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Research Article

Acute Myeloid Leukemia in Children in Resource Limited Setting: Experience from a Tertiary Paediatric Oncology Center of Eastern India

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Abstract

Introduction: Acute myeloid leukemia (AML) is a difficult disease to treat in resource limited settings. Data from India is limited to identify trends or shortcomings and plan remedial strategies. Objective: To analyze the clinical profile and outcome in children with AML treated with daunorubicin- based induction protocol in a Pediatric oncology centre.

Methodology: This study looks at the outcomes of 27 patients with pediatric AML treated at our centre from January 2018 and June 2020. They were treated with daunorubicin based induction followed by consolidation with high dose cytarabine.

Results: The complete remission rate in this study is 66.7%. Toxicity related deaths were seen in deaths were seen in 25.9% cases. The relapse rate is 22.2%. Event free survival (EFS) in the cohort at 2.5 years was 51.8%.

Conclusion: This study demonstrates good EFS with the use of daunorubicin based protocol in resource limited settings as compared to previously reported studies. The toxicity related deaths specially in induction can be further reduced if we can ensure early referral of patients and prompt treatment.

Keywords: Pediatric Acute Myeloid Leukaemia; Survival; Outcome; Daunorubicin

Introduction

Acute leukemia is the commonest malignancy encountered in childhood accounting for nearly one-third of all childhood cancers. Acute myeloid leukemia (AML) comprises 15 to 20% of pediatric acute leukemias. Though outcomes of pediatric acute lymphoblastic leukemia (ALL) have much improved in recent years, similar results have not been reciprocated with pediatric AML. Pediatric Acute myeloid leukemia (AML) remains a difficult disease to treat in resource limited settings like India [1]. On the other hand, Western literature reports progressive improvements in prognosis for children AML over the years. Complete remission (CR) rates as high as 90 % and overall survival (OS) rates up to 65 % have been reported in pediatric AML [2,3]. This improvement in outcomes can be attributed to modernized flow cytometry based diagnostic techniques, standardized treatment protocols, better supportive care measures, and ability to salvage relapses using hematopoietic stem cell transplantation and newer drugs. But all these improvements may not be available in developing nations. Especially adequate supportive care may not be available in resource limited settings. Hence, improvement in the survival of pediatric AML in resource limited settings remains challenging. Data from India regarding pediatric AML is limited. As a corollary, there is a limited understanding of shortcomings in these resource limited settings. This makes it difficult to identify trends and plan remedial measures to improve patient survival.

Objective

To analyze the clinical profile and outcome in children with AML treated with daunorubicin- based induction protocol in a tertiary care center.

Methodology

- **Study type**: Retrospective observational study.

- **Study Setting:** Undertaken between January 2018 and June 2020 in a tertiary Paediatric Oncology Center.
- **Inclusion criteria:** <18-years, presenting with a diagnosis of de novo AML.
- **Exclusion criteria:** Acute promyelocytic leukemia, Down syndrome and secondary AML.
- **Classification and Stratification:** Genetic classification by a combination of karyotyping with G banding technique and FISH analysis for t(8;21), inv 16, t(15;17), MLL gene rearrangements in all children. Stratified based on the WHO classification to standard, intermediate and high-risk groups.
- **Intervention:** Treated with anthracycline-based induction 1 (daunorubicin 60 mg/m^2/day for 3 days given over 2 h as infusion and cytarabine 100 mg/m^2/day given as continuous intravenous infusion for 10 days) (DA), induction 2 (daunorubicin 50 mg/m^2/day for 3 days given over 2 h as infusion and cytarabine 100 mg/m^2/day given as continuous intravenous infusion for 8 days) followed by consolidation with 2 cycles of high-dose (3g/m^2) cyatarabine (HIDAC). Stem cell transplantation was not performed.
- **Analysis:** Data extracted from the medical records. Patient identity was masked. Descriptive statistics are reported. Kaplan-Meier method was used for survival analysis with Log Rank (Mantel-Cox) for test of significance. SPSS package was used for analyses (SPSS version 13.0; SPSS Inc. Chicago). P values < 0.05 are considered significant.

Outcome

- Proportion of cases achieving remission
- Event free survival (EFS)

Results

A total of 36 cases of AML were diagnosed at our centre during the study period. Of these, 27/36 patients underwent treatment and 9/36 (25%) did not consent to treatment at our centre. The 6 patients refused consent due to various reasons. Some wanted treatment at other centre, while a few decided on trying alternative methods of medicine. The median age of the patients was 11.3 years (range 1-17 years), 18/27 (66.7%) patients were male. 6/27 (22.2%) Patients had t(8;21) which was the most common recurrent genetic abnormality followed by 4/27 (14.8%) patients with inv (16). Most of the patients, 11/27 (40.7%) belonged to the intermediate risk group of genetic risk stratification (Table 1). Fever was the most common presenting symptom seen in 24/27 (88.9%) patients. Median presenting WBC count was 13,600 (range: 600-3,56,000). (Table 1). Hyperleucocytosis was seen in 3 patients (11%). No patient had CNS disease.

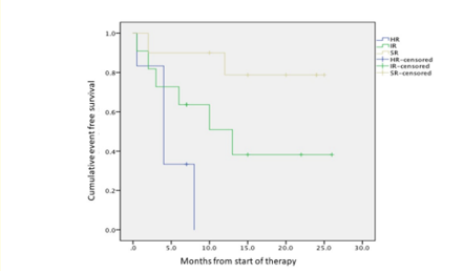
	SR	IR	HR
N (%)	10 (37%)	11 (40.7%)	6 (22.3)
Median Age (Years)	9.3	10.6	12.8
Median WBC (X 10^3)	17.5	6.8	33.1

Table 1: Patient Profile as per risk group.

(SR = standard risk, IR = intermediate risk, HR = high risk).

DA induction chemotherapy was administered to all patients. Complete remission (CR) was achieved in 18/27 (66.7%) patients. CR after first cycle of DA induction was achieved in 17/27 (62.9 %) patients. Only 1 patient was in partial remission after first induction who achieved CR after second cycle induction.

The median duration of follow-up of study patients was 17.7 months (range 5-23 months). The Event free survival (EFS) of the entire cohort at 2.5 years was 51.8%. EFS in patients with good, intermediate, poor risk cytogenetics are 80%, 45.5%, and 16.7 % respectively (p value = 0.01). EFS of intermediate risk (IR) and high risk (HR) group was 45.5% and 16.7% respectively. Mean EFS in months for standard risk (SR) 21.2 months (95% CI: 16.4-26.0), IR: 13.9 months (95% CI: 7.5-20.3), and HR: 4.8 months (95% CI: 2.4- 7.1) (Figure 1). The number of induction deaths were 6/27 (22.2%). Amongst, 5 (18.5%) of these were due to sepsis while one (3.7%) was due to refractory disease. There was one death during HIDAC. 6 patients have relapsed so far (22.2%).



Overall Comparison			
	Chi-Square	Degree of freedom	p value
Log Rank (Mantel-Cox)	9.197	2	0.010

Figure 1: Kaplan Meier Curve, EFS based on cytogenetic risk stratification.

Discussion

Though great advances have been made in the treatment of pediatric Acute Lymphoblastic Leukaemia (ALL), pediatric AML is still remains a difficult disease to treat with relatively poor outcomes. Also, there is paucity of published literature as to Indian data on pediatric AML. Table 2 provides a summary of studies on pediatric AML reported from India [4-8]. If we analyse this data, one would realise that there is barely any uniformity of treatment protocols being followed at various centres. This along with the fact that we have much fewer patients than that of pediatric ALL makes data interpretation difficult. It is imperative that the Pediatric oncology centres of the country come together to collate the available data on pediatric AML so that we can select the protocol most suited to our resource limited settings.

Centre, time period, Author [Ref]	Sample size	Age (yrs)	Treatment Protocol Used	Complete Remission (%)	Refractory (%)	Toxic deaths (%)	Relapse (%)	Event Free Survival (%)
AIIMS, 2005-09, Gupta., *et al*. [4]	60	1-18	(3+7 HAM) HIDAC x 3	77.1	20	5.7	48.5	NS
SGRH, 2005-10 Yadav., *et al*. [5]	35	NS	MRC UK 12	NS	NS	45	26	22
AIIMS 2008-13, Bahl., *et al*. [6]	130	8-18	DA/ADE. HIDAC X3	62	NS	6.1	NS	28
CMC, 2012-14 Philip., *et al*. [7]	23	<15	AML BFM 98	70	NS	24.2	31.7	35.5
CI, 2012-14 Radhakrishnan., *et al*. [8]	65	<18	DA/ADE. HIDAC X2	72	NS	NS	NS	28
Current study	27	<18	DA HIDAC X2	66.7	3.7	25.9	22.2	51.8

Table 2: Summary of studies on childhood AML from India after 2005.

NS: Not Stated.

AIIMS: All India Institute of Medical Science, Delhi; SGRH: Sir Ganga Ram Hospital, Delhi; CI: Cancer Institute, Chennai; CMC: Christian Medical College, Vellore; CI: Cancer Institute, Adyar, Chennai.

The CR rate (66.7%) in our study is quite comparable to those reported from other centres in India. In our study, standard risk patients have very encouraging EFS (80%), demonstrating the feasibility of DA regimen in resource limited settings. One of the reasons among others why our high-risk patients had relatively poor outcome was because most of these patients could not undergo further intensive chemotherapy or allogenic stem cell transplantation due to financial constraints. Treatment cost in pediatric AML still remains formidable, hindering equitable access to healthcare. Many of our patients sadly opted for cheaper alternative medicine for treatment due to cost issue, thereby affecting outcomes. The overall mortality during induction in our study was 22.2% and there was one death during HIDAC consolidation in our study. The deaths due to toxicity were relatively lower as compared to other similar studies. It may thus be logical to conclude that the DA regimen is more feasible and better suited for use in patients in resource limited setting as ours. The DA regimen fared favorably as compared to mitoxantrone based regimen or even other daunorubicin based regimen like ADE. This may be explained by the fact that more intense induction regimens might even further increase treatment related mortality in resource limited settings as ours. Relapse rates (22.2%) were lower as compared to other studies. Benefits were partly offset by slightly higher toxicity-related deaths (25.9%) possibly because around 50% of the patients came in poor condition presenting with sepsis or disseminated fungal infections.

Cytogenetic profile in our study was similar to other studies and was the only factor that significantly predicted survival [9,10]. In a recent study by Tyagi et al, the 34.3% revealed favourable cytogenetic rusk group with intermediate risk group having the highest number of patients just like our study. This study showed loss of

Y chromosome to be the most common genetic abnormality detected in 12.9% patients [10]. In our study, t(8;21) was the most common recurrent genetic abnormality.

Limitation

This was a single center study; multicentric study would be better.

Many high-risk patients could not undergo allogenic stem cell transplantation even when indicated by protocol due to financial constraints.

Conclusion

Overall the study shows encouraging results in treatment of children with AML even in resource limited settings with the use of DA regimen. This highlights the fact that conformity to a standard protocol and optimization of supportive care can improve outcome in Pediatric AML. But we also need to raise awareness at the ground level to ensure early referral to an appropriate centre so that the children get admitted at a more salvageable stage so that the mortality specially the induction deaths can be reduced further.

Source of Funding

Nil.

Conflict of Interest

Nil.

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