CHILDHOOD ACUTE LEUKEMIA IN TANZANIA; CLINICAL PRESENTATION, HEMATOLOGICAL PARAMETERS AND SURVIVAL RATE TWO YEARS FROM DIAGNOSIS.

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CHILDHOOD ACUTE LEUKEMIA IN TANZANIA; CLINICAL PRESENTATION, HEMATOLOGICAL PARAMETERS AND SURVIVAL RATE TWO YEARS FROM DIAGNOSIS.

By

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October, 2014

CERTIFICATION

The undersigned certify that she has read and hereby recommends for acceptance by the Muhimbili University of Health and Allied Sciences a dissertation entitled *'**childhood acute leukemia in Tanzania; clinical presentation, hematological parameters and survival rate two years from diagnosis'*** in partial fulfillment of the requirements for the degree of masters of medicine in Pediatrics and Child Health Muhimbili University of Health and Allied Sciences.

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Date

DECLARATION AND COPYRIGHT

I, **Judith Cosmas Lamosai**, Declare that this **dissertation** is my own original work and that it has not been presented and will not be presented to any other University for a similar or any other degree award.

Signature..... Date.....

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DEDICATION

To my husband Wolfgang and my sons Nathan and Ethan for always are there for me. And to my dear parents Mr. and Mrs. Cosmas Sirili Lamosai for showing me the value of education. I will always remain grateful and kind to all of you.

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ABSTRACT

Background: Acute childhood leukemia is a progressive malignant disease of the blood forming tissues arising within the bone marrow, characterized by the uncontrolled proliferation of immature leukocytes and their precursors replacing the normal hematopoietic cells of the bone marrow leading to bone marrow failure. There are two main types of acute leukaemia i.e. Acute Lymphoblastic Leukaemia (ALL) in which lymphoid progenitor cells undergo dysregulated proliferation, with clonal expansion and accounts for 77% of all leukemias occurring in children. Acute Myeloid Leukaemia (AML) on other hand is myeloid dysregulation and accounts for 11% of cases of childhood leukemias. With modern scientific and technological advances cure rate for childhood leukemia is possible in 90% among those with ALL and 76% among those with AML. However, in countries with limited resources cure rates are relatively lower. Description of the clinical presentation and survival rate of children with acute leukemia in Tanzanian is important so that necessary changes can be made to improve the outcome. In Tanzania there is lack of data on the clinical presentation, and survival rate of children with acute leukemia.

Objective: The broad objective of this study was to determine the clinical presentation, hematological parameters and survival rate two years from diagnosis in children aged less than 18 years with acute leukemia in Tanzania.

Materials and Methods: A retrospective hospital based cohort study was conducted at Ocean Road Cancer Institute (ORCI) and Muhimbili National Hospital (MNH), Dar Es Salaam (DSM) Tanzania, including data from 1st January 2008 to 31st December 2011. Data were collected from patient files using a questionnaire. Data collected were analyzed using statistical package for the social sciences (SPSS) version 20.

Results: A total of 193 patients' files were reviewed during this study. More than half of the patients were males (56.5%) with male to female ratio of 1.3: 1. Mean age at presentation was 8.23 years ± 4.73SD. (Range 1 – 18 years), 68.4% were 10 years and below. Majority (79.8 %) had ALL of which 56 % were males with mean age of 7.82 yrs ±4.49SD, for AML the mean age was 9.87 yrs ± 5.33 SD. Common presenting features

were found to be pallor/anemia (78.8%), fever and lymphadenopathy (70.5%), splenomegally (56%) and hepatomegally (53.4%). Thirty two percent had White Blood Cell (WBC) count >50 K/ul, 23% had platelet count <20 K/ul and 60% had severe anemia. For ALL survival rate was 66% at one year and 40% at two years from diagnosis; and for AML survival rate was 19% at one year and there was no survivor at two years from diagnosis.

Conclusions: Childhood acute leukemia in ORCI and MNH Tanzania commonly presents with pallor/anemia, fever and lymphadenopathy. More than half of the patients presented with severe anemia, splenomegaly and hepatomegaly. WBC count >50 K/ul is highly associated with increased mortality. Two years survival rate from diagnosis is poor especially for AML.

Recommendations: Clinicians should have a high index of suspicion for acute leukemia for children who present with persistent fever and anemia. Community health education is required in order to increase community awareness and to emphasize on early health care seeking behavior.

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LIST OF ABBREVIATIONS

ALL	Acute lymphoblastic leukemia
AML	Acute myeloblastic leukemia
BMA	Bone marrow aspiration
CNS	Central nervous system
CXR	Chest x ray
DFS	Disease free survival
DIC	Disseminated intravascular coagulation
DM	Diabetes mellitus
DS	Down syndrome
DSM	Dar Es Salaam
EFS	Event free survival
Hb	Hemoglobin
IT	Intra thecal
MNH	Muhimbili National Hospital
MRC	Medical Research Council
MUHAS	Muhimbili University of Health and Allied Sciences
ORCI	Ocean Road Cancer Institute
OS	Overall survival
PCP	Pneumocystic Carinii/ Jeroves Pneumonia
PI	Principal Investigator
SCA	Sickle cell anemia
UKALL2003	United Kingdom Acute Lymphoblastic Leukemia 20d03 protocol
WBC	White Blood cell Count

Definition of terms

1. Anemia – hemoglobin level < 11 g/dl
2. Severe anemia- hemoglobin level < 7 g/dl
3. Bleeding – spontaneous bleeding from any body part
4. Multiple swellings – swellings in more than one anatomical site including abdominal or neck swelling
5. Other swellings – body swelling other than neck and abdominal swelling

1.0 INTRODUCTION AND LITERATURE REVIEW

Acute childhood leukemia is a progressive malignant disease of the blood forming tissues arising within the bone marrow. It is characterized by uncontrolled proliferation of immature leukocytes and their precursors replacing the normal hematopoietic cells of the bone marrow leading to bone marrow failure. This is because the malignant cells have abnormally increased proliferating rate with decreased spontaneous apoptotic rate. It is mainly divided into two groups; Acute lymphoblastic leukemia (ALL) and acute myeloblastic leukemia (AML). ALL is characterized by malignant transformation occurring in a single abnormal progenitor cell which expands by uncontrolled self multiplication. Malignant transformation occurs as a result of spontaneous mutation occurring in B cell, T cell lineage or their precursors. AML is characterized by malignant transformation and proliferation of myeloid lineage cell precursors including monocytes, granulocytes, erythrocytes and megakaryocytes [1-3]

Etiologies of most childhood leukemias involve genetic-environmental interaction; viral factors have also been implicated. The initiating genetic event occur to hematopoietic cells during fetal development in uterus for most precursor B cell ALL and some AML. This first event is enough to create a malignant clone for some leukemias but for some, further genetic change is required occurring probably postnatal [1-4].

People with an abnormal number of chromosomes and chromosomal translocation (chromosomal abnormalities) have an increased risk of developing leukemia. Environmental factors like ionizing radiation (diagnostic or therapeutic) exposure prenatally or postnatally, chemicals e.g. benzene and drugs e.g. cyclophosphamide increase the risk of developing leukemia. Little evidence is available to supports the role of viral transformation in causing leukemia [1-3.]

Worldwide childhood leukemia accounts for 41% of all childhood malignancies, with ALL making 75-77% of childhood leukemia while AML contributing 11-15% [1, 2]. Studies done in Cote d'voire and Nigeria showed that acute leukemia account for 4% and 16.9% of all childhood malignancies respectively [5, 6.]

Studies done in Kenya in 2012 and 1999 showed that ALL accounts for 15% and 7.6% of all childhood malignancies respectively [8,9]. Similar studies done in Egypt (Cairo), Nigeria and Sudan showed that ALL accounts for 87%, 65.5% and 19.8% of all childhood leukemia respectively [7,10, 11.] Acute myeloid leukemia has a low prevalence compared to ALL. Studies done in Nigeria and Kenya showed that AML accounts for 37% and 5.1% among all childhood malignancies [9, 10.]

In Tanzania an unpublished study done by Chirande Lulu regarding clinicalpathological characteristics in childhood malignancies found that ALL accounted for 10.6% of all malignancies occurring in children [12.]

Incidences of leukemia show higher rates in developed countries than in developing countries. This can be explained by good diagnostic facilities which go hand to hand with the economic status of the country [4.]

Acute lymphoblastic leukemia occurs more common in boys than in girls at all age group with a peak incidence between 2 – 6 years [1, 13, 14.]

1.1 Clinical presentation of childhood leukemia.

Manifestations of leukemia occur as a result of replacement of bone marrow by malignant cells and/or secondary to bone marrow failure.

Initial manifestations include anorexia, fatigue, irritability, low grade fever and bone or joint pain with or without joint swelling. As the disease advances features of bone marrow failure become evident including pallor, fatigue, bleeding e.g. epistaxis, petechie, purpura, ecchymosis or mucous membrane hemorrhage and fever secondary to infection. Features reflecting proliferative nature of the disease include lymphadenopathy, splenomegaly and less commonly hepatomegaly. Features of increased intracranial pressure indicating CNS involvement include papilledema, retinal hemorrhage and cranial nerve palsies. Bone tenderness and/or joint swelling can be present in patients with bone or joint pain. Deep bone pain without tenderness may occur with bone marrow involvement. Respiratory distress syndrome may occur as a result of anemia or obstructive airway problem as a result of large anterior mediastinal mass in the thymus or nodes. Respiratory symptoms are common in adolescent boys with T- cell ALL which also present with higher leukocyte counts. Median leukocyte count at presentation is 33,000. Half to three quarters of patients have leukocyte count <20,000. Three quarters of patients have thrombocytopenia, 30-68% have hepatosplenomegaly, 5% present with CNS symptoms. Testicular and ovarian involvement can also occur. Patients can also present with acute kidney injury, stroke, disseminated intravascular coagulopathy and tumour lysis syndrome as complications. Features common to AML but uncommon to ALL include subcutaneous nodules (blueberry muffin lesions), gingival infiltrations, CNS symptoms, DIC and chloromas (granulocytic sarcomas). Chloromas are commonly associated with the M2 subtype of AML with t (8; 21) translocation [1-3].

In a study done by Ma *et al* in Hong Kong regarding clinical presentation among children with ALL, bone and joint pain were found to be commonest presenting features followed by fever, hepatosplenomegally and lymphadenopathy [15].

Similar study done by Yasmeen *et al* in Pakistan showed that commonest features at presentation were fever and anemia which accounted for 86%, lymphadenopathy 75%, hepatomegally 67% and splenomegally 58%. In 34% of their patients initial WBC count was >50,000/mm3 while in 54% of patients hemoglobin (Hb) was <7g/dl and 33% had platelet count <20,000. Only 5% of patients presented with CNS disease[13.]

Togo did a study in Bamako which showed that 75% of children diagnosed with ALL were cachectic at presentation, 83% had lymphadenitis, splenomegally and hepatomegally. Seventeen percent had neurologic involvement while 83% had initial WBC count >50,000/mm3. [14]

Another study done by Williams *et al* in Nigeria showed that 54% of AML patients had chloromas[10], while Nakimbugwe in Uganda found that acute leukemia commonly presents with anemia (93.2%) and fever (89.3%) [16.]

1.2 Prognostic indicators

Adverse prognostic indicators include male gender, age less than one year or above ten years, high WBC count at diagnosis, poor response to induction therapy, unfavorable cytogenetic like presence of Philadelphia chromosome and high level of minimal residual disease at 28 days[1, 3, 17]

In a study done by S. M. NG *et al* in Malaysia showed that age less than one year, high WBC count, high hemoglobin level (≥ 11g/dl), and male gender had significant relationship to prognosis [18]

Another study which was done by Johnston *et al* in United Kingdom showed that male sex is a poor prognostic indicator[19].

Similar study conducted in Poland by Badowska also showed that male sex is a poor prognostic indicator, it also showed that Hb > 10 g/dl is associated with poor prognosis[20].

1.3 Diagnosis

Diagnosis of a child with suspected leukemia begins with proper history taking and physical examination. Early involvement of hematologist and pediatric oncologist is important in work up of a child with suspected leukemia. Initial evaluation involves complete blood count and differential count (diagnosis and risk assessment), peripheral blood smear (diagnosis), bone marrow aspirate (diagnosis), bone marrow trephine biopsy (diagnosis), lumbar puncture for CSF cytospin (diagnosis, prognostic indicator), immunophenotyping (diagnosis), cytogenetic (diagnosis, prognostic indicator), molecular genetics (diagnosis, prognostic indicator) and chest radiograph (diagnosis) [21].

In ALL bone marrow is replaced by homogenous infiltrate of lymphoblasts >25%. Lymphoblasts are small approximately 14 micrometers in diameter with scant cytoplasm and no granules. Nucleus lacks nucleoli or have small indistinct one. For AML 30% of nucleated cells in the aspirate must be blast cells of myeloid origin. Myeloblasts are characterized by multiple large nucleoli, delicate chromatin, and gray blue cytoplasm and Auer rods [1, 22].

In Tanzania cytogenetic and molecular genetics are not done due to lack of resources.

1.4 Treatment

Treatment of acute leukemia includes chemotherapy and supportive care due to complications which can arise secondary to the disease itself or as a result of treatment.

1.4.1 Chemotherapy

Children diagnosed with leukemia are treated following regimens which are developed by national or international cooperative groups. Treatment is primarily by chemotherapy as leukemia is a systemic disease and it consists of several phases. Initial therapy known as remission induction lasting for 4 weeks is designed to eradicate leukemic cells from the bone marrow. In this; patients are given drugs like dexamethasone or prednisone, vincristine, asparaginase, daunorubicin). The next phase known as consolidation/intensification focuses on CNS therapy in order to prevent later CNS relapse. Intensification (cytarabine, cyclophosphamide, etoposide, dexamethasone, asparaginase, doxorubicin, MTX, 6-MP, vincristine); consolidation (MTX, 6-MP, cytarabine, cyclophosphamide). The last phase known as maintenance phase aims at removing residual disease, it takes 2 – 3 years depending on the protocol used, (drugs like MTX, 6-MP, vincristine pulses, glucocorticoid). Bone marrow transplant is necessary for some high risk patients especially those with Philadelphia chromosome [1-3.]

Treatment of AML involves the use of intensive multi agent chemotherapy in order to induce remission. Almost all chemotherapy regimens include combination of an anthracycline (most often daunorubicin [daunomycin]) with cytosine arabinoside (cytarabine). Other drugs include fludarabine, etoposide, amsacrine, dexamethasone, 6-thioguanine, cyclophosphamide, and mitoxantrone. This intensive chemotherapy causes severe pancytopenia and patients are at greater risk of infections, bleeding and anemia. Infections and bleeding are the major causes of mortality and these patients require good supportive care to help them recover. After remission is attained, matched sibling donor bone marrow or stem cell transplant help to achieve long term disease free survival in 60 – 70% of patients and help to prevent relapse [1-3.] For further information on the medications used, refer appendix 2.

1.4.2 Supportive care

Supportive care include use of intravenous fluid to reduce blood viscosity in patients with high WBC counts which puts them at risk of stroke, allopurinol (urate oxidase) to prevent renal failure which can occur as a result of high levels of serum uric acids, blood and platelet transfusion for hematologic derangements, empirical antimicrobial therapy for infection in patients with febrile neutropenia and Pneumocystic Carinii/Jeroves Pneumonia (PCP) prophylaxis during and for several months following treatment completion. [1-3]

1.5 Complications

These can occur as a result of disease itself or secondary to treatment. Acute complications include tumor lysis syndrome, renal failure, sepsis, bleeding, thrombosis, encephalopathy and seizures. Long

term complications include secondary malignancy, growth hormone deficiency, learning disability and cognitive defects[1]

1.6 Outcome of childhood leukemia

Factors affecting outcome include, age of the patient, initial leukocyte count at diagnosis, sex of the patient and response to induction treatment [1-3]. Factors associated with poor prognosis include age less than one year (Infantile ALL) or above 10 years, initial WBC count >50 k/uL, male sex and poor response to induction treatment. Other factors associated with poor outcome though not reflected in this study include unfavorable cytogenetic feature like presence of Philadelphia chromosome and hypodiploidity. Moreover AML carries a poor prognosis as compared to ALL. [1]

Studies in developed countries showed that 5 years survival rate for children with ALL range between 70-86% while in developing countries survival rates are lower 38% [1, 23-25]

A study done by Quah in Singapore showed that AML survival was poor with 30% disease free survival (DFS) after 2 years, for ALL DFS at 2 years was 62%. It was also found that patients who had marked hepatosplenomegally at diagnosis (enlarged liver and/or spleen >or =10cm below coastal margin) had significant shortened survival in patients with ALL[26.]

In a study done by Togo in Mali regarding characteristic of children with ALL found that 33.3% of patients died 5 years after starting treatment.(5years survival rate 66.7%) [14]

Dakka N *et al* in Morocco found that 5 year survival rate of ALL was 38% [25]

The same study done in Nigeria by William showed that only 18% of ALL patients were alive after one year following standard chemotherapy [10.]

In another study conducted in Uganda by Nakimbugwe showed that, initial response to treatment for ALL was 39.7% and for AML was 26.7%. Cure rates at 2 years for ALL was 17.5% and for AML was 2.9% with overall cure rate of 20.4%. Mortality rate for ALL was found to be 68% while for AML was 11.6% with overall mortality rate of 79.6%. For both types of leukemia there was no patient who was alive at 5 years from diagnosis[16.]

2.0 PROBLEM STATEMENT

In developed countries significant progress has been made in treatment of childhood leukemia. This has led to high cure rates and hence high survival rates of about 80 - 90% for ALL and 76% for AML in these settings. Mortality rates for acute lymphoblastic leukemia (ALL) directly correlate to country income. In developing countries 5 years survival rates are poor, about 38% for ALL. This is because developing countries with limited resources like Tanzania have poor health care system and delivery of effective cancer therapy is difficult leading to low survival rates. Also patients have limited access to curative treatment because of low social economic status. [1, 15, 25 27]

A study conducted in Pakistan showed that ALL commonly present with fever and anemia, lymphadenopathy, hepatomegally and splenomegally. Half of their patients had severe anemia, 34% had WBC > 50,000/mm3, and 33% had platelet count <20,000/mm3. [13] A study which was done in Uganda showed that acute leukemia commonly presents with anemia and fever. [16]

In Tanzania there is lack of published data on clinical presentation and survival rate of children with acute leukemia.

This study aimed to determine the clinical presentation and survival rate of children with acute leukemia at ORCI and MNH Tanzania from January 1, 2008 to December 31st, 2011. The findings of this study are therefore expected to fill the existing knowledge gap in our setting.

3.0 RATIONALE

In order to improve leukemia outcomes in developing countries, a better understanding of the disease`s clinical presentation is required.

Description of the clinical presentation of children with acute leukemia in Tanzanian is important so that necessary changes can be made to improve the outcome of these children and increase the survival rate.

This study aimed to provide baseline data on clinical presentation of children diagnosed with acute leukemia (ALL and AML) at ORCI and MNH Tanzania from January 1st, 2008 to December 31st, 2011 and determine survival rate two years from diagnosis with current treatment regimen (UK ALL 2003).

3.1 Research questions

1. What is the clinical presentation and hematological parameters of children with acute leukemia at ORCI and MNH Tanzania?

2. What is the association between the prognostic indicators and mortality in children with acute leukemia at ORCI and MNH Tanzania

3. What is the survival rate of children with acute leukemia two years from diagnosis at ORCI and MNH Tanzania**?**

4.0 OBJECTIVES

4.1 Broad objective

To determine the clinical presentation, hematological parameters and survival rate of children under age 18 yrs with acute leukemia two years from diagnosis at ORCI and MNH Tanzania.

4.2 Specific objectives

4.2.1. To determine the clinical presentation of children with acute leukemia at ORCI and MNH Tanzania.

4.2.2. To determine the hematological parameters at presentation in children with acute leukemia at ORCI and MNH Tanzania

4.3 Secondary Objective

4.3.1. To determine and compare the survival rate two years from diagnosis of children with ALL and AML at ORCI and MNH Tanzania.

4.3.2 To determine the association between selected prognostic indicators and mortality in children with acute leukemia at ORCI and MNH Tanzania.

5.0 MATERIALS AND METHODS

5.1 Study design

Retrospective hospital based cohort study where information was obtained through medical file review.

5.2 Study area

The study was conducted at ORCI and MNH, DSM Tanzania. ORCI has been the only referral center giving care for patients with malignancies in Tanzania. In April 2011 pediatric oncology unit was transferred from ORCI to MNH, which has a bed capacity of 53. Currently MNH is the only referral center providing service for children with malignancies in Tanzania. MNH is one of the four tertiary hospitals in the country; it is also a teaching hospital for MUHAS which has undergraduate and postgraduate students. In 2012 roughly 250 children were diagnosed to have malignancies at MNH and out of these 29% were having acute leukemia. There is inpatient service and outpatient service. In Tanzania patients with malignancies are treated for free, the cost being covered by the Government. The medications are funded by the Government and multiple donors and are given to patients free of charge except for some expensive ones like L-asparagines which the patient has to contribute.

5.2.1 Treatment at ORCI and MNH Tanzania

In ORCI and MNH Tanzania children with ALL are treated following UKALL (United Kingdom acute lymphoblastic leukemia) 2003 protocol comprising of 5 phases; induction, consolidation, interim maintenance, delayed intensification and maintenance. Patients are grouped into two, low risk group who are given regimen A of treatment and high risk group who are given regimen B of treatment. Low risk group is characterized by WBC at presentation $\leq$ 50K/ul, age between 1 and 10 years and complete remission following induction phase of treatment. Girls with low risk are treated for 112 weeks and boys for 164 weeks.

High risk group is characterized by WBC count at presentation >50K/ul, age below one year or above 10 years and poor response following induction phase of treatment. In this group girls are treated for 114 weeks and boys for 166 weeks.

Initially children with confirmed AML were not treated at ORCI, they were sent home on palliation. From June 2008 children with AML were treated with 6 thioguanine, etoposide and cytarabine as per an unpublished regimen utilized in the Tata Memorial Hospital in Mumbai India or were treated as per modified arm of the Medical Research Council AML trial 15(MRC AML 15) protocol. MRC AML 15 protocol include induction therapy which has two courses (course 1 and course 2) followed by consolidation phase which also has two courses (course 3 and course 4). From late 2012 AML

patients are no longer given treatment at MNH. This is because the drugs used to treat AML are very toxic and the supportive care is limited in our setup. The drugs are given in high dose and they tend to cause profound pancytopenia. At this time patients require aggressive supportive care including isolation in special rooms to prevent infections, timely blood product transfusion and antibiotic therapy of which constant availability is a problem in our setup. When patients attain remission, they need to undergo bone marrow transplant so that they can be able to produce enough normal hematopoietic stem cells. This will help them stay in remission for a long time if relapse does not occur. In Tanzania bone marrow transplantation is not done and the patients need to go outside the country to get it done.

5.2.2 Archiving of medical records

Patient files are kept in the hospital`s medical records, but medical files for children with malignancies are kept in a separate place within the oncology unit. The files for the deceased are kept in the same room but separate place from those of live patients.

5.2.3 Challenges

There is no constant supply of drugs

Staff number is not sufficient; during the study period there were no specialists in the oncology ward as compared to now where there are three specialists. Also there is inadequate number of pathologists, there are only 9 pathologists serving the whole Hospital. Nurses are also not enough, there are only 24 nurses working in the pediatric oncology unit.

There is no pediatric oncologist and we depend on pediatric oncologists from outside the country.

5.3 Study population and participants

All patients under age 18 years with clinical or confirmed diagnosis of Acute Leukemia in ORCI and MNH records from 1st January 2008 to 31st December 2011.

5.3.1 Inclusion criteria

All patients under age 18 yrs with a diagnosis of acute leukemia whose medical files had enough information within these four years were included in the study.

5.3.2 Exclusion criteria

All patients under 18 yrs with a diagnosis of acute leukemia whose files did not have information on presenting symptoms, signs and/or hematological parameters.

5.4 Sample size calculation

The following assumptions were used for calculation of sample size for comparing survival rates among ALL and AML:

- Survival rate after 5 years among patients with ALL = 38% [25]
- Survival rate after 5 years among patients with AML = 15% (assuming 23% difference)
- 5% significance level of a 2-sided test
- Power of 80%
- Ratio of ALL to AML =3 given that in a previous study, 73% of children with acute leukemia had ALL [12]

For an alpha level of 0.05, a minimum sample size of 38 with AML and 114 with ALL will be adequate to detect 23% difference in survival rate among children with acute leukemia with 80% power.

5.6 Sampling technique

In this study all patients' files which met the inclusion criteria were included by consecutive enrollment. The data in the records showed there were 264 children with acute leukemia in the four years of the study. Files which could be traced were 193, so the file retrieval rate was 73%.

5.7 Data collection method

Patients with a diagnosis of acute leukemia from January 2008 to December 2011were identified from register books and the patient file numbers were noted. Then using the file numbers, files were traced from patient`s records. From patients' files, variables on patient demography that is age, sex, and residence; date of presentation; disease presentation basing on symptoms the patients presented with; also the physical findings like pallor, splenomegaly, lymphadenopathy, hepatomegaly, bruising, bone or joint tenderness or joint swelling and presence of subcutaneous nodules. If a sign was not reported in the file it was considered as not present. Also recorded were the initial laboratory investigation results including hemoglobin level in g/dl, WBC count in K/uL, platelet count in K/uL and diagnosis being ALL or AML. Outcome within two years from diagnosis was recorded for all patients diagnosed with acute leukemia within these four years; that is either the patient is alive, dead or unknown status. Unknown status means there was no information regarding the status of the patient within two years from diagnosis. Also recorded was date of death if reported, date last seen for those who were alive and those with unknown status and time from presentation to date last seen or date of death. All these were entered in a questionnaire developed by the author.

A research assistant, whom I trained for one day on how to fill the questionnaire before the start of data collection, assisted with collection of data.

5.7.8 Key variables

Age, sex, patient symptoms, physical findings at presentation, initial laboratory investigation results, diagnosis, date of death or date last seen, time from presentation to date last seen or date of death.

6.0 DATA MANAGEMENT AND ANALYSIS

Data cleaning was done prior to analysis to check for errors and inconsistencies. Data analysis was done using Statistical Package for the Social Sciences (SPSS) version 20. Patient characteristics were described using frequencies and percentages for categorical variables, for continuous variables means (standard deviations) were calculated. The chi-square test was used to compare percentages. Kaplan Meier survival curves comparing different groups were plotted. Groups include; diagnosis (ALL and AML), sex (male and female), WBC count at presentation (≤ 50K/uL and > 50K/uL) and age groups (≤ 10 yrs and > 10 yrs). Comparison of the survival curves was done using the Log rank test. P values of less than 0.05 were considered statistically significant.

7.0 ETHICAL CONSIDERATION

Ethical approval to conduct the study was granted by Muhimbili University of Health and Allied Sciences Ethical Review Board and permission to do the study was obtained from the Hospital`s management. Data collected were kept confidential by not using patient names or file numbers in the questionnaires and during data entry, instead unique study numbers were assigned to each participant.

This study being retrospective, it was not possible to obtain consent from the children or their parents/guardian instead the permission to do the study was obtained from the Executive Directors of the Hospitals.

8.0 RESULTS

8.1 Social demographic characteristics and diagnosis of the patients studied

During the study period a total of 193 patient files with a diagnosis of acute leukemia were reviewed. File retrieval rate was 73% (193/264). Only two files were excluded from this analysis because of incomplete data. More than half (56. 5%) were males with male to female ratio of 1.3: 1. Mean age at presentation was 8.23 years ± 4.73SD. (Range 1 – 18 years), 68.4% were aged 10 years and below. Included in this group were two children who were below one year. One was seven months and the other was 10 months, both had clinical diagnosis of ALL. ALL was more common with a prevalence of 79.8%, of which 85 (55%)were males and 69(45%) were females with mean age of 7.82 yrs ±4.49SD, for AML 23(59%) were males and 16 were females with the mean age of 9.87 yrs ± 5.33 SD.

Close to half of the patients (40.9%) were from Dar Es Salaam (DSM), 9.3% were from Kilimanjaro, 7.8% from Zanzibar, 6.2% from Morogoro, 5.7% from Arusha, 5.2% from Singida. Other regions contributed smaller percentages. Mean duration of symptoms (from onset to reaching MNH/ORCI) was 12 weeks±13.112 SD (range 1 – 96weeks). This is as seen in Table 1

Table 1. Social Demographic characteristics and diagnosis of children under 18 years with acute leukemia at ORCI and MNH Tanzania 2008 to 2011 (n=193)

Characteristics	Frequency	%
Sex		
Male	109	56.5
Female	84	43.5
Age Group(years)		
*≤ 10	132	68.4
>10	61	31.6
Diagnosis		
ALL	154	79.8
AML	39	20.2

*2 were under one year

8.2 Hematological parameters of the studied patients at presentation

Of all children with acute leukemia, 32% presented with WBC count above 50 K/uL. Almost all (95%) had anemia; that is hemoglobin level below 11g/dl and 60% had severe anemia; that is hemoglobin below 7g/dl. Twenty three percent had platelet count below 20K/uL. These hematological parameters are summarized in Table 2

Table 2. Hematological parameters at presentation among children under 18 years with acute leukemia attended at ORCI and MNH DSM 2008 to 2011(n=193)

Parameter	Frequency	%
WBC (K/uL)		
≤ 50	132	68.4
>50	61	31.6
Platelet count(K/uL)		
≥20	148	76.7
< 20	45	23.3
Hemoglobin (g/dl)		
<7	115	59.6
7-10.9	69	35.7
≥ 11	9	4.7

8.3 Common presenting symptoms and signs in children with acute leukemia

Common presenting symptom in children with acute leukemia was found to be fever (70.5%), others are as shown in Figure 1 below

Common presenting signs were found to be pallor (78.8%), lymphadenopathy (70.5%), fever (66.8%), splenomegally (56%) and hepatomegally (53.4%). Bleeding accounted for 11.4%. This is shown in Figure 2 below

Figure 1. Presenting symptoms among children aged under 18 years with acute leukemia attended at ORCI and MNH DSM 2008 to 2011(n=193)

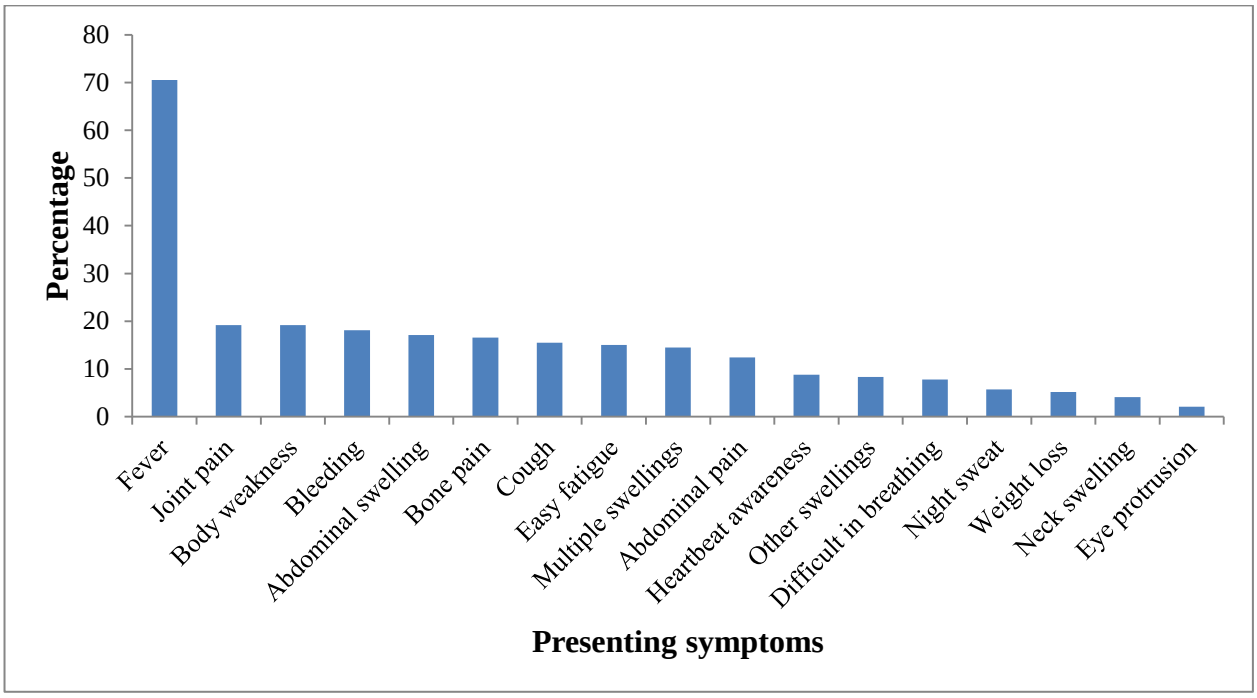
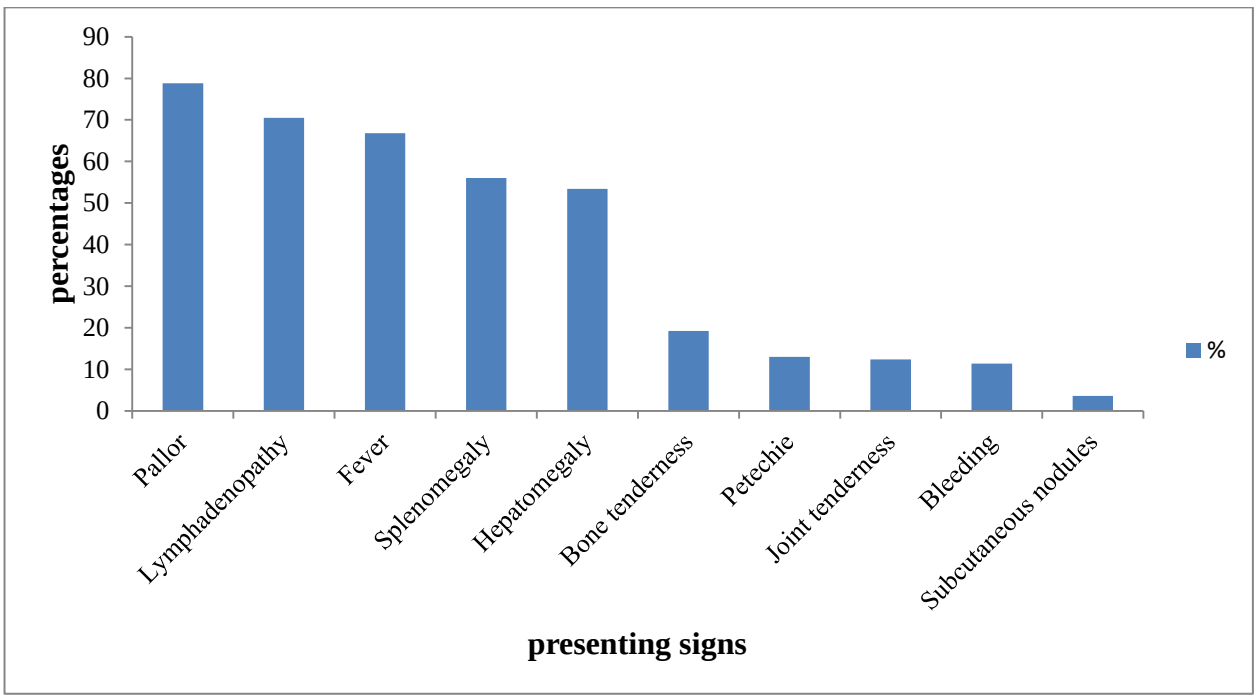


Figure 2. Presenting signs among children aged under 18 years with acute leukemia attended at ORCI and MNH DSM 2008 to 2011(n=193)



8.4 Association between selected prognostic indicators and mortality in children aged under 18 years with acute leukemia attended at ORCI and MNH DSM 2008 to 2011(n=193)

Majority (62%) of children with WBC count above 50 K/uL died within two years from diagnosis as compared to 45% of those with WBC count below 50 K/uL The difference between the two groups is statistically significant (p value = 0.023).

The results from this study show that 48% of all males with acute leukemia died within two years from diagnosis as compared to 54% among females. The difference between the two groups is not statistically significant. (p value = 0.419).

It also shows that 59% of all children above 10 years died within two years from diagnosis as compared to 47% below 10 years; again the difference between the two groups is not statistically significant (p value = 0.098).

More than half (61%) of the patients with anemia (as defined by hemoglobin level <11g/dl) died within two years from diagnosis as compared to those without anemia (43%).This is summarized in Table 4

Table 3. Association between selected prognostic indicators and mortality among children under 18 years with acute leukemia attended at ORCI and MNH DSM 2008 to 2011. (n= 193)

Variable	Frequency	Dead (%)	X^2 (df)	P-values
Sex				
Male	109	52 (48)	0.653 (1)	0.419
Female	84	45 (54)		
Age at presentation(years)				
≤10	132	62(47)	2.736(1)	0.098
>10	61	36 (59)		
WBC (K/uL)				
≤50	132	59 (45)	5.168 (1)	0.023
>50	61	38 (62		
Hb (g/dl)				
<11	184	94 (60.6)	1.022 (1)	0.351
≥11	9	3 (42.9)		

8.5. Survival rate in children with acute leukemia

Figure 3 shows that for ALL survival rates were 66% at one year and 40% at two years from diagnosis. For AML survival rate was 19% at one year and there was no survivor at two years from diagnosis. The difference between the two groups is statistically significant. (Log rank p value = 0.0001)

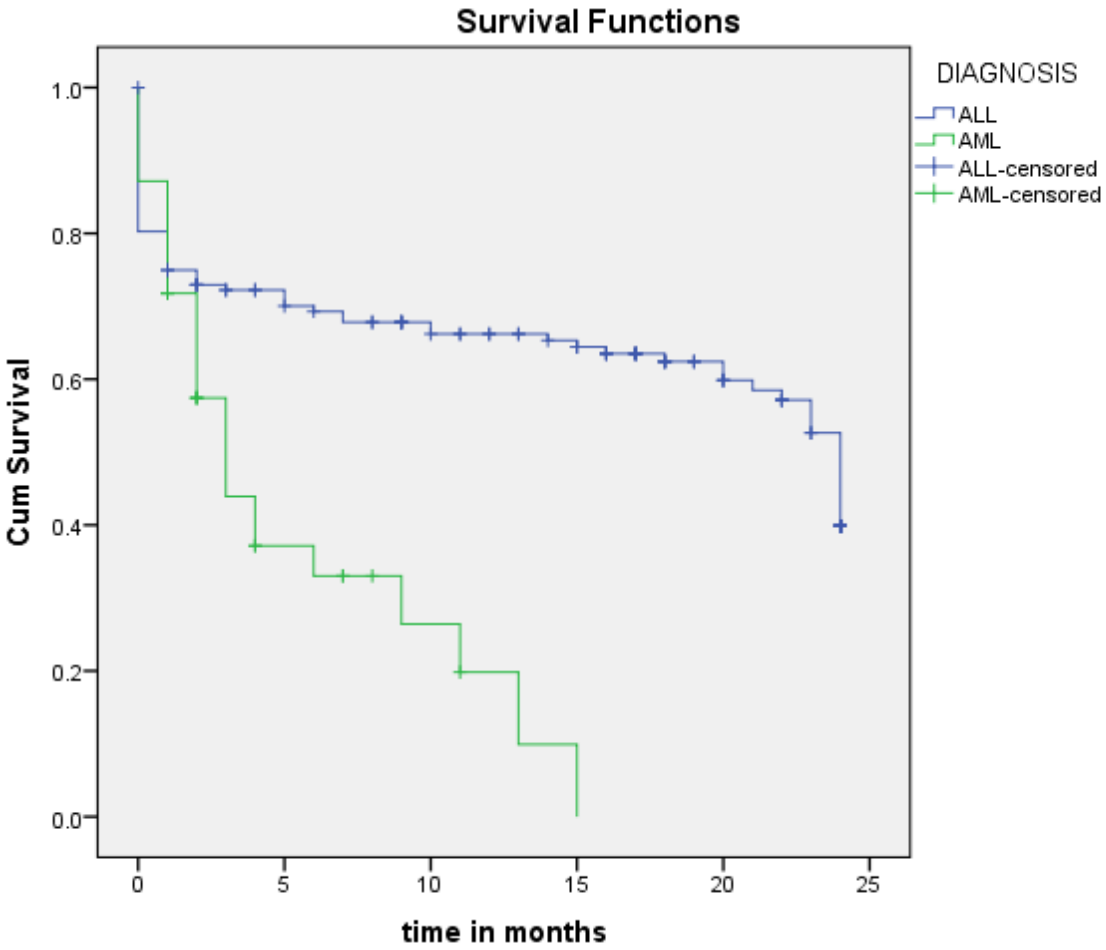


Figure 3. Kaplan Maier Survival curve showing survival probability for children with ALL and AML.

Figure 4 shows that those who had WBC count > 50 K/uL had survival rate of 50% at 12 months and 25% at 24 months, for those with WBC count ≤ 50 K/uL it was 65% at 12 months and 40% at 24 months. There is a statistically significant difference between the two groups. (Log rank p value = 0.010).

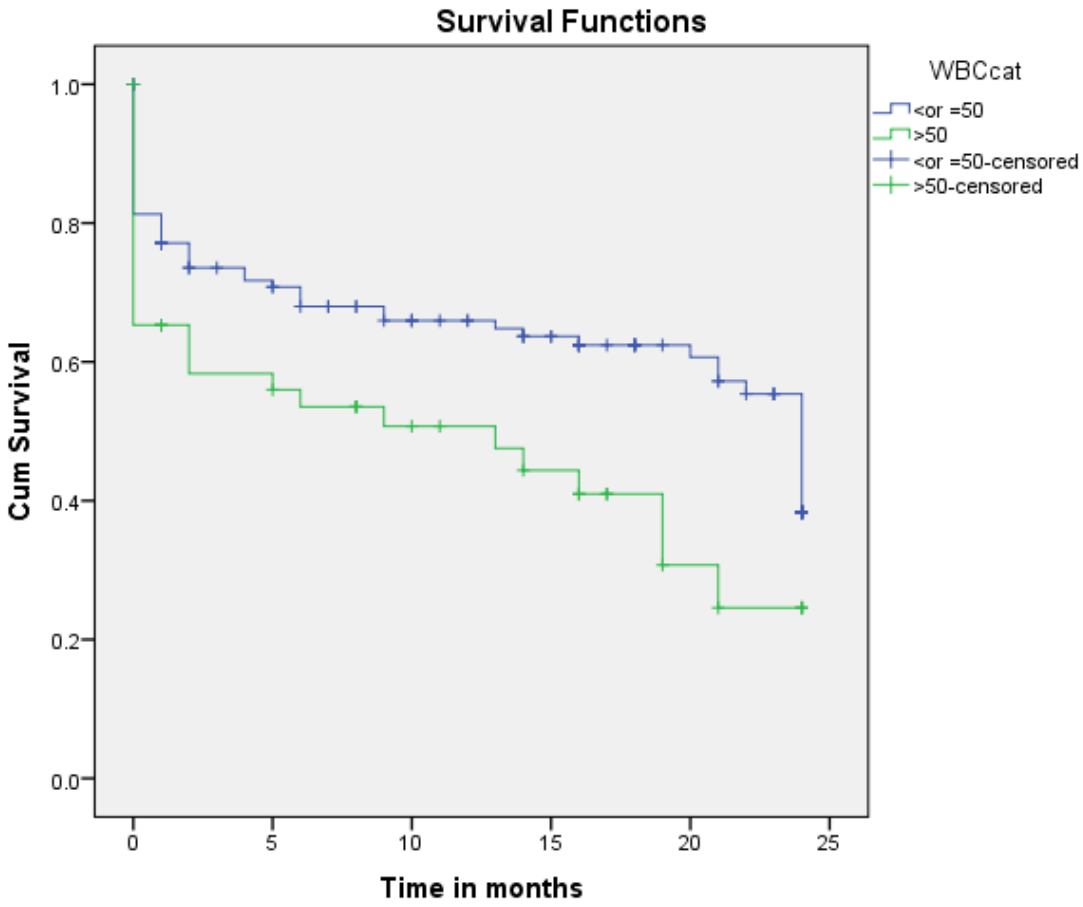


Fig 4. Kaplan Meier survival curve showing survival probability in children with WBC count ≤50 K/uL and those with WBC count >50 K/uL.

Figure 5 shows that survival rate for males was 60% at 12 months and 40% at 24 months, for females it was 60% at 12 months and 25% at 24 months. The difference between the two groups is not statistically significant. (Log rank p value = 0.660)

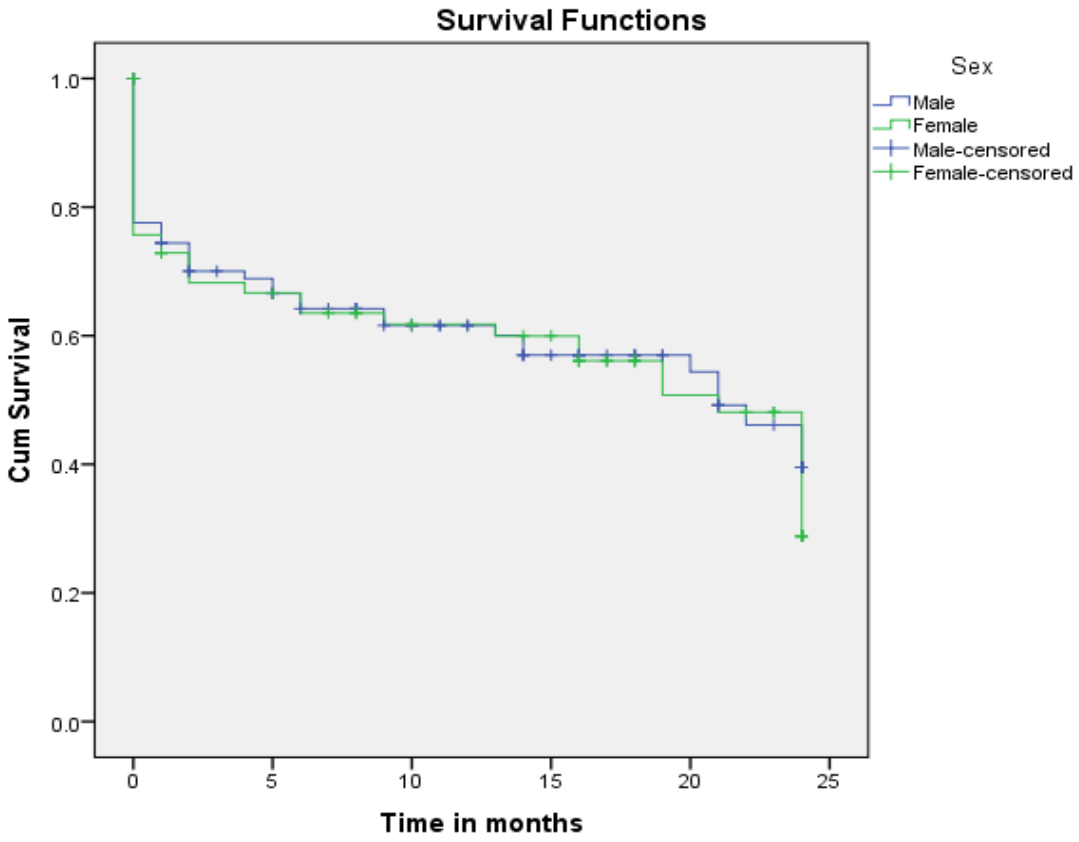


Fig. 5 Kaplan Maier survival curve showing survival probability between males and females.

Figure 6 shows that survival rate for those who were ≤ 10 years was 65% at 12 months and 40% at 24 months, for those > 10 years it was 55% at 12 months and 25% at 24 months. The difference between the two groups is not statistically significant. (Log rank p value = 0.060)

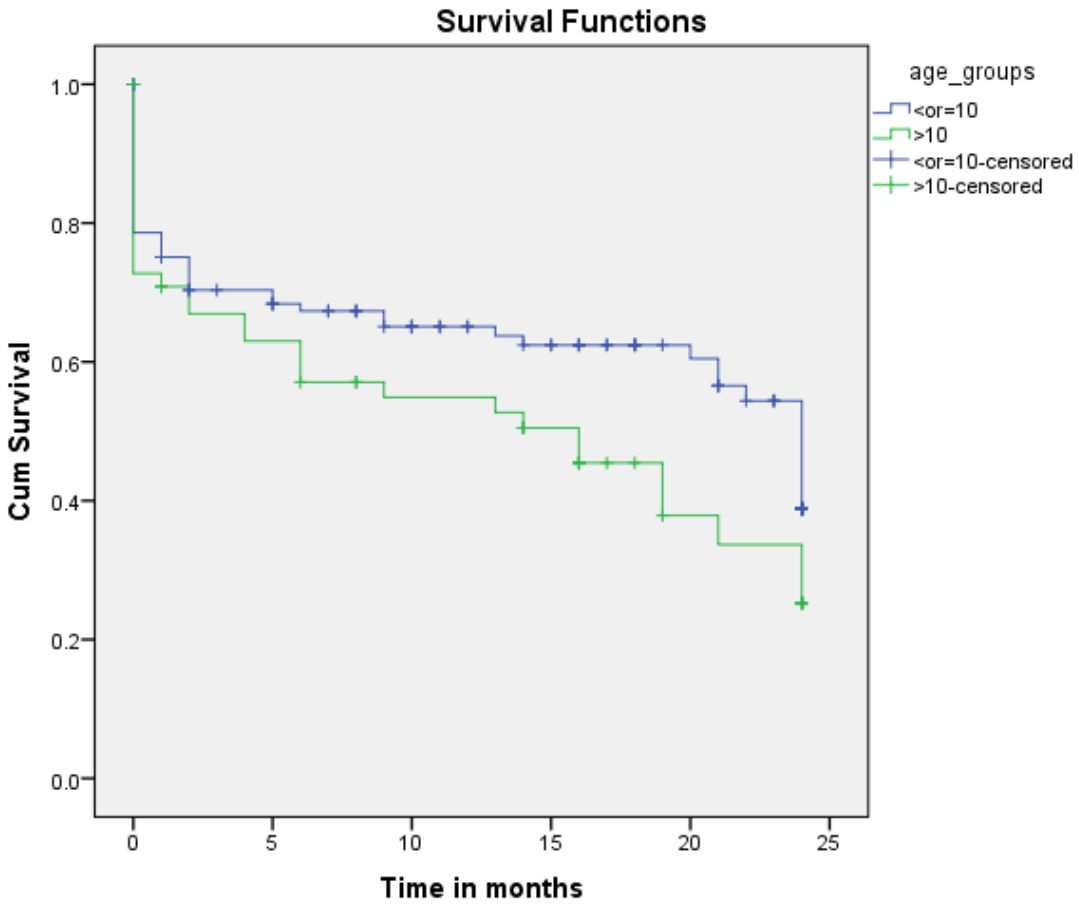


Fig 6. Kaplan Maier survival curve showing survival probability between children aged ≤ 10 years and those > 10 years.

8.6 Other findings from the study

Small percentage of children (11%) had other illnesses. Eleven children had pediatric acquired immune deficiency syndrome (PAIDS), 4 had sickle cell anemia (SCA), 2 had Down's syndrome (DS), 1 had pulmonary tuberculosis (PTB), 1 had nephrotic syndrome (NS), 1 had cerebral palsy (CP) and 1had diabetes mellitus (DM)

Twenty two patients were misdiagnosed at presentation leading to delayed diagnosis of acute leukemia, among these eight were diagnosed as having SCA, eight lymphoma and six were diagnosed as having tuberculosis.

Thirteen (7%) patients died before starting treatment.

9.0 DISCUSSION

In this study acute leukemia has been found to be associated with high mortality. ALL has been found to be more common (79.8%) and it occurs more in boys. This is consistent with the literature that ALL is more common in children and it occurs more in boys than in girls at all age groups. It is also consistent with the findings from studies which were conducted in Cairo and Nigeria which showed that ALL account for 87% and 65.5% of all childhood leukemia respectively[10, 11.]

At two years from diagnosis approximately one fifth of the children with ALL and one fifth of children with AML had unknown status. The unknown status could either mean the patient is dead and the information has not been given to the hospital or the patient has stopped treatment and maybe they decided to seek alternative therapy from either outside the country, spiritual services or traditional healers. There is great possibility for those who stopped treatment to be dead because of the progressive nature of the disease.

9.1 Clinical presentation and hematological parameters of children with acute leukemia at ORCI and MNH Tanzania

More than three quarters of patients presented with pallor (anemia), about three quarters presented with fever and lymphadenopathy and slightly more than half presented with splenomegally and hepatomegally. This finding suggests that children with acute leukemia at ORCI and MNH present with high burden of leukemic cells. Consistent with these findings are the results from a study which was conducted by Nakimbugwe in Uganda which showed that acute leukemia commonly present with anemia and fever [16]. These findings are also similar to the findings from a study which took place in Pakistan by Yasmeen *et al* which showed that 34% of their patients presented with WBC count > 50,000/mm3, 54% had hemoglobin <7g/dl and 33% had platelet count <20,000/mm3, common features at presentation were fever and anemia (86%) followed by lymphadenopathy, hepatomegally and splenomegally[13]. Bleeding which occurs secondary to thrombocytopenia occurred in one fifth of patients at presentation.

9.2 Association between selected prognostic indicators and the adverse outcome

In this study three prognostic indicators were selected for association with outcome; these are age at diagnosis, sex and WBC count at presentation.

High WBC count above 50 K/uL is found to be highly associated with increased mortality; this is consistent with the literature and other studies in Africa [18]. High WBC count is caused by the malignant proliferation of the immature leukocytes and their precursors.

More than half of all children over ten years died within two years from diagnosis; although this was not statistically significant, it is supported by the literature that older age is a bad prognostic indicator for acute leukemia. Age less than one year is also a bad prognostic indicator; in this study only two children were below one year, and they both died within one week of admission. A study which was conducted in Malaysia also showed that age < 1 year is associated with increased mortality[18].

Although male sex is known to be a risk factor for bad prognosis, the data in this study show that more females died during the study period. It was found that more than half of all females died within two years from diagnosis as compared to approximately half of all males. This is in contrast to the literature and other studies done in Africa, UK and Poland which showed that male sex is a poor prognostic indicator[18-20].

Majority of children had anemia and more than half had severe anemia. Of those with anemia 60.6% died within two years from diagnosis as compared to 43% of those without anemia. The difference is not statistically significant but this can be explained by the small number of children without anemia. This is in contrast to studies which were conducted in Malaysia and Poland which showed that hemoglobin level above 11g/dl and above 10g/dl respectively was associated with poor outcome [18, 20].

9.3 Survival rate in children with acute leukemia

In this study ALL survival at two years was 40% and for AML there were no survivors beyond 15 months. Studies done in Morocco and Mali showed that ALL survival at five years was 38% and 33.3% respectively [14, 25]. The high survival rate observed in this study is because of the survival analysis time. Survival rate in this study was determined at two years as opposed to five years as was done in the other two studies. If the survival rate in this study was to be determined at five years; it would be much lower than the rates observed in the other two studies.

Mean duration of symptoms of three months is very long for acute leukemia because the disease has progressive nature. One factor which could have contributed to late presentation is the fact that majority of the patients were from outside Dar Es Salaam (DSM). The cost of transporting the patient and the parent/guardian to DSM may have contributed to delayed presentation at ORCI/MNH. This may contribute to poor survival rate because if the patient presents late, the disease may be at an advanced stage, hence less chances of survival. Another factor which contributes to prolonged duration of symptoms is the presence of concomitant illnesses. Presence of these other illnesses could have masked the symptoms and signs of acute leukemia leading to delayed diagnosis and hence made treatment of leukemia more complicated. Misdiagnosis which could have contributed to delayed diagnosis could be because of lack of awareness of acute leukemia to health care workers. Delayed

presentation as reflected by mean duration of symptoms together with delayed diagnosis could have contributed to poor survival rates.

Few patients died before starting treatment. It is thought that this could be due to the disease being at an advanced stage at presentation or due to the complications of the disease.

10.0 STUDY STRENGTH AND LIMITATIONS

10.1. Strength of the study

Even though the study was done retrospectively and research assistant was used, the author collected most of the data and cross checked the data collected by the assistant daily to ensure completeness of the data. Also the author entered and analyzed the data personally.

This study has helped us to know the two years survival rate of children with acute leukemia in our setting.

10.2 Limitations of the study

1. Some data were not reported in the files and were taken as not present; this may have underestimated the results on clinical presentation in this study

2. Survival rate was calculated for two years because it was not possible to get records past 2008 so it was difficult to get retrospective follow up information for all patients for longer periods; this is because outcome had to be determined within the same time period for all patients

11.0 CONCLUSION

Children with acute leukemia in Tanzania commonly presents with pallor/anemia, fever and lymphadenopathy. More than half of the patients presented with severe anemia, splenomegally and hepatomegally. WBC count >50K/uL is highly associated with increased mortality. Two years survival rate from diagnosis is poor especially for AML.

12.0 RECOMMENDATIONS

1. Clinicians should have a high index of suspicion for acute leukemia for children who present with persistent fever and anemia
2. Community health education to increase community awareness and to emphasize on early health care seeking behavior
3. Standardized checklist of presenting symptoms and signs to enable capturing of all the features and avoid missing data.

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APPENDIX NO 1: QUESTIONNAIRE

Questionnaire number:

Hospital name:

Hospital Registration Number:

Part One: Sociodemographic characteristics

1. Age in years
2. Sex 1. Male 2. Female
3. Residence (region)
4. Date of admission /presentation
5. Referral from

Part two: Diagnosis

6. Symptom duration
7. Weight
8. Diagnosis 1. ALL 2. AML

   Any other diagnosis

9. Date of diagnosis
10. Days from presentation to diagnosis
11. Method of diagnosis
12. Number of days admitted (inpatient)
13. Reason for admission
14. Number of visits made (outpatient)

Part three: Physical findings at presentation

15. Fever 1. No 2. Yes
16. Pallor 1. Yes 2. No
17. Lymphadenopathy 1. Yes 2. No
18. Splenomegaly 1. Yes 2. No
19. Hepatomegaly 1. Yes 2. No
20. Bruising/petechie 1. Yes 2. No
21. Bleeding 1. Yes 2. No
22. Bone/joint pain/swelling 1. Yes 2. No
23. Subcutaneous nodule 1. Yes 2. No

Part four: Initial laboratory investigation results

24. Hemoglobin level
25. WBC count
26. Platelet count

Part five: Medication

27. What treatment regimen was the patient on

Part six: Outcome

28. Survival two years from diagnosis 1. Alive 2. Dead 3. Unknown status
29. If dead, date of death
30. If status unknown, date last seen

APPENDIX NO 2: SUMMARY OF CHEMOTHERAPEUTIC DRUGS USED.

DRUG	CLASS	MECHANISM OF ACTION	COMMON SIDE EFFECTS
Asparagines	Antineoplastic drug	Catalyses the hydrolysis of asparagines to aspartic acid	Hypersensitivity reaction
Cyclophosphamide	Alkylating agent	Interfere with cell replication through its metabolite phosphoramide mustard which forms DNA crosslinks leading to cell death.	Nausea, vomiting, bone marrow suppression
Cytarabine (Ara C)	Antimetabolite	Interfere with pyrimidine synthesis by rapidly converting to cytosine arabinoside triphosphate which damage DNA	Anorexia, nausea, vomiting, diarrhea
Vincristine	Vinca alkaloid	Arrest mitosis at metaphase	Peripheral neuropathy, hyponatremia, constipation, hair loss
Daunorubicine	Cytotoxic antibiotic	Interfere with DNA replication by intercalating with DNA in cancer cells	Painful injection, leucopenia, GI symptoms
Dexamethasone	Glucocorticoid	Anti-inflammatory effect	Infections, weight gain
Doxorubicin	Cytotoxic antibiotic	Intercalation of DNA thereby inhibiting DNA replication	Nausea, vomiting, neutropenia, pain over injection site,

			mucositis
Etoposide	Cytotoxic agent	Topoisomerase inhibitor	Hypotension, hair loss, constipation or diarrhea
Mercaptopurine (6MP)	Antimetabolite	Interfere with synthesis and function of DNA and RNA through inhibition of the enzyme phosphoribosyl pyrophosphate amidotransferase which is the rate limiting enzyme of purine synthesis	Pancytopenia, liver toxicity

APPENDIX NO 3. ALL PROTOCAL

UKALL 2003 REGIMEN A.

NCI Stratification

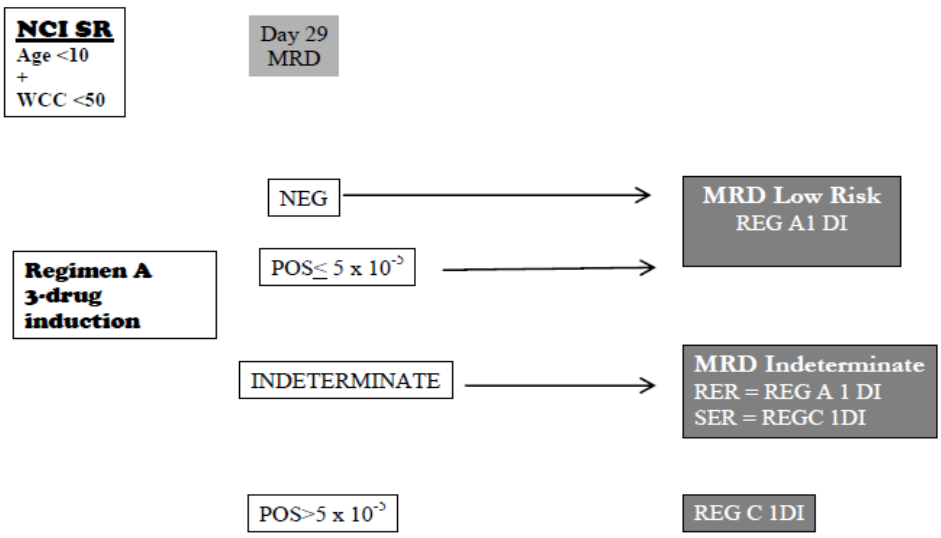
Patients treated on regimen A must be before their 10th birthday and have a highest white cell count before starting treatment less than 50x109/L.

MRD Stratification

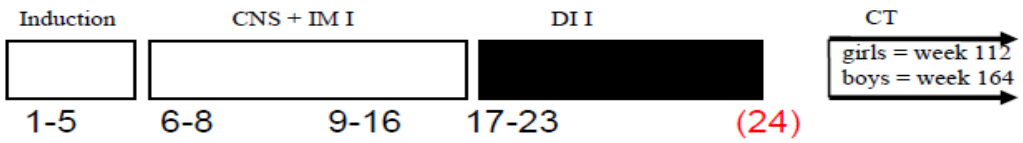
MRD High Risk patients will receive Regimen C with one delayed intensification and should change treatment at day 35.

MRD Low Risk patients will receive one delayed intensifications.

MRD Indeterminate patients will receive Regimen C with 1 DI (from D35) if slow responders and Regimen A with 1 DI if rapid responders at day 15



Summary of Regimen A.
Regimen A consists of the following phases:
1. Three drug induction (duration 5 weeks) with **dexamethasone** as steroid of choice.
2. Intensification/CNS-directed phase (duration 3 weeks) with **6-mercaptopurine**;
3. Interim maintenance I (duration 8 weeks) with **dexamethasone** and **6-mercaptopurine**;
4. Delayed intensification I (duration 7 weeks) with **6-mercaptopurine** in reconsolidation;
5. Maintenance chemotherapy with **dexamethasone and 6-mercaptopurine** to end of week 112 for girls and end of 164 for boys.



UKALL 2003 REGIMEN A: DETAILS OF TREATMENT.

Schedule A - Remission induction – phase I (See flowchart 1.**)**
This phase runs for 35 days from day 1 (beginning of week 1) to day 35 inclusive (end of week 5) (i.e. 5 weeks in total).
a) **Fluids** All patients should be adequately hydrated (at least 2-2.5 l/m2/24hrs. given parenterally for the first 48 hours.
b) **Allopurinol** 100 mg/m2 oral three times daily should start 24 hours before chemo-

therapy and continue for 5 days.
c) **Dexamethasone** 6 mg/m2/day (maximum dose 10 mg/day in induction only) for **28 days** and then tapered over the next 7 days. The steroid should be divided into two doses per day.
d) **Vincristine** 1.5 mg/m2 (maximum single dose 2 mg) IV weekly for five weeks starting on day 2 and continuing on days 9, 16, 23 and 30.
e) **Pegylated L-asparaginase (Oncaspar)** 1000iu/m2 **IM** , on day 4 and day 18
f) **Intrathecal methotrexate On days 1, 8 and 29.** Dose by age:<2yrs: 8mg; 2yrs: 10mg; 3yrs or more: 12 mg. NB Patients who have CNS disease at presentation should receive weekly doses until two clear CSF samples are obtained- see page 24. Do not schedule vincristine on the same day as the intrathecal methotrexate.
g) **6-mercaptopurine** 75 mg/m2/day orally starting on day 29 (beginning week 5) (if neutrophils > 0.75 and platelets > 75) and continuing for 4 weeks in total (to end of consolidation, week 8) Doses should be taken at least one hour after the evening meal, without milk products. Dose adjustments are described in Appendix C.
h) **Bone marrow Aspirates** Bone marrow should be checked at day 8, 15 and 29.
Patients with adverse risk cytogenetics should switch to Regimen C at day 15. Day 29 BM2 and MRD High Risk patients and MRD indeterminate patients with slow early response at day 15 should switch to Regimen C at day 35. Day 29 BM3 patients are off-protocol.
i) Co-trimoxazole (trimethoprim and sulphamethoxazole)
This drug is given as PCP prophylaxis orally on 2 consecutive days throughout treatment ***from the start of induction.*** This dosage is lower than that recommended in previous studies, but has been found to be equally effective in CCG studies. The dose is tabulated below. Please ensure separation of the days on which oral Methotrexate and Cotrimoxazole doses are given during maintenance courses.
If a child remains cytopenic after being off chemotherapy for three weeks or more, then stop the co-trimoxazole. Reintroduce co-trimoxazole once both thiopurine and methotrexate are back at standard dose. If cytopenias recur once the co-trimoxazole is reintroduced, then it should be stopped for at least two months and an alternative form *CYP ALL* 14 *Interim Guidelinev3 July 2011* 14

of prophylaxis used instead (see below). The alternative drug should then be continued for the duration of the antileukaemic therapy

The maintenance of adequate doses of thiopurine and methotrexate should take precedence over continuing co-trimoxazole. If co-trimoxazole is stopped, however, it must be remembered that the child is at increased risk of PCP. Nebulised pentamidine or oral Dapsone are alternative drugs.

Surface area Co-trimoxazole Trimethoprim Sulphamethoxazole
0.5-0.75 m2 240 mg bd 40 mg bd 200 mg bd
0.76-1.0 m2 360 mg bd 60 mg bd 300 mg bd
over 1.0 m2 480 mg bd 80 mg bd 400 mg bd

See also appendix D for details of alternative PCP prophylaxis regimens.

Regimen A: Consolidation/CNS phase, phase II (See flowchart 2.)

This phase runs for 21 days from day 1 (beginning of week 6) to day 21 inclusive (end of week 8) i.e. 3 weeks. Patients should have an ANC >0.75 x109/L and platelets of >75x109/L.
Patients with refractory CNS disease at diagnosis will receive cranial irradiation during consolidation starting at day 36.
a) **Intrathecal methotrexate** Days 1, 8 and 15 Dose by age:<2yrs: 8mg; 2yrs: 10mg; 3yrs or more: 12 mg. Do not schedule vincristine on the same day as the methotrexate.
b) **6-mercaptopurine** 75mg/m2/day orally continuing to day 21 (end of week 8) Doses should be taken at least one hour after the evening meal, without milk products. Dose adjustments are described in Appendix C.
Regimen A: Interim maintenance I – phase III (See flowchart 3.)
This phase runs from day 1 (beginning of week 9) to day 56 inclusive (end of week 16) (i.e. 8 weeks). Patients should have an ANC >0.75 x109/L and platelets of >75 x109/L to start.
a) **Dexamethasone** 6 mg/m2/day orally, divided into twice-daily doses each day
on days 1-5 (week 9) and days 29-33 (week 13).
b) **Vincristine** 1.5 mg/m2 (maximum single dose 2 mg) IV on day 1 (week 9)
and day 29 (week 13).
c) **6-mercaptopurine** 75 mg/m2/day orally, daily on days 1-49 (weeks 9-15) but **not**
days 50-56 (week 16). Doses should be taken at least one hour after the evening meal without milk products. Dose adjustments are described in Appendix C. The omission of 6-mercaptopurine for days 50-56 is in line with the relevant CCG protocol.
d) **Oral methotrexate** 20 mg/m2 orally weekly during weeks beginning on days 1, 8,
22, 29, 36, 43 and 50 (weeks 9-16). Note none is given day 15 as an intrathecal dose is given during that week should be a single dose taken with 6-mercaptopurine. Dose adjustments are described in Appendix C.
e) **Intrathecal methotrexate** on day 1 week 11. Dose by age: <2yrs: 8mg; 2yrs: 10mg; 3yrs or more: 12 mg. Do not schedule vincristine on the same day as IT methotrexate. *CYP ALL* 16 *Interim Guidelinev3 July 2011* 16

Regimen A: Delayed intensification I – phase IV (See flowchart 4.)

This phase runs from day 1 (beginning of week 17) to day 49 inclusive (end week 23) i.e. 7 weeks. To start, ANC should be >0.75x109/L and platelets of >75x109/L. Once begun, therapy during weeks 17 – 20 is not interrupted for myelosuppression alone. Therapy due day 1, week 21 should be delayed until ANC >0.75x109/L and platelets of >75x109/L and once begun should not be interrupted solely for myelosuppression. Any serious infection, such as Varicella, pneumocystis pneumonia, or neutropenia with fever, and presumed or proven infection, warrants chemotherapy interruption at any time during DI.
Part 1; weeks 17 – 20:
a) **Dexamethasone** 10mg/m²/day orally for 7 days on days 2- 8 (week 17) and 16-22 (week 19). No taper. Divide into two daily doses, adjusted upward to nearest 0.25 mg, as tablet size dictates. (Liquid preparation is acceptable).
b) **Vincristine** 1.5 mg/m² (2.0 mg max) IV push on days 2 (week 17), 9 (week 18) and 16 (week 19).
c) **Doxorubicin (Adriamycin)** 25 mg/m² IV on days 2 (week 17),9 (week 18) and 16 (week 19) given over a period of 1 hour.
d) **Pegylated L-Asparaginase (Oncaspar)** 1000 iu/m2 IM on day 4 (week 17)
e) **Intrathecal methotrexate** on day 1 (week 17). Dose by age: <2yrs: 8mg; 2yrs: 10mg; 3yrs or more: 12 mg. Do not schedule vincristine on the same day as IT methotrexate.
Part 2; weeks 21-23:
f) **Cyclophosphamide** 1,000 mg/m² IV over 20-30 min day 29 (week 21). Give 125mls/m2 /hr of Dextrose /Saline infusion for 30 minutes before the cyclophosphamide and for 3.5 hours afterwards, i.e. 4 hours in total. Do not add potassium. Mesna is not needed.
g) **Mercaptopurine.** All patients receive MP 60 mg/m2/day during delayed intensification**.** The drug is given daily by mouth for 14 days from day 29 (beginning of week 21) to day 42 (end of week 22). No dose adjustments are made during this block.Doses should be taken at least one hour after the evening meal, without milk products.
h) **Cytarabine (ara-C).** 75mg/m2/day by IV push or subcutaneously – 8 doses in two pulses of 4 days each; days 30-33 (week 21) and days 37-40 (week 22).
i) **Intrathecal methotrexate.** Days 29 (week 21) and 36 (week 22). Dose by age: <2yrs: 8mg; 2yrs: 10mg; 3yrs or more: 12 mg.*CYP ALL* 17 *Interim Guidelinev3 July 2011* 17

Regimen A: Maintenance – phase V (See flowchart 7.)

Maintenance runs from day 1 cycle 1 (beginning of week 24) in 12-week cycles to end of week 112 for girls and end of week 164 for boys. The cycle in progress is stopped when the end of therapy is reached. This period equates to 2 years from the start of interim maintenance I for girls and 3 years for boys.
Maintenance should begin when the ANC is >0.75 x 109/l and the platelet count is >75 x 109/l. Only 6-mercaptopurine and oral methotrexate will be interrupted for myelosuppression and not made up. Days off therapy for intercurrent infections are counted as days of maintenance and not made up. Omit the Vincristine and steroid pulse if it falls in the last week of therapy. *Anaemia* occurring in the course of maintenance therapy should be treated with transfusion and the dose of drug is maintained. If *persistent anaemia* occurs (i.e., haemoglobin below 8 g/dl) investigate for Parvovirus infection. Please contact trial co-ordinators for advice.
a) **Dexamethasone** 6 mg/m2/day orally, divided into twice-daily doses on days 1-5,
29-33 and 57-61 of each cycle.

b) **Vincristine** 1.5mg/m2 (maximum single dose 2 mg) IV on days 1, 29, and 57 of
each cycle.
c) **6-mercaptopurine** 75mg/m2/day orally daily throughout maintenance. Doses should be taken at least one hour after the evening meal without milk products.
Dose adjustments are described in Appendix C.
d) **Oral methotrexate** 20 mg/m2 orally during weeks beginning days 1, 8, 22, 29, 36, 43,
50, 57, 64, 71 and 78 of each cycle. Note none is given in the third week of each cycle as an intrathecal dose is given during that week. Dose adjustments are described in Appendix C.
e) Intrathecal methotrexate on day 15 of each cycle.
Dose by age: <2yrs: 8mg; 2yrs: 10mg; 3yrs or more: 12 mg. Do not schedule vincristine for the same day as intrathecal methotrexate.
f) Bone marrow examination should be carried out at the same time as the End of Treatment intrathecal methotrexate. NB the end of treatment marrow should always be done BEFORE chemotherapy is stopped to prevent confusion due to “rebound” marrows.
END OF REGIMEN A *CYP ALL* 18 *Interim Guidelinev3 July 2011* 18

16. UKALL 2003 REGIMEN B.

NCI Stratification

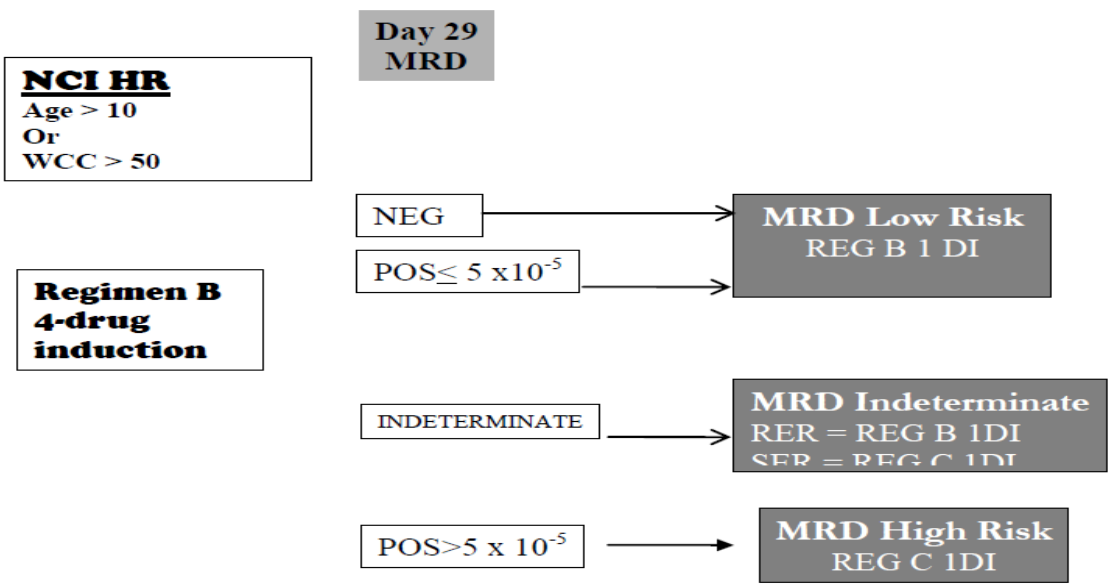
This regimen (B) is for patients defined as at high risk of relapse because of their age (□10 years) or presenting white cell count (□50x109/L).

MRD Stratification

MRD Low Risk patients will receive one delayed intensification.

MRD High Risk patients will receive Regimen C with 1 DI and should change treatment at day 35.

MRD Indeterminate patients will continue on Regimen B + 1DI if they have a rapid response and Regimen C + 1 DI (from D35) if they have a slow response at day 8.



Summary of Regimen B.

Regimen B consists of the following phases:
1. Four drug induction (duration 5 weeks) with **dexamethasone** as steroid of choice.
2. Standard BFM consolidation (duration 5 weeks) with **6-mercaptopurine**;
3. Interim maintenance I (duration 8 weeks) - **dexamethasone and mercaptopurine**;
3. Delayed intensification I (duration 7 weeks); **6-mercaptopurine** in reconsolidation;
4. Maintenance chemotherapy with **dexamethasone and 6-mercaptopurine** to end of week 114 for girls and end of week 166 for boys.



Prevention of Tumour Lysis

Treatment centres should have a policy for the prevention and treatment of Tumour Lysis syndrome in patients with high white cell counts or bulky disease. Consideration should also be given to the use of Recombinant Urate Oxidase (Rasburicase) *instead of* Allopurinol in patients with very high white cell (> 100 x 109/l) counts or bulky disease (Mediastinal mass or large abdominal lymph nodes).*CYP ALL* 20 *Interim Guidelinev3 July 2011* 20

UKALL 2003 REGIMEN B: DETAILS OF TREATMENT.

The convention for day/week numbering is that a new module of therapy begins on day 1 of whatever week of treatment has been reached.

Regimen B: Remission induction – phase I (See flowchart 8.)

This phase runs for 35 days from day 1 (beginning of week 1) to day 35 inclusive (end of week 5).

a) **Fluids:** All patients should be adequately hydrated (at least 2-2.5 l/m2/24hrs given parenterally for the first 48 hours).

b) **Allopurinol:** 100 mg/m2 oral three times daily should start 24 hours before chemotherapy and continue for 5 days.

c) **Dexamethasone:** 6 mg/m2/day (maximum dose 10 mg/day in induction only) for 28 days and then tapered over the next 7 days. The steroid should be divided into two doses per day.

d) **Vincristine:** 1.5 mg/m2 (maximum single dose 2 mg) IV bolus weekly for five weeks starting on day 2 and continuing on days 9, 16, 23 and 30.

e) **Daunorubicin:** 25 mg/m2 IV over 1 hour on days 2, 9, 16, and 23.

f) **Pegylated L-asparaginase: (Oncaspar)** 1000 iu/m2 IM**,** on day 4 and day 18.

g) **Intrathecal methotrexate: On days 1, 8 and 28** Dose by age: <2yrs: 8mg; 2yrs: 10mg; 3yrs or more: 12 mg. NB Patients who have CNS disease at presentation should receive weekly doses - see page 24. Do not schedule vincristine on the same day as the intrathecal methotrexate.

h) **6-mercaptopurine:** 60 mg/m2/day orally starting on day 29 (beginning week 5) (if neutrophils > 0.75 and platelets > 75) and continuing for five weeks in total (to end of week 9). Doses should be taken at least one hour after the evening meal without milk products. Do not increase dosage for ANC>2.0.

i) **Bone marrow:** Check marrow status on days 8 and 29. Send Day 29 Marrow for MRD .

Patients with M3 marrow at day 29 are off protocol and should continue therapy on high risk arm of R3. Day 29 BM2, MRD High Risk and MRD indeterminate patients with slow early response at day 8 should change to regimen C at day 35**.**

j) Co-trimoxazole (trimethoprim and sulphamethoxazole)

This drug is given as PCP prophylaxis orally on 2 consecutive days throughout treatment from the start of induction. The dose is tabulated below. Please ensure separation of the days on which oral Methotrexate and Cotrimoxazole doses are given during maintenance courses.

If a child remains cytopenic after being off chemotherapy for three weeks or more, then stop the co-trimoxazole. Reintroduce co-trimoxazole once both thiopurine and methotrexate are back at standard dose. If cytopenias recur once the co-trimoxazole is reintroduced, then it should be stopped for at least two months and an alternative form of prophylaxis used instead (see below). The alternative drug should then be continued for the duration of the antileukaemic therapy

The maintenance of adequate doses of thiopurine and methotrexate should take precedence over continuing co-trimoxazole. If co-trimoxazole is stopped, however, it must be remembered that the child is at increased risk of PCP. Nebulised pentamidine or oral Dapsone are alternative drugs.

Surface area Co-trimoxazole Trimethoprim Sulphamethoxazole
0.5-0.75 m2 240 mg bd 40 mg bd 200 mg bd
0.76-1.0 m2 360 mg bd 60 mg bd 300 mg bd
over 1.0 m2 480 mg bd 80 mg bd 400 mg bd

See also appendix D for details of alternative PCP prophylaxis regimens.

Regimen B: Standard BFM Consolidation – phase II (See flowchart 9.)

This phase runs for 35 days from day 1 (beginning of week 6) to day 35 inclusive (end of week 10) i.e. 5 weeks. To be eligible to enter standard BFM consolidation, patients must be in remission, and have an ANC >0.75x109/L and platelets of >75x109/L. If the blood count has not recovered and marrow is hypocellular M1, delay the start of consolidation one week and repeat the bone marrow to confirm M1 status. Patients with refractory CNS disease at diagnosis will receive cranial irradiation during consolidation starting at day 36.
a) Cyclophosphamide: 1,000 mg/m² IV over 20-30 minutes on days 1 and 15. Give125mls/m2/hr of Dextrose/ Saline infusion for 30 minutes before cyclophosphamide and for 3.5 hours afterwards, i.e. 4 hours in total. Do not add potassium. Mesna is not needed.
b) **Cytarabine** (ara-C): 75mg/m2/day by IV push or subcutaneously – 16 doses in four pulses of 4 days each; days 2-5, 9-12, 16-19 and 23-26.
c) **6-Mercaptopurine**: Continue 6-mercaptopurine, 60mg/m2/day to Day 28 of standard BFM consolidation. (5 weeks in total from the start in week 5 of induction). Doses should be taken at least one hour after the evening meal without milk products. Do not increase dosage for ANC>2.0.
d) **Intrathecal methotrexate**: once a week for three doses on days 1, 8 and 15. Dose by age: <2yrs: 8mg; 2yrs: 10mg; 3yrs or more: 12 mg. These doses are in line with CCG recommendations. There is no intravenous vincristine in this phase. *CYP ALL* 23 *Interim Guidelinev3 July 2011* 23

Regimen B: Interim maintenance I – phase III (See flowchart 10.)

This phase runs from day 1 (beginning of week 11) to day 56 inclusive (end of week 18) i.e. 8 weeks. Patients should have an ANC >0.75 x109/L and platelets of >75x109/L.
a) **Dexamethasone:** 6 mg/m2/day orally, divided into twice daily doses each day on days 2-6 (week 11) and days 30-34 (week 15).
b) **Vincristine:** 1.5 mg/m2 (maximum single dose 2 mg) IV on day 2 (week 11) and day 30 (week 15).
c) **6-mercaptopurine:** 75 mg/m2/day orally, daily on days 1-49 (weeks 11-17), but not days 50-56 (week 18). Doses should be taken at least one hour after the evening meal without milk products. Dose adjustments are described in Appendix C. The omission of 6-mercaptopurine for days 50-56 is in line with the relevant CCG protocol.
d) **Oral methotrexate** 20 mg/m2 oral weekly during weeks beginning on days 8, 15, 22, 36, 43 and 50 as single dose taken with 6-mercaptopurine. Dose adjustments are described in Appendix C.
e) **Intrathecal methotrexate** on days 1 and 29. Dose by age: <2yrs: 8mg; 2yrs: 10mg; 3yrs or more: 12 mg. Do not schedule vincristine on the same day as IT methotrexate. *CYP ALL* 24 *Interim Guidelinev3 July 2011* 24

Regimen B: Delayed intensification I – phase IV (See flowchart 11.)

This phase runs from day 1 (beginning of week 19) to day 49 inclusive (end week 25) i.e. 7 weeks. Patients should have an ANC >0.75x109/L and platelets of >75x109/L. Once begun, therapy during weeks 19-22 is not interrupted for myelosuppression alone. Therapy due day 1 week 23 should be delayed until ANC >0.75x109/L and platelets of >75x109/L. and once begun should not be interrupted solely for myelosuppression. Any serious infection, such as Varicella, pneumocystis pneumonia, or neutropenia with fever, and presumed or proven infection, warrants chemotherapy interruption at any time during DI.
Part 1; weeks 19 – 22:
a) **Dexamethasone** 10 mg/m²/day orally for 7 days on days 2-8 (week 19) and 16-22

(week 21). No taper. Divide into two daily doses, adjusted upward to nearest 0.25 mg, as tablet size dictates. (Liquid preparation is acceptable).
b) **Vincristine** 1.5 mg/m² (2.0 mg max) IV push on days 2 (week 19), 9 (week 20) and 16 (week 21).
c) Doxorubicin (Adriamycin) 25 mg/m² IV on days 2 (week 19), 9 (week 20) and 16 (week 21) given over a period of 1 hour.
d) **Pegylated L-Asparaginase: (Oncaspar)** 1000 iu/m2 IM on day 4 (week 19)
e) **Intrathecal methotrexate** on day 1 (week 19). Dose by age: <2yrs: 8mg; 2yrs: 10mg; 3yrs or more: 12 mg. Do not schedule vincristine on the same day as intrathecal methotrexate.
Part 2; weeks 23 – 25:
f) **Cyclophosphamide** 1,000 mg/m² IV over 20-30 min day 29 (week 23). Give 125mls/m2 /hr of Dextrose /Saline infusion for 30 minutes before the cyclophosphamide and for 3.5 hours afterwards, i.e. 4 hours in total. Do not add potassium. Mesna is not needed.
g) **Mercaptopurine. All** patients receive MP 60 mg/m2/day during delayed intensification 1**.** The drug is given daily by mouth for 14 days from day 29 (beginning of week 23) to day 42 (end of week 24). No dose adjustments are made during this block. Doses should be taken at least one hour after the evening meal, without milk products.
h) **Cytarabine (ara-C).** 75mg/m2/day by IV push or subcutaneously – 8 doses in two pulses of 4 days each; days 30-33 (week 23) and days 37-40 (week 24).
i) **Intrathecal methotrexate.** Days 29 (week 23) and 36 (week 24). Dose by age: <2yrs: 8mg; 2yrs: 10mg; 3yrs or more: 12 mg. *CYP ALL* 25 *Interim Guidelinev3 July 2011* 25

Regimen B: Maintenance – Phase V (See flowchart 14.)

Maintenance begins from day 1 cycle 1 (beginning of week 26) in 12-week cycles to end of week 114 for girls and to the end of week 166 for boys. The cycle in progress is stopped when the end of therapy is reached. Omit the Vincristine and steroid pulse if it falls in the last week of therapy. This period of continuing treatment equates to 2 years from the start of interim maintenance I for girls and 3 years for boys.
Maintenance should begin when the ANC is >0.75 x 109/l and the platelet count is >75 x 109/l. Only 6-mercaptopurine and oral methotrexate will be interrupted for myelosuppression and not made up. Days off therapy for intercurrent infections are counted as days of maintenance and not made up. *Anaemia* occurring in the course of maintenance therapy should be treated with transfusion and the dose of drug is maintained. If *persistent anaemia* occurs (i.e., haemoglobin below 8 g/dl) investigate for parvovirus infection. Please contact trial co-ordinators for advice.
a) **Dexamethasone:** 6 mg/m2/day orally, divided into twice-daily doses on days 1-5, 29-33 and 57-61 of each cycle.
b) **Vincristine:** 1.5 mg/m2 (maximum single dose 2 mg) IV on days 1, 29, and 57 of each cycle.
c) **6-mercaptopurine:** 75 mg/m2/day orally, daily throughout maintenance. Doses should be taken at least one hour after the evening meal without milk products. Dose adjustments are described in Appendix C.
d) **Oral methotrexate:** 20 mg/m2 orally during weeks beginning on days 1, 8, 22, 29, 36, 43, 50, 57, 64, 71 and 78 of each cycle. Note none is given in the third week of each cycle as an intrathecal dose is given during that week**.** Dose adjustments are described in Appendix C.
e) **Intrathecal methotrexate:** On day 15 of each cycle. Dose by age: <2yrs: 8mg; 2yrs: 10mg; 3yrs or more: 12 mg.
f) **Bone marrow examination** should be carried out at the same time as the **end of treatment** intrathecal methotrexate. NB the end of treatment marrow should always be done BEFORE chemotherapy is stopped to prevent confusion due to “rebound” marrows.

APPENDIX NO 4. AML PROTOCALS

1 TATA MEMORIAL HOSPITAL

(DEPT. OF MEDICAL ONCOLOGY)

THERAPY FOR AML PATIENTS ON ORAL PROTOCOL

Name: _____ Hospital No: _____

Initial Therapy: From ____/____/____ to ____/____/____

(1) T. Allopurinol (100 mg) 1 – 1 – 1

(2) Syp Cital 2 tsp – 2 tsp – 2 tsp in ½ glass water

(3) Check urine pH thrice a day: it should be 7

Supportive Care:

(1) To be continued for entire period of chemotherapy.
(2) _____ liters of water to be taken every day.
(3) To eat home cooked, fresh food.
(4) Fruits, salads, soups encouraged (well cleaned).
(5) T. Clotrimazole 1 – 1 – 1 to be sucked every day.
(6) Hexidine mouth wash 4 times per day.
(7) Betadine Sitz bath twice a day.
(8) T.Septran / Septran DS 1 - 1 tab every Saturday & Sunday only.
(9) To check urine sugar twice a day and report if urine sugar positive.
(10) To keep at least 2 platelet donors checked and ready.

Chemotherapy:

(1) T. Prednisolone (20 mg/m^2): _____ with breakfast; _____ with dinner. X 21 days

(2) C. Omeprazole (20 mg): _____ with breakfast; _____ with dinner. X 21 days

(3) T. 6 TG (40 /m^2): _____ tab 2 hrs after dinner. X 21 days

(4) C. Etoposide (50 mg/m^2): _____ after Lunch X 21 days

Cycle #: _____: ____/____/____ to ____/____/____

#: _____: ____/____/____ to ____/____/____

#: _____: ____/____/____ to ____/____/____

#: _____: ____/____/____ to ____/____/____

- Please do CBC every 15 days or earlier if necessary.
- Please do BUN/S.Cr/LFT prior to each new cycle of chemotherapy.
- Please give supportive care with blood/platelets/antibiotics, etc as and when necessary.
- Please contact me at 022 – 4147000 Ext: 4534; 022 – 4177217 direct; or banavali_2000@yahoo.com or Fax: 022 – 4146937 if necessary.

- Please send patient for Follow up at Tata Memorial Hospital on ____/____/____

Dr. Shripad Banavali, MD

Cons. Hem – Oncologist

2. MRC AML 15

INDUCTION

Please note that Ara-C, cytosine arabinoside, cytarabine and cytosine refer to the same **cytotoxic compound.**

1. ADE schedules

Course 1 ADE 10+3+5

Cytosine Arabinoside 100 mg/m2 12-hourly by i.v. push on days 1-10 inclusive (20 doses).
Daunorubicin 50 mg/m2 daily by 1-hour i.v. infusion on days 1, 3 and 5 (3 doses).
Etoposide 100 mg/m2 daily by 4-hour infusion on days 1-5 inclusive (5 doses).

Course 2 ADE 8+3+5

Cytosine Arabinoside 100 mg/m2 12-hourly by i.v. push on days 1-8 inclusive (16 doses).
Daunorubicin 50 mg/m2 daily by 1-hour i.v. infusion on days 1, 3 and 5 (3 doses).
Etoposide 100 mg/m2 daily by 4-hour infusion on days 1-5 inclusive (5 doses).

Note: All drug doses should be reduced by 25% for children aged less than one year.

CONSOLIDATION

1. MRC Consolidation

Course 3 MACE

Amsacrine 100 mg/m2 daily by 1-hour i.v. infusion (in 5% dextrose) on days 1-5 inclusive (5 doses).
Cytosine Arabinoside 200 mg/m2 daily by i.v. infusion over 19 hours on days 1-5 inclusive (5 doses).
Etoposide 100 mg/m2 daily by 4-hour i.v. infusion on days 1-5 inclusive (5 doses).
NOTE: Amsacrine must not be infused in 0.9% sodium chloride: precipitation or flocculation occurs. However all MACE drugs can be administered in 5% dextrose.

Course 4 MidAC

Mitoxantrone 10 mg/m2 daily by 1-hour infusion on days 1-5 inclusive (5 doses).
Cytosine Arabinoside 1 g/m2 12-hourly by 2-hour i.v. infusion on days 1-3 inclusive (6 doses).
NOTE: It is recommended that Prednisolone (0.5% Predsol) eye drops are used 2 hourly
(2 drops per eye) during the course of MidAC and be continued for 5 days after the course finishes.

Note: All drug doses should be reduced by 25% for children aged less than one year.

2. Cytosine consolidation - High-dose Ara-C (3 g/m2)

Course 3

Ara-C 3 g/m2 given i.v. over 4 hours 12-hourly on days 1, 3

and 5 (six doses).

Course 4

Ara-C 3 g/m2 given i.v. over 4 hours 12-hourly on days 1, 3 and 5 (six doses).

NOTE: Prednisolone (0.5% Predsol) eye drops must be used 2-hourly (2 drops per eye) during each course of high-dose Ara-C, and be continued for 5 days after the course finishes.

NB: In children under 1 year the Ara-C 3.0 g/m2 should be calculated from the patient's weight in kilograms as 100 mg/kg per dose.

MYLOTARG THERAPY DURING CONSOLIDATION

Administration of Mylotarg

Patients are only eligible to receive Mylotarg if their liver function tests do not exceed twice normal. Any patient who experienced side-effects attributed to Mylotarg in course 1 **should not be randomised for Mylotarg in consolidation**. Mylotarg will be given at a dose of 3mg protein /m2 on day 1 of course 3.

Patients should not be given azole antifungal drugs until day 5 after the administration of Mylotarg and for patients who have been taking a prophylactic azole this should be discontinued 5 days before the Mylotarg dose is due.

The patient should receive premedication with paracetamol and i/v chlorphenamine 1 hour before starting the Mylotarg infusion. Paracetamol may be repeated as necessary in the event of fever and chills occurring. Vital signs must be monitored during the infusion and for 4 hours following its completion.

The reconstituted dose of Mylotarg should be diluted in 100ml sodium chloride 0.9% and infused over 2 hours. When aseptically prepared under controlled, validated conditions in the pharmacy, the diluted dose may be stored for up to 16 hours at room temperature and must be protected from light (applies during infusion also). It is important to note that the infusion must be completed within 20 hours after reconstitution.