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Original Article

Treating Acute Myeloid Leukemia among Children with Down Syndrome

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Abstract

Background: Down Syndrome (DS) children with acute myeloid leukemia (AML) have unique differences in clinical features, epidemiologic nature, and biologic patterns of disease compared with AML in children without DS. **Aims and Objective:** AML in DS children should be considered distinct disorder from AML in Non DS population and treatment needs to be customized for this population. In this retrospective study spanning from 2014 to 2019 we present our experience of managing leukemia in children with DS. **Materials and Methods:** From 2014 and 2019, 72 children aged below 18 years were managed at our institute with acute myeloid leukemia (AML). Out of these 72 children with AML, 7 children were with DS which was confirmed by karyotyping. Majority of these children had M7 while M2 and M4 subtypes were seen in one child each. On conventional karyotyping in addition to trisomy 21 additional cytogenetic abnormalities were seen in 4 patients. Two children had trisomy 8. One child had deletion of 11 chromosomes and one had translocation between 8 and 21 chromosomes. **Results:** All 7 children were administered intensive chemotherapy with curative intent after informed parental consent. All 7 children achieved complete remission. Four out of 7 children had complications related to severe neutropenia. **Conclusion:** All patients of DS with AML should be offered chemotherapy with curative intent. Endeavour should be to give less aggressive chemotherapy protocol to bring down treatment related mortality.

Keywords: *Acute myeloid leukemia, curative intent, Down syndrome*

Introduction

Down syndrome (DS) is the most common genetic anomaly with incidence ranging from 1 in 600 to 1 in 1000 live births.[1] This syndrome is recognized by characteristic dysmorphic features and developmental abnormalities. Children affected with DS have trisomy of 21 chromosome, and besides characteristic features, extra genetic material of 21st chromosome also renders them uniquely susceptible to myeloid leukemia.[2] DS children with myeloid leukemia exhibit unique differences in clinical features, epidemiologic nature, and biologic patterns of disease compared with myeloid leukemia among children who do not have DS.[3] Children with DS have 500 fold increased incidence acute megakaryoblastic leukemia (AMkL) which is a subtype of myeloid leukemia[4] AMkL is rare among children without DS and is associated with poor survival.[5] Paradoxically outcomes of AMkL in children with DS are better than general population.[6,7] Nearly all DS AMkL cases are positive for somatic mutations of the GATA1 gene which is not present in non DS population with AMkL.[8] This finding suggest that DS AMkL should be considered distinct disorder from AMkL in Non DS population and treatment needs to be customized for this population. In this retrospective study spanning from 2014 to 2019 we present our experience of managing leukemia in children with DS.

Objectives

Objective of presenting this case series is to highlight the distinctive features of acute myeloid leukemia (AML) in children with DS and to increase awareness among referring pediatricians about better prognosis for AMl in these children as compared to general population.

Methods

It is a retrospective study spanning 5 years from 2014 to 2019. Descriptive statistics design has been used to describe 6 cases of AML in children with DS managed during these 5 years.

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Table 1: Base line characteristics at the time of diagnosis

Patient number	Age (months)	Sex	Duration of symptoms (days)	EMD (yes/no)	Fever	Hepatomegaly (yes/no)	Splenomegaly (yes/no)	Presentation Hb (gm/dL)	Presentation TLC ($\times 10^9$/L)	Peripheral blood blasts%	Presentation platelets ($\times 10^9$/L)	LDH, above ULN (yes/no)
1	48	Male	60	No	No	Yes	Yes	9	9.4	40	40	Yes
2	14	Male	100	No	Yes	Yes	Yes	9.4	6.1	11	11	Yes
3	25	Female	30	No	Yes	Yes	No	7.2	61	60	53	Yes
4	26	Male	120	Yes	Yes	Yes	Yes	7.4	32	62	131	No
5	24	Male	45	No	Yes	Yes	Yes	5.9	2.5	12	120	Yes
6	32	Male	60	No	Yes	Yes	No	4.9	1.9	0	30	No
7	18	Female	90	No	Yes	Yes	Yes	6.5	52	71	15	No

EMD –Extramedullary disease; Hb – Hemoglobin; TLC – Total leukocyte counts; LDH – Lactate dehydrogenase; ULN – Upper limit of normal

Case series

From 2014 and 2019, 72 children aged below 18 years were managed at our institute with AML. Out of these 72 children with AML, 7 children were with DS which was confirmed by karyotyping. Clinical features of these 7 children are summarized in Table 1. Fever, hepatomegaly and splenomegaly were the common presenting features. Only one child (Patient number 4) had extramedullary disease and he had significant delay of 120 days between onset of symptoms and presentation. All but one child had blasts cells present on peripheral smear. All patients were subjected to bone marrow aspiration and biopsy. AML was further sub classified on morphology as per French American British classification [Table 2]. Majority (5/7) of these children had M7 while M2 and M4 subtypes were seen in one child each (Patient number 5 and 1 respectively). Bone marrow samples were sent for conventional karyotyping as well as polymerase chain reaction for established translocations and mutations. On conventional karyotyping in addition to trisomy 21 additional cytogenetic abnormalities were seen in 4 patients. Two children had trisomy 8 (Patient number 1 and 6). One child had deletion of 11 chromosomes (Patient number 3) and one had translocation between 8 and 21 chromosomes (Patient number 5). None of these 7 children had history of preceding transient myeloproliferative disorder. All 7 children were administered intensive chemotherapy after informed parental consent [Table 3]. Briefly chemotherapy consisted of induction, consolidation (high dose cytosine arabinoside [AraC]) and maintenance (monthly cycles of 6thioguanine and low dose AraC) for 18 months. Etoposide was administered during induction phase [Table 3]. CNS directed therapy was administered by intrathecal AraC, during each cycle of induction and consolidation followed by 3 monthly during maintenance chemotherapy. All patients were treated in single room with reverse barrier nursing. As per our institutional protocol we do not use antifungal prophylaxis in children with AML during induction chemotherapy. Septran prophylaxis was started during maintenance chemotherapy.

Results

Outcomes of treatment have been summarized in Table 3. Early response to treatment was evaluated by peripheral blood blast clearance after end of induction chemotherapy at D + 7. Granulocyte colony stimulating factor (G-CSF) was used in all patients in dose of 5 mcg/kg subcutaneously. G-CSF was started on D + 8 of chemotherapy. G-CSF was administered till two consecutive reports of ANC > 500/mm^3. Median days of use were 10 days (Range 4–14 days) during induction cycles. No patients were given prophylactic antibiotics or antifungals. All 7 patients are currently under follow-up, patient number 1 and 2 have been followed up for more than 60 months. Remaining 5 children have been under follow-up for median duration

of 24 months (9–48 months) at the time of writing. Assessment for minimal residual disease was not done for any of these children during follow-up because as it is not part of our institutional protocol.

Discussion

Incidence of AML among pediatric population is estimated to be 7.7 cases per million,[9] accounting for 18% of all childhood leukemia.[10] Unlike Acute lymphoblastic leukemia, treatment of AML is associated with poor prognosis and significant relapse rates. Almost 50%–80% patients in India suffer severe toxicity, relapse or refractory disease.[11] Radhakrishnan *et al*. evaluated and found twodrug induction regimen to be more suitable then the conventional three drug induction regimen in order to reduce treatment related toxicity among sick patients.[12] In India cure rates have been inferior for pediatric malignancies when compared to developed countries.[13] With improvement is supportive care and standardization of treatment protocols, improved survival has also been reported in pediatric AML management in India.[14] Abandonment of therapy is common in the Indian/low middle income country scenario. Socioeconomic factors and long-term morbidity associated with DS also play part in failure to complete therapy in AML.[15] Historically patients with DS with AML were considered to have high risk disease and patients with DS who developed AML were not administered protocol based therapy largely owing to DS *per se* In a large multi centre study from India 54% patients of AML were not given any form of therapy due to various reasons.[16] Though there is no study from India, one can safely assume that higher percentage of DS with AML do not get any form of treatment due to reasons discussed above. In last three decades outcomes have improved dramatically once patients with DS were treated according to tailor made protocols for them.[17] Initial study of 12 patients with DS published in 1992 was first one to show excellent outcomes with chemotherapy protocol with AraC as backbone. In this study 3-year event free survival (EFS) was 100% for patients of DS compared to only 28% for non DS patients.[18] Since then more than 10 studies have been published studying patients of DS with AML and all have reported significantly better outcome in these patients in comparison to non DS AML.[17] One of recently published results is from COG-A2971 study which included 132 patients of DS with AML. In this study induction consisted of oral thio guanine (T), continuous infusion of AraC (A) and daunorubicin (D) also known as TAD protocol. Consolidation was as per Capizzi regimen with high dose AraC (3 g/m^2) and L asparginase. There was no maintenance chemotherapy. Five-year overall survival and EFS rates were impressive 84% and 79%.[19] Therapy reduction and its outcome were studied in 170 patients treated with International Ml-DS 2006 trial. In this study, lower cumulative dose of etoposide was used along with AraC and Idarubicin (AIE) during induction. There was no maintenance chemotherapy. Despite being less intensive, there were comparable results as far as disease outcomes were concerned.[20] This proved the concept that altered drug metabolism in myeloid leukemic-DS cells and the altered capacity for DNA repair in normal DS cells both permit and necessitate reduced exposures to cytotoxic therapies for optimal survival benefit. Two groups have published findings after studying large number of DS with AML.

Table 2: French American British classification and cytogentic abnormalities of all 7 patients

Patient number	FAB classification	Additional cytogenetic abnormalities	PCR/FISH for translocations
1	M4	Trisomy 8	Negative
2	M7	None	Negative
3	M7	Del 11	Negative
4	M7	None	Negative
5	M2	t(8;21)	t(8;21)
6	M7	Trisomy 8	Negative
7	M7	Add (5) (p15), del 7 (p13)	Negative

FAB – French American British classification; PCR – Polymerase chain reaction; FISH – Fluorescent *in situ* hybridization

Table 3: Treatment and outcome details

Patient number	Induction-1	Number of induction cycles	Absolute day 7 blast count	Severe neutropenic complications (yes/no)	Remission status	Type of consolidation	Follow-up duration (months)
1	TAD	4	100	Yes	CR	HaM	>60
2	TAD	4	0	Yes	CR	HaM	>60
3	3+7	2	100	No	CR	HiDAC	48
4	3+7	1	0	No	CR	HiDAC	36
5	AIE	2	200	Yes	CR	HiDAC	24
6	AIE	2	0	Yes	CR	HiDAC	18
7	3+7	1	0	No	CR	HiDAC	09

TAD-6 – Thioguanine (100 mg/m^2 × 4 days), Cytosine arabinoside (200 mg/m^2 daily as continuous infusion × 4 days), Daunorubicin (20 mg/m^2 daily over 1 h infusion × 4 days); AIE – Cytosine arabinoside (100 mg/m^2 continuous infusion × 7 days), Idarubicin (12 mg/m^2 as 4 h infusion × 3 days), Etoposide (150 mg/m^2 as 1 h infusion × 3 days), 3+7 (Idarubicin 12 mg/m^2 × 3 days + cytosine arabinoside 100 mg/m^2 daily as continuous infusion × 7 days); HaM – High dose cytosine arabinoside, mitoxantrone (cytosinearabinoside 1 g/m^2 as a 4 h infusion every 12 h × 3 days, Mitoxantrone 10 mg/m^2 as 30 min infusion × 2 days; HiDAC – High dose cytosine arabinoside (3 g/m^2 as a 3 h infusion × 3 days); CR – Complete remission

Based on these findings we have modified our induction protocol to less intensive 3 + 7 or ADE from 2017 onward. Anthracycline cardiotoxicity is more pronounced in children with DS. Cardiac assessment in all patients was done by baseline echocardiography and repeated at 06 monthly intervals till the follow-up period. No patient exceeded cumulative threshold dose of anthracycline and we did not find any evidence of cardiac toxicity in any of the patient. In present study all patients developed febrile neutropenia during induction, out of which 4 patients who received 3 drug induction developed severe complications necessitating intensive care. All patients successfully recovered with good supportive care. Though these are small numbers, they do indicate that addition of third drug during induction increases severe neutropenic complications. In our study, we used prophylactic G-CSF in all patients with no adverse outcomes even though some studies have documented higher risk of relapse with G-CSF.[21,22] Our policy of use of G-CSF in children with AML post induction chemotherapy is guided by various publications in literature where G-CSF has not been associated with increased risk of relapse.[23] In a Cochrane review where 19 studies with more than 5000 patients were analyzed, relapse rates did not increase due to use of CSFs.[24] Shortening the duration of neutropenia in children with AML is very important in our setting but authors would like to caution that long-term follow-up is required to assess the risk of relapse in these children due to use of G-CSF. With advances in cytogenetics it is clear that besides trisomy 21, DS children with AML may show additional chromosomal abnormalities.[25] Recent study has suggested that normal karyotype, besides trisomy 21 may indicate poor prognosis among this specific group of children.[26] In our study only 2 children (Patient number 2 and 4) did not have additional cytogenetic anomaly while other 5 had additional trisomy (Patient number 1 and 6), deletion (Patient number 3 and 7), or translocation (Patient number 5). However, this is too small a series to comment on significance of these anomalies in terms of management or prognosis. Additional cytogenetic abnormalities are important especially in long-term outcome. We intend to follow-up these children to better understand effects of additional cytogenetic abnormalities.

Conclusion

DS children are particularly susceptible to AML, which is relatively uncommon disorder among children without DS. However, prognosis among DS children is much better than non-DS children for AML. During this time period, 65 non DS AML children were also treated. At 2 years of follow-up, 38 children were in remission giving an OS of 58.4% in this cohort. To conclude all patients of DS with AML should be offered chemotherapy, as they show excellent response to AraC, which was remains keystone in any chemotherapy protocol. Endeavour should be to give less aggressive chemotherapy protocol to bring down treatment related mortality. G-CSF should be judiciously used from D + 8 during induction to bring down duration and complications of febrile neutropenia in these patients.

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Conflicts of interest

There are no conflicts of interest.

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