

Acute myeloid leukaemia in children: Experience at a tertiary care facility of Pakistan

Zehra Fadoo,¹ Naureen Mushtaq,² Saima Alvi,³ Muhammad Ali⁴

Department of Paediatrics, Aga Khan University Hospital, Karachi,^{1,2} Department of Paediatrics & Child Health, British Columbia University, Vancouver,³ Department of Paediatrics, Division of Haematology and Oncology, the Hospital for Sick Children, University of Toronto, Canada.⁴

Abstract

Objective: To document the demographics and outcome of children with Acute Myeloid Leukemia (AML) treated at a tertiary care facility of Pakistan.

Methods: A retrospective study was conducted at Aga Khan University on children (less than 15 years) diagnosed to have AML between January 2000 to May 2007. Total 40 cases were diagnosed out of which 37 charts were available for review.

Results: The average age of presentation was 8.5±4.5 years and 75% were males. The most common presenting feature was fever in 83% followed by bleeding in 41% and pallor in 39%. Initial WBC of > 100,000 was seen in 19% of patients. The most common FAB subtype was M4 39%. Twenty three patients underwent treatment out of which 12 patients are alive and in remission. Majority were followed up around 2 years and 6 months. Out of the 11 patients who died three had resistant disease, four relapsed and rest died due to sepsis mostly during induction.

Conclusions: The most common sub type in our study is AML M4 although AML M2 is reported as predominant subtype. About a third of the patients could not start or complete therapy due to financial constraints. The overall survival for our patients who completed therapy was 52%.

Keywords: Acute Myeloid Leukemia (AML), Childhood cancer, Clinical presentation, Treatment, Outcome (JPMA 62: 125; 2012).

Introduction

Acute leukaemias represent neoplasm of the haematopoietic cell precursors manifested as clonal expansion of myeloid and lymphoid haematopoiesis. Acute Myelogenous Leukaemia (AML) represents group of haematological malignancies that arise within bone marrow precursors of myeloid, monocyte, erythroid and megakaryocytic cell lineages.¹

Contrary to Acute Lymphoblastic Leukaemia of the late 1970's only modest improvement in the long-term survival of children with AML has been observed. However, over the last few years' treatment modification, intensification, introduction of new chemotherapeutic agents, targeted therapy and concomitant haematopoietic stem cell transplantation in high risk patients has improved overall survival in children with AML up to 50-60%.²⁻⁴

Acute Myeloid Leukaemia represents 15%-20% of all leukaemias in children less than 14 years of age with Acute Leukaemia constituting 30% of all childhood malignancies. Literature has shown that estimated incidence of childhood AML is 5-7 per million people per year and the frequency

remains static throughout childhood with slight increase in adolescence.² There is no sex predilection but there is some difference in certain ethnic and racial groups.⁵ A few predisposing factors such as environmental, genetic and acquired also increase the risk of AML.² The diagnosis of AML is established with a combination of morphologic, immunophenotypic and cytogenetic features.

To date very little information is available from our country on the frequency, subtype, presentation and outcome of childhood acute myeloid leukaemia. The majority of published data focuses on morphology and refers to both adults and children.⁶⁻⁸ Our study is a single centre based study and may not reflect the overall presentation and outcome of Paediatric AML in our country.

Patients and Methods

A retrospective descriptive study was conducted at the Aga Khan University Hospital, Karachi, Pakistan on children (less than 15 years) from January 2000 to May 2007. Forty cases were diagnosed as AML during this period and 37 charts were available for analysis.

Results

From January 2000 to May 2007, 40 children <15 years were diagnosed as AML. Of these 37 charts were available for review. Out of these 37 patients only 23 (62%) had undergone complete treatment. Remaining children's parents refused treatment or were referred elsewhere due to financial constraints or other social problems.

There were 9 (25%) females and 28 (75%) males. Average age at diagnosis was 8.5±4.5 years (6mo-15 years) and median of 10 years. Varied clinical presentations were found. Fever was the most common presenting feature in 31 (83%) followed by, bleeding/bruising in 15 (41%) and pallor in 14 (38%). One patient had associated Downs syndrome and two patients presented with bilateral proptosis.

Hyperleukocytosis is one of the important prognostic indicators. In our study 17 (46 %) patients had W.B.C between 0-20,000 x10⁹/L, 13 (35%) had 20,000- 100,000x10⁹/L and 7 (19%) patients had WBC >100,000x10⁹/L at presentation.

High LDH of >1000 IU/L was found in 50% patients. The most common FAB (French-American-British) subtype was M4 39% followed by M2 16 % M3 and M6 each 14 % and M5 3% (Table-1).

CNS (central nervous system) disease was present in 5 (13%) patients. M4 was the predominant subtype in CNS positive children. One of these patients also had hyperleukocytosis.

The patients were initially treated on POG (Pediatric Oncology Group) 9421-DAT (daunomycin, cytosine arabinoside and Thioguanine) based protocols, from 2000-2002 and then changed to Medical Research Council (MRC) AML 10 protocol. The children with APLM-M3 (Acute Promyelocytic Leukaemia) were treated with chemotherapy and All Trans

Table-1: Patient's characteristics.

Sex	Alive	Expired
Male	07	08
Female	05	03
Fab Classification		
M2	02	02
APML	04	-
M4	04	05
M5	01	-
M6	01	02
Treatment Options		
MRC	04	04
DAT	04	07
COG based ATRA	04	
CNS Disease (Total 5)*		
*2 left against medical advise	02	01

FAB classification: French American British. APLM: Acute Promyelocytic Leukaemia. MRC: Medical Research Council. DAT: Daunomycin, Cytosine Avabioside and Thioguanine. COG: Children Oncology Group. CNS: Central Nervous System.

Table-2: Treatment Scheme applied in 23 patients with AML diagnosed at Aga Khan University Hospital (Jan 2000-May 2007).

Phase of Chemotherapy	Drug	Dose	Administration & Duration
Induction (Course 1&2)	Daunomycin	45mg/m2	IV Day 1-3
	Ara-C	100mg/m2	IV Day 1-7
	6TG	100mg/m2	PO day1-7
	*Ara-C	40mg/m2	IT Day 1 only
Consolidation (Course 1 & 3)	VP 16	100mg/m2	IV Day1-5
	Mitoxantrone	10mg/m2	IV Day1-4
	*Ara-C	40mg/m2	IT Day 1 only
Consolidation (Course 2)	Ara-C	1 gm/m2	IV Day 1-5 Q12Hrly
MRC Based Therapy			
Induction (Course 1 & 2)	Ara-C	100mg/m2	IV Day 1-8 Q12Hrly
	Daunorubicin	50 mg/m2	IV Day1, 3 & 5
ADE	VP 16	100mg/m2	IV Day1-5
	Triple IT (HC, Ara-C, MTX)		Day 1 only
Post Induction (Course 3)	Idarubicin	10mg/m2	IV Day 1-2
	Cytarabine	200mg/m2	IV Day 1-5
	VP 16	100mg/m2	IV Day1-5
Consolidation (Course 4)	Ara-C	3gm/m2	IV Day1,2,8 and 9
	Asparaginase	6000/mgm2	IV Day 2& 9
CLASP (Course 5)	Mitoxantrone	10mg/m2	IV Day1-5
	Mida A	Ara-C	1gm/m2
ATRA based APLM Therapy			
Induction	Daunorubicin	50mg/m2	IV Day3-6
	Ara-C	200mg/m2	IV Day 1-7
	ATRA	45mg/m2	PO till complete response
Consolidation (Course 1 & 2)	Ara-C		IT day 1 only
	ATRA	45mg/m2	PO Day 1-7
Maintenance	Daunorubicin	50 mg/m2	IV Day 1-3
	ATRA	45mg/m2	PO Day1-7 alternate week for 1 year
	6MP	60 mg/m2	PO daily 1 year
	Methotrexate	20 mg/m2	PO once a week for 1 year

* Note CSF positive patients should receive total 6 doses of Triple IT in a period of 3 weeks following diagnosis of AML.

HC hydrocortisone, Ara-C cytarabine, MTX methotrexate, VP-16 etoposide, ATRA all trans retinoic acid, IV intravenous, PO oral, IT intrathecal.

retinoic acid (ATRA) based on COG (Children Oncology Group) protocol with one year of maintenance therapy. The details of chemotherapy are further explained in Table-2.

Three patients out of twenty three had resistant disease and their FAB subtypes were M6 and M4. Resistant disease was defined as no remission (marrow blasts > 20%) even after two courses of induction therapy. These patients were then put on palliative/supportive care only. Relapses

were seen in 4 and in one patient with Down's syndrome. Three were isolated BM (bone marrow) relapse and 1 had BM and CSF (cerebro-spinal fluid) combined. Three opted for further therapy; two went into second remission and received Bone Marrow Transplant successfully, while the others succumbed to their disease. Four children died due to sepsis, 2 during induction therapy and 1 died during re-induction of relapsed disease. One patient had hyperleukocytosis and died due to sepsis and acute renal failure prior to any therapy.

Thus at the time of analysis, 52% (12/23) of those patients who completed treatment, are alive and in remission. The average length of follow up for these patients is 2 years and 6 months (range 12 months to 72 months).

Discussion

Over the last couple of years the prognosis for children with AML has shown improvement. Some of the trials have quoted a complete remission rate of more than 90% with an overall survival rate of about 50-60% as half of them will experience relapse.¹ Though the main reason of treatment failure in AML is the recurrent/resistant disease, death due to treatment related toxicities and infections also contribute to the overall morbidity and mortality.⁹ In the Medical Research Council (MRC) AML10 trial, the overall survival rate was found to be 57%, showing marked improvement as compared to the previous trials but treatment related mortality was nearly 14%.¹⁰

The clinical presentation of AML maybe diverse and nonspecific, but is usually directly related to the leukaemic infiltration of the bone marrow, with resultant cell lines depression. Patients typically present with signs and symptoms of fatigue and pallor, bleeding, fever and infections due to myelosuppression of red cells, platelets, and white cells, respectively. Other features of presentation may include bone pains, hepatomegaly and splenomegaly, granulocytic sarcomas in orbit or periorbital area or at times with involvement of spinal cord presenting as spinal cord compression.²

In our study we have evaluated the different clinical presentations and laboratory data of children with AML. The average age of diagnosis of AML was 8.5 ± 4.5 years with marked male predominance, 75% compared to 25% females. Although this has also been observed in other studies^{6,7,11} our data may be biased due to gender preference in our society. The outcome observed was better in females. Fever is considered as the most common presentation of AML.^{1,2} In our patients it was found in 83% followed by bleeding/bruising in 41% and pallor in 39% of patients. Factors such as WBC, morphologic classification (FAB classification), and biological

characteristics such as immunophenotype and cytogenetic are considered as prognostic markers. White Blood Cell counts have also important relationship with the prognosis in AML. Various studies have shown a WBC count of $<20,000$ cells/ml³ is associated with a better prognosis, and a WBC of $>100,000$ cells/ml³ is associated with unfavourable outcome.^{12,13} In our study 19% of patients had white cell count > 100000 cells/ml³.

Metabolic derangements are important features that can be present in these patients at the time of diagnosis or arise secondary to therapy. This is dependent on the tumour cells burden and leukaemic cell turnover rate. Children can present with mild to severe hyperuricaemia, hyperkalaemia, hyperphosphataemia, and hypocalcaemia.² One of our patients who presented with metabolic derangements died in induction phase of chemotherapy due to tumour lysis syndrome and acute renal failure. Patients with M3 AML (APL) and M5 AML (monocytic) are more likely to show signs of DIC with associated laboratory abnormalities such as prolonged prothrombin time (PT), partial thromboplastin time (PTT), and decreased fibrinogen.² In our study four patients had APML (3 females and 1 male) and all are alive till the time of evaluation.

CNS disease is more common in M4 and M5 AML as well as those with high white cell count.² In our study five patients had CNS disease and all were with M4 subtype.

Till a few years back AML was classified on the basis of morphologic appearance using the FAB classification. Because of the limitations of this classification and lack of consistency or association with underlying biology, the World Health Organization (WHO) recently developed a system for comprehensive AML classification based on cytogenetics, disease biology, and clinical history.^{2,14} Cytogenetics looking at specific molecular translocations found in AML were available at our institute only after 2004, thus for this study, we only used morphological FAB for further classification. In our study the most common FAB subtype found was M4 38% followed by M2 16%, M3 and M6 each 14 % then M5 3% although internationally AML M2 and M4 has been reported as predominant subtype.^{2,15,16} This is followed by M1 20%, M5 15% (note age < 2 years M5 is nearly 50%), M3 5%-10%, M6 $< 5\%$, M7 3% and M0 $<3\%$. Even the studies carried out in adult population are predictive of M2 subtype as the most common. This difference has also been reported in another study from our institution and other studies carried out elsewhere in our country.⁶⁻⁸

From 2000-2002 the children were treated on the POG 9421-DAT based therapy and then the therapy was changed to MRC- AML 10 based protocol. AML M3 was treated with ATRA plus chemotherapy based on COG protocol with one year maintenance. Improved outcome has

been reported with the use of MRC AML 10 protocol which was also observed in our study.¹⁷ As cytogenetics were not available for majority of patients thus risk stratification could be done and all were treated with the same regimen except for those with APML who were considered good risk and treated using ATRA based protocol.

Recurrence of childhood myeloid leukaemia is associated with poor outcome.¹⁸ In our study 23 patients were able to complete their treatment. Those who were not able to complete treatment either had financial constraints or refused any treatment. The outcome of these patients is unknown as none came for follow-up. The patients with resistant disease were only offered supportive care.

Out of 23, 12 (52%) patients were in remission and in our follow up at the time of analysis. Three out of the four patients with relapsed disease were treated with second line therapy using FLAG. Two patients who achieved second induction remission underwent bone marrow transplantation successfully. Although Down's syndrome patients have a better prognosis but unfortunately our patient relapsed and the family decided for no further treatment. The average length of follow up period of our patients after completion of therapy was 2 years and 6 months with the longest survival being 6 years.

Resistant disease, relapses and infections are the most common attributable factors for deaths in AML which was also seen in our patients.

Over the years outcome of AML patients has improved because of diagnostic and prognostic factors, subgroup-risk directed treatment, targeted therapy and stem cell transplantation. With the progress in the understanding of biology of AML and development of new molecular targeted therapy in combination with chemotherapy and better supportive care, survival of children with acute myeloid leukaemia will further improve.

Our study is a single institution based study and may not be able to depict the overall status of children with AML in our country. Further data from other centres or multicenter studies are needed to demonstrate the overall incidence and survival of children with AML in Pakistan.

Although this study may not be comparable to the survival data from the more developed countries, it is enough to encourage physicians to at least try and treat these patients and refer them as early as possible. With improved resources, availability of targeted therapies and haematopoietic stem cell transplantation, development of better diagnostic facilities especially cytogenetics and better supportive care, we can

achieve a better overall survival rate.

Conclusion

Majority of children were males however survival was better in females. About a third of the patients in our study could not start or complete therapy due to financial constraints. Even with these limitations overall survival for our patients who completed therapy was 50%.

References

1. Rubnitz JE, Gibson B, Smith FO. Acute Myeloid Leukemia *Pediatr Clin North Am* 2008; 55: 21-51.
2. Pizzo PA, Poplack, DG, editors. Principles and Practice of Pediatric Oncology. Philadelphia: Lippincott Williams & Wilkins, 2006; 591.
3. Areeci RJ, Sande J, Lange B, Shannon K, Franklin J, Hertchinson R.. Safety and efficacy of gemtuzumab ozagamicin in pediatric patients with advanced CD 33+ Acute Myeloid Leukemia. *Blood* 2005; 106: 1183-8.
4. Ortego JJ, Diazde Heredia C, Olive T, Bastida P, Llorca A, Armadans L, et al. Allogeneic and autologous bone marrow transplantation after consolidation therapy in high risk acute myeloid leukemia in children. Towards a risk - oriented therapy. *Haematologica* 2003; 88: 290-9.
5. Children's Oncology Group. Aplenc R, Alonzo TA, Gerbing RB, Smith FO, Meshinchi S, Ross JA, et al. Ethnicity and survival in childhood acute myeloid leukemia: a report from the Children's Oncology Group. *Blood* 2006; 108: 74-80.
6. Haroni MS, Adil SN, Shaikh MU, Kakepoto GN, Khurshid M. Frequency of fat subtype in acute myeloid patients at Aga Khan University Hospital Karachi. *J Ayub Med Coll Abbottabad* 2005; 17: 26-9.
7. Zaki S, Burney IA, Khurshid M. Acute myeloid leukemia in children in Pakistan: an audit. *J Pak Med Assoc* 2002; 52: 247-9.
8. Hassan K, Ikram N, Shah SH. A morphological pattern of 234 cases of leukemia. *J Pak Med Assoc* 1994; 44: 145-8.
9. Creutzig U, Zimmermann M, Reinhardt D, Dworzak M, Staij J, Lehnbecher T.. Early deaths and treatment related mortality in Children undergoing therapy for Acute Myeloid Leukemia: Analysis of multicentre clinical trials in AML-BFM 93 and AML - BFM 98. *J Clin Oncol* 2004; 22: 4384-93.
10. Riley LC, Hann IM, Wheatley K, Stevens RF. Treatment-related deaths during induction and first remission of acute myeloid leukemia in children treated on the Tenth Medical Research Council Acute Myeloid Leukemia trial (MRC AML10). The MRC Childhood Leukaemia Working Party. *Br J Haematol* 1999; 106: 436-44.
11. Viana MB, Cunha KC, Ramos G, Murao M. Acute myeloid leukemia in childhood: A Fifteen years experience in a single institution. *J Pediatr (Rio J)* 2003; 79: 489-96.
12. Creutzig U, Zimmermann M, Ritter J, Henze G, Graf N, Loffler H, et al. Definition of a standard-risk group in children with AML. *Br J Haematol* 1999; 104: 630-9.
13. Meshinchi S, Arceci R J. Prognostic factors and risk-based therapy in pediatric acute myeloid leukemia. *Oncologist* 2007; 12: 341-55.
14. Vardiman JW, Harris NL, Brunning RD. The World Health Organization (WHO) classification of the myeloid neoplasms. *Blood* 2002; 100: 2292-302.
15. Burning R. Atlas of Tumor Pathology. Tumors of the Bone Marrow. (Atlas of Tumor Pathology 3rd series). Washington, 1993; 51.
16. Ghosh S, Shinde SC, Kumaran GS, Sqr RS, Dhord SR, Bachrinath SR, et al. Haematologic and immunophenotypic profile of acute myeloid leukemia: an experience of Tata Memorial Hospital. *Indian J Cancer* 2003; 40: 71-6.
17. Tan RM, Quah TC, Aung L, Liang S, Kirk RC, Yeoh AE. Improved outcome in childhood acute myeloid leukemia in Singapore with the MRC AML 10 protocol. *Pediatr Blood Cancer* 2007; 48: 262-7.
18. Rubnitz JE, Razzouk BI, Lensing S, Pounds S, Pui CH, Riberio RC. Prognostic factors and outcome of recurrence in childhood acute myeloid leukemia. *Cancer* 2007; 109: 157-63.