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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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A B S T R A C T

Introduction: Acute myeloid leukaemia (AML) is a difficult disease to treat in resource-limited settings. Data from India is limited to identifying trends or shortcomings and planning remedial strategies.

Objective: To analyse the clinical profile and outcome in children with AML treated with daunorubicin-based induction protocol in a Paediatric oncology centre.

Methodology: This study looks at the outcomes of 27 patients with paediatric 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% of 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 the daunorubicin-based protocol in resource-limited settings as compared to previously reported studies. The toxicity-related deaths especially in induction can be further reduced if we can ensure early referral of patients and prompt treatment.

Keywords: Paediatric 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 leukaemia (AML) comprises 15 to 20% of paediatric acute leukaemias. Though outcomes of paediatric acute lymphoblastic leukaemia (ALL) have much improved in recent years, similar results have not been reciprocated with paediatric AML. Paediatric Acute myeloid leukaemia (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 with AML over the years. Complete remission (CR) rates as high as 90% and overall survival

(OS) rates up to 65% have been reported in paediatric AML.[2,3] This improvement in outcomes can be attributed to modernised flow cytometry-based diagnostic techniques, standardised treatment protocols, better supportive care measures, and the 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 paediatric AML in resource-limited settings remains challenging. Data from India regarding paediatric 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 analyse the clinical profile and outcome in children with AML treated with daunorubicin-based induction protocol in a tertiary care centre

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 leukaemia, Down syndrome and secondary AML
- **Ethical Approval:** Ethical clearance was taken for the study

Classification & Stratification

Genetic classification by a combination of karyotyping with G banding technique and FISH analysis for t(8;21), inv 16, t(15;17), and MLL gene rearrangements in all children

Stratification 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 (3 g/m^2) cyatarabine (HIDAC). Stem cell transplantation was not performed.

Analysis

Data extracted from the medical records. The patient's identity was masked. Descriptive statistics are reported. Kaplan-Meier method was used for survival analysis with Log Rank (Mantel-Cox) for the 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.. Some wanted treatment at another centre, while a few decided to try alternative methods of medicine. The median age of the patients was 11.3 years (range 1–17 years), and 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. The 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.

Table 1.Patient Profile as per Risk Group

Variables	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

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 the first cycle of DA induction was achieved in 17/27 (62.9 %) patients. Only 1 patient was in partial remission after the first induction and achieved CR after the second cycle induction.

The median duration of follow-up of study patients was 17.7 months (range 5–23 months). The EFS of the entire cohort at 2.5 years was 51.8%. EFS values in patients with good, intermediate, and poor risk cytogenetics were 80%, 45.5%, and 16.7 % respectively (p value = 0.01). EFS values of the intermediate risk (IR) and high risk (HR) groups were 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 was 6/27 (22.2%). Amongst these, 5 (18.5%) 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%).

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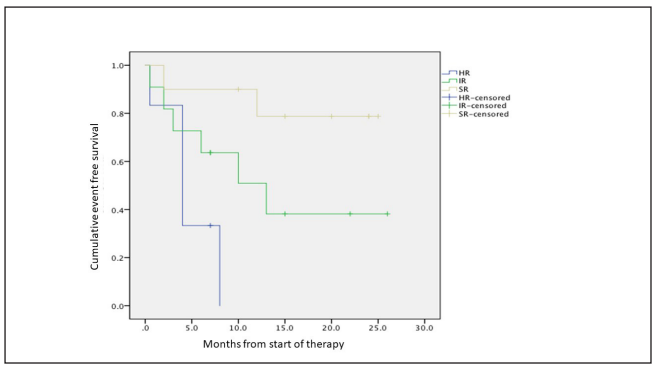

Figure 1.Kaplan Meier Curve, EFS Based on Cytogenetic Risk Stratification

Table 2.Overall Comparison

Test	Chi-Square Value	Degree of Freedom	p Value
Log Rank (Mantel-Cox)	9.197	2	0.010

Discussion

Though great advances have been made in the treatment of paediatric Acute Lymphoblastic Leukaemia (ALL), paediatric AML still remains a difficult disease to treat with relatively poor outcomes. Also, there is a paucity of published literature regarding Indian data on paediatric AML. Table 3 provides a summary of studies on paediatric 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 paediatric ALL makes data interpretation difficult. It is imperative that the Paediatric oncology centres of the country come together to collate the available data on paediatric AML so that we can select the protocol most suited to our resource-limited settings.

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 regimens in resource-limited settings. One of the reasons among others why our high-risk patients had relatively poor outcomes was because most of these patients could not undergo further intensive chemotherapy or allogeneic stem cell transplantation due to financial constraints. Treatment costs in paediatric AML still remain formidable, hindering equitable access to healthcare. Many of our patients sadly opted for cheaper alternative medicine for treatment due to cost issues, 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 a resource-limited setting such as ours. The DA regimen fared favourably as compared to the 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 such 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.

The 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., 34.3% revealed a favourable cytogenetic risk group with the intermediate risk group having the highest number of patients just like our study. This study showed loss of the Y chromosome to be the most common genetic abnormality detected in 12.9% of patients.[10] In our study, t(8;21) was the most common recurrent genetic abnormality.

Table 3.Summary of Studies on Childhood AML from India After 2005

Centre, Time Period, Author	Sample Size	Age (Years)	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

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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

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

Limitation

- This was a single-centre study; a multicentric study would be better.
- Many high-risk patients could not undergo allogeneic stem cell transplantation even when indicated by protocol due to financial constraints.

Conclusion

Overall the study shows encouraging results in the treatment of children with AML even in resource-limited settings with the use of a DA regimen. This highlights the fact that conformity to a standard protocol and optimisation of supportive care can improve outcomes in Paediatric 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, especially the induction deaths can be reduced further.

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Conflict of Interest: None

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