Review Article

Acute leukemia in children: A review of the current Indian data

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Abstract

Acute leukemias are the most common diagnostic group of childhood cancer. This review summarizes the published literature on reported current outcomes of childhood acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML) from India. Overall survival in ALL ranged from 45% to 81% (commonly >60%) and event-free survival ranged from 41% to 70% (commonly >50%). Outcome data for AML was patchy with varying duration of follow-up, but it can be inferred that 50–80% of treated patients had experienced an event (toxic death, refractory disease or relapse). It is imperative that going forward focus should be on collaborative efforts, which promote treatment of patients on risk-stratified adapted protocols based on local infrastructure, improvement in supportive care and encourage prospective multi-center clinical trials.

Key words: Acute lymphoblastic leukemia, acute myeloid leukemia, child, India, outcomes, survival

Introduction

Leukemias (>95% of which are acute) constitute the most common diagnostic group of childhood cancers worldwide, and in India.[1,2] Remarkable progress has been made in the treatment of acute lymphoblastic leukemia (ALL, which constitute 75–80% of childhood acute leukemias) with 5-year overall survival rate reaching 90% in the high-income countries (HICs).[3] Advances in acute myeloid leukemia (AML), while not so spectacular, have been steady with 5-year overall survival rates approaching 70%.[4] There is limited longitudinal data on childhood cancer survival trends from India. Nevertheless, there is published evidence that there has been progress in the outcomes of childhood ALL In India although the magnitude of progress has been more modest.[5,6] The data on AML are too scant to make any meaningful conclusions.

The purpose of this review is to summarize the published literature on reported current (defined as publications from the year 2000 onward) outcomes of childhood ALL and AML from India. As recent efforts of collaboration gather pace with prospective multi-center studies being developed under the aegis of the Indian Pediatric Oncology Group (InPOG), such a review is timely and will provide useful baseline information.

Methods

A search of PubMed using keywords "leukemia," "child," and "India" was done independently by both co-authors in October 2015. The search was limited to studies published from the year 2000 onward. Any study, which reported outcomes on survival, related to ALL and AML (excluding acute promyelocytic leukemia) was included. Other outcomes of interest were mortality, relapse, and treatment abandonment. The results of the searches were compared and merged. The reference list of every included study was searched to identify any other eligible studies. Moreover, Google Scholar was searched to identify all citations to the included studies and these were then also assessed for inclusion in this review. The data were extracted and displayed in a tabular form.

Results

Acute lymphoblastic leukemia

Nine studies were included (one population-based and the other eight hospital-based), which covered variable time periods (range 1985–2011) [Table 1]. Together, they constituted 3761 children with ALL with some overlap (two studies reported patients from Cancer Institute, Chennai,[5,7] and two studies reported patients from the All India Institute of Medical Sciences[5,10]). Median age of children ranged from 5 to 10 years, baseline white blood cell (WBC) count of >50,000/mm^3 was seen in 23–37%, T-cell disease in 21–50%, and central nervous system disease in 2–6% of the patients. Cytogenetic analysis was done only in a small proportion of patients in three studies with TEL-AML1 in 9.4–13.7% and BCR-ABL in 1.8–7% of patients.[8,11,13] MCP-841 (and consequently cranial radiotherapy) was used in majority of the patients with absence of risk-group stratification.

There was selective reporting of outcomes with varying duration of follow-up (generally 5 years). There was also a selection bias with either inclusion of only those families who were "committed," "willing," and "able to remain close," or inclusion of everyone but exclusion of those who abandoned at the stage of survival analysis except in the study by Kulkarni *et al*.[9] With these caveats, overall survival ranged from 45% to 81% (commonly >60%) and event-free survival ranged from 41% to 70% (commonly >50%) among the hospitals. The overall survival outcomes when including all those diagnosed, regardless of initiation or completion of treatment was more modest 33% in the cohort from the Post Graduate Institute of Medical Education and Research, Chandigarh,[9] and 39% in the only report from the population-based cancer registries.[7] Toxic deaths, where reported, ranged from 2% to 13% in induction and 4–24% anytime during treatment. As 83–95% (commonly <90%) of children with ALL were in remission at the end of induction, it implies that around 10% children had an event (mortality or refractory disease) in induction. Relapse rates ranged from 18% to 41% (commonly ~30%).

Acute myeloid leukemia

Six studies were included (one population-based and the other five hospital-based) which covered variable time periods (range 1990–2014) [Table 2] and together they constituted 336 children with AML. The treatment protocols were variable with the use of two or three drug induction.

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Table 1: Summary of studies on childhood acute lymphoblastic leukemia from India published after the year 2000

	Study ID										
	Population-based	Hospital based									
	Swaminathan *et al.*, 2008[7]	Magrath *et al.*, 2005[5]		Bajel *et al.*, 2008[8]	Kulkarni *et al.*, 2009[9]	Arya *et al.*, 2010[10]	Yadav *et al.*, 2012[11]	Mukhopadhyay *et al.*, 2013[12]	Gupta *et al.*, 2015[13]	Radhakrishnan *et al.*, 2015[14]	
Study overview											
Institute	MMTR	CI	TMH	AIIMS	CMC	PGIMER	AIIMS	SGRH	NSCBCRI	RGCI	CI
Time period	1990-2001		1990-1997		1985-2003	1990-2006	1992-2002	NS	2004-2011	1996-2009	2005-2011
Number	343	168	652	228	307	762	254	98	500 321 pediatric 2-12 years 179 adolescent 13-18 years	212	238
Age (years)	0-14	Median 10	Median 7.2	Median 7.6	Median 6 (1-14)	Median 5	NS	NS	Median 10 (2-18)	Median 6 (1-18)	Median 10 (0.9-30)
Gender (male:female)	1.8:1	NS	NS	NS	1.8:1	3.2:1	3.9:1	NS	1.5:1	3.5:1	1.8:1
Disease											
T-cell	NS	43.10%	20.70%	31.80%	22%	NS	31%	NS	50.4%	23.90%	39.4%
WBC >50,000	NS	34.50%	24.60%	31.10%	23.10%	26.3%	28.3%	NS	NS	36.80%	34%
CNS	NS	NS	NS	NS	6.2%	3.1%	6%	NS	NS	2.3%	3.4%
Treatment details											
Protocol	NS		MCP841		Modified BFM 76/79	Modified UKALL X	MCP 841	NS	MCP 841	MCP 841, others	Modified BFM 95
RT	NS		All		All	All except <3 years age	All except <3 years age	NS	NS	NS	All except <3 years age
Induction outcomes											
CR	NS	86.90%	94.80%	83.30%	91.60%	83.40%	87.80%	NS	NS	NS	NS
Toxic deaths	NS	NS	NS	NS	2%	12.8%	11.0%	NS	NS	NS	3.3%
Resistant	NS	NS	NS	NS	6.40%	1.20%	1.20%	NS	NS	NS	NS
Abandoned	NS	NS	NS	NS	NS	6.60%	NS	NS	NS	NS	NS
Overall outcomes											
Toxic death	NS	16.70%	10.60%	22.80%	3.80%	20.90%	24.00%	NS	NS	NS	NS
Relapses	NS	41.10%	28.80%	30.50%	30.40%	20.30%	17.90%	NS	Children 20% Adolescents 41%	NS	31%
OS	38.7% at 5 years	45% at 4 years	67% at 4 years	58% at 4 years	59.8% at 5 years	46% at 5 years (including abandonment)	67% (follow-up not specified)	70.5% at 2.5 years	Children 78% Adolescents 60% (follow-up not specified)	81.4% at 5 years	NS
EFS	NS	43% at 4 years	60% at 4 years	41% at 4 years	56% at 5 years	43% at 5 years (including abandonment)	51.6% (follow-up not specified)	60% at 2.5 years	Children 70.2 Adolescents 52% (follow-up not specified)	72.1% at 5 years	63.4% at median follow-up 32.7 months
DFS	NS	NS	NS	NS	53.9% at 5 years	NS	61.9% (follow-up not specified)	NS	Children 72.4% Adolescents 56% (follow-up not specified)	75.6% at 5 years	NS

Contd...

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	Study ID									
	Population-based	Hospital based								
	Swaminathan *et al*., 2008[7]	Magrath *et al*., 2005[5]	Bajel *et al*., 2008[8]	Kulkarni *et al*., 2009[9]	Arya *et al*., 2010[10]	Yadav *et al*., 2012[11]	Mukhopadhyay *et al*., 2013[12]	Gupta *et al*., 2015[13]	Radhakrishnan *et al*., 2015[14]
Abandoned	NS	<4%	10.98% (censored in analysis)	30.2% opted for no therapy, and 14.6% abandoned treatment	NS	NS	NS	NS	5.5%
Comments		Only patients able to remain close to the treatment center during the period of induction and consolidation were considered eligible for entry on protocol, in order to ensure effective follow-up	Treatment was initiated only for those families with adequate commitment (about 50% of all)		Those willing for the treatment and regular follow-up were accrued				

AIIMS=All India Institute of Medical Sciences, CI=Cancer Institute, CMC=Christian Medical College, CNS=Central nervous system, CR=Clinical remission, DFS=Disease free survival, EFS=Event free survival, MMTR=Madras Metropolitan Tumor Registry, NS=Not specified, OS=Overall survival, PGIMER=Post Graduate Institute of Medical Education and Research, RGCI=Rajiv Gandhi Cancer Institute, RT=radiotherapy, SGRH=Sir Ganga Ram Hospital, NSCBCRI=Netaji Subhas Chandra Bose Cancer Research Institute, TMH=Tata Memorial Hospital, WBC=White blood cell

Swaminathan *et al*. reported a 5-year overall survival of 30% in the Madras Metropolitan Tumor Registry.[7] Although there was selective reporting of outcomes from the hospital-based cohorts with varying duration of follow-up, it can be inferred that 50–80% of treated patients had experienced an event (toxic death, refractory disease or relapse). In addition, a large proportion of patients opted not to take treatment. Toxic deaths overall ranged from 6% to 45% and during induction from 3% to 25% with higher deaths in the three drug induction protocol. Relapse rates ranged from 26% to 48% with higher relapse rate in the two-drug induction protocol.

Discussion

Based on these results, there is currently a significant gap in the outcomes of ALL and AML in India as compared to that reported from HIC.[3,4] However, before we further dissect the data and infer from it, it is important to put these results in a national context. According to GLOBOCAN estimates (http://globocan.iarc.fr), there are nearly 25,000 children diagnosed with cancer in India every year and around 9000 of these have leukemia. Even with these conservative estimates, there would be 90,000 children with leukemia in a decade in India.

Our analysis of 3761 children with ALL and 336 children with AML over a time period spanning two to three decades, represents a tiny fraction of the total childhood leukemia burden. One can argue that these "missing patients," many of whom are likely to be from rural or smaller urban areas, are likely to have an outcome worse than that seen in the hospital-based cohorts in this review and probably more closer to that reported from the only population-based study. This happens because hospital-based cohorts would often exclude those who opt not to take treatment or abandon treatment.

What are the outcomes of those children who are treated but the outcome data are missing. Some of this information can be found in the gray literature where institutions publish the abstract of their work.[6,20] These often do not get published but can provide us useful information. Still the majority of outcome information is not captured. In recognition of the need of data collection, recent efforts of developing online hospital-based cancer registries dedicated to childhood cancer such as IndiaPod (https://indiapod.org) and Pond4kids (https://www.pond4kids.org) as well as funding for data managers will address this gap.[21] Currently, over 8000 newly diagnosed children with cancer are being registered on IndiaPod every year (Jennifer Lowe, personal communication).

Similar to observations from studies in other low–middle income countries (LMIC) and prior studies from India, our results confirm there are broadly three reasons for poor outcome of children with acute leukemias; treatment abandonment, relapses, and toxic deaths.[6,22,23]

Treatment abandonment is attributable to a complex interplay of biological, socio-economic and treatment-related factors prevalent in India.[24] Biological differences (a relatively greater proportion of older children, T-cell disease, high WBC count, BCR-ABL, t(1:19) and a lesser proportion of TEL-AML1), host factors (comorbidities such as malnutrition, tuberculosis, hepatitis B, multidrug resistant bacterial infections, and potential pharmacogenomic factors), poor infrastructure (lack of adequate

Table 2: Summary of studies on childhood acute myeloid leukemia from India published after the year 2000

	Study ID					
	Population-based	Hospital based				
	Swaminathan *et al.*, 2008[7]	Gupta *et al.*, 2011[15]	Yadav *et al.*, 2011[16]	Philip *et al.*, 2015[17]	Bahl *et al.*, 2015[18]	Radhakrishnan *et al.*, 2015[19]
Study overview						
Institute	MMTR	Hematology, AIIMS	SGRH	CMC	Oncology, AIIMS	CI
Time period	1990-2001	2005-2009	2005-2010	2012-2014	2000-2011	2008-2013
Number	60	35	23	23	130	65
Age	0-14 years	Mean 12.4 years (1-18 years)	NS	<15 years	8-18 years	Median 11 years (1-17 years)
Gender (male:female)	1.2:1	1.9:1	NS	NS	NS	2.25:1
Treatment details	NS	Induction (3+7 ± HAM) and consolidation (HD-AraC 3 cycles)	MRC UK AML 12	AML BFM 98	Induction (3+7) and consolidation (HD-AraC 3 cycles)	Induction (DA or ADE) and consolidation (HD-AraC 2-3 cycles)
Induction outcomes						
CR	NS	77.1% after 1 and 94.3% after 2 cycles of induction	NS	NS	NS	62% after 1 cycle DA 88% after 2 cycles ADE
Toxic deaths	NS	2.8%	22%	24.7%	NS	4.6% (DA - 0% and ADE - 11%)
Refractory	NS	20% after 1 cycle, 0% after 2 cycles	NS	NS	NS	NS
Abandoned	NS	2.8%	NS	NS	NS	NS
Overall outcomes						
Toxic death	NS	5.7%	45%	NS	NS	6.1%
Relapses	NS	48.5%	26% (includes refractory)	NS	NS	NS
OS	30.3% at 5 years	NS	26% alive	70.4% at 1 year	Median 32.4 months	36% (median follow-up 11.5 months) Median 14.6 months
EFS	NS	NS	22% alive and disease free	NS	NS	28% (median follow-up 11.5 months) Median 12.6 months
DFS	NS	Median 13 months 4 years DFS 40%	NS	NS	Median 15.8 months	NS
Abandoned	NS	5.7%	NS	NS	NS	NS
Comments		All patients analyzed - none excluded	28 did not take treatment	24 did not take treatment	Most of data combined with adult data	

AIIMS=All India Institute of Medical Sciences, CI=Cancer Institute, CMC=Christian Medical College, CR=Clinical remission, DFS=Disease free survival, EFS=Event free survival, MMTR=Madras Metropolitan Tumor Registry, NS=Not specified, OS=Overall survival, SGRH=Sir Ganga Ram Hospital, AML=Acute myeloid leukemia, DA=Doxorubicin, Cytarabine, ADE=Cytarabine, Doxorubicin, Etoposide

and trained manpower, and poor supportive care), and lack of appropriate uniform national risk-stratified protocols, explain not only the relatively poorer outcome (higher relapses and toxic deaths) in India compared to HIC, but also the variation in outcomes seen within India. In contrast, for AML, no clear biological differences have been demonstrated between India and HIC, and it is likely that optimal treatment and supportive care are crucial to improving outcomes. The pursuit of more intense treatment (and arguably greater clinical remission rates and lesser relapse rates) has to be balanced with increasing toxic deaths as a consequence. There is a suggestion in the AML studies included in this review, that those with three drug induction had a greater response and lower relapse rate but a higher toxic death rate offsetting the advantage gained by the increase in treatment intensity. However, the small number of patients and centers involved prevents any meaningful conclusions.

It is imperative that going forward focus should be on addressing all three issues. Treatment abandonment requires holistic support to families through provision of financial support, lodging, psychological support, transportation, food subsidies, establishment of a parent support group, and a patient tracking system.[25]

Reduction of relapse rates requires adoption of appropriate risk-stratified (including minimal residual disease if feasible) adapted treatment regimens based on the experience, infrastructure, and supportive care available at a center as proposed in recent guidelines.[26,27] Steroid prephase in ALL should be used for slow cytoreduction, as well as preventing metabolic and infectious complications. In children with AML ineligible for standard intensive regimens due to co-morbidities or financial reasons, outpatient oral metronomic chemotherapy may be used as a bridge to standard therapy with response rates of 89%, including 62% complete remissions.[28]

Reduction of toxic deaths would require systematic improvement in supportive care through the use of local and international insights which include timely prevention and management of tumor lysis syndrome including the use of low-dose rasburicase,[29] aggressive management of hyperleukocytosis including through use of L-asparaginase,[30]

addressing malnutrition through upfront nutritional risk assessment and intervention,[31] early detection, prevention and treatment of hepatitis B using lamivudine or entecavir,[32] as well as tuberculosis and other multidrug resistant infections through strict infection control policies, and adequate transfusion support through promotion of voluntary platelet and blood donor registries.[33]

Most importantly, collaborative efforts, which promote treatment of patients on common protocols and encourage prospective multi-center clinical trials, are required. Collaboration among individuals and institutions regionally, nationally, and internationally has been fundamental to the remarkable progress made in Europe and North America in childhood cancer generally,[34] and in ALL and AML specifically where[3,4] nearly all children with cancer are registered in co-operative groups and majority enter clinical trials.[35-37] The experiences of collaborative groups in LMIC such as Morocco, Central America, Brazil, and the iBFM are the examples that such groups can be successful and that regional and national collaboration contribute greatly to improve the survival and outcome of childhood cancers.[23] In contrast, there has been a notable lack of prospective multi-center studies from India in relation to all childhood cancers including ALL and AML with one exception.[5] Recent efforts by InPOG on promoting clinical trials and the development of the InPOG-ALL-15-01 trial are welcome developments in this regard. They have the potential of bringing about a quantum leap in childhood cancer outcomes in India, just as the seminal MCP-841 study did for ALL by improving survival rates from <20% to nearly 60%.[5]

Finally, it is important to point out the lack of data from India on late effects. This is particularly relevant for ALL as historically the majority of the patients have received cranial radiotherapy as part of their treatment. Rajendranath *et al*. have recently reported that 15% of children with ALL (all of who were treated on the MCP-841 protocol with cranial radiation exposure of 18–24 Gy) had neurocognitive impairment.[38] This knowledge and consequent therapeutic adjustments would ensure that with adoption of risk-stratified intensive tailored treatments in future, we improve survival while reducing late effects in children with acute leukemia in India.

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Conflicts of interest

There are no conflicts of interest.

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