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IMPROVED OVERALL AND EVENT FREE SURVIVAL WITH ADAPTED BERLIN-FRANKFURT-MUNSTER (BFM)RISK STRATIFIED TREATMENT IN PEDIATRIC ACUTE LYMPHOBLASTIC LEUKEMIA-SINGLE CENTRE EXPERIENCE FROM SOUTH INDIA

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ABSTRACT

BACKGROUND: Paediatric acute lymphoblastic leukemia (ALL) has a reported five year overall survival reaching over 90% in high income countries(HICs).Overall survival in India ranged from 45-81%(commonly > 60%) and Event free survival ranged from 41-70%(commonly > 50%)

AIM: To analyse the outcome with a uniform protocol adapted from Berlin-Frankfurt-Münster (BFM) protocol used in all Pediatric ALL patients.

METHOD: After institutional research board approval , records of consecutive children with newly diagnosed with B cell and T cell Acute lymphoblastic leukemia/lymphoma (ALL) between 1 and 14 years of age at the time of diagnosis and underwent treatment in the institution from 1/1/10 to 31/12/18 were reviewed .Patient treatment was stratified according to BFM relapse risk criteria to standard risk(SR), Intermediate risk(IR) and high Risk(HR).

RESULTS: One hundred and twenty eight children consecutively treated for acute lymphoblastic leukemia/ lymphoma with ages ranging from 1-14 years were analysed. The estimated 5year overall survival and Event free survival by Kaplan meier method were 82.3+/- 3.4% and 79.8+/- 3.6%.

CONCLUSIONS: Adherence to globally accepted treatment regimens along with best supportive care can bring out results similar to HICs.

KEYWORDS : Childhood Acute Lymphoblastic Leukemia, Risk Stratified Treatment, Survival

INTRODUCTION

Approximately 50-200 per million children gets affected with childhood cancer [i]. Acute lymphoblastic leukemia (ALL) accounts for around one thirds of this .According to population based cancer registries, the age adjusted rate(AAR) of incidence of Leukemia in India among boys and girls ranges between 0-101.4 and 0-62.3 per million respectively [ii].

The first documented transient remission of childhood ALL was in 1948 by Sydney Farber using Aminopterin[iii].In 1961, Frei et al combined Methotrexate with 6 mercaptopurine (6MP) to achieve 2 year overall survival rate of 20%.[iv]The current combination " Total therapy" concept consisting of Remission induction , CNS directed therapy with Intrathecal methotrexate and High dose intravenous methotrexate, Intensification and Maintenance was initiated by Pinkel et al[v]. Prophylactic cranial irradiation was later replaced by CNS directed intravenous methotrexate owing to the long term complications like second cancers, neurocognitive impairment and multiple endocrinopathies. [vi, vii]. Age at diagnosis, initial leukocyte count,the cytogenetics of the clone and the initial response to therapy are identified risk factors which predict prognosis [viii].

Berlin-Frankfurt-Münster (BFM) and the Associazione Italiana di Ematologia Pediatrica (AIEOP) studies, proved that Minimal residual disease (MRD)assessment is the best predictor of prognosis in both B and T cell ALL.[ix,x]. Accurate risk stratification, best supportive care and strict protocol adherence in combination cheomterapies have resulted in > 85% event free survival and > 90% overall survival rate in most collaborative trials [xi,xii,xiii,xiv,xv,xvi,xvii,xviii,xix].

Different publications from India including single centre outcomes and population registries show an overall survival over a wide range from 40-81% and event free survival 28-70%.[xx,xxi]The overall survival was 33% in a cohort from Post graduate institute , Chandigarh when including all those diagnosed, regardless of initiation or completion of treatment[xxii] and was 39% in a report from a population based cancer registry.[xxiii]The estimated 5 year overall survival, EFS and disease free survival was 59.8%, 56%, and 53.9%, respectively as reported from Christian Medical College , Vellore.[xxiv]The 5 year overall survival was 40% and event free survival 28% as reported from from another single centre in South India [xxv]. We put forward our experience within a single centre with an adapted protocol.

MATERIALS AND METHODS:

This was a cross sectional , single centre observational study. After Institutional Research Board approval records of consecutive children with newly diagnosed with B cell and T cell Acute lymphoblastic leukemia/lymphoma (ALL) between 1 and 14 years of age at the time of diagnosis and underwent treatment in the institution from 1/1/10 to 31/12/18 were reviewed. Diagnosis was based on the presence of 20% or more lymphoblasts in the bone marrow(BM) or peripheral blood(confirmed by flow cytometry) or by lymph node biopsy and immunohistochemistry. [xxvi] B-ALL patient treatment was stratified according to BFM relapse risk criteria to standard risk(SR), Intermediate risk(IR) and high Risk(HR). Conventional Karyotyping,

Fluorescent in situ hybridization (FISH), and Polymerase chain reaction (PCR) were used in risk stratification. All patients were treated with BFM based protocol with adaptations and received 4-drug (Vincristine/ Daunorubicin/ L Asparaginase/ Prednisolone) induction and Phase 2 with cyclophosphamide, cytosine arabinoside, and 6-mercaptopurine (6-MP), consolidation with oral 6-MP and IV methotrexate (MTX), 2 gm/m^2 x 4 for SR and IR B-ALL and 5 gm/m^2 x 4 for HR B-ALL, T-ALL, and CNS disease. Phase I reinduction utilized adriamycin and dexamethasone in addition to vincristine and asparaginase . The Phase 2 reinduction regimen closely mirrored Phase 2 induction but only lasting two weeks. Maintenance therapy consisted of oral daily 6-MP, weekly MTX and monthly doses of Dexamethasone and IV Vincristine for 104 weeks. Prophylactic intrathecal MTX was given during induction, consolidation, reinduction and once in three months during maintenance . Febrile neutropenia protocols were enforced. Filgrastim was given prophylactically between cycles to target ANC > 0.5 x 10^6/uL. Prednisolone Response was assessed on day 8 by measuring absolute blast count on the peripheral blood , after 7 days of prednisone and one dose of intrathecal methotrexate (MTX) during the week 1. Prednisone good response (PGR) was defined as less than 1 x 10^9/L blasts. BM morphology was evaluated for treatment response on day 33. Complete remission (CR) was defined as less than 5% marrow blasts and no extramedullary disease. Those children failing to achieve CR by day 33 were moved to high risk consolidation protocol . BM relapse was defined as reappearance of >25% lymphoblasts in the marrow and CNS relapses were confirmed by morphology on CSF cytospinned slides. .Combined relapses meant recurrence in both BM and extramedullary site(s). OS and EFS were assessed by Kaplan-Meier method.

RESULTS:

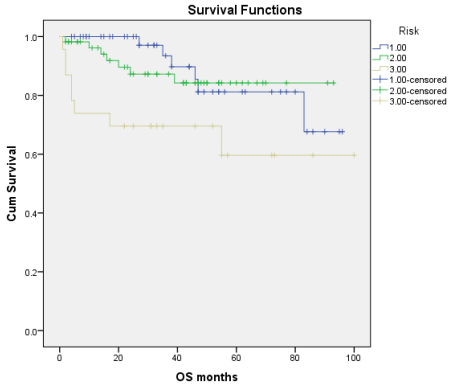
One hundred and twenty eight children consecutively treated for acute lymphoblastic leukemia/ lymphoma with ages ranging from 1-14 years were analysed . Mean age was 5.97 years (range 1-14 years).Male patients predominated the cohort n= 69(53.9%).Majority of patients were found to have immuno phenotypically B cell ALL n =113 (88.3%) against T cell ALL n=15(11.7%).Peripheral blood blasts ranged between 0-98%(mean 26.42%) Mean blasts percentage in the bone marrow aspirate was 72.6%. Cytogenetic reports were available for 114 patients (89%).Clinically relevant translocations were detected in 15 patients (11.71%).The commonest detected translocation in the cohort was t(12:21)(n=10;7.81%). The other chromosomal translocations detected were t(1:19) (n= 3; 2.3%) and t(9:22) (n=2; 1.52%). No MLL mutations were detected in the cohort.Eight patients in the cohort had CNS involvement at presentation(6.3%), either as a motor weakness or as presence of blasts in the CSF.On Risk stratification , Forty nine (38.2%)children were stratified into standard risk,56(43.75%) into intermediate risk and 23(17.9%) patients to high risk. Ninety (70.3%)patients had Good prednisolone response. Fifteen (11.7%)patients had poor prednisolone response. The remaining couldnot be categorized as there were no circulating blasts prior to initiation of steroids(18%). There were four induction deaths(3.125%), two due to Gram negative blood stream infection (1.52%), one due to invasive mucormycosis (0.76%), One patient died due to refractory congestive cardiac failure (0.76%).One hundred and thirteen patients (92.18%) were found have achieved CR during reassessment on Day33.Six patients had not achieved CR and were reallocated to high risk. Minimal Residual disease analysis by bone marrow flowcytometry during reassessment was utilized to determine risk for the consecutive last 62 patients in the cohort(48.4%). One patient died during salvage chemotherapy for refractory disease after induction. One child was censored from the cohort as lost to follow up as there was change in treatment centre. There were no treatment abandonments. Twenty two children relapsed (17.18%). Nine children had very early relapse(7.03%);ie within 18 months of initial diagnosis while continuing therapy as per the protocol. Seven children had early relapses (5.4%)ie more than 18 months from the initial diagnosis but within 6 months of cessation of therapy. Six children had late relapses(4.68%) (ie six months after cessation of frontline therapy).Eighteen children died in relapse (14.06%). One child underwent Allogenic stem cell transplant(0.76%) after salvage therapy and in CR 2.Three children went into CR2 after late relapse and salvage therapy and are continuing chemotherapy.The Kaplan Meier estimated 5year overall survival of the cohort was 82.3 +/- 3.4%.The estimated 5 year Event free survival by Kaplan Meier method for the cohort was 79.8+/- 3.6%.

Table 1: The demographic details of the Cohort

		Number	Percentage
1	Sex		
	Male	69	53.9
	Female	59	46.1
2	Phenotype		
	B	113	88.3
	T	15	11.7
3	CNS disease at presentation		
	Absent	120	93.8
	Present	8	6.3
4	Prednisolone response		
	Good	90	70.3
	Poor	15	11.7
	Cannot be commented upon	23	17.96
5	Risk stratification		
	Standard	49	38.3
	Intermediate	56	43.9
	High	23	18

FIGURE 1:

Shows the Kaplan Meier 5year estimated overall survival of the cohort according to risk stratification.The OS for standard , intermediate and high risk disease was 83.62% with Standard error 4.447, 81.42% with SE 4.047 and 66.62% with SE 9.47 respectively.



DISCUSSION:

The childhood ALL outcome in India has lagged behind the developed nations owing to the high rates of treatment abandonment, lack of awareness and education, financial support, limitation in quality of care provided, lack of better understanding of disease biology and risk stratified approach implementation due to compromises made to understand the disease biology in view of the lack of financial back up.[23,,,,].The induction mortality ranging from 2% - 5.3% in centres like CMC, Vellore and RCC, Trivandrum to upto 17% in resource limited settings of public health reflects the significance of supportive care and strict following of febrile neutropenia protocols which would improve the overall outcome [23,26,].

In our cohort, Males to females had a ratio of 1.16:1, which was very different from the previously published literature from India where it was male predominant cohort [22, 23]. The Median age of presentation in the cohort was 5.97years, much higher than described in literature.[]Patients with T cell ALL were 11.7% , much lower than described in published literature from India[22].The presence of CNS disease at diagnosis was present in 6.3 % patients similar to the results published from another centre from South India [26].Toxic deaths during Induction was 2.34%, close to the best reported in the literature from India[26].The estimated 5 year overall survival in our cohort was 82.3%+/-3.4% comparable to the best 5 year OS published from India.[] The estimated 5 year event free survival by Kaplan meier method in our study was 79.8%+/- 3.6%, higher than the best published report from India[36].

Application of local and international insights in systematic improvement of supportive care by enforcement of strict infection control policies, close monitoring and aggressive management of

Tumour lysis syndrome and ensuring adequate transfusion support along with address of nutritional requirements leads to reduction in Induction mortality and improves the overall survival.[, ,].Further, close monitoring for strict risk categorization and timely reallocation to tailor therapy will improve overall and event free survival.

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