ORIGINAL **A**RTICLE

Analysis of outcomes and prognostic factors of acute lymphoblastic leukemia patients treated by MCP841 protocol: A regional cancer center experience

Akhil Kapoor, Ashok Kalwar, Narender Kumar[1], Mukesh Kumar Singhal, Surender Beniwal, Harvindra Singh Kumar

Department of Oncology, Acharya Tulsi Regional Cancer Treatment and Research Institute, Sardar Patel Medical College and Associated Group of Hospitals, Bikaner, Rajasthan, [1]Department of Oncology, Delhi State Cancer Research Institute, New Delhi, India

Background: A dramatic improvement in the survival of acute lymphoblastic leukemia (ALL) patients in the last three decades has been observed. MCP 841 protocol is an old but effective tool with tolerable toxicities. The objective of this study was to estimate the relapse-free survival of ALL patients treated uniformly with MCP 841 protocol on the basis of various prognostic factors. **Materials and Methods:** The study design was retrospective and it was conducted in a regional cancer center of Northwest India. Three hundred and ten ALL patients who underwent treatment with MCP 841 protocol and regular follow-up for up to 5 years were selected for this study. Relapse-free survival was calculated by Kaplan–Meier analysis and Cox regression analysis was used to calculate the hazards ratio (HR) using Statistical Package for the Social Sciences (SPSS) software for windows version 20.0. **Results:** Fifty-four percent patients were <15 years of age and 69% were males. 53.2% patients were in remission at the end of 5 years of starting the treatment. Relapse-free survival at 5 years by Kaplan–Meir analysis for B-cell ALL was 62% [HR 0.67 {95% confidence interval (CI) 0.47-0.95}] with patients with unknown lineage taken as reference] while for T cell it was 28% [HR 1.41 (95% CI 1.19-1.63), P 0.001]. Patients with total leukocyte count (TLC) <1 lakh/cmm at presentation, relapse-free survival was 68% and those with TLC >1 lakh/cmm had 41% survival [HR 2.14 (1.76-2.48) with, $P < 0.001$]. **Conclusion:** MCP 841 protocol is a useful tool for the treatment of ALL in children when more aggressive protocols can not be used.

Key words: Acute lymphoblastic leukemia (ALL), MCP 841 protocol, Northwest India, prognostic factors, survival analysis

INTRODUCTION

There has been a dramatic improvement in the survival outcome of acute lymphoblastic leukemia (ALL) patients with a better understanding of molecular biology, the use of combination chemotherapy protocols, risk stratification using clinical, genetic, and molecular parameters, improvements in supportive care, along with effective central nervous system (CNS) prophylaxis. MCP 841 protocol has emerged to be an effective tool with tolerable toxicities and thus, is useful even for developing countries. BFM 90, BFM-95, and UKALL-XI protocols are widely used in Western countries but rarely used in limited resource settings due to their higher toxicities.. Survival outcome in childhood ALL has reached over 80% in resource-rich nations.[1-4] However, reports from various institutions in India suggest that the outcome is inferior to that achieved in the developed nations due to poor management of infections, leading to toxic deaths and also increased incidence of relapse.[5-10] The patient population of India differs markedly from the Western population with respect to the prevalence of illiteracy, poverty, malnutrition, and chronic infectious diseases. Although multiple studies have been performed across the world;

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Quick Response Code:	**Website:** www.jmsjournal.net	
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there is a deficiency of data available on the prognostic factors, response to treatment, and research on the biology of ALL from the Northwest Indian perspective. Our institute, being a regional cancer center, treats a significant proportion of ALL patients who are provided with the best possible treatment within resource and financial constraints. We present the findings of a retrospective study designed to estimate the relapse-free survival of ALL patients treated uniformly with MCP 841 protocol on the basis of various prognostic factors. The identification of prognostic factors and toxicities would help to determine the management lacunae and would lead to an overall improvement in the quality of care of ALL patients.

MATERIALS AND METHODS

A total of 310 previously untreated ALL patients from Northwest India presenting to our oncology outpatient department (OPD) from June 2002 to June 2008 who took treatment and were on regular follow-up for 5 years were selected in this retrospective hospital-based study. Diagnosis of ALL was confirmed by bone marrow (BM) aspiration on the first visit. Cytochemistry was performed using myeloperoxidase stain. Detailed clinical history, physical examination, peripheral blood film (PBF), and biochemical profiles, including liver and renal function tests, were performed at the initial presentation. Cerebrospinal fluid (CSF) was obtained for cytology in patients suspected of CNS disease at presentation. CSF-positive patients and those having L3 (French-American-British criteria) were not included in this study.

The MCP 841 protocol, first used in India, includes effective drugs given in such a way that the minimal supportive care is required; this factor is the main reason for the reduction in costs. The approximate cost of complete course of treatment with MCP 841 protocol in the Indian setting is about 3000 USD (2,00,000 INR); however, the cost is highly dependent on the costs of hospital admission and transfusion. In our regional cancer center, these costs were minimal because of funding by the government. Apart from this, most of the chemotherapy drugs were provided free of cost, further cutting the costs and making the treatment available within the reach of poor families. Data were obtained from the records of these 310 carefully selected patients and were analyzed. Ethical approval was not required for this study as the study was retrospective and the patients who were selected were treated with a standard institutional protocol.

Immunophenotyping (IPT) was performed in 205 patients who could afford it out of 310 cases using a panel of monoclonal antibodies, which included CD2, 4, 5, 7, 8, 10, 11b, 15, 19, 20, 36, 13, 33, HLA-DR, and surface immunoglobulin (sIg). Common ALL was defined as

CD10-positive with all T-cell markers as negative. T-cell ALL was defined as either CD5- or CD7-positive with or without additional T-cell markers but with negative B-cell antigens. The patient's guardians were counseled regarding the need for strict adherence to the protocol and need for timely follow-up. They were also provided assistance with local accommodation and travel passes.

Treatment protocol

All patients were uniformly treated with MCP841 protocol. Risk stratification was not done in patients treated at our center. All patients were treated with standard MCP 841 protocol. The treatment protocol is outlined in Table 1. Patients received two induction cycles (I1 and I2), repeat

Table 1: Table showing the MCP841 protocol with the various phases, along with the drugs used with their doses

Phase	Chemotherapy drug	Dose and schedule
Induction 1 (I1)*	Vincristine	1.4 mg/m^2 IV, days 1, 8, 15, 22, and 29
	Daunorubicin	30 mg/m^2 IV, days 8, 15, and 29
	L-Asparaginase	6,000 IU/m^2 SC×10 doses, days 2-20 alternate day
	Prednisolone	40 mg/m^2 PO, days 1-28
	Methotrexate	IT, days 8, 15 and 22
Induction 2 (I2)*	6-Mercaptopurine	75 mg/m^2 PO, daily, days 1-7 and days 15-21
	Cyclophosphamide	750 mg/m^2 IV, days 1 and 15
	Methotrexate	12 mg IT, days 1, 8, 15 and 22
	Cranial irradiation	200 cGy daily×10 days (total 2,000 cGy)
Repeat Induction-1 (RI1)	Same as I1	Doses and schedule as per I1
Consolidation (C)	Cyclophosphamide	750 mg/m^2 IV, days 1 and 15
	Vincristine	1.4 mg/m^2 IV, days 1 and 15
	Cytarabine	70 mg/m^2 SC, every 12 hours×6 doses, days 1-3 and days 15-17
	6-Mercaptopurine	75 mg/m^2 PO, daily, days 1-7 and days 15-21
	Prednisone	40 mg/m^2 PO, days 1-7
Maintenance (M, 6 cycles)	Vincristine	1.4 mg/m^2 IV, on day 1
	Daunorubicin	30 mg/m^2 IV, on day 1
	L-Asparaginase	6,000 IU/m^2 SC, on days 1, 3, 5 and 7
	Methotrexate	15 mg/m^2 PO, once a week, missing every 4th week for a total of 12 weeks. Begin on day 15
	6-Mercaptopurine	75 mg/m^2 PO, daily, 3 weeks out of every 4 for a total of 12 weeks. Begin on day 15

IV = Intravenous; SC = Subcutaneous; PO = Per oral; IT = Intrathecal

induction (RI1), consolidation (C), and six maintenance cycles (M). CNS prophylactic therapy included cranial irradiation (2,000 cGy) for children above the a1ge of 3 years. Patients less than 3 years were treated with an alternative regimen (I2A) containing high dose cytarabine with granulocyte colony-stimulating factor (G-CSF) support. All patients received 12 weekly intrathecal injections of methotrexate during the induction and consolidation phases of therapy in a dose of 8 mg, 10 mg, and 12 mg in children under 2 years, 2-3 years, and more than 3 years of age, respectively. The total duration of therapy was 2 years.

The patients were hospitalized in the leukemia ward of our hospital to start the induction protocol. Complete blood count (CBC) was performed biweekly (thrice weekly if the patient had thrombocytopenia) and PBF was performed weekly. CSF examination was performed monthly during the induction and consolidation phases to detect early CNS relapse. During the maintenance phase, lumbar puncture was performed only when clinically indicated. BM examination was performed at the end of induction therapy. Complete remission (CR) was defined as less than 5% lymphoblasts in a normocellular BM in the absence of clinical evidence of disease. Patients with more than 5% blasts at the end of induction regimen were considered as nonresponders. Relapse was defined as the presence of unequivocal malignant blast cells (>25%) in the BM or on histological or cytological documentation of blasts in extramedullary sites after the achievement of CR.

The relapses were classified on the basis of the sites of relapses, that is, BM, CNS, and testi(e)s. BM relapse was suspected on the basis of blood counts and/or clinical manifestations. CSF was examined in patients presenting with headache and vomiting. In case of bone marrow relapse, clinical examination of testes and a CSF study were mandatory to rule out concurrent testis and CNS disease, respectively. In cases with nontender testicular enlargement, fine-needle aspiration cytology (FNAC) was performed to confirm the etiology. The presence of unequivocal blasts in CSF irrespective of CSF cell count and/or new onset cranial nerve palsy was considered as CNS leukemia.

Supportive care

At the start of the protocol, the patients' relatives were counseled to deposit blood in our hospital's blood bank in advance for the timely management of hematological complications. Patients with high total leukocyte count (TLC) were prescribed allopurinol 100-600 mgm in two to three divided doses for the prevention of uric acid nephropathy. Patients with TLC >1 lakh/cmm received intravenous (IV) hydration 4 L/sqm, along with the injection sodium bicarbonate. Serum electrolytes were monitored in such patients due to the high risk of tumor lysis syndrome.

Cotrimoxazole was coadministered with oral prednisolone for pnemocystis carinii prophylaxis. Povidone iodine gargle was given to maintain good oral hygiene and clotrimazole lozenges were used for prophylaxis of fungal infections. Febrile neutropenic patients were treated with IV antibiotics. After sending blood for culture and sensitivity, empirical choice was ceftazidime/ceftriaxone with amikacin. The addition of fluconazole was considered if fever persisted for more than 72 h after starting IV antibiotics. Blood transfusions were given if the hemoglobin level was below 8 g/dL and platelets when the count was below 20,000/cmm or in the presence of bleeding.

Statistical analysis

The 5-year relapse-free survival was calculated on the basis of B-cell versus T-cell ALL, TLC at presentation >1 lakh/cmm, age at presentation, sex, common acute lymphoblastic leukemia antigen (CALLA) positivity, the presence of blasts in PBF on day 15 of induction, and completion of protocol within prescribed time. Kaplan–Meir survival curves were plotted and log-rank (Mantel–Cox) test was performed for the comparison of survival curves; statistical significance (P value) and chi-square values were calculated. The mean survival with 95% confidence interval (CI) was also calculated. Assuming the proportional hazards assumption to be true in this calculation, Cox regression analysis was performed by forward stepwise (likelihood ratio) method and hazard ratio with 95% CI was also obtained. All statistical calculations were performed using Statistical Package for the Social Sciences (SPSS) software for windows version 20.0 (IBM Corp., Armonk, NY, USA).

RESULTS

The characteristics of patients at presentation are depicted in Table 2. Out of 310 patients, 215 (69%) were males, with the male/female ratio being 2.2:1. One hundred and sixty five (53.2%) patients were in remission at the end of 5 years of the starting of treatment. Nineteen patients (6.1%) were nonresponders or died during induction. A total of 126 patients (40.6%) relapsed in 5 years from the start of the treatment. Most of these relapses ($n = 113$, 89.6%) occurred while the patients were on treatment. Table 3 shows the timing of relapse of these patients. The most frequent site of relapse was BM ($n = 114$, 90.4%) followed by CNS ($n = 7$, 5.5%), testis ($n = 3$, 2.4%), and solitary bone ($n = 2$, 1.6%). Thus, BM, CNS, and testicular relapse rates were found in 39.1%, ($n = 114$ of 291), 2.4% ($n = 7$ of 291), and 1% ($n = 3$ of 291) of the patients, respectively.

Overall, the 5-year survival was 53.2%. Relapse-free survival at 5 years by Kaplan–Meir analysis for B-cell ALL was 62% while for T cell it was 28% ($P < 0.001$) [Figure 1]. The mean survival for B and T lineages was

Table 2: Table showing baseline characteristics of patients with reference to demographic and hematologic parameters

Variables	Number (%)
Gender	
Male	215 (69)
Female	95 (31)
Age (years)	
<3	23 (7.4)
3-10	71 (22.9)
11-15	75 (24.1)
16-20	83 (26.8)
>20	58 (18.7)
Immunophenotype	205 (66.1)
B-lineage	166 (81)
T-lineage	39 (19)
CALLA	85 (27.4)
Positive	21 (24.7)
Negative	64 (75.2)
TLC count (lakh/cmm)	
☐1	188 (60.6)
<1	122 (39.4)
Day 15 PBF	
With blast	191 (61.6)
Without blast	119 (88.4)
Protocol completed within designated time	
Yes	270 (87)
No	40 (13)

CALLA = Common ALL antigen; TLC = Total leukocyte count; PBF = Peripheral blood film

Table 3: Table showing the number of relapses as per the phase of treatment

Phase	Number of relapses (%)
Induction	49 [38.9]
Induction-2nd (I2)	20 (40.8)
Repeat Induction-1st (RI1)	29 (59.2)
Consolidation	27 [21.4]
Maintenance (M)	37 [29.4]
M1	13 (35)
M2	9 (24)
M3	7 (18.9)
M4	6 (16.2)
M5	1 (2.7)
M6	1 (2.7)
3rd year	10 [7.9]
4th year	2 [1.6]
5th year	1 [0.8]
Total	126

Note: 19 (6.1%) patients were non responders or died during induction. The value in square brackets represents the percentage out of all phases

Figure 2: Survival plot showing 5-year relapse-free survival probability with total leukocyte count (TLC) at presentation against time
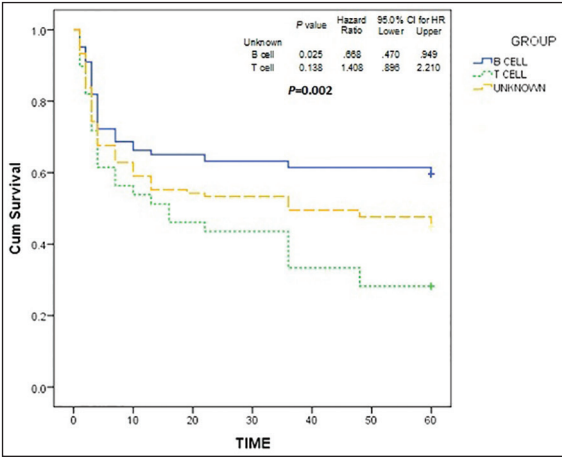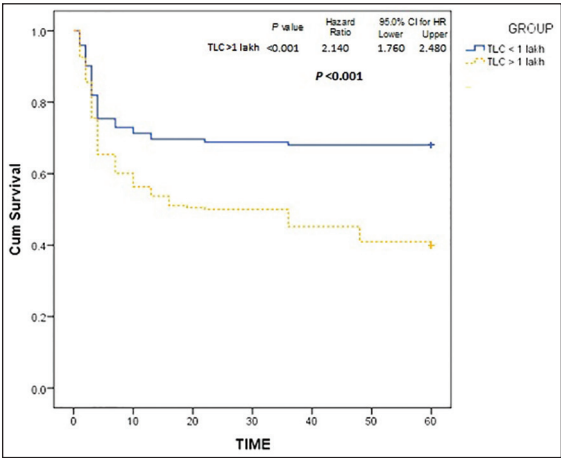

Figure 1: Kaplan–Meier survival plot showing 5-year relapse-free survival probability for T-cell ALL and B-cell ALL

39.35 months and 26.38 months, respectively [hazards ratio (HR) 1.41, 95% CI 1.19-1.63, P 0.002]. Table 4 summarizes the results of statistical tests for survival analysis for various subgroups. In patients with day 15 PBF without blast, relapse-free survival was 65% while in those with persistent blast, it was 45% ($P < 0.001$). In patients with TLC <1 lakh at presentation, relapse-free survival was 68% and in those with TLC >1 lakh had

41% survival with a mean survival of 42.51 months and 30.99 months, respectively (HR 2.14, 95% CI 1.76-2.48, $P < 0.001$) [Figure 2]. CALLA-positive patients had 95% survival while CALLA-negative patients had only 20% survival (HR 2.46, 95% CI 1.48-4.09, $P < 0.001$). For the <3 years age group, survival was 30% (HR 2.90 with reference to 3-10 years age group, 95% CI 1.55-5.44, $P < 0.001$), for the >20 years age group it was 15%, for the 3-10 years age group and 11–15 years age group it was 65% and 64%, respectively, while for the 16-20 years age group, it was 59% ($P < 0.001$,) [Figure 3]. The mean survival time for <3 years age group was 21.34 months, for 3-10 years, 11-15 years, and 16-20 years, it was 41.59 months, 40.82 months, and 40.20 months, respectively, while for >20 years, it was 18.34 months (HR 3.39, 95% CI 2.09-5.51, $P < 0.001$). However, the data were not statistically significant for males (50%) versus females (60%) (P 0.24).

Table 4: Table showing survival estimates (Kaplan–Meier and Cox regression) according to various prognostic variables

Subgroup	Mean survival in months (95% CI)	Hazard ratio (95% CI)	P value
Lineage			
B-cell	39.35 (35.28-43.42)	0.67 (0.47-0.95)	0.002
T-cell	26.38 (18.64-34.12)	1.1 (1.19-1.63)	
Unknown	33.26 (28.07-38.46)	1.00	
TLC at presentation			
<1 lakh/cmm	42.51 (37.93-47.08)	1.00	<0.001
>1 lakh/cmm	30.99 (27.17-34.79)	2.14 (1.76-2.48)	
Age group (years)			
<3	21.35 (10.80-31.89)	2.90 (1.55-5.44)	<0.001
3– 10	41.59 (35.67-47.51)	1.00	
11– 15	40.82 (34.86-46.78)	1.06 (0.62-1.83)	
16– 20	40.21 (34.62-45.78)	1.21 (0.73-2.03)	
>20	18.34 (12.65-24.04)	3.39 (2.09-5.51)	
Blast at day 15			
Present	32.26 (28.48-36.03)	1.80 (1.26-2.58)	0.001
Absent	41.20 (36.44-45.96)	1.00	
CALLA			
Positive	56.39 (52.96-59.81)	0.08 (0.03-0.22)	<0.001
Negative	14.05 (04.43-23.66)	2.46 (1.48-4.09)	
Unknown	32.13 (28.64-35.61)	1.00	

Note: The category with the hazard ratio HR = 1.0 is considered the reference category with which other categories are compared to; CI = Confidence interval; TLC = Total leukocyte count; CALLA = Common ALL antigen

Figure 3: Kaplan–Meier plot showing agewise 5-year relapse-free survival probability plotted against time

DISCUSSION

ALL is a hematologic malignancy, which is potentially curable. The last few decades have seen the use of modern combination chemotherapy protocols with highly effective CNS prophylaxis. Despite these developments, the prognosis of ALL patients remains poor in developing counties due to the lack of resources and delay in diagnosis. Also, there are reports suggestive of a different biology of ALL in India as compared to the Western world. T-cell ALL is more frequent in India[11-13] though the overall incidence of ALL is threefold lower in India as compared to the USA. These differences in the biology of the disease are thought to affect both the disease extent and results of the treatment. Also, the Third World countries are known for the prevalence of malnutrition and chronic infectious diseases. These environmental factors are thought to adversely influence the tolerance to intensive combination chemotherapy regimens, leading to increased toxicity of the treatment. This study was designed to address these issues with a target to improve the future management of ALL patients.

The authors would like to highlight the use of high dose cytarabine in children less than 3 years of age. A recent study by Mirouliaei *et al.* showed that cranial radiotherapy of 18-24 Gy in children suffering from ALL lead to growth hormone deficiency after clonidine stimulation test in 44%
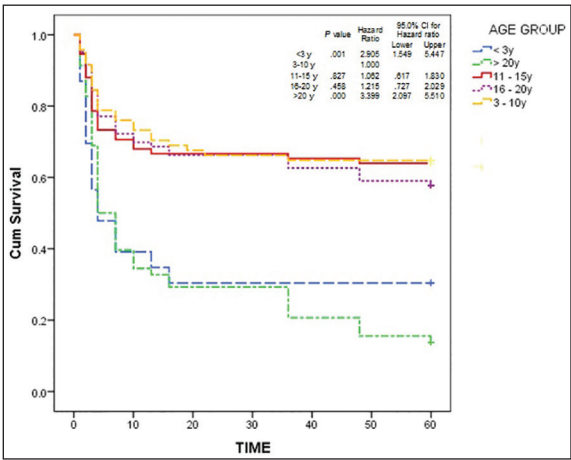
of the patients and in 50% of these cases, within 1 year of whole brain radiation. They recommended a reduction in the dose of radiotherapy in such patients wherever possible.[14] It has been reported that somatotroph hormone axis is more sensitive to radiation in children than in adults. Follin *et al.* concluded that ALL survivors, treated with a moderate dose of prophylactic cranial radiotherapy, have a central adrenal insufficiency 20 years after diagnosis. An increased awareness of the risk for an adrenal insufficiency is of importance and lifelong surveillance of the entire hypothalamic-pituitary axis is recommended in these patients. These manifestations are more likely to occur if cranial radiotherapy is given to younger children in whom brain development is still in process.[15] Thus, the institutional protocols of some leading cancer care centers in India are using high dose cytarabine (I2A protocol) as an alternative to cranial radiation in children <3 years of age.

An important feature of patient characteristics in our study is a definite male preponderance (M:F = 2.2:1). This is in contrast to figures from the Western countries. Dana Farber consortium protocol 91-0 study reported a sex ratio of 1.1:1.[16] However, in an Indian study by Arya *et al.*, this ratio was 3.6:1.[17] These data strongly reflect the poor care of female children in India and the preferential treatment of male siblings.

Another important difference, which deserves to be highlighted is TLC at presentation. In our study, 60% patients had TLC >1 lakh/cmm. This is in clearly a great excess when compared with both Indian and Western studies.[10,16-19] A possible explanation is that in most of these studies, only childhood ALL patients were enrolled while in our study, every ALL patient was enrolled irrespective of age. Also, since our center caters to a population living in highly remote areas that are far from proper health care facilities, there is high chance that patients presented late with an increased burden of the disease. These factors also possibly explain the high relapse rate in our study. TLC at

presentation proved to be a highly significant ($P < 0.001$) prognostic factor for relapse-free survival. Some centers use I2A protocol (high dose cytarabine) in patients with high TLC counts (>1 lakh/cmm) at presentation, apart from using it for eradicating blasts from CNS in children <3 years.

T-cell ALL has been correlated with poor prognosis in many studies.[20,21] It is associated with higher TLC at diagnosis, the male gender, older age, and mediastinal mass. Also, these patients are at a higher risk of induction failure.[22] In our study, the incidence of T-cell ALL was 19%. This was in line with the data presented by Advani *et al.* (20.7%).[10] However, another Indian study by Arya *et al.* reported a 31% incidence of this phenotype.[17] Another recent Eastern Indian study reported 50.4% incidence of T-cell immunophenotype.[8] Western studies have reported <10% incidence.[16] These data clearly establish the difference in the biologies of ALL in India from the Western world.

Patients with persistent circulating leukemic cells at 7-10 days after the initiation of combination chemotherapy have been found to be at increased risk of relapse.[23] The rate of clearance of peripheral blasts has been found to be of prognostic significance in both T-cell and B lineage ALLs. In our study, a strong positive correlation was noted between day 15 PBF without blast and relapse-free survival supporting its role as an important prognostic factor.

Precursor B-cell ALL is defined by the expression of cytoplasmic CD79a, CD19, HLA DR, and other B cell-associated antigens. It accounts for 80-85% cases of childhood ALL. Around 90% precursor B-cell ALLs express CD10 surface antigen (known as common ALL antigen; CALLA). The absence of CD10 is associated with MLL translocations, particularly t (4; 11) and a poor outcome. [24] CALLA-positive patients had a much better 5-year relapse-free survival than CALLA-negative patients in our study (95% versus 20%, HR 2.46, $P < 0.001$).

Age at diagnosis has a strong prognostic significance, reflecting different underlying biologies of ALL in different age groups.[25] The better prognosis in young children (1-10 years) is partially explained by the more frequent occurrence of favorable cytogenetic features in the leukemic blasts including hyperdiploidy with 51 or more chromosomes and/or favorable chromosome trisomies, or the ETV6-RUNX1;t (12; 21), also known as the TEL-AML1 translocation.[25,26] Approximately 80% of infants with ALL have an MLL gene rearrangement.[27-29] This subgroup presents typically with very high TLC counts and an increased incidence of CNS involvement, resulting in a poor overall survival. Our data showed the best 5-year relapse-free survival probability for 3-10 years age group (70%) followed by 11-15 years and 16-20 years age groups. Those <3 years and >20 years had poorer survival probability (15-30%).

BM was the most common site of relapse in our study (90.4%). This was in accordance with both Indian and Western studies.[8,16,17,30] CNS relapse was observed in 2.4% of the patients who achieved remission. In an Indian study by Raje *et al.*, this figure was 1.76%.[31] These data correlated well with that of foreign studies.[32] The overall 5-year survival in our study was 53.2%, which was clearly lesser than not only Western but also other Indian studies.[16,17] This could be attributed to the higher incidence of high-risk disease and differences in tumor biology in the Northwest Indian scenario.

The MCP 841 protocol is an important landmark in the advancement of treatment and outcomes of childhood ALL in India. However, this protocol has some drawbacks, one of the biggest being that there is no risk stratification to either intensify or deintensify treatment.

Drawbacks of the study

The study being a retrospective one, suffers from the usual drawback of the availability of limited data in the records of a busy cancer center. Although cytogenetics and reverse transcription polymerase chain reaction (RT-PCR) tests are being now routinely performed in ALL patients, they were sparingly done few years back at our center. Also, IPT reports entry in the records were limited, thereby restricting our analysis to B-cell versus T-cell and CALLA-positive versus CALLA-negative patients. Hence, it was not possible to find out the detailed correlation seen between outcome and these reports.

CONCLUSIONS

The data presented in this study clearly indicate the need of more aggressive treatment and more research on the biology of ALL in the Indian setting. The greater distance of dedicated cancer centers, apart from ignorance, illiteracy, poverty, and belief in an alternate system of medicine can be implicated as the root causes of poor prognosis of ALL in India. MCP 841 protocol is a useful tool for treatment of ALL in children when more aggressive protocols cannot be used.

Conflicts of interest

There are no conflicts of interest.

AUTHOR'S CONTRIBUTION

AKal conceived the idea, collected data and designed the study. AKap collected data, wrote the paper, performed statistical analysis and reviewed the literature. MKS, SB and HSK helped in data collection. NK performed statistical analysis and interpreted the results. All the authors approved the final manuscript.

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