Acute Myeloid Leukemia in Children: Experience from Tertiary Cancer Centre in India

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Abstract There is paucity of data in pediatric Acute Myeloid Leukemia (AML) from developing countries. We analyzed the outcomes of 65 consecutive patients with pediatric AML treated at our centre from January-2008 to May-2013. The median event free survival (EFS) and overall survival (OS) were 12.6 and 14.6 months respectively. Patients with good-risk cytogenetics had a better EFS ($p = 0.004$) and OS ($p = 0.01$). Overall, these results are not comparable to that observed in other centres globally and leaves scope for further improvement. This includes implementing allogeneic bone marrow transplantation as a treatment for all children with high-risk AML.

Keywords Acute Myeloid Leukemia · Chemotherapy · Survival

Introduction

The prognosis for children with acute myeloid leukemia (AML) has improved greatly over the last three decades. Complete remission (CR) rates as high as 90 % and overall survival (OS) rates up to 65 % have been reported in pediatric AML [1, 2]. There is no standard induction chemotherapy regime for treatment of pediatric AML. There is lack of available evidence from the literature that shows superiority of a three drug over a two drug induction

chemotherapy regimen in pediatric AML. There is also a paucity of data on outcome in pediatric AML from developing countries like India [3]. Treatment of AML in resource poor settings is challenging because of lack of supportive care facilities, high cost of treatment and poor access to stem cell transplantation [3].

Patients and Methods

We analyzed the data of all consecutive pediatric patients with AML, <18 years of age who were admitted at our centre from 1st January 2008 to 31st May 2013. Diagnosis of AML was confirmed by bone marrow aspiration morphology and flow cytometry. Patients were stratified for risk according to the bone marrow cytogenetic analysis report [4]. Patients with t(8;21) or inv(16) in the leukemic cells were classified as having favourable cytogenetics, patients with normal karyotype, acquired +21 or t(9;11) were classified as having intermediate cytogenetics and patients with complex cytogenetics (three or more karyotype abnormalities), -5/del 5q, -7/del 7q, +8, t(8;16), t(11q23), t(16;21), t(9;22), t(1;22), inv(3), t(3;3), t(6;9), t(7;12) or del 9q abnormalities were classified as high risk cytogenetics. Detection of mutations in FLT-3 and NPM was not performed.

During the study period two different treatment protocols were used to treat pediatric AML at our centre. Patients received induction chemotherapy with either daunorubicin and cytarabine (DA) or daunorubicin, cytarabine and etoposide (ADE). Induction with DA regimen consisted of daunorubicin 60 mg/m²/day for 3 days given over 2 h as infusion and cytarabine 100 mg/m²/day given as continuous intravenous infusion for 7 days. Induction with ADE regimen consisted of cytarabine

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200 mg/m²/day given as intravenous bolus in two divided doses for 10 days during the first and for 8 days during the second induction. Daunorubicin 50 mg/m²/day was given over 2 h as infusion for 3 days and etoposide 100 mg/m²/day was given over 2 h as infusion for 5 days. Patient who received DA induction chemotherapy were given one cycle of induction followed by three cycles of consolidation with high dose cytarabine given at a total dose of 18 gm/m² (3 g/m² twice daily alternately for 3 days). Patient who received ADE induction chemotherapy were given two cycles of induction followed by two cycles of consolidation with high dose cytarabine (HIDAC) given at a total dose of 18 gm/m². The DA regimen was administered at our institute from January 2008 to June 2012 and the ADE regimen from June 2012 to May 2013. Bone marrow studies were performed at the end of first induction, patients in DA regimen were given supportive care if their bone marrow was not in complete remission (CR), and patients in ADE arm were given second induction irrespective of their remission status and given supportive care if they did not achieve remission after second induction. Patients with AML M3 were not included in the analysis. Chemotherapy related toxicity was analyzed using the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI-CTCAE) version 4 criteria [5].

Event was defined as death due to any cause or recurrence of leukemia. Event free survival (EFS) was calculated from date of initiation of treatment to date of relapse, death or last follow-up. OS was calculated from date of initiation of treatment to date of death or date of last follow-up. EFS and OS were estimated using Kaplan–Meier method and variables were compared using the log rank test. *p* value <0.05 was considered significant. Categorical variables were compared using Chi square test. Statistical analysis was done using SPSS software (IBM SPSS Statistics Version 9).

Results

A total of 72 cases of AML were diagnosed at our institute during the study period of which 65/72 patients underwent treatment and 7/72 refused consent to treatment. The seven patients refused consent as either they wished to try alternative treatment or have it closer to home. The median age of the patients was 9 years (range 1–17 years), 45/65 (69 %) patients were male. The commonest French American British (FAB) sub-type was AML M2 (26 %) Fever was the most common presenting symptom seen in 39/65 (60 %) patients. Infections at presentation was observed in 17/65 patients (26 %), with pneumonia and

soft tissue cellulitis being the most common. Baseline demographic data are shown in Table 1.

DA induction chemotherapy was administered to 39/65 (60 %) patients and ADE induction chemotherapy to 26/65 (40 %) patients. Stratification for risk by cytogenetics was available for 44/65 (67 %) patients, of which 18/44 (41 %) patients were classified as good, 14/44 (32 %) patients were classified as intermediate and 12 (27 %) patients were classified as high risk. CR was achieved in 47/65 (72 %) patients. CR after first cycle of DA induction was achieved in 24/39 (62 %) patients. CR after first cycle of ADE induction was achieved in 18/26 (69 %) patients and after second cycle ADE induction in 23/26 (88 %) patients. Median days of neutropenia was 19 and 16 days in ADE

Table 1 Patient characteristics at presentation

Characteristic	Number
Gender	
Male	45/65 (70 %)
Female	20/65 (30 %)
Median age	11 years (1–17 years)
Presenting complaints	
Fever	39/65 (60 %)
Bleeding	16/65 (24 %)
Fatigue	6/65 (9.2 %)
Cytogenetics	
High risk	12/65 (18 %)
Intermediate risk	13/65 (20 %)
Good risk	18/65 (28 %)
NA	22/65 (34 %)
Upfront infections	18 (26 %)
Pneumonia	10/18
Cellulitis	5/18
Others	2/18
Type of induction	
DA	39/65 (60 %)
ADE	26/65 (40 %)
FAB subtype	
M2	20/65 (31 %)
M4	14/65 (22 %)
M5	5/65 (8 %)
M6	7/65 (11 %)
M7	3/65 (4 %)
Not specified	16/65 (24 %)
Median hemoglobin	6.7 gm %
Median WBC	16,700/dL
Median platelets	65,000/dL

DA Daunorubicin and Cytarabine; ADE Cytarabine, Daunorubicin and Etoposide; FAB French, American and British; WBC White Blood Cells; NA Not available

and DA arm respectively. Comparison between the DA and ADE regimens is shown in Table 2.

The median duration of follow-up of study patients was 11.7 months (range 0.3–53.13 months). The OS and EFS of the entire cohort was 36 and 28 % respectively. The median EFS and OS were 12.6 and 14.6 months respectively (Fig. 1a, b). EFS in patients with good, intermediate, poor risk cytogenetics and where it was not available was 62.27, 30.29, 12.5 and 11.1 % respectively (p value = 0.004; Fig. 2a). The only factor which significantly predicted EFS and OS was stratification of risk by cytogenetics. OS in patients with good, intermediate, poor

risk cytogenetics and where it was not available was 62.27, 43.75, 15.63 and 27.78 % respectively (p value = 0.01; Fig. 2b). There was 1/39 (2 %) death during induction in the DA regimen and 3/26 (11 %) in the ADE regimen. The cause of death during induction in the DA arm was due to refractory disease and all the three patients in the ADE arm died due to infections. There was one death during HIDAC consolidation due to sepsis. Two patients with high risk cytogenetics underwent matched sibling allogeneic stem cell transplant, one of them has relapsed and died while the other patient is in CR at 2 years follow-up.

Discussion

Treatment of AML in children is intense and requires excellent health care infrastructure. It is also associated with significant financial burden for the family especially in resource poor settings [6]. There is paucity of published data from India on pediatric AML, treatment protocol and cytogenetics based risk stratification. It is important to get data from developing countries so that standardised protocols suitable to local setting can be designed to improve outcomes. Table 3 provides a description of studies on pediatric AML reported from India.

There has been no published study in the pediatric literature comparing a three drug induction regimen with a two drug induction regimen in pediatric AML. Patients in resource poor setting tend to present in moribund condition and have serious infection at presentation. It may be more suitable to use the DA regimen rather than more toxic ADE regimen as induction chemotherapy in such patients. Mortality due to induction in pediatric AML from Western

Table 2 Comparison between DA and ADE regimens

	DA (n = 39)	ADE (n = 26)	p value*
CR	24 (62 %)	23 (88 %)	0.52
EFS	29 %	32 %	0.6 ⁺
OS	36 %	40 %	0.4 ⁺
Anti-fungal use	14 (35 %)	14 (53 %)	0.16
Growth factor use	4 (10 %)	7 (26 %)	0.84
Blood culture positivity	10 (25 %)	8 (30 %)	0.6
Induction deaths	1 (2 %)	3 (11 %)	0.14
Median days neutropenia	16	19	0.63
Cytogenetics			
Good	10 (25 %)	8 (30 %)	0.05
Intermediate	8 (20 %)	5 (19 %)	
Poor	5 (13 %)	7 (26 %)	
NA	12 (31 %)	10 (38 %)	

DA Daunorubicin and Cytarabine; ADE Cytarabine, Daunorubicin and Etoposide; CR Complete Remission; EFS Event Free Survival; OS Overall Survival; NA Not available. * Chi square test. ⁺ Log Rank

Fig. 1 Kaplan Meier survival curves. **a** Event free survival (EFS) for study patients. **b** Overall survival (OS) for study patients

Fig. 2 Kaplan Meier survival curves. **a** Comparing EFS for various cytogenetic risk groups. **b** Comparing OS for various cytogenetic risk groups

Table 3 Studies on pediatric AML outcome from India

Study [reference]	Time era	No. of patients	Age range [Median]	CR %	OS % (median follow up)
Jain et al. [10]	2006–2009	24	1.1–18 (12.5)	79	25
Sharavat et al. [11]	2007–2009	44	1–18 (8.5)	81.8	36.2 (24 months)
Mukhopadhyay et al. [12]*	2004–2006	30	0.25–18 (12)	–	30 (19 months)
Banavali et al. [13]*	1998–2003	26	3–25 (13)	62	38.4
Trehan et al. [14]*	2002–2006	32	1.5–13 (8)	65.6	23 (30)
Borker et al. [15]*	2003–2008	20	2.3–17 (11)	66.6	44 (17.9)
Present study	2008–2013	65	1–18 (11)	72	36 (11.7)

CR Complete remission, * conference abstract

countries have been reported between 3.8 and 11.5 % [7, 8]. The overall mortality during induction in our study was 6.5 % and there was only one death during HIDAC consolidation in our study underlines that disease relapse rather than toxicities were responsible for the poor outcomes. However, we have not included patients who were not treated because of their moribund condition or those who refused treatment, the outcomes would be inferior if these patients were also analysed.

Cytogenetic profile in our study was similar to western population and was the only factor that predicted survival [4]. The reason why patients with intermediate or poor risk cytogenetics patients had inferior outcomes compared to western data was because majority of these patients could not undergo allogeneic stem cell transplantation due to financial constraints [9].

Although our study is not a randomized trial we didn't find a difference in survival between DA and ADE arm, however there can be inherent bias as patients who were not fit would have been given DA rather than ADE chemotherapy. The median follow-up in our study was

only 11.6 months even though patients were recruited from 2008 to 2103 because 60 % of patients were enrolled between 2011 and 2013. The follow-up with ADE being much shorter than DA regimen. Even though a high CR rate was achieved with both regimens, overall survival continued to remain poor due to disease relapses among the intermediate and high risk patients. Increasing coverage with allogeneic stem cell transplant in both intermediate and high risk cytogenetics patients might help improve outcomes. We are currently doing cytogenetic testing, FLT3 and NPM mutational analysis for all pediatric AML patients and offering low cost subsidised matched sibling allogeneic stem cell transplant to all patients with high risk AML.

This study gives a picture of real life scenario in a teaching cancer hospital. All patients were treated without any economic consideration. The major drawbacks of our study was that patients who relapsed were not given salvage treatment and majority of patients with high risk features did not receive allogeneic stem cell transplantation. We are currently conducting a randomised trial

comparing DA versus ADE induction in pediatric AML [CTRI REF/2014/09/007540]. This hopefully will give us a better idea of the survival patients with AML, and thereby curing the majority.

Compliance with Ethical Standards

Conflict of interest None.

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