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The efficacy and long-term side effects of prophylactic cranial radiation therapy in childhood acute lymphocytic leukaemia (ALL) in Johannesburg, South Africa

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UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

The Efficacy And Long-Term Side Effects Of Prophylactic Cranial Radiation Therapy In Childhood Acute Lymphocytic Leukaemia (ALL) In Johannesburg, South Africa

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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of Master of Medicine in Radiation Oncology

April, 2021

DECLARATION

I, Nonkululeko Mlaba, declare that this thesis is my own work. It is being submitted for the degree of Master of Medicine in Radiation Oncology at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other university.

_____

Dr Nonkululeko Mlaba

_____day of _____20_____in_____

DEDICATION

This study is dedicated to my family and friends. Thank you for the love, support, and motivation. I want to thank my husband in particular, for his constant encouragement and confidence in my abilities; even when I doubted myself.

Publications and presentations
This work has never been published.

It has never been presented at a congress.

ABSTRACT

Background

Relapse disease is the main source of treatment failure in acute lymphoblastic leukaemia despite improvements in the efficacy of upfront treatment. Even with improved outcomes globally, low to middle income countries continue to experience inferior cure rates. There is paucity of local data to help inform and modify adopted international protocols.

Objective

The aim of this study was to evaluate the efficacy of prophylactic cranial irradiation as part of multimodal treatment of acute lymphoblastic leukaemia in preventing relapse, identify factors associated with relapse, and long-term sequelae of prophylactic cranial radiation in a population of paediatric patients in Johannesburg, South Africa.

Materials and Methods

This was a retrospective analysis of patients' medical records of acute lymphoblastic leukaemia treated in a public academic institution in Johannesburg, who received prophylactic cranial irradiation as part of the modified BFM-95 protocol. Records of fifty-one (51) patients treated from 2009 to 2016 were included in the study. Five-year overall survival and event-free survival as well as cumulative incidence of relapse were estimated using the Kaplan-Meier analytic method. Cox regression model was used for analysis of prognostic factors, estimating hazard ratios with 95% confidence intervals. For growth evaluation, z-scores were generated from height measurement and the generalized estimation model was used to analyse height differences between two radiation doses [12 Gy and 18Gy] and association between height and clinical variables.

Results

The estimated 5-year overall survival (OS) and event-free survival (EFS) was 64% (95% CI: 49% - 75%) and 57% (95%CI: 42% - 70%) respectively.

In total, 18 out of 51 (35%) patients experienced relapse with an incident rate of 7.0%, (95% CI, 4.4% – 11.1%), translating to a cumulative probability of relapse at 3 and 5 years being 33% (95%

CI: 19% – 56%) and 45% (95% CI, 27% – 73%) respectively. The bone marrow was a frequent site of relapse with an incidence rate of 4.6%, (95% CI, 2.6% – 8.2%) occurring in 12 out of 18 patients whilst fewer cases occurred in the central nervous system, incidence rate of 2.3%, (95% CI, 1.0% – 5.2%). Of the six (6) patients that experienced relapse in the central nervous system, only one had isolated central nervous system recurrence.

Unfavourable cytogenetics (MLL rearrangement or BCR-ABL), and non-adherence to maintenance phase of the ALL treatment were predictors significantly associated with an increased risk of relapse [($p=0.04$) and ($p<0.001$].

There was a high rate of mortality in the subgroup of patients that experienced relapse, 88% (16/18).

There were differences in height z-scores observed between the 12 Gy and 18Gy radiation doses which were marginally statistically significant ($p=0.053$). Children treated with 12 Gy were able to maintain normal growth with an average height z-score>0. By contrast, children who were treated with 18Gy had negative average z scores in the first 3 years after completing treatment but thereafter experienced growth velocity. A small proportion of patients 4/51 (7.8%) had significant neurocognitive impairment requiring special remedial education.

Conclusion

The outcomes were poor in this study with low overall and event-free survival and high incidence of relapse. However, prophylactic cranial irradiation still appears to be effective in preventing CNS relapse for both the medium and high-risk groups with acceptable side effect profiles. Poor compliance with treatment and unfavourable cytogenetics were important prognostic factors for relapse.

These results are comparable to the experience of low to middle income countries that utilize international adopted acute lymphoblastic leukaemia treatment protocols. Strategies to better understand the unique biology and conditions that impact outcomes in low to middle income countries continue through international collaborative trials should be encouraged to improve on progress made in acute lymphoblastic leukaemia management and producing protocols suitable for diverse populations.

Keywords: ALL, CNS relapse, LMIC, prophylactic cranial irradiation

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LIST OF ABBREVIATIONS/NOMENCLATURE

ACTH: Adrenocorticotropic hormone

ALL: Acute lymphoblastic leukaemia

BFM-95: Berlin-Frankfurt-Munster-95 protocol

BM: Bone Marrow

CEO: Chief Executive Officer

CHBAH: Chris Hani Baragwanath Academic Hospital

CI: Confidence Interval

CMJAH: Charlotte Maxeke Johannesburg Academic Hospital

CNS: Central nervous system

COG: Children's Oncology Group

CRM: Competing Risk Methods

CSF: cerebrospinal fluid

DNA: Deoxynucleic Acid

EFS: Event Free Survival

GH: Growth hormone

Gy: Gray (unit dose of radiation)

GEE: Generalizing Estimating Equation model

HIV: Human immunodeficiency virus

HPTA: Hypothalamic-Pituitary-Thyroid Axis

HR: Hazard Ratio

LMIC: Low and Middle Income Country

HIC: High-income countries

6MP: 6-mercaptopurine (used in LMIC)

MRD: Minimal Residual Disease

MXT: Methotrexate

OS: Overall Survival

RT: Radiotherapy

TSH: Thyroid stimulating hormone

WBC: White blood cells

WHO: World Health Organisation

1 Introduction

1.1 Background

Acute lymphoblastic leukaemia (ALL) is the most common cancer in childhood worldwide, accounting for approximately 30% of childhood cancer [1]. It also remains at the top in Sub-Saharan Africa (South Africa 27.4% and Namibia 22.7%) [2]. In the 1960s ALL caused more deaths compared to other cancers with less than 10% of children surviving but improvements in treatment modalities over the years resulted in remarkable five-year overall survival rate greater than 85%. Early successes in leukaemia control are attributable to the introduction of central nervous system (CNS) directed therapy which involves prophylactic cranial irradiation with or without intrathecal methotrexate [3]. Even with improvements in outcomes, relapse is still a major cause of treatment failure estimated to affect 15% - 20% of patients with markedly reduced overall survival of 30%-40% [4, 5]. Relapsed disease can be found in different anatomic sites and commonly occurs in the bone marrow and less commonly other extra-medullary sites such as the CNS and testis. CNS relapse rates approach 5%-11%, a significant reduction from historical rates exceeding 60% experienced prior to the introduction of CNS-directed therapy, which classically involved craniospinal or prophylactic cranial irradiation [6]. Factors associated with increased risk of relapse are extensively reported in literature and include age, leukocytosis at diagnosis, presence of leukaemic cells in the CNS (even from iatrogenic introduction during a traumatic lumbar puncture), high risk genetic abnormalities such as Philadelphia chromosome, t(1;19), t(4;11), and T-cell ALL and minimum residual disease [5, 7].

Among contributing factors to improved survival outcome was adoption of risk-based stratification protocols developed through collaborative research clinical trials. Patients with favorable features are treated with less toxic regimens whereas more aggressive regimens are reserved for those with more high-risk disease. Different stratification schemas are used to categorize patients into standard, medium and high risk and the latter receives intensified chemotherapy, intrathecal chemotherapy, prophylactic cranial irradiation and haematopoetic stem cell transplant post induction. Sadly, the impressive ALL outcomes seen in high-income countries have not translated to low and middle-income countries [8]. Cure rates are still lower in developing countries due to the epidemiology and pathobiology (adverse risk factors at diagnosis), lack of dedicated multidisciplinary oncology units and poor access to care [9]. In South Africa, cure rates range between 50%-75% for the reasons mentioned above [10, 11]. In particular, black and mixed ethnicity children in the United States and South Africa have been observed to exhibit poor prognosis despite equal access to effective treatment [10-12]. Consequently, most South African paediatric oncology units including our institution have been reluctant to de-intensify treatment for black children classified in the standard and medium risk disease categories. Adopted international protocols have been modified, with all black children classified and treated as medium or high risk and receiving CNS-directed therapy which includes prophylactic cranial irradiation.

Prophylactic cranial irradiation is an effective form of CNS-directed therapy but its efficacy is offset by debilitating late complications which include secondary neoplasms, endocrinopathy, neurocognitive dysfunction, and neurotoxicity [13]. In earlier studies, a high rate of these toxicities was observed when doses of 24 Gy were used and craniospinal instead of cranial volumes were

treated. To minimize the toxicity, doses were reduced to 12-18 Gy without loss of efficacy, cranial instead of craniospinal irradiation is used and reserved for the subgroup with the highest risk of relapse [14]. CNS-related late effects are still a concern even at low doses especially for the developing brain because of the negative impact in health-related quality of life and daily functioning. Some centres have eliminated cranial irradiation in their protocols replacing it with more intensive systemic and intrathecal chemotherapy, accepting the small risk of CNS relapse in high-risk patients. It is the aim of cancer treatment generally, including that of ALL to refine and maintain high cure rates whilst minimizing adverse effects of treatments and improving quality of life.

It is our hypothesis that there are differences in outcomes between South Africa and high-income countries (HIC) in children with acute lymphoblastic leukaemia which will inform future management. Understanding the South African epidemiology and experience is key for the success of ALL management as local treatment strategies are adapted from international studies and protocols.

1.2 Problem Statement and justification

The effectiveness of prophylactic cranial irradiation in reducing CNS as well as systemic relapse among high-risk ALL paediatric patients is well recognized but this efficacy is countered by significant long-term toxicity associated with prophylactic cranial irradiation. The effectiveness and long term sequelae of prophylactic cranial irradiation whilst well documented in HIC have not been documented to the same extent in South Africa.

1.3 Literature review

Acute lymphoblastic leukaemia is the most common childhood malignancy; its incidence peaks between the ages of 2 and 5 years, and is more common in boys [1, 3]. According to the South African National Cancer Registry, the leukaemia age-standardized incidence is 11.9 new cases per million for the age range 0-14 years for the period 1997-2007, highest at 15.5 per million in the 0-4 age group and more common in boys than girls [2]. Clinical presentation of ALL depends on the extent of bone marrow and extramedullary infiltration by leukaemic cells. Symptoms maybe vague (pallor, bleeding, fever) due to haematopoetic failure or life-threatening oncologic emergencies (superior vena cava syndrome secondary to mediastinal lymphadenopathy and CNS haemorrhage or thrombosis due to hyperleukocytosis [1]. Common extramedullary sites are CNS and rarely, testes, ovaries and the eyes or orbits.

ALL is a malignant disorder of lymphoid progenitor cells. The World Health Organization (WHO) classifies ALL as B or T lymphoblastic leukemia based upon cell lineage. Diagnostic evaluation includes clinical examination and specialized tests on bone marrow aspirate and trephine to determine the leukaemia phenotype and presence or absence of cytogenetic abnormalities. CNS leukaemia diagnosis requires cytological confirmation of presence of blasts in the CSF or clinical signs such as facial nerve palsy, brain, or eye involvement or a tumour mass involving the CNS on imaging studies. Risk group stratification incorporates prognostic factors such as patient's clinical features at the time of diagnosis (age, sex); disease characteristics (white blood cell count, tumor immunophenotype, cytogenetic findings) and measurement of initial response to therapy (minimum or measurable residual disease) and risk assignment [15, 16].

Before the universal use of CNS-directed therapy, most patients relapsed with CNS disease, despite fewer than 5% of patients having CNS leukemia at diagnosis [1,3,13]. Earlier trials

demonstrated that craniospinal irradiation produced dramatic reduction in isolated CNS relapse but was associated with significant morbidity. Approximately 50% of children who received doses of 24Gy developed hypothalamic-pituitary dysfunction, hyperprolactinemia and central precocious puberty; brain radionecrosis ranging from subclinical CNS changes detected by magnetic resonance imaging (MRI) (atrophy, leukoencephalopathy, calcifications, or grey matter abnormalities) to overt clinical neurocognitive dysfunction, focal neurologic signs and seizures; secondary brain tumours [1,3]. Spinal radiation was associated with myelosuppression and musculoskeletal hypoplasia. These complications prompted researchers to investigate strategies to de-escalate radiation volumes and doses[17]. Prophylactic cranial irradiation replaced craniospinal irradiation and treatment doses were reduced and, in some centres prophylactic cranial irradiation completely replaced by intrathecal methotrexate [12, 17].

Endocrine deficiencies in the hypothalamic-pituitary-axis (HPTA) are the commonest late complication following cranial irradiation with damage at the level of the hypothalamus. The development, severity, and frequency of the HPTA dysfunction is related to the total dose given, dose per fraction, age at treatment, time since treatment and female gender. The somatotrophic axis is the most radiosensitive pathway [18]. A retrospective childhood cancer survivor study of a large cohort of adults treated with cranial radiotherapy of which 72% had leukaemia reported the prevalence of growth hormone (GH) deficiency to be 46%, gonadotrophin deficiency at 10.8%, thyroid stimulating hormone deficiency in 7.5% and ACTH deficiency in 4% over a long period of 27 years (range: 10 -47 years) [19]. GH deficiency usually manifests early (mean of 2.6 years), followed by gonadotrophin hormones and hyperprolactinemia after 3.6 years, ACTH at 6 years and TSH at 11 years. It is therefore recommended to conduct regular follow-up clinical evaluation which includes linear growth and pubertal staging at baseline and annually after radiotherapy and

should be conducted until final height and pubertal maturity has been reached. According to collaborative trials, cranial irradiation doses reported to correlate with pituitary dysfunction are as follows, GH deficiency ≥18 Gy, central precocious puberty ≥18 Gy, TSH deficiency ≥ 30 Gy, hyperprolactinemia ≥ 50 Gy.

At the Charlotte Maxeke Johannesburg Academic Hospital, a slightly modified Berlin-Frankfurt-Munster (BFM) 1995 protocol (appendix 6) is used because most patients are black. The standard risk group was dropped, and the population is divided into medium and high-risk groups as follows:

A) Medium Risk Group

1. Leukaemic blasts<1000/ul in peripheral blood on Day 8 after 7-day Prednisone induction pre-phase
2. Complete remission on Day 33 (M1 marrow) and/or mediastinal mass<30% initial size
3. No t(9:22) or BCR/ABL recombination
4. No t(4:11) or MLL/AF4 recombination

B) High Risk Group

1. Leukaemic blasts ≥1000/ul in peripheral blood on Day 8 after 7-day Prednisone induction pre-phase
2. No complete remission on Day 33 (M1 marrow) and/or mediastinal mass>30% initial size
3. t(9:22) or BCR/ABR recombination
4. t(4:11) or MLL/AF4 recombination

All patients received CNS-directed therapy during induction and in the intensification phase. Intrathecal methotrexate is initially given followed by high-dose methotrexate or prophylactic cranial irradiation depending on the age of the patient. Intrathecal methotrexate and intrathecal hydrocortisone are preferred for patients younger than 6 years of age unless they fall in the high risk stratification wherein lower doses of prophylactic cranial irradiation (12 or 12.6 Gy) are given between ages 3-6 years. Patients older than 6 years and those with overt CNS disease at diagnosis received prophylactic cranial irradiation dose of 18Gy irrespective of risk group. Preventative CNS irradiation is given at the end of the intensive chemotherapy treatment which end of re-induction phase for the medium risk and consolidation phase for the high-risk group and before the maintenance phase.

1.4 Aims and objectives

Aim

To determine the rate of relapse, factors associated with relapse in paediatric patients with acute lymphoblastic leukaemia, and long-term sequelae of prophylactic cranial radiation therapy in a population of patients diagnosed with ALL and who received prophylactic cranial radiation therapy.

Study objectives

The objectives of this study are:

1. Primary objective

- To determine the incidence of relapse, anatomic sites and risk factors associated with relapse in children who received prophylactic cranial radiotherapy.

2. Secondary objectives
    - Overall outcome of patients
    - To describe the long-term effects associated with prophylactic cranial irradiation

2 Study Methods

2.1 Study design and setting

This is a retrospective analysis of paediatric patients with ALL utilizing data collected from the paediatric oncology departments located at Chris Hani Baragwanath Academic Hospital (CHBAH) and Charlotte Maxeke Academic Hospital (CMJAH) and treated at the Radiation Oncology department at CMJAH in the period from 2009 to 2015.

2.2 Study population and study sample

The study population include children between ages 1-18 years. A total number of 51 patients with the diagnosis of Acute Lymphoblastic Leukaemia (ALL) were included for data analysis in our study.

2.2.1 Inclusion criteria

- Any patient who received prophylactic cranial irradiation for ALL as part of CNS-directed therapy between 2009-2015
- Children between ages 1-18 years

2.2.2 Exclusion criteria

- ALL patients who only received intrathecal chemotherapy for CNS-directed therapy
- Patients whose medical records were missing or not retrievable

2.3 Diagnosis of Acute Lymphoblastic Leukaemia (ALL)

The diagnosis is established when at least 25% blasts on bone marrow trephine or CSF. CNS involvement is diagnosed by performing a lumbar puncture and denoted by presence of >5cells/uL or lymphocytes.

Immunophenotype: Surface antigen considered positive if at least 20% expression of leukaemic expressed specific antigen with more than 98% fluorescence intensity compared to controls.

Cytogenetics: ploidy is determined by measuring DNA content using flow cytometry. [15, 16].

2.4 Response criteria

Complete Response is evaluated at Day 33 and defined as less than 5% blasts in the bone marrow, absence of leukemic blasts in peripheral blood and cerebrospinal fluid and no evidence of disease at any other site.

Relapse is defined as more than 25% blast cells in the bone marrow, meningeal or CNS leukaemia or combination of bone marrow and CNS leukemia.

2.5 Time to relapse

Time to relapse is classified according the BFM protocol as:

Very early = relapse occurring within 18 months from first diagnosis

Early = after 18 months of first diagnosis but within 6 months after end of therapy

Late = after 18 months but more than 6 months after end of therapy.

2.6 Data collection and management

Demographic, clinical, laboratory, height and weight data were collected from patients' medical records and captured on the REDCap database, and thereafter imported to an excel spreadsheet for ease of analysis. It included age (date of birth), sex, race, WBC, immunophenotype, ploidy, mediastinal mass, CNS involvement, testes involvement (for males), risk-classification, relapse and anatomic site, mortality, school grade at time of treatment and during follow-up, special school attendance or referral (yes/no), and patient's weight and height; at diagnosis, post-radiation and subsequently annually (see Appendix 1 for sample of data collection sheet).

2.7 Data processing and statistical analysis

Using Stata software version 15, different commands assisted in cleaning the data. Data cleaning processes included checking for duplicates, missing values, recoding and categorising variables. There was a process of ensuring quality assurance. Data analysis was also done using Stata 15 software.

2.7.1 Data analysis

Demographic, clinical and outcome characteristics of all patients were summarized using descriptive statistics. Frequency and percentages were used to present categorical variables and statistical measures such as mean, median, inter-quartile range, minimum and maximum values used to describe continuous variables. Differences in the distribution of variables among patient subsets was analysed using Pearson's Chi square test or Fischer's exact tests, where applicable.

Overall and event-free survival were calculated using the Kaplan-Meier (KM) method also known as the product-limit estimate. Event-free survival (EFS) was calculated from the time of diagnosis to the date of an event (any relapse or mortality from any cause) or date of last follow-up. Overall

survival (OS) was defined from time of diagnosis to death. Differences between high and medium risk groups were compared using log-rank tests. Cox proportional -hazard regression analysis was used for univariate and multivariate analysis of prognostic factors with 95% confidence intervals. All variables with a $p<0.05$ were considered as statistically significant.

The cumulative incidence of relapse was estimated using the complement of KM method and calculated as one minus the survival probability. In this approach, a patient that is alive at the end of the study or develops an intervening or competing event (an event other than event of interest) is censored and this event is considered non-informative or independent of the event of interest. This method has been criticised for overestimating the cumulative incidence as it does not adjust for competing events. An alternative approach is to adopt the Competing Risk Method (CRM) or cumulative incidence function pioneered by Kalbfleisch and Prentice in 1980 [20]. This method is useful when there is/are competing event (failure) which are considered formative and may preclude the onset of the event of interest, or may modify the probability of the onset of the event of interest. This method would have been useful in defining the site-specific but there is no access to the requisite software.

Cox proportional-hazard regression analysis was used to identify predictor variables associated with relapse and factors with a with a $p<0.05$ were considered as statistically significant.

Height measurements were converted to Z-scores using the National Department of Health's Road to Health growth charts (adapted from USA's Centre for Disease Control) to evaluate growth as a proxy for radiation effects on the hypothalamic-pituitary axis. Z scores or standard scores are used to describe mathematically how far above and below the population mean or median the raw score is. The average differences in z-scores between the two different radiation therapy doses (12Gy and 18Gy) was analysed by the generalized estimating equation (GEE) and a graph plotted; a

$p<0.05$ was considered statistically significant. The GEE model was also used to assess the association between RT dose and clinical variables that might influence changes in height z-scores.

Similarly, the proportion of patients needing special education was described.

2.8 Ethics

Permission to access patients' medical records was obtained from the Chief Executive Officers (CEO) of the two academic hospitals (Appendix 2 and 3).

Ethics approval was sought from the Human Research Ethics Committee (HREC) of The University of the Witwatersrand. The Ethics clearance certificate number M181086 (Appendix 4).

3 Results

3.1 Patients' characteristics

Table 1: Patients' characteristics [demographics and clinicopathological parameters]

Characteristic	Frequency (n=51)	Percentage (%)
Age (years)		
≤10	37	72
>10	14	28
Sex		
Female	18	35
Male	33	65
Race		
Black	48	94
White	2	4
Asian (Indian)	1	2
Risk stratification		
Medium	21	41
High	30	59
WCC (10^3 dL)		
≤50	34	67
>50	17	33
Immunophenotype		
B-ALL	33	65
T-ALL	13	27
Mixed B-cell	4	8
Cytogenetics		
t(9:22)or BCR/ABL recombination	3	6
t(4:11) or MLL/AF4 recombination	6	12
Favourable translocation	16	51
No translocations	26	31
Complete Remission		
Yes	33	66
No	17	34
Relapse		
Yes	18	35
No	33	65
Relapse site		
Isolated CNS	1	6
Isolated BM	12	67
Combined CNS and BM	5	27

A total of 51 patients diagnosed with ALL treated with the modified BFM-95 protocol who received cranial irradiation between 2009 and 2016 were eligible for analysis. The median

follow-up time was 4.8 years. The median age was 8 years (range: 1-17), and there were more male compared to female patients (Table 3.1).

More than half (59%, n=30) of the patients were classified as high-risk while the remaining (41%, n=21) were medium risk. A third of the patients (31%, n=16) had white blood cell count (WCC) more than 50,000 cells/dL at diagnosis. The median platelet count was 52,000/dL (range 7000-584,000/dL) and the median hemoglobin (Hb) was 7.1 g/dl (range: 1.6 - 16.6 g/dl), with most of the patients (98%, n=50) presenting with anaemia (Hb ≤ 12) at diagnosis.

Commonly observed clinical features at presentation were lymphadenopathy of the head and neck region followed by hepatosplenomegaly. Extramedullary manifestation of ALL was seen in a small proportion of patients; CNS involvement in 2 (4%) patients, testicular and eye involvement in 1 (2%) patient.

Regarding response to treatment, the proportion of patients who had good response to prednisone on day 8, defined as fewer than 1000u/L blasts in the peripheral smear was 60% (n=31). Initial complete response defined as < 5% blasts in the bone marrow, absence of blasts in the peripheral blood and CSF and no evidence of local disease initially on day 33 (post-induction) was attained in two thirds (66%, n=33) of the patients post-induction. Patients with minimum residual disease (MRD) post-induction were treated with high risk blocks because day 33 MRD was identified as an independent prognostic factor for relapse. Remission is again measured as above on week 12 (post consolidation) for these patients. Unfortunately, end of consolidation remission data was not collected for this study.

3.2 Overall outcomes

Following a median follow-up time of 4.8 years, the estimated probability of overall survival (OS) for this patient population was 69% (95% CI: 54%-79%) at 3 years, 64% (95% CI: 49%-75%) at 5 years and 52% (95% CI: 34%-68%) at 10 years (Figure 3.1).

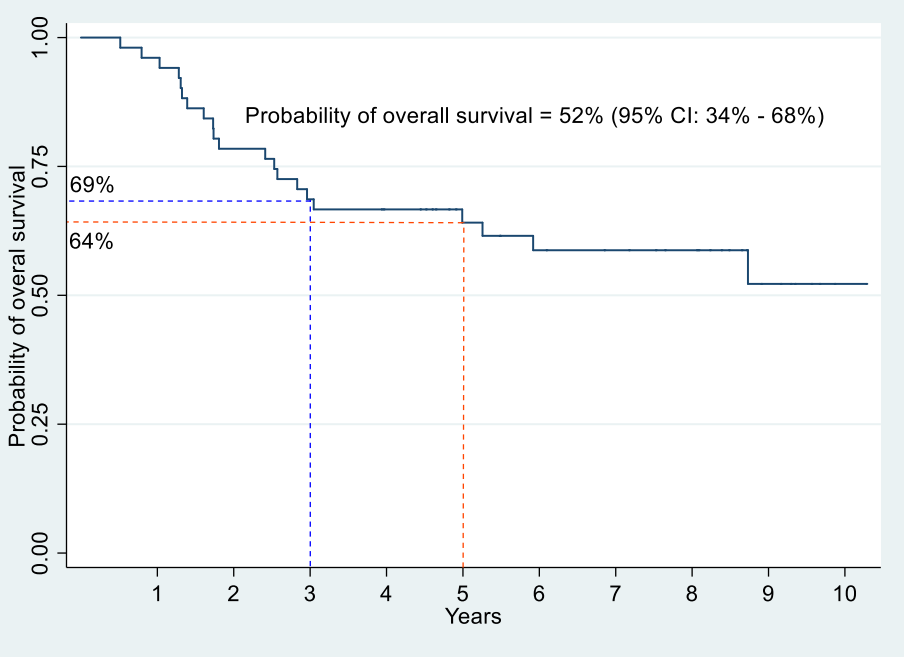


Figure 3.1: Kaplan-Meier curve estimate of overall survival for the patient population

A total of 21 (41%) patients died and a significant number of patients who experienced relapse 17/18 (94%) had died at the time of analysis indicated the poor prognosis related to relapse. The median time to death was 4.5 years with the majority occurring within 3 years of diagnosis. Of the patients that demised after relapse, 59% (n=10) were less than 10 years of age and 41%, (n=7) were above the age of 10years. Relapse occurred very early (<18months) in 41 % (n=7); early (between 18 - 36months) in 35 % (n=6) and late (>36 months) in 24 % (n=4).

The probability of an event free survival (EFS) was 67% (95% CI: 52%-77%) at 3 years and 57% (95% CI: 42%- 70%) at 5 years.

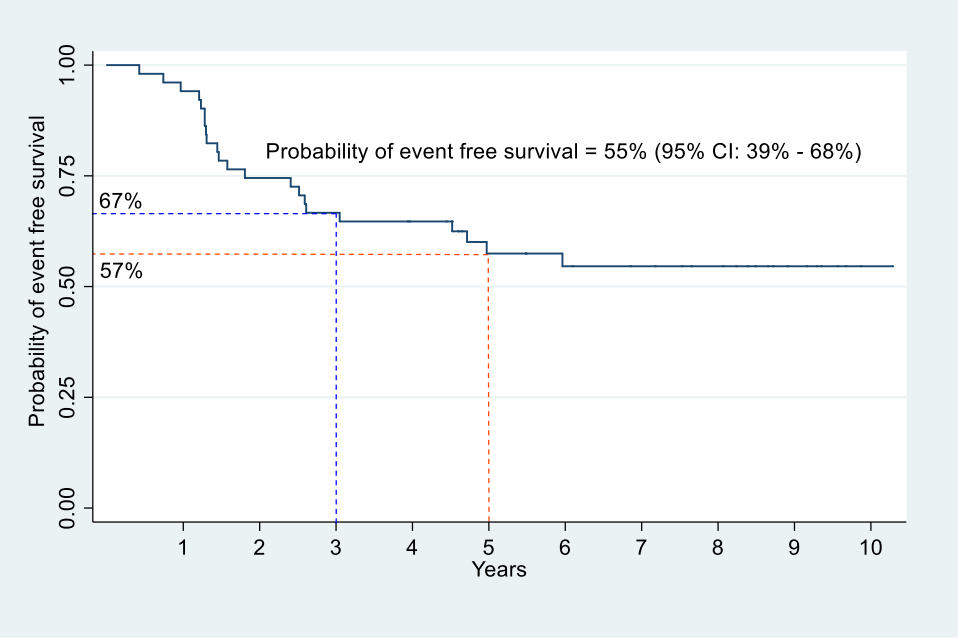


Figure 3.2: Probability of event-free survival (EFS) for the patient population

The Kaplan-Meier curve showing the estimates of EFS split by risk group stratification is shown in figure 3.3 below and shows no difference in the probability of developing an event overall, however the curves separate with longer-term survival, suggesting a trend towards a difference between the two groups.

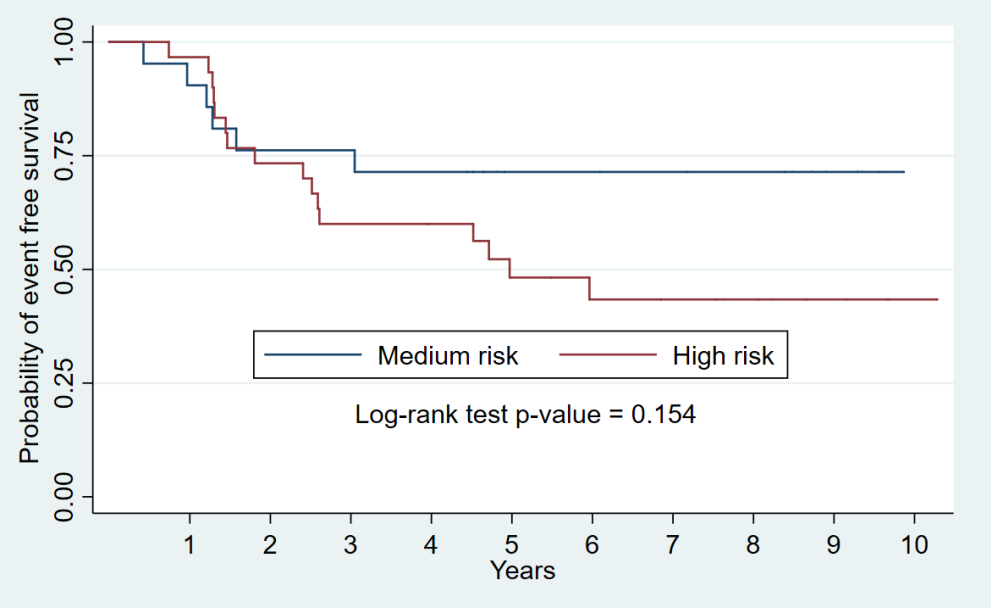


Figure 3.3: Kaplan-Meier estimate of event-free survival between the risk groups

3.3 Relapse: overall and central nervous system (CNS)

A total of 18 (35%) out of the 51 patients had relapse and of these, two-thirds relapsed in the bone marrow 67% (n=12), while 27% (n=5) had CNS relapse (isolated and combined) with only one patient having isolated CNS relapse. The median time to relapse was18.5 months (14.7-31.7). As shown in figure 3.4, eight (8) patients experienced early relapse occurring within 18 months of diagnosis and the remaining ten (10) had late relapse occurring more than 18 months post diagnosis, of these only 4 patients had very late relapse occurring more than 36 months after diagnosis. Relapse in the central nervous system was relatively early in 14.9 months (8.9 - 17.6) compared to relapse in the bone marrow at 29.5 months (15.2 - 55.4) but this difference was not statistically significant (p-value 0.134).

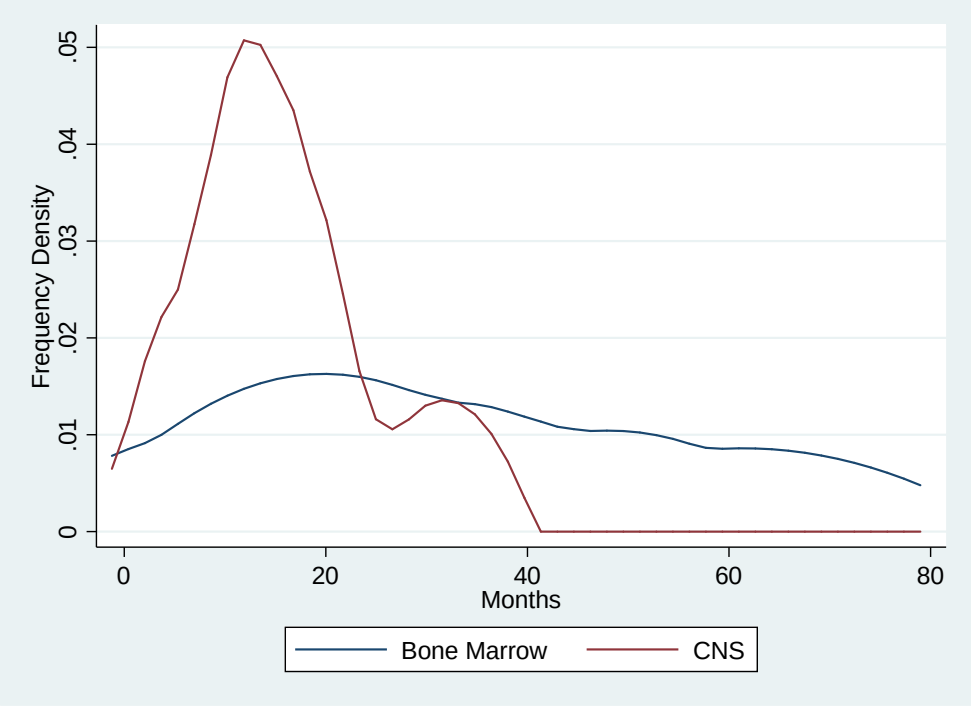


Figure 3.4: Time pattern of relapse

Figure 3.5 shows the overall cumulative incidence rate of relapse was 7.0%, (95% CI, 4.4% – 11.1%) (i.e. 7.0 cases per 100 person-years or 70 cases per 1000 person-years). Cumulative probability of overall relapse at 3 and 5 years was 33% (95% CI: 19% – 56%) and 45% (95% CI, 27% – 73%) respectively.

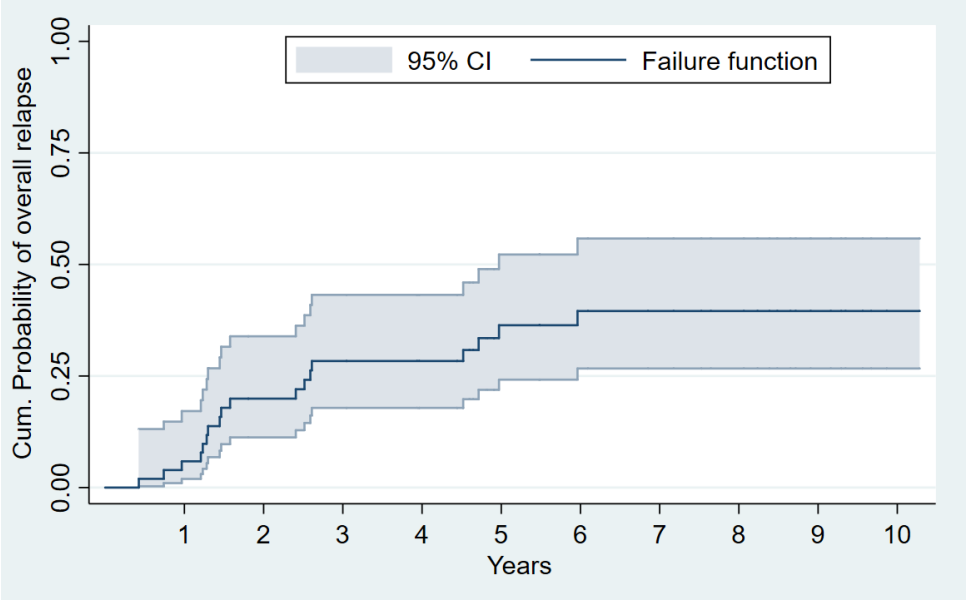


Figure 3.5: Cumulative probability of overall relapse

CNS relapse occurred in 12% (n=6) of the patient studied, and 33% (n=6) of patients who had relapse. CNS relapse had an incidence rate of 2.3%, (95% CI, 1.0 % – 5.2 %) (i.e. 2.3 cases per 100 person-years or 23 cases per 1000 person-years). Cumulative probability of CNS relapse at 3 was 14% (95% CI: 6% – 32%), see figure 3.6. All CNS relapses occurred before 5 years.

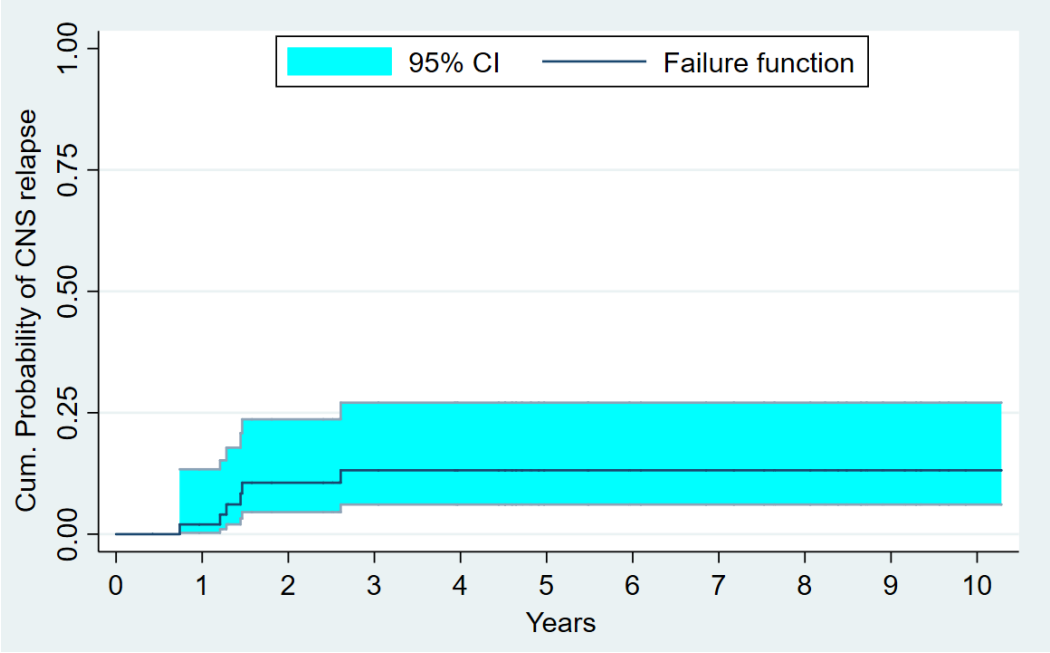


Figure 3.6: Cumulative probability of CNS relapse

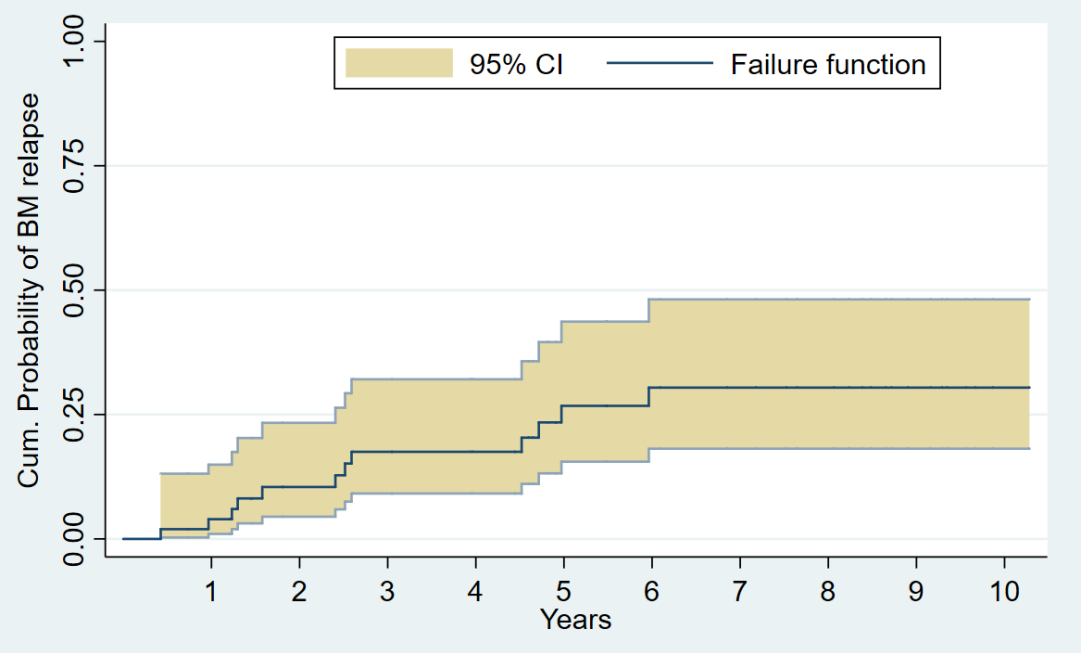


Figure 3.7: Cumulative probability of bone marrow relapse

Bone marrow (BM) relapse occurred in 12% (n=6) of the patient studied, and 67% (n=12) of all patients who had relapse. With an incidence rate of 4.6%, (95% CI, 2.6 % – 8.2 %), BM relapse occurred in 46 cases per 1000 person-years. Figure 8 indicates the cumulative probability of BM relapse at 3 and 5 years was 19% (95% CI: 9 % – 38 %) and 31% (95% CI: 16 % – 57 %) respectively.

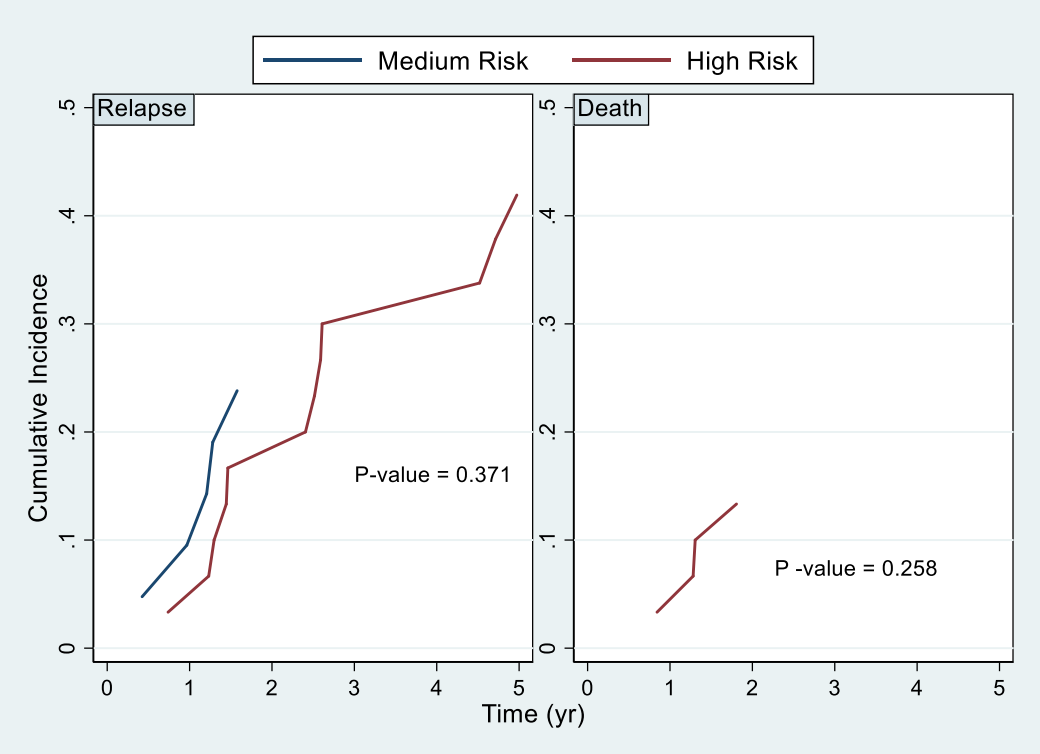


Figure3.8: Probability of relapse and death between risk groups: CRM

Analysis using the competing risk function, adjusting for patients who failed (died) before the main event of relapse, showed a trend towards a higher cumulative incidence of relapse and death in the high risk group; which whilst not statistically significant, is clinically relevant in figure 3.8 above.

3.3.1 Risk factors associated with relapse

Because of the small sample size, the analysis focused on variables contributing to overall ALL relapse and could not tease out those associated with individual sites such as CNS or bone marrow.

Table 2.2: Univariate analysis of laboratory and clinical factors and their association with relapse

Variable	No Relapse	Relapse	Total	Chi square	p-value
Age (years) at diagnosis, n (%)					
≤10	24 (72)	13 (72)	37 (72)	0.00	0.965
>10	9 (28)	5 (28)	14(72)		
Sex, n (%)					
Female	11 (33)	6 (33)	17(33)	0.00	0.983
Male	22 (67)	12 (67)	34(67)		
Immunophenotype, n (%)					
B-cell All	19 (58)	14 (78)	33(65)	1.30	0.522
T-cell All	11 (33)	3 (17)	14(27)		
Mixed B-cell lineage	3 (9)	1 (5)	4(8)		
Cytogenetics n (%)					
t(9;22) and t(4;11) [unfavourable]	4 (12)	5 (28)	9 (18)	9.52	**0.008**
NIL translocations	15 (46)	1 (6)	16 (31)		
Other t(12;21) [favourable]	14 (42)	12 (66)	26 (51)		
Risk Stratification, n (%)					
Medium	16 (48)	5 (28)	21 (41)	1.57	0.210
High	17 (52)	13 (72)	30 (58)		
Completed ALL treatment protocol, n (%)					
Yes	33 (100)	12 (67)	45 (88)	29.23	**<0.001**
No	0 (0)	6 (33)	6 (12)		
White Cell Count, n (%)					
≤50 000 d/L	24 (73)	10 (56)	34 (67)	1.06	0.303
>50 000 d/L	9 (27)	8 (44)	17 (33)		
Day 8 Prednisone Response, n (%)					
Good	23 (70)	7 (41)	30 (60)	2.95	0.086
Poor	10 (30)	10 (59)	20 (40)		
Day 33 Complete Remission, n (%)					
Yes	21 (64)	11 (65)	32 (64)	0.07	0.793
No	12 (36)	6 (35)	18 (36)		

Clinical and laboratory variables known to confer a high risk of relapse were tested in a logistic regression model and interactions among factors with a p-value ≤ 0.25 included in the cox-regression model for multivariate analysis.

The mean age of patients who experienced relapse was 6 years at diagnosis versus 8 years for those who did not have relapse and this was not statistically significant (p=0.438). The univariate analysis shown in table 3.2 above, demonstrated that unfavourable cytogenetics [t (4;11)/MLL rearrangement or [t (9;22)/BCR-ABL] (p=0.008) and the patients who failed to complete the full 3-year ALL treatment protocol (p<0.001) had a statistically significant impact on relapse.

In the multivariate cox regression analysis, patients who had no genetic alterations (no translocations) and those who received and completed the full intended 3-year ALL treatment protocol had a markedly reduced risk of relapse which was less than 10% which are statistically significant albeit with confidence intervals; [HR=0.06 (0.004 – 0.93), (p = 0.044)] and [HR=0.06 (0.01 – 0.30) (p=0.001)] respectively. Regarding genetics, children with the more common and favourable prognostic genetic translocations such as [t (12; 21)/ETV6-RUNX1] did not show a low risk of relapse, [HR=0.55 (0.10 – 2.93), p=0.486].

Table 3.3: A multivariate regression model to determine impact of variables on relapse

Variable	Hazard Ratio (95% CI)	P value
Age at diagnosis	1.03 (0.88 – 1. 19)	0.737
Sex		
Female	1	
Male	0.87 (0.18 – 4.19)	0.866
Cytogenetics		
BCR/MLL	1	
Nil Translocations	0.06 (0.004 – 0.93)	**0.044**
Favourable translocations	0.55 (0.10 – 2.93)	0.486
Risk stratification		
Medium	1	
High	2.04 (0.35 – 11.74)	0.425
Completed ALL treatment protocol		
No	1	
Yes	0.06 (0.01 – 0.30)	**0.001**
Day 8 Prednisone Response		
Poor	1	
Good	0.46 (0.10 – 2.14)	0.326
Day 33 Complete Remission		
No	1	
Yes	3.42 (0.73 – 16.12)	0.120
White Cell Count		
≤50 000 d/L	1	
>50 000 d/L	1.19 (0.32 – 4.38)	0.792

Immunophenotype		
B-cell All	1	
T-cell All	1.65 (0.34 – 7.94)	0.532
Mixed lineage	0.78 (0.05 – 13.05)	0.862

Other prognostic factors such as age at diagnosis, gender, white cell count at diagnosis, immunophenotype, response to therapy at Day 8 and Day 33 had no impact on the risk for relapse. Further information on the blast biology such as DNA index or ploidy indicating chromosome losses or gains in blasts cells which have been shown to have prognostic significance was not collected for this analysis. There were very few cases (n=3) with extramedullary disease at presentation and thus it was also not possible to test for association either.

3.4 Side effects of cranial irradiation

All the patients received cranial radiation as part of the CNS-directed therapy, the median age at the start of prophylactic cranial radiation therapy was 9 years (range = 2 – 17), and 7 years (range= 2 - 15) for the 12Gy and 10 years (range=6 - 17) for 18Gy doses respectively. Final height was evaluated at 6 months to 11 years post irradiation.

The characteristics were balanced between the two dose groups and as per protocol, younger patients below the age of 6 were likely to be treated with the lower dose schedule compared to older children. The median pre-radiation therapy or baseline height z-scores for the two dose groups was 0.53 (95% CI: -0.84-0.41) for 12Gy (n=24) and 0.099(95% CI: -0.3-0.72) for 18Gy (n=25).

Post-radiation at year 5 for 12Gy (n=11) the height z-score was -0.08(95% CI: -1.27-0.36) and for 18Gy (n=17) the z-score was -0.02 (95% CI: -0.46-0.73).

Differences in height were observed between the two doses and were marginally statistically significant (p=0.053). Children were able to maintain normal growth with a height velocity or positive average.

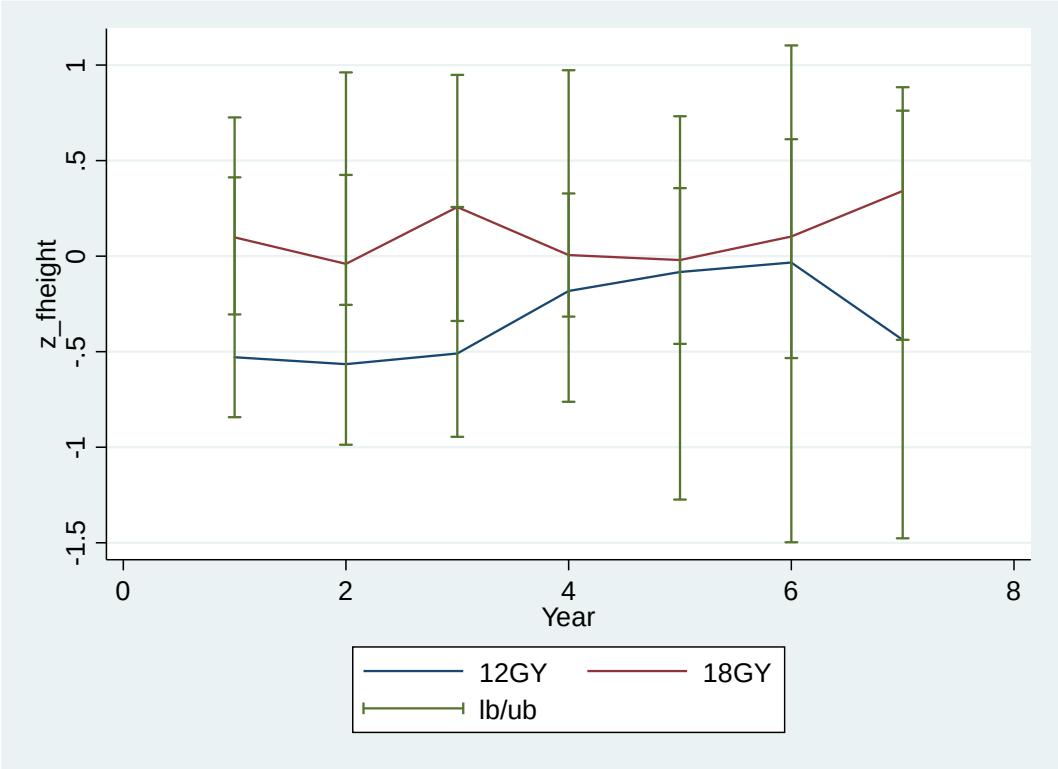


Figure 3.9: Effect of RT dose on changes in height

Table3. 4: Univariate analysis for changes in z-height scores using the generalizing estimating equation model (GEE)

Variable	Estimate (CI)	p-value
Gender Female	-0.16(-0.7-0.38)	0.565
Ethnicity	0.27(-0.36-0.91)	0.394
WCC	-0.0007(-0.004-0.002)	0.640
Cytogenetics	0.06(-0.31-0.42)	0.747
Radiation dose	-0.06(-0.15-0.02)	0.161
Age at RT years	-0.2(-0.23—0.16)	<0.00001

Age was found to be associated with changes in height in both univariate and multivariate analysis. Young age at RT was associated with a 0.2 and 0.19 decrease in height annually in univariate and multivariate analyses which were statistically significant ($p<0.0001$). In addition, being female resulted in 0.24 decrease in height was statistically significant on multivariate analysis ($p=0.043$)

Table3.5: Multivariate analysis: association between changes in height and clinical parameters using (GEE)

Variable	Estimate (CI)	p-value
Gender Female	-0.24(-0.47—0.007)	**0.043**
Ethnicity	0.2(-0.06-0.46)	0.125
WCC	-0.0007(-0.002-0.0097)	0.404
Cytogenetics	0.02(-0.18-0.23)	0.827
Radiation dose	-0.01(-0.05-0.03)	0.570
Age at RT years	-0.19(-0.23- -0.16)	**<0.00001**

Only four (4) patients were reported to be in special school, indicating neurocognitive impairment, all others were in regular school. These patients were all male and received prophylactic cranial irradiation below the age of 10. Half of the patients were in the medium risk group whilst the other half was stratified as high risk. Equally, half received a dose of 12 Gy for prophylactic radiation therapy and the other half received a dose of 18 Gy.

Of the 28 long term survivors, 6 patients completed post-matric qualifications and 13 were in high school.

4 Discussion

Relapse or recurrent disease in ALL affects approximately 15%-20% of paediatric patients after initial therapy and confers poor prognosis with inferior survival outcomes ranging from 20%-50% [21]. Low to middle income countries report worse cure rates compared to their high-income counterparts despite managing ALL with same treatment protocols [22, 23]. It is imperative to understand what drives these differences and how the gaps can be narrowed.

This was a retrospective study of children with ALL treated at a tertiary academic institution aimed at describing outcomes amongst those who received prophylactic cranial radiotherapy post-intensive therapy, the incidence of relapse, factors associated with relapse and side effects associated with preventative cranial irradiation.

The results demonstrated overall inferior outcomes, high relapse rate experienced during the maintenance phase of the ALL treatment protocol and was significantly associated with unfavourable cytogenetic aberrations at diagnosis and non-adherence to the maintenance therapy.

4.1 Survival outcomes

The 5-year overall survival (OS) and event-free survival (EFS) were lower at 64% and 57% respectively compared to HIC that report survival rates more than 80% but like outcomes seen in other LMIC [24, 25]. A study conducted in India reported EFS rates of 63.4% with the introduction of BFM-95. Similarly, disease-free survival was 67% among coloured children in the Western Cape following the implementation of the risk stratified BFM-90 and BFM-95 protocols [9]. The international protocols are typically modified to suit local risk factors and conditions. The commonly cited reasons behind inferior outcomes in LIMC are a possible different biology of ALL (higher proportion of T-cell immunophenotype and race), advanced stage at presentation leading to infections and other complications causing treatment interruptions or prolongation. In addition, low socio-economic status that precludes treatment intensification and supportive care in LMIC because of financial constraints and associated comorbid conditions such as malnutrition have been shown to contribute to suboptimal outcomes [26]. Most of these factors are not well studied and exploration of their impact on survival was

beyond the scope of this study; only diagnostic features and initial treatment response known to increase the risk of relapse were studied.

There was a significantly higher mortality rate (94%) amongst patients who relapsed compared to 50% reported in the literature[25, 27]. Factors that predict for mortality after relapse are: short duration of initial remission (within 36 months), relapse in the bone marrow (isolated or combined) which was documented in this population.[28] Salvage treatment for relapsed disease uses the same risk-based standard chemotherapy at high doses and haematopoietic stem cell-transplant but most patients are refractory to treatment. Unfortunately, data on the salvage therapy offered to our patients upon relapse was not collected.

4.2 Risk factors for ALL relapse

The 5-year cumulative incidences of overall relapse, isolated bone marrow and relapse involving the CNS were much higher at 33%, 14% and 31% respectively compared to developed countries which report incidence of relapse rates ranging from 15% -20% [21, 29, 30] but comparable to other LMIC [24,25]. Like these studies, the bone marrow was the commonest anatomic site of relapse and relapse occurred during the 3-year initial treatment protocol (median time of 18 months). Relapse is believed to arise from drug-resistant clones present at diagnosis and responsible for early relapses in contrast to the generation of new mutant clones responsible for 'second leukaemia' observed in late relapsed disease. The latter still retain some chemotherapy sensitivity[27]. This hypothesis is supported by the correlation between induction failure, relapses in CNS-sanctuary site harbouring resistant clones and early relapses. The small proportion of patients with CNS relapse in our study had early relapse supporting this hypothesis.

Adverse cytogenetic features such as t (9; 22)/BCR-ABL1/Philadelphia ALL and t(4;11)/MLL re-arrangement positive cases were significantly associated with relapse. Philadelphia ALL is frequently found in adolescents and when combined with leukocytosis, slow response to early therapy and treated with standard chemotherapy drugs, the outcomes are extremely poor[7, 15]. Addition of a tyrosine kinase to induction phase of treatment has improved outcomes but unfortunately, it was not available in our institution in the period under analysis. Mixed lineage

leukaemia rearrangement also predicts poor outcomes in infants and unfortunately, there are no targeted agents for this pathway[31]

Failure to complete the ALL treatment protocol is usually attributable to patient non-compliance or abandonment of treatment and/or physician-initiated treatment interruptions because of treatment toxicity during the maintenance [23, 32, 33]. Durable remission after complete remission is dependent on compliance with 6-mercaptopurine (6-MP) and methotrexate (MTX) for a period of 2 years. Bhatia et al [34] found that adherence rates falling below 90% were associated with an increased risk of relapse with an attributable risk of 33%. It was highest in the adolescent age-group with forgetfulness often cited as a reason for non-compliance. Compliance is measured by mean white cell count which must be in the range of $2\text{-}3x10^9$/L, levels of 6-MP metabolites (6-thioguinine nucleotide) in the erythrocytes or the activity of the enzyme thiopurine methyltransferase responsible for degrading 6-MP if resources are available. The authors also found that socio-demographic and economic characteristics helped explain non-adherence; low-income households amongst Asian-Americans and in contrast, low maternal levels of education were risk factors amongst African American households.

Other studies have also reported similar unfavourable socio-economic and cultural reasons for non-compliance. Educational, socio-economic, language and communication barriers between staff and parents contributed to poor compliance in Black patients in Johannesburg, South Africa compared to their Caucasian counterparts; only half of the Black children attended clinic visits on the designated days compared to 90% of the Caucasian children [33]. By contrast, these studies observed that white parents were more likely to report toxic effects of the treatment compared to black parents because of their understanding of the disease. Parental understanding of ALL was not explored in this research.

In a COG trial, up to a third (31%) of relapses were attributed to non-adherence which was more prevalent among African Americans, Hispanics children representing a population with lower socio-economic status and consequent poor health outcomes [5]. Ninety-four (94%) of this population was black and early reports indicated that outcomes among black children were poor even when conditions of treatment were equivalent [9-11]. These outcome disparities have reduced significantly over time but some differences among minority groups which correlate with low socio-economic status persist. Some studies have recommended the inclusion of socio-

economic status and race in risk stratification to account for treatment intensification. In our population, patients are admitted during the intensive treatment period to closely monitor and promptly respond to treatment-related complications. However, maintenance treatment is offered on an outpatient basis thus children and parents may find it hard to adhere to clinic visits and medication when they are feeling well, resulting in down-ward treatment-drift. It is difficult to identify if these issues were prevalent in our population as neither the socio-economic status nor measures of adherence to drug therapy and visits were quantified in this study.

Comorbid immunodeficiencies, malnutrition, pre-existing organ dysfunction can all negatively affect treatment outcomes and are also not incorporated in risk-stratification. Tests for HIV infection were available for this population and only 2 patients were positive but were on antiretroviral medications and their disease well controlled.

An elevated risk of mortality and relapse disease is linked to a high white cell count at diagnosis. This trait was not found to be a predictor of poor outcomes in this population presumably due to confounding adverse immunophenotypic (T-cell biology in a third of patients), genetic alterations such as lower incidence of favourable hyperdiploidy or chromosomal rearrangements (ETV6-RUNX1) that do not have poor prognosis or as yet undefined intrinsic biological, endocrine, metabolic factors. Continued refinement and intensity of treatment are also known to have eliminated the adverse impact of leukocytosis at diagnosis. Extramedullary disease in the liver and CNS at diagnosis was associated with lower survival and event -free -survival and the hypothesis is that this feature represents a high burden of disease making it difficult to clear clonal cells [35].

There was a trend towards a difference in outcomes between the medium and high-risk groups with higher hazards of death [HR 2.6(0.96-7.21], p=0.05 on univariate analysis, for the high-risk group. Although not statistically significant, it is clinically significant that mortality was exclusively observed in the high-risk subgroup confirming dismal outcomes and highlighting the need for individual level risk identification, and development of novel drugs and or treatment modalities without added toxicities.

Neither early response to treatment nor failed induction were associated with poor patient outcomes or risk of relapse in this population, likely because these factors were already used for stratification and the patients were treated with high-risk protocol. In this population a relatively

higher proportion of patients (34%, n=17) failed induction compared to 2-3% reported in developed countries [5, 25]. Patients with no complete remission after induction usually never achieve remission and if they do, experience early relapse and high mortality rates [5, 25]. Whilst the prognostic significance of rapid clearance of blasts in the peripheral blood and bone marrow on days 8 and 15 of commencing therapy was identified in earlier studies, subsequently minimal residual disease (MRD≥ 0.01%) shown to be a more reliable independent predictor of poor prognosis irrespective of prednisone response, clinical or genetic features and thus used to adjust therapy [16, 27].

4.3 Side effects of prophylactic cranial radiation therapy

Growth evaluation has been elucidated as a surrogate for growth hormone deficiency as this hormone is the first and only endocrine abnormality observed in prophylactic cranial irradiation because panhypopituitarism requires higher total cranial radiation doses. Whilst other studies have demonstrated statistically and clinically significant reduction in final height, there was a trend towards height impairment with the dose of 18 Gy which was not statistically significant [36, 37]. Shorter follow up time (median time of 5 years) and a small sample size may be the cause. Conflicting findings have also been reported in the literature regarding the effect on the hypothalamic-pituitary axis of doses less than 20 Gy, with some articles citing no impact on endocrine function with doses lower than 20 Gy [18,19].

The prevalence of children needing special school which is an indicator of the clinical impact caused by neurocognitive impairment was low in this population at 7% (n=4). There was no comparator group or objective neuropsychological testing to categorically conclude if this was related to CNS-directed therapy (cranial irradiation or intrathecal methotrexate). Indeed, this could represent a normal variation in development, unrelated to ALL severity or therapy or, genetic polymorphism all of which can affect brain structure and function. However, the literature reports a low incidence of cognitive impairment at low doses used for prophylactic cranial irradiation[18]. A study conducted in South Africa assessing the cognitive profile of children post preventative cranial radiation therapy found visuospatial deficit which affects learning, and a similar international study comparing CNS-directed intrathecal chemotherapy and cranial irradiation also demonstrated slow information processing and diminished

adaptability potentially affecting academic performance despite normal intelligence quotient (IQ) scores [38, 39].

5 Limitations

This is a retrospective study from a single institution in Johannesburg with resultant inferior levels of evidence. The sample size was too small to draw definite conclusions about causality and in making treatment recommendations or modifications. Difficulty was encountered in reviewing patient records retrospectively with considerable missing information and inconsistencies in data capturing in medical files.

In addition, it was challenging to clearly define risk factors for CNS relapse since prophylactic cranial irradiation was given to all patients, and there was no control group that only received intensified intrathecal or systemic chemotherapy.

In this study, the Kaplan-Meier approach was appropriate for estimating the cumulative incidence of relapse because the competing event which was death was experienced by more than 90% of the patients who had relapse. Similarly, when estimating the site-specific relapse cumulative incidence rates, there are no competing events in the presence of multiple failure events (death and other anatomic site relapse) [20].

Measurement of pituitary hormones are not routinely done to evaluate pituitary function and would have been a more objective measure of hypothalamic-pituitary dysfunction.

The risk of second neoplasms, a common complication among long-term survivors observed in patients who received cranial irradiation is not reported in this study. Longer follow-up periods are needed to quantify this often-debilitating adverse effect.

6 Conclusion

Relapse ALL disease was associated with a remarkably high rate of mortality in this population. Despite supportive care, salvage treatment requiring more intensive systemic therapy, allogenic stem transplant and re-irradiation when used is associated with increased risk of treatment-related toxicity further contributing to poor outcomes. In order to achieve improved outcomes, it

is important to better understand reasons behind non-completion of the treatment protocol and the biology of ALL in the black paediatric population as well as the pathophysiology of relapse.

Although prophylactic cranial radiation therapy is associated with adverse effects, it is effective, inexpensive, easily accessible, and convenient for low to middle income countries. When resources and the biology of ALL allow, the goal should be to convert to intensive intrathecal and systemic chemotherapy for upfront ALL management, in line with developed countries to minimize side effects and increase salvage therapy options, and in so doing strike a perfect balance between beneficence and non-maleficence.

7 Recommendations

A bigger sample size and or a prospective study will be useful in clarifying if prophylactic cranial irradiation protocol is still-

The poor survival rate observed in this study and a solitary case of CNS relapse reinforces the current adoption and adaptation of the BFM-95 protocol and not allocating children of black ethnicity into the standard risk groups and continuing with intense CNS-directed therapy for both medium and high-risk groups.

With up to 80% of childhood cancers in LIMC, there is a need for collaborative evaluation of epidemiology, biology and needs unique to our diverse populations. In addition, registries that track and evaluate the efficacy and appropriateness of adopted protocols will improve outcomes.

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UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

FACULTY OF HEALTH SCIENCES

PLAGIARISM DECLARATION TO BE SIGNED BY ALL HIGHER DEGREE STUDENTS

SENATE PLAGIARISM POLICY: APPENDIX ONE

I DR NONKULULEKO. Z. MCABA (Student number: 8902724J) am a student registered for the degree of MMed (Radiation Oncology) in the academic year 5th.

I hereby declare the following:

- I am aware that plagiarism (the use of someone else's work without their permission and/or without acknowledging the original source) is wrong.
- I confirm that the work submitted for assessment for the above degree is my own unaided work except where I have explicitly indicated otherwise.
- I have followed the required conventions in referencing the thoughts and ideas of others.
- I understand that the University of the Witwatersrand may take disciplinary action against me if there is a belief that this is not my own unaided work or that I have failed to acknowledge the source of the ideas or words in my writing.
- I have included as an appendix a report from "Turnitin" (or other approved plagiarism detection) software indicating the level of plagiarism in my research document.

Signature:  Date: 25/11/2020

Appendix Two [2]

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL

Enquiries:
Ms. N. Mzila
Office of the Clinical Director
Email:Nolwazi.Mzila@gauteng.gov.za
Tell: (011): 488-4812
17 September 2018

Dear Dr. N. Z. Mlaba

STUDY TITTLE: The Efficacy and Long – Term Side Effects Of Prophylactic Cranial Radiation Therapy in Child Acute Lymphocytic Leukaemia (ALL) In Johannesburg, South Africa.

Permission to conduct the above mentioned study is provisional approved. Your study can only commence once Ethics approval is obtained. Please forward a copy of your Ethics Clearance Certificate as soon as the study is approved by the Ethics Committee for the CEO's office to give you the final approval to conduct the study.

Supported / ~~not supported~~

Dr. M.I. Mofokeng
Clinical Director
DATE: 18/9/2018

Approved / not approved

Ms. G. Bogoshi
Chief Executive Officer
DATE: 18.09.2018

Appendix three [3]

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

MEDICAL ADVISORY COMMITTEE

CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL

PERMISSION TO CONDUCT RESEARCH

Date: 2nd October 2018

TITLE OF PROJECT:

The efficacy and long-term side effects of prophylactic cranial radiation therapy in childhood acute lymphocytic leukaemia (ALL) in Johannesburg, South Africa.

UNIVERSITY: Witwatersrand

Principal Investigator: Dr N Z Mlaba

Department: Radiation Oncology

Supervisor : Dr J Kotzen

Permission Head Department (where research conducted): Yes

The Medical Advisory Committee recommends that the said research be conducted at Chris Hani Baragwanath Academic Hospital. The CEO / management of Chris Hani Baragwanath Academic Hospital is accordingly informed and the study is subject to:-

- Permission having been granted by the Committee for Research on Human Subjects of the University of the Witwatersrand.
- The Hospital will not incur extra costs as a result of the research being conducted on its patients within the hospital
- The MAC will be informed of any serious adverse events as soon as they occur
- Permission is granted for the duration of the Ethics Committee Approval.

.....
Recommended
(On behalf of the MAC)
Date: 2/10/2018

.....
Approved/Not Approved
Hospital Management
Date: 03 10 2018

Appendix four [4]

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R14/49 Dr Nonkululeko Z Mlaba

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M181086

NAME: (Principal Investigator)	Dr Nonkululeko Z Mlaba
DEPARTMENT:	Radiation Oncology Charlotte Maxeke Johannesburg Academic Hospital
PROJECT TITLE:	The efficacy and long-term side effects of prophylactic cranial radiation therapy in childhood acute lymphocytic leukaemia (ALL) in Johannesburg, South Africa
DATE CONSIDERED:	26/10/2018
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr J Kotzen and Prof J Poole
APPROVED BY:	Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	29/10/2018

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary on the Third Floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in October and will therefore be due in the month of October each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature

Date 21/11/2018

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix five [5]

Title: The efficacy and long-term side effects of prophylactic cranial radiation therapy in childhood acute lymphocytic leukaemia (ALL) in Johannesburg, South Africa

Data collection Sheet

Variable	CNS relapse	No CNS relapse
Risk group Medium high		
Age group <6 years >6 years		
Sex Female Male		
Race group Black Other		
HIV status Yes No		
WCC <50000 >50000		
Location Urban Rural		
Phenotype Pre-B-ALL T-ALL Not available		
Cytogenetic findings t(9:22)or BCR/ABR recombination t(4:11) or MLL/AF4 recombination		
Day 8 Prednisone response Yes No		
Complete remission on D33 Yes		

No		
CNS involvement Yes No		
Mediastinal Mass Yes No		
Testes involvement Yes No		
Time to relapse Very early Early Late		
Special schooling Yes No		
Decreased Growth Hormone levels Yes NO		
Second malignancy Yes No		

ALL – BFM – 95 (MODIFIED).

STRATIFICATION CRITERIA

A. MEDIUM RISK GROUP

1) Leukemic Blasts < 1000/µl in peripheral blood on Day 8 after 7-day Prednisone induction Pre Phase.
2) Complete remission on Day 33 (M1 marrow) and/or mediastinal mass <30% initial size
3) No t (9:22) or BCR/ABL recombination
4) No t (4:11) or MLL/AF4 recombination

B. HIGH RISK GROUP

1) Leukemic Blasts ≥ 1000/µl in peripheral Blood on Day 8
2) No complete remission on Day 33 and/or mediastinal mass > 30% initial size
3) t (9:22) or BCR/ABL recombination
4) t (4:11) or MLL/AF4 recombination

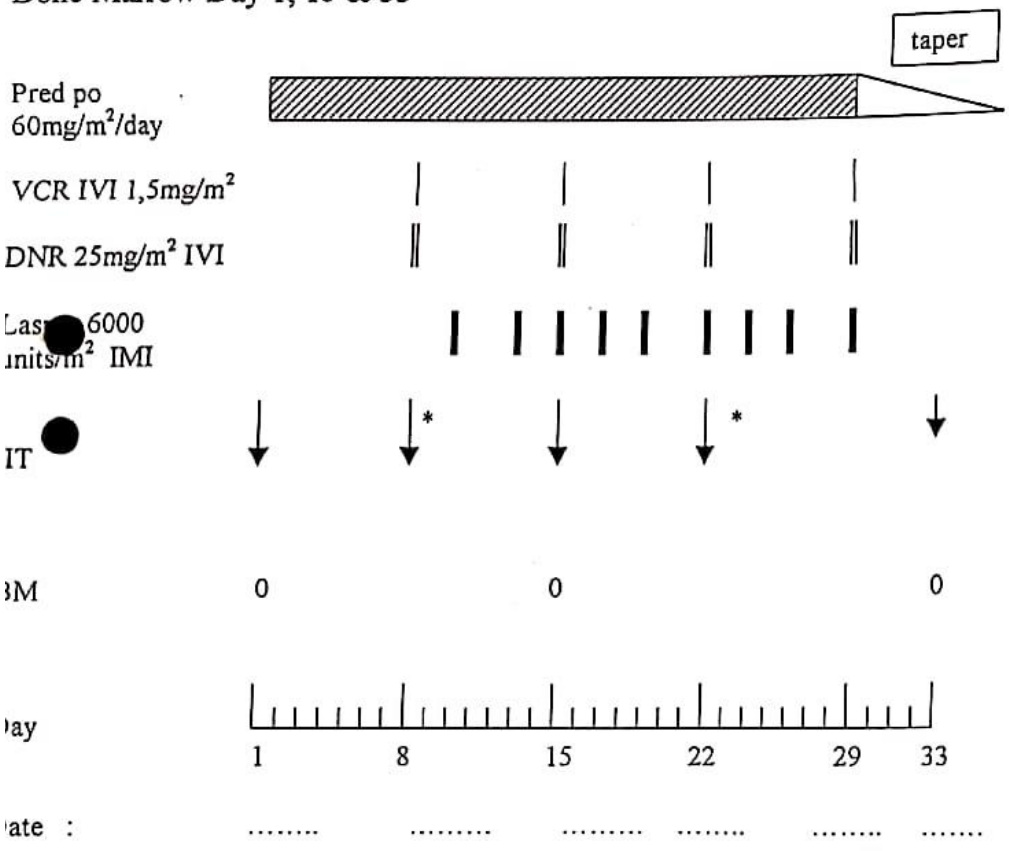
ALL BFM – 95 (MODIFIED)

PHASE I – INDUCTION

Prednisone: 60mg/m^2/day po: Day 1 – 28, then taper over 7 days
Vincristine: 1,5mg/m^2/day IV1: Day 8, 15, 22 & 29
Daunorubicin: 25mg/m^2/day IVI: Day 8, 15, 22 & 29
L'asparaginase: 6000 units/m^2/day IMI: Monday, Wednesday, Friday x 9 doses
Intrathecal Methotrexate: Day 1, 15 & 33
(< 1 year 6mg; 1-2 yrs 8mg; 2-3 yrs 10mg; ≥ 3 yrs 12mg)
Intrathecal Hydrocortisone : Day 1, 15 & 33
(< 1 year 8mg; 1-2 yrs 10mg; 2-3 yrs 12mg; ≥ 3 yrs 15mg)
Intrathecal Ara C (Cytosar): Day 1
(< 1 year 20mg; 1-2 yrs 30mg; 2-3 yrs 50mg; ≥ 3 yrs 70mg)

* If CNS disease at diagnosis – Triple IT on Day 0, 8, 15, 22 & 33

Bone Marrow Day 1, 15 & 33



If CNS disease at diagnosis – Triple IT on Day 0, 8, 15, 22 & 33

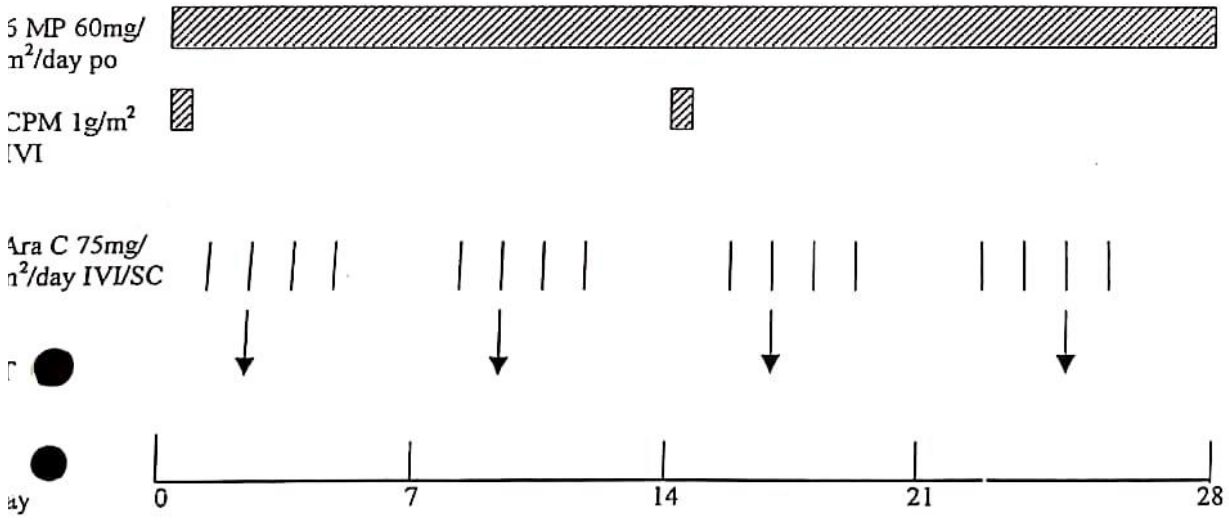
ALL – BFM – 95 (MODIFIED)

PHASE II – CONSOLIDATION (MEDIUM RISK)

To commence within 1 week of induction Day 33

Requirements :
1) CR – BM + CNS
2) Good general condition and no serious infections
3) WCC > 2,0; Neutrophils > 0,5; Platelets > 50

Cyclophosphamide: 1000mg/m^2/day IVI: Day 0, 14
Cytosine Arabinoside (Ara C): 75mg/m^2/day IVI / SC: Days 1 – 4; 8 – 11, 15 – 18, 22 – 25
6 M[illegible]captopurine: 60mg/m^2/day po: Day 0 – 28
Intrathecal Methotrexate weekly x 4 (< 1yr 6mg; 1-2yrs 8mg; 2-3yrs 10mg; ≥3yrs 12mg)
Intrathecal Hydrocortisone weekly x 4 (< 1yr 8mg; 1-2yrs 10mg; 2-3yrs 12mg; ≥3yrs 15mg)
Co[illegible]moxazole: 3mg/kg TMP po daily on 3 consecutive days/week



Note:
1) Requirement for 2nd Cyclophos – WCC > 1,0, neutrophils > 0,3, Platelets > 50
2) Each Ara C block must be given as a block – requirements are WCC > 0,5, Platelets > 30. If an Ara C Block must be postponed, 6 MP must be stopped as well and recommenced when Ara C recommences Total dose of 6 MP must be 28 days.
3) Trend of counts is more important than absolute value.

GH RISK :

To commence HR blocks within 1 week of Day 33 induction
Block HR-1, 2 & 3 x 2 ie 6 blocks altogether given 4 weekly
G-CSF to commence 48 hours after completion of each block until neutrophils > 5,0.

4 x HDMTX
2 x HDCyodx. → 12Gy Cranial irradiation

ALL BFM – 95 (MODIFIED)

PHASE III – CNS INTENSIFICATION

< 6 years

Prehydration x 6 hours with alkalinizing fluids prior to each HD Methotrexate

High dose Methotrexate: 7g/m^2/dose – 10% over 1 hour } Day 0, 14, 28
- 90% over 23 hours}

Intrathecal Methotrexate and Intrathecal Hydrocortisone: Day 1, 15, 29 (ie. during Methotrexate infusion)
(Doses – see Phase I & II)

6 Mercaptopurine: 25mg/m^2/day po Day 0 – 35 nocte
Cotrimoxazole: 3mg/kg TMP daily x 3 consecutive days/week

(see separate sheet for administration Instructions)

> 6 years

Prophylactic Cranial Irradiation 18 Gy

Methotrexate: 75mg/m^2 IVI push: Day 0, 14, 28
6 Mercaptopurine: 75mg/m^2/day po: Day 0 – 35 given nocte
Cotrimoxazole: 3mg/kg TMP daily x 3 consecutive days/week

ALL – BFM – 95 (MODIFIED)

PHASE V – MAINTENANCE

To begin approximately 2 weeks after Phase IV completed
BM aspirate at beginning of maintenance and at completion

Vincristine: 1,5mg/m^2 IVI 4 weekly
Prednisone: 40mg/m^2 PO daily x 5 days 4 weekly
Methotrexate: 20mg/m^2 PO weekly
Or 75mg/m^2 IVI 2 weekly
6 Mercaptopurine: 75mg/m^2 PO daily given nocte
Intrathecal Methotrexate and Hydrocortisone 12 weekly
(Doses – see Phase I)
Co-trimoxazole: 3mg/kg TMP PO on 3 consecutive days/week

Dose management of 6 MP / Methotrexate

WCC/µl	% dose 6 MP / Methotrexate
< 1000	0
1000 – 2000	50%
2000 – 3000	100%
> 3000	to 150%

Maintenance therapy to continue till 3 years from diagnosis