 5 years (33.3%). There were 100 (58.5%) male children in the study. Among the mothers of children in this study 77 (45.0%) were unemployed while 53 (31.0%) of fathers were in salaried employment and 40 (23.4%) fathers were self employed.

Table 1: Demographic characteristics of the study population

	Number of patients	Percent
Sex		
Female	71	41.5
Male	100	58.5
Age		
Below 2 years	16	9.4
3 to 5 years	57	33.3
6 to 9 years	50	29.2
10 to 15 years	48	28.1
Father's occupation		
Salaried	53	30.99
Self employed	40	23.39
Unemployed	24	14.04
No response	54	31.58
Maternal occupation		
Salaried	15	8.77
Self employed	29	16.96
Unemployed	77	45.03
No response	50	29.24

Figure 2 shows that Central and Eastern provinces contributed the highest number of participants with these regions being represented by 61 (35.7%) and 42 (24.6%) patients respectively. Western and North Eastern provinces had the lowest number of patients in the study.
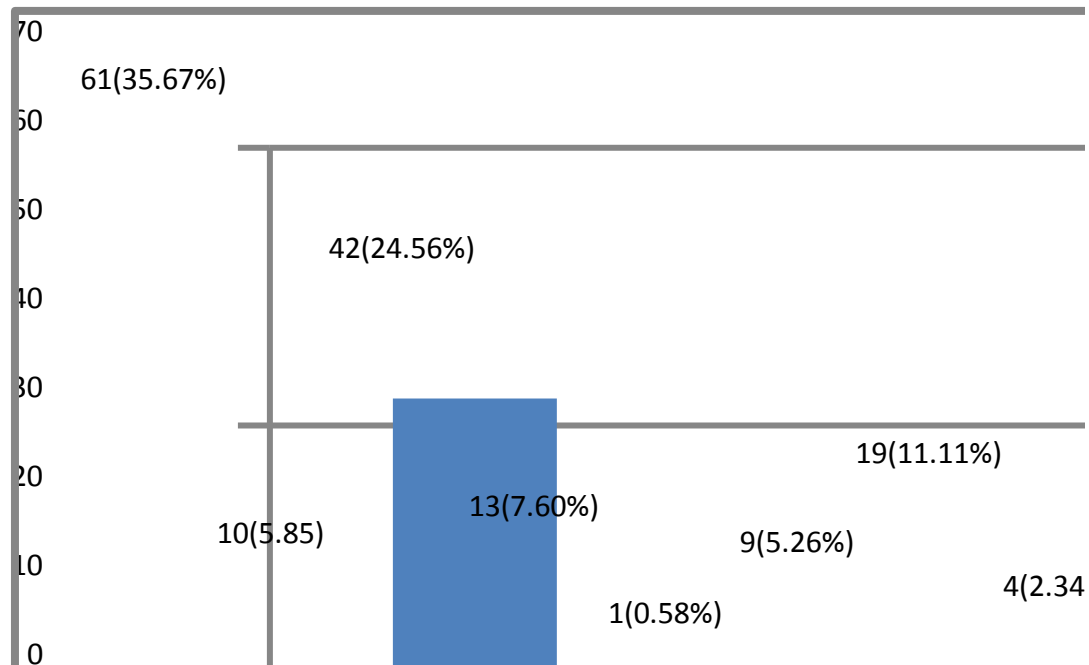
Figure 2: Residence of Pediatrics patients presenting with ALL at KNH

3.2   Prevalence of ALL Subtypes

The prevalence of various subtypes of ALL based on morphological classification in children seen at KNH are presented in Figure 1. L2-T-precursor cells were the predominant classification occurring in 137 (80.1%) of patients followed by L1-B-precursor cells, seen in 16 (9.4%) of cases. Only one (0.6%) child had and L3-B cells. Among the 17 children with uncharacterized ALL diagnosis 14 (82.4%) had histopathological report showing 2 cases with B cells, and 1 case with Precursor-T cells.
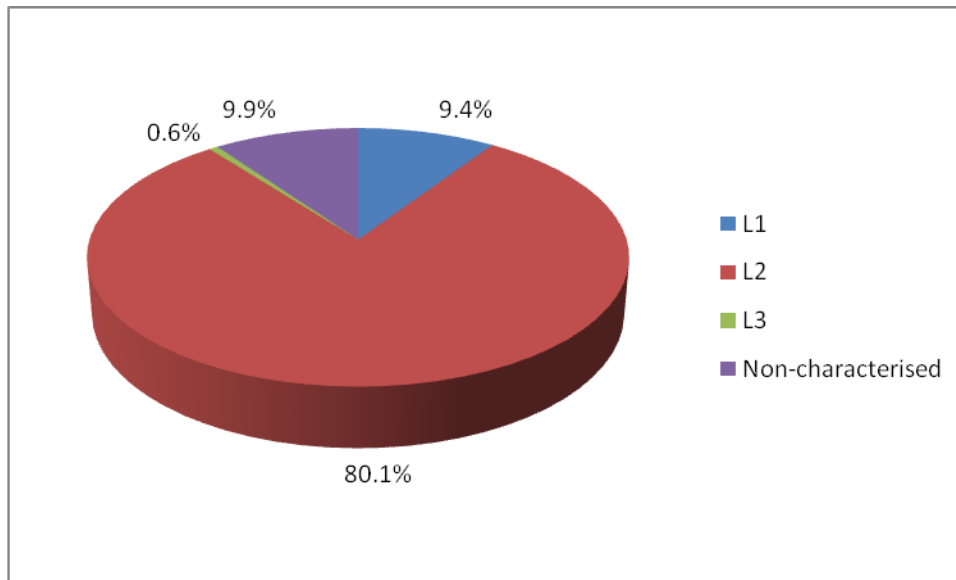
Figure 3: Prevalence of various sub - types of ALL at KNH between 2001 and 2012 based on morphological classification

None of the cases of the ALL in this study reported a family history of ALL. Figure 4 shows that metastasis or infiltration had occurred in 20 (11.8%) cases at the time of diagnosis and that the most common site of metastasis was the CNS.
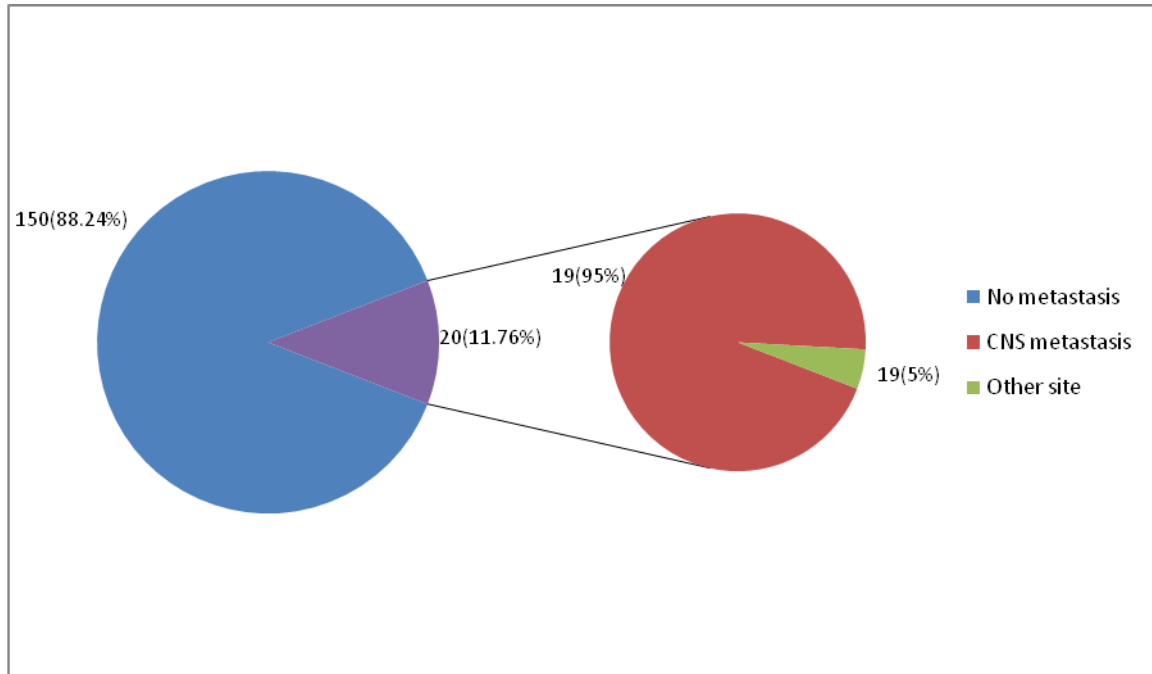
Figure 4: Metastatic sites at diagnosis of ALL in pediatric patients at KNH

The most common clinical feature among ALL patients was anemia in 147 (86.0%) children, Table 2. Other common clinical features were lymphadenopathy 83 (48.5%) and hepatomegaly 82 (48.0%). Except for hyperuricemia, the clinical features of ALL did not show statistically significant associations with subtype of ALL diagnosis (**p** values > 0.05, Table 2). Hyperuricemia was the least common presentation but was a frequent presentation among non characterized ALL (5 out of 17) while it was not reported in L1 or L3 subtypes and only occurred in 11(8.0%) L2 cases (**p** = 0.025).

Table 2: Clinical features among children presenting with ALL at KNH for the period 2001-2010

	L1(n=16)	L2 (n=137)	L3 (n=1)	Non characterised (n =17)	Total (n =171)	P value
Anemia	15	114	1	17	147 (86.0)	0.218
Lympadenopathy	7	68	0	8	83 (48.5)	0.939
Hepatomegaly	5	68	0	9	82 (48.0)	0.402
Splenomegaly	7	51	0	8	66 (38.6)	0.781
Neutropenia	7	46	0	6	59 (34.5)	0.819
Bleeding	2	46	1	7	56 (32.8)	0.103
Hyperuricemia	0	11	0	5	16 (9.4)	0.025

3.3 Chemotherapeutic Management of ALL

Among the 171 children with ALL 150 (87.7%) were managed on KNH 1 regimen. Eight cases (4.7%) were managed using alternative regimens (either KNH 2, n =2 or "other regimen", n = 6) while 13 (7.6%) had not had any treatment instituted (Table 3). One hundred and fifty one (88.3%) patients had undergone induction phase and 87(50.9%) of the patients had proceeded till maintenance phase.

Table 3: ALL treatment regimens and type of patients managed using different regimens at KNH (percentages in brackets)

	Type of regimen			
	KNH 1	**KNH2 or Other**	**Total**	**P value**
Age, n = 171				
Below 2 years	13(8.67)	0(0)	13(8.23)	0.363
3 to 5 years	52(34.67)	2(25)	54(34.18)	
6 to 9 years	44(29.33)	5(62.5)	49(31.01)	
10 to 15 years	41(27.33)	1(12.5)	42(26.58)	
ALL subtype, n = 171				
L1	15(10)	1(12.5)	16(10.13)	0.450
L2	123(82)	6(75)	129(81.65)	
Non-characterized	12(8)	1(12.5)	13(8.23)	
Blood film, n = 138				
Positive blasts	114(87.69)	8(100)	122(88.41)	0.596
Negative blasts	16(12.31)	0(0)	16(11.59)	
Histology classification, n = 153				
Positive blasts	141(96.58)	7(100)	148(96.73)	1.000
Negative blasts	5(3.42)	0(0)	5(3.27)	
Metastasis, n = 157				
Yes	19(12.75)	1(12.50)		1.000
No	130 (87.25)	7 (87.50)		
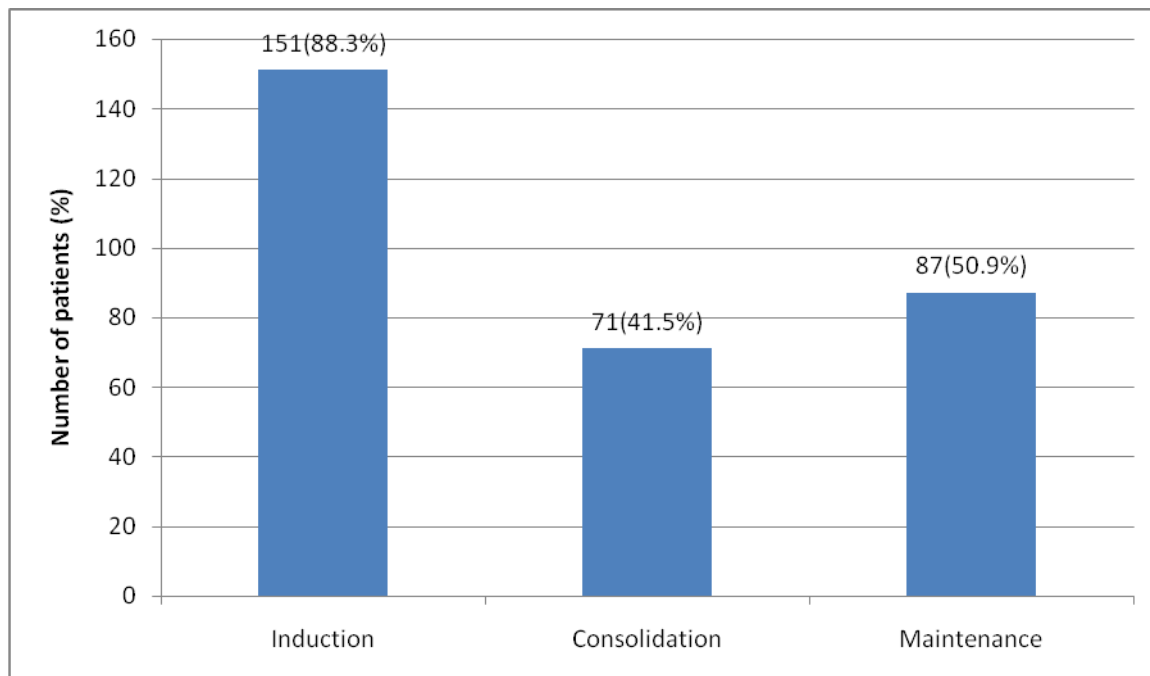
Phases of Treatment

Figure 5: Phases of ALL treatment undergone by pediatric patients at KNH

The type of regimen used in treating ALL did not show independent association with age of children, but all the 13 children aged 2 years or less were managed using KNH 1 regimen (**P** = 0.363). Most patients on both regimens had L2 subtype ALL representing 6 (75.0%) and 123 (82.0%) of patients managed using KNH 2 or other regimen and KNH 1 regimen, respectively (Table 3). All the patients with positive blasts either on blood film (n = 8) or histology (n = 7) were managed using KNH 1, KNH 2 and other regimen but these associations between regimen type and blood film or histology classifications were not statistically significant.

3.4 Clinical Outcomes of ALL Management

A total of five outcomes related to ALL chemotherapeutic management were investigated among the patients in this study (Table 4). Remission occurred following treatment in 105 (61.4%) cases. However, the most commonly occurring treatment outcome was mortality. During the study, 110 deaths occurred giving a case fatality rate of 64.3% among childhood cases of acute lymphoblastic leukemia at KNH. Eighty (46.8%) patients relapsed. The average duration to relapse of acute lymphoblastic leukemia was 12.98 months ((SD ±9.9), range 1 to 41 months. Extravasations and treatment failure rarely occurred (Table 4).

Out of the sixty one patients who were alive, 33 (54.1%) were followed up and duration of survival during and after treatment was established, while 28 (45.9%) were lost to follow-up. The absolute determination of the quality of live (QOL) including infection free live, activities, happiness and fulfillment was beyond the scope of this study.

Only 34(22.7%) of the 158 children in whom therapy was initiated achieved complete cure while 124(77.3%) did not get cured. Cure in this case refers to those who were able to achieve remission up to and including maintenance phase. Twenty three (67.6%) of those that achieved cure were alive while 11 (32.4%) died which indicates that the chances of survival after complete cure is higher than if the patient fails to achieve cure.

Table 4: Clinical outcomes of children with ALL at KNH during the period 2001-2010

Outcome	Number	Percent	
			28 (45.9%) QOL not established
Alive	61	35.67	33(54.1%) QOL established
Dead	110	64.33	
Extravasations			
Yes	5	2.92	
No	166	97.08	
Relapse			
Yes	80	46.78	
No	42	24.56	
Unknown	49	28.65	
Remission			
Yes	105	61.4	
No	25	14.62	
Unknown	41	23.98	
Treatment failure			
Yes	19	11.11	
No	112	65.5	
Not determined	40	23.39	

The common relapse sites are shown in Figure 6 below. ALL relapse occurred most frequently in the CNS, 60 (67.4%) followed by the bone marrow, 15 (16.9%). The site of relapse did not show statistically significant association with mortality (**p** values > 0.05).
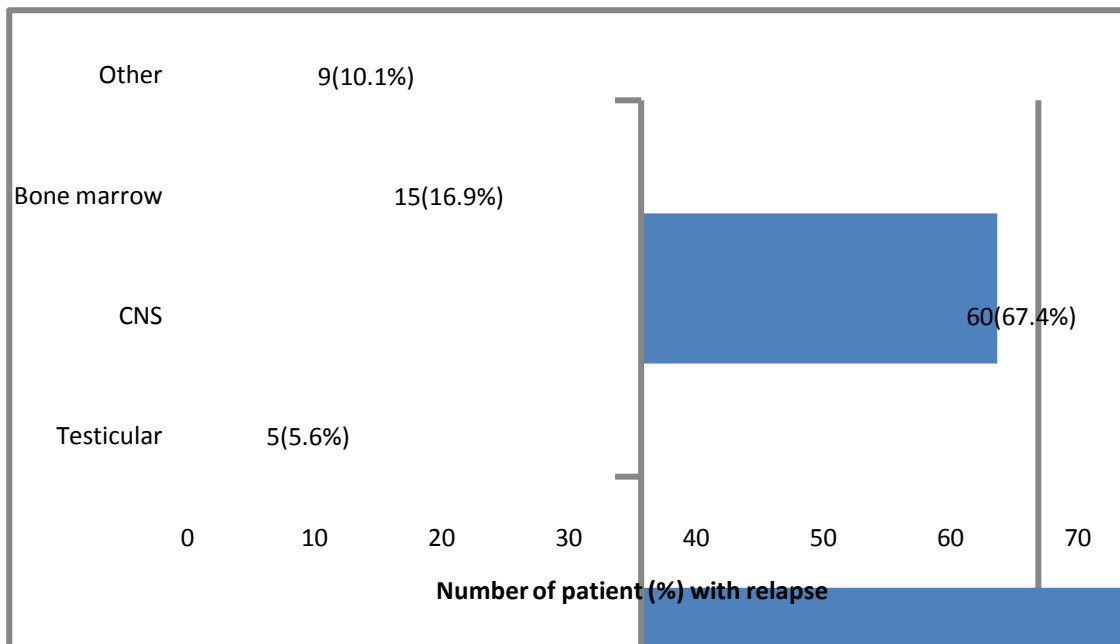
Figure 6: Sites of relapse among children with ALL at KNH

These treatment outcomes did not show a statistically significant association with the type of chemotherapeutic regimen used to treat ALL (Table 5). However, all the five cases of extravasations occurred in patients managed using KNH 1 regimen.

Table 5: Clinical outcomes of children with ALL at KNH according to treatment regimen

	Type of regimen		
	KNH 1	**KNH2 or Other**	**P value**
Outcome, n = 158			
Alive	59(96.72)	2(3.28)	0.712
Dead	91(93.81)	6(6.19)	
Extravasations, n = 158			
Yes	5(100)	0	1.000
No	145(94.77)	8(5.23)	
Relapse, n = 122			
Yes	77(96.25)	3(3.75)	1.000
No	41(97.62)	1(2.38)	
Unknown			
Remission, n = 130			
Yes	102(97.14)	3(2.86)	0.579
No	24(96)	1(4)	
Treatment failure, n = 131			
Yes	108(96.43)	4(3.57)	1.000
No	19(100)	0	

Survival Functions According to Regimen

The median duration of follow up of patients with ALL was 17.97 months, range 2 days to 9.1 years. Kaplan Meier survival functions for patient on the two main regimens are shown in figure 7 below. As shown in the figure, patients on KNH regimen 1 had cumulatively higher survival probabilities. However, results of the log rank test comparing survival probabilities for patients on the two regimens showed that the two groups of patients did not have statistically significantly different cumulative survivals, (**p** =0.279).
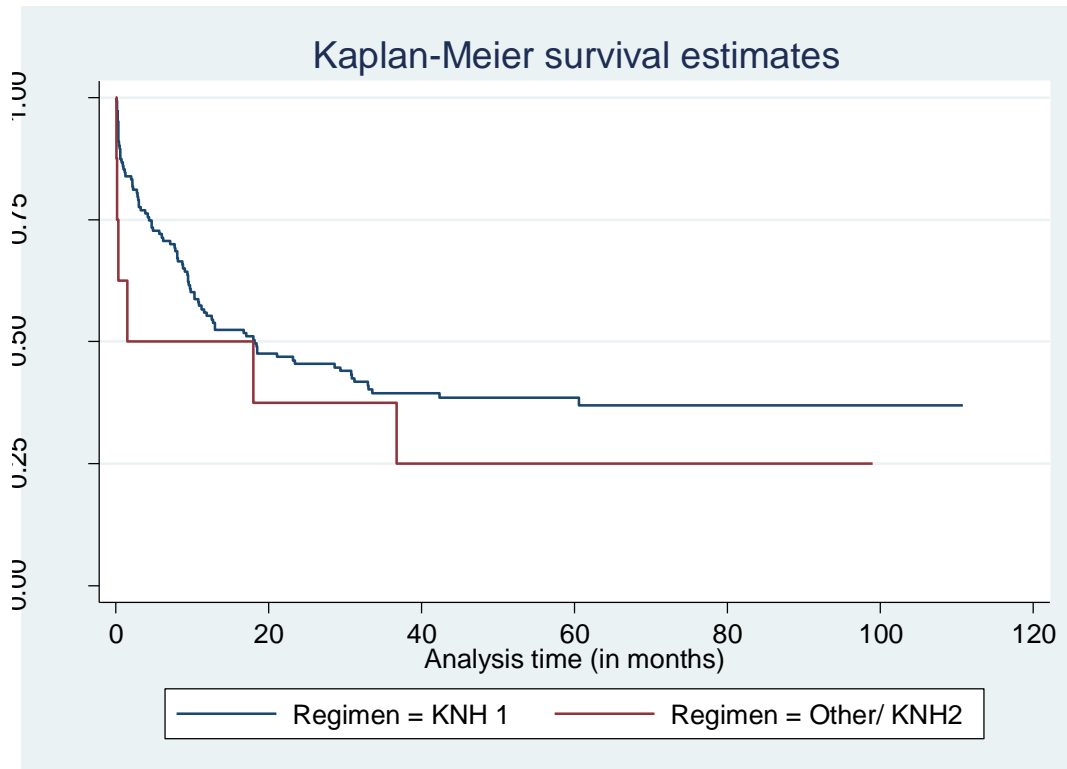
Figure 7: Kaplan - Meier Survival Estimates

3.5 Factors Correlated to the Treatment Outcomes of ALL in KNH

Mortality as an outcome of treatment did not show a statistically significant positive association with any of the basic demographic characteristic of the patients including: age ($p = 0.985$), sex ($p = 0.97$), maternal occupation ($p = 0.098$) or paternal occupation ($p = 0.119$). The patient characteristics that showed significant association with mortality as a treatment outcome were: blood film ($p = 0.011$), failure to initiate a regimen ($p = 0.005$) and absence of remission ($p < 0.0010$), Table 5. Specifically, most patients who died (94.6%) had positive blasts on blood film compared to 79.6% of patients who survived and had positive blasts. All the 13 patients for whom therapy was not initiated died.

Table 6: Clinical outcomes of children with ALL at KNH in relation to various factors (Percentages in brackets)

	Outcome		
	Alive **n (%)**	**Dead** **n (%)**	**P value**
Blood film, n = 146			
Positive blasts	43(79.63)	87(94.57)	0.011
Negative blasts	11(20.37)	5(5.43)	
Histology classification, n = 153			
Positive blasts	58(96.67)	102(97.14)	1.000
Negative blasts	2(3.33)	3(2.86)	
Regimen initiated, n = 171			
No	0(0)	13(11.82)	0.005
Yes	61(100)	97(88.18)	
Metastasis, n = 170			
Yes	9(15)	11(10)	0.332
No	51(85)	99(90)	
Treatment phase during remission, n = 171			
Failure	11(18.03)	55(50)	< 0.001
Induction	3(4.92)	18(16.36)	
Consolidation	24(39.43)	26(23.64)	
Maintenance	23(37.70)	11(10)	

The associations between the clinical features of patients on presentation with ALL and the outcome of chemotherapeutic management are shown in table 6. Two of these clinical features: bleeding (**p** < 0.001) and splenomegaly (**p** = 0.032) showed statistically significant associations with the outcome of mortality. For splenomegaly, 44.6% of the children who died had splenomegaly compared to 27.9% of the children who survived. Bleeding was also more common among the children who died (42.7%) compared to those who survived (14.8%).

Table 7: Clinical features among children presenting with ALL at KNH and mortality

	Alive (n = 61)	Died (n = 110)	P value
Anemia	52(85.25%)	95(86.36%)	0.822
Lympadenopathy	34(55.74%)	49(44.55%)	0.161
Hepatomegaly	31(50.82%)	51(46.36%)	0.576
Splenomegaly	17(27.87%)	49(44.55%)	**0.032**
Neutropenia	26(42.62%)	33(30.0%)	0.096
Bleeding	9(14.75%)	47(42.73%)	**<0.001**
Hyperuricemia	3(4.92%)	13(11.82%)	0.176

3.6 Regimen change

A total of 31 (18.13%) patients had their chemotherapeutic regimen changed. Four of the patients were changed to KNH 2 regimen and the remaining 27 to "other" chemotherapeutic regimens. The reason for regimen change was not commonly documented in the clinical notes. In instances where documentation was available the reasons for regimen change were as follows: treatment failure (n = 3), cost (n = 1) and other reasons (n = 1). Seven (36.84%) out of the 19 cases of treatment failure had their regimen changed as did 17(15.45%) of the children who died. Change of regimen did not show statistically significant association with mortality ($p = 0.204$), remission ($p = 0.792$) or treatment failure ($p=0.399$).

The findings of the multivariable logistic regression analysis of the factors associated with mortality are shown in Table 8. In this adjusted analysis two factors namely bleeding and blood film findings showed independent statistical association with mortality. The odds of death among children with a negative blood film blast was 80% lower (OR = 0.2, 95 CI 0.06-0.68) compared to that of children with a positive blast. The odds of death among children presenting with bleeding was five-fold higher than that of children who did not have bleeding.

Table 8: Logistic regression analysis of independent predictors of chemotherapeutic outcome (mortality) among ALL pediatric patients at KNH

	Odds Ratio(OR)	P- value	[95% Conf. Interval]
No splenomegaly	1.00		
Splenomegaly	**1.75**	**0.16**	**0.80-3.79**
No bleeding	1.00		
Bleeding	**5.19**	**0.00**	**1.93-13.95**
Positive blood film	1.00		
Negative blood film	0.20	0.01	0.06-0.68

CHAPTER FOUR: DISCUSSION

Demographic characteristics of the study population.

The percentage age distribution in this study showed that most patients were aged below 5 years and specifically between 3 to 5 years (33.3%).

The age distribution is closely related to the findings by Ries *et al* in the USA who found the peak age in ALL incidence to be between 2-5 years, with a decrease to the lowest incidence of ages 8 years and above. In this study, it was concluded that incidences of ALL among children aged 2-3 years was approximately four fold greater than that of infants and nearly ten fold greater than that of adolescents above 15 years[11]. Similar findings have been documented by Shah *et al* in England and Wales where the peak age was around 3-4 years and then it declines with progress in age [12].The male preponderance in our study also agrees with the study carried out by Lisa *et al* [51].

Prevalence of ALL subtypes

In this study, L2-T-precursor cells were the predominant classification occurring in 80.1% of patients followed by L1-B-precursor cells (9.4%). Only one (0.6%) child had and L3-B cells.

The prevalence of ALL subtype strongly agrees with the study carried out by Kadan *et al* which found out that black children seem to have higher incidence of T-cell ALL than other races, this according to FAB classification of ALL is ALL-L 2 [30].

Clinical features among children presenting with ALL

In this study, the most common clinical feature among ALL patients was anemia. Other common clinical features were lymphadenopathy and hepatomegaly.

These findings are similar to those that have been documented by Karen *et al* that patients with acute lymphoblastic leukemia commonly have physical signs of anemia including pallor and cardiac flow murmur. About 10-20% also present with left upper quadrant fullness and early satiety which is splenomegaly [53].

Chemotherapeutic Regimen

The use of the locally modified regimen which excludes L-Asparaginase by such a big percentage is by far a contrast to the international standards of the popular studies mostly in developed countries where L-Asparaginase is central to the treatment guidelines and protocols. This regimen has shown high cure rates and more favorable outcomes than our regimen in major studies [50].

Our study was unable to conclusively give a fair comparison across regimens due to the small number of patients that were put on the second regimen 2(1.3%) which includes L-Asparaginase compared with 150(94.9%) that were put in the KNH1 regimen.

Clinical Outcomes of ALL Management

Our cure rates of 22.7% are by far too low in comparison to the internationally reported cure rates of 90% in a study done by Hunger *et al* which was attributed to improved diagnosis and treatment [52].The number of survivors in this study of 23 patients (14.6%) is also low compared to the reports from meta-analysis done by Pui et al [50] which reported survival rates of 70-80 %.

The poor outcome for both the cure rates and survival rates could not be immediately established in this study as most of them were statistically insignificant. However, most of the international studies have included L- asparaginase as part of the treatment regimens and protocols unlike our settings. The efficacy of regimens with L-asparaginase could not be conclusively established in our study due to the small number of patients who used the regimen in our case (n=2), compared to other regimens without L-asparaginase that is KNH 1 and other (n=156) [48, 50].

According to Lund *et al* the poor therapeutic outcome can possibly be in addition to other factors due to the T-cell subtype (ALL-L2) of acute lymphoblastic leukemia which in their study not only has poor outcome but also high mortality than other subtypes [56].Given that the most predominant subtype in KNH is T-cell, it can be theorized as one of the reason for the high mortality.

Factors Correlated to the Treatment Outcomes of ALL in KNH

The patient characteristics that showed significant association with mortality as a treatment outcome were: blood film ($p = 0.011$), failure to initiate a regimen ($p = 0.005$) and absence of remission ($p < 0.0010$).

The findings in this study however are a contrast to the findings by Hussein *et al* who successively established a correlation between age and mortality. In their study they found out that younger children aged 1-10 years had better response to therapy than those who are older than 10 years. But the study strongly agrees that slow early response to therapy or absence of remission lead to high mortality [54].

Two of the clinical features: bleeding ($p < 0.001$) and splenomegaly ($p = 0.032$) showed statistically significant associations with the outcome of mortality.

Related findings have been documented by Asim *et al* in their study who found out that hemorrhage (bleeding) was the second major reason for mortality at 10.8% among acute lymphoblastic leukemia patients only to all infections combined which was attributed to 85% of the total mortality [55]. The association of splenomegaly with mortality was not comparable to any known study yet.

CHAPTER FIVE

5.0 CONCLUSION

The most predominant subtype of ALL was found to be L2-T precursor cell with 137cases (80.1%) followed by L1 B precursor cells with 16 cases (9.4 %) and lastly L3 or B cell with 1case (0.6%). Seventeen cases (9.9%) were not characterised.

Mortality was the most commonly occurring treatment outcome with 110 deaths giving a case fatality rate of 64.3% among childhood cases of ALL in Kenya. Initial remission occurred in 105 cases (61.4%). Eighty (46.8%) of patients had a relapse, and the commonest site of relapse was CNS at 60 (67.4%).

Cure rate was 34 (22.7%) of the 158 children in whom therapy was initiated compared to 124(77.34%) children who did not get cured. Twenty three (67.6%) of those that achieved cure were alive while 11 (32.4%) died. Extravasations and treatment failure at the initial stages of therapy rarely occurred.

Among the 171 children with ALL, 150 (87.7%) were managed on KNH 1 regimen. Eight cases (4.7%) were managed using alternative regimens (either KNH 2, n =2 or "other regimen", n = 6) while 13 (7.6%) had no treatment instituted.

The patient characteristics that showed significant association with mortality as a treatment outcome were: blood film (p = 0.011), failure to initiate a regimen (p = 0.005), absence of remission ($p < 0.0010$).

Clinical features that showed statistically significant associations with the outcome of mortality were bleeding ($p < 0.001$) and splenomegaly ($p = 0.032$).

5.1 RECOMMENDATIONS

A controlled study comparing two regimens that is the KNH 1 and L- asparaginase based regimen is recommended. This is due to the limited number of patients on the L- asparaginase regimen at KNH which couldn't give a conclusive comparison and dependable results.

The poor cure rates and overall survival during and after treatment compared to the international findings are very alarming. A qualitative study on true causes of mortality and poor outcomes apart from the regimens instituted needs to be done.

Most patients came from Central and Eastern Provinces of Kenya. A relationship between geographical location and ALL needs to be established by an epidemiological study.

A five or more year event free survival (EFS) study needs to be done to establish the survival rates and factors related to the same.

The rate of loss to follow-up was very significant. Some of it could have been attributed to the long distances that patients travelled to get treatment at KNH. We recommend for establishment of satellite sites to deal with satellite patients from outside Nairobi.

Policy makers and other stakeholders in ALL therapy should revise the guidelines on ALL treatment in the light of poor outcomes as we wait for a controlled study to establish the overall efficacy of newer regimens.

ALL like other aggressive childhood cancers has proved to be fatal without proper management, therefore in agreement with the 66th WHO general assembly paper emphasis should be put on non-communicable diseases by allocation of more resources on research, awareness, diagnosis and treatment by various governments including the government of Kenya.

As a clinical pharmacist together with my colleagues wish to play a major role in the revision and implementation of up to date chemotherapeutic regimens in not only for ALL but also other oncology guidelines.

5.2 STUDY LIMITATIONS

The anticipated sample size of 384 files which could have given us unprecedented sensitivity and precision was not achieved due to unavoidable reasons. Consequently, the precision for this study was reduced to 0.07(7%) from the intended 0.05(5%), by the sample size of 171. The 2% precision difference however did not alter the study adversely. In addition, the study was retrospective in nature and therefore the information obtained from the records could not be verified or clarified.

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APPENDICES

APPENDIX 1:   DATA COLLECTION FORM

Study eligibility checklist

Date --   Study serial number-----------------

Data Collector's initials --

File study code number ---

Inclusion Criteria (if any of the inclusion statement below is marked "NO" the file is not

included in the study.

YES (   )   NO (   ) Patient is below 15 years

YES (   )   NO (   ) Patient has been diagnosed with ALL

YES (   )   NO (   ) Patient diagnosed before Jan 2001 & Dec 2010

A)   Participant's Details

1.   Age(years) [   ]

2.   Sex   M[   ]   F[   ]

3.   Weight (kg) [   ]

4.   Body Surface Area (BSA) in M^2 [   ]

5.   Age at diagnosis (years) [   ]

6.   Residence: Current [   ] Permanent[   ]

7.   Parents Occupation: Father: Salaried [   ] Self-Employed[   ] Unemployed[   ]

                    Mother: Salaried [   ] Self-Employed[ ] Unemployed[   ]

8.   Parents education level:

Father: Non-formal [   ] Primary [   ] Secondary[   ]   College/Univeristy[   ]

Mother: Non-formal [ ] Primary [   ] Secondary[   ]   College/Univeristy[   ]

9.   Year of diagnosis date[ ]Month[ ]Year20[   ]

B)   Information about the disease

10.   Subtype of ALL: L 1 [   ]   L2[   ]   L3[   ] Not characterized [   ]

11.   If not characterized histopathological report present:Yes[   ]   No[   ]

12.   IF yes cell type identified:Precursor-B cells[   ] Precursor-T cells[   ] B-cells[   ] Non[   ]

13.   Any history of ALL in the family? Yes [   ]   No[   ]

14.   Had the disease metastasized at diagnosis? Yes[   ]   No[   ]

15.   If disease metastasized, site? CNS[   ]   Testicular[   ]   Other[   ]

16.   Histological classification: BMA +ve blasts[   ]   -ve blasts[   ]

17.   Blood films if available: +ve blasts[   ]   -ve blasts[   ]

18.   Clinical signs: Lymphadenopathy[   ] Splenomegally[   ] Hyperuricemia[   ]

Neutropenia[   ] Anaemia [   ] Bleeding[   ]hepatomegally[   ]

19.   Philadelphia chromosome if test available: +ve[   ]   -ve [   ]

C)   Treatment information

20.   Regimen instituted: Date[ ]Month year[   ] Year[   ]

   British regimen [   ] KNH regimen 1[   ]KNH Regimen 2 [   ] Other[   ]

21.   Phases of treatment underwent Induction [   ] Consolidation[   ] Maintenance[   ]

22.   Supportive treatment given (Tick where applicable)

Antiemetic   [   ]   Platelets [   ]   Antibiotics [   ] Allopurinol [   ]   Whole

blood [   ]   IV Fluids [   ]   Neupogen[   ]   Other[   ]

D)   Treatment outcomes

23.   Death[   ] Date[   ] Month[   ]Year[   ]

24.   Treatment failure:Yes[   ]No[   ]

25.   Extravasations? YES[   ]   NO[   ]

26.   Complete remission? YES[   ]   NO[   ]

27.   If complete remission at? Induction[   ]   Consolidation[   ]   Maintenance[   ]

28.   Relapse of the disease: YES[   ]   NO[   ]

29.   Time to occurrence of relapse, in months[   ]

30.   If relapse, type of relapse? Testicular[   ]CNS[   ] Bone marrow[   ]Other[   ]

31.   Change of regimen? YES[   ]   NO[   ]

32.   If regimen changed to which one? British regimen [   ] KNH regimen 1[   ]KNH

Regimen 2 [   ] other[   ]

33.   Any other reasons for drug change if any? ADR/Toxicities[   ] Non availability of drug[   ]

Prohibitive cost[   ] Treatment Failure[   ] Co-morbidity[   ] Other[   ]

34.   Response to any therapy given after relapse if applicable:Remision[   ] No remission[   ]

35.   Overall outcome at end of therapy: Alive[   ]Dead[   ]

36.   If dead:Date[   ]Month[   ]year[   ]

E)   Quality of Life (QOL)

37.   Surviving since diagnosis and after treatment?

<3 months   [   ]   3-<6 months [   ]

 6-<12 months [   ]   12-<18 months [   ]

 18-<24 months [   ]   ≥24 months   [   ]

APPENDIX 2: ETHICS APPROVAL

UNIVERSITY OF NAIROBI
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P O BOX 19676 Code 00202
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KENYATTA NATIONAL HOSPITAL
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Tel: 726300-9
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Ref: KNH-ERC/A/81

17th April 2012

Dr. Bob Nyaribari Agwata
Dept.of Pharmaceutics & Pharmacy Practice
School of Pharmacy
University of Nairobi

Dear Dr. Agwata

RESEARCH PROPOSAL: "A TEN YEAR RETROSPECTIVE STUDY ON THE THERAPEUTIC MANAGEMENT AND CLINICAL OUTCOMES OF ACUTE LYMPHOBLASTIC LEUKEMIA AMONG CHILDREN AT KENYATTA NATIONAL HOSPIAL, KENYA (JANUARY 2001-DECEMBER 2010" **(P122/03/2012)**

This is to inform you that the KNH/UoN-Ethics & Research Committee (ERC) has reviewed and **approved** your above revised research proposal. The approval periods are 17th April 2012 to 16th April 2013.

This approval is subject to compliance with the following requirements:

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

For more details consult the KNH/UoN -ERC website **www.uonbi.ac.ke/activities/KNHUoN**

Yours sincerely

PROF A.N. GUANTAI
SECRETARY, KNH/UON-ERC

c.c.   The Deputy Director CS, KNH
        The Principal, College of Health Sciences, UON
        The Dean, School of Pharmacy, UON
        The Chairman, Dept. of Pharmaceutics and Pharmacy Practice, UON
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