ORIGINAL ARTICLE

Mortality in paediatric acute myeloid leukaemia

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Abstract

Objective: To analyse the common causes of death in paediatric acute myeloid leukaemia cases at a tertiary care facility.

Methods: The retrospective study was conducted at the Paediatric Oncology Department of the Combined Military Hospital, Rawalpindi, Pakistan, and comprised newly-registered cases of acute myeloid leukaemia aged <18 years from January 1, 2012, onwards and who completed their treatment before January 31, 2019. Data was retrieved from medical records and was analysed using SPSS 23.

Results: Of the 206 cases, 130(63.1%) were males and 76(36.9%) were females. Overall mean age at diagnosis was 5.96±3.57 years (range: 9 months to 15 years). Of the total, 6(2.9%) patients died before the start of treatment. Of the remaining, 43(21.5%) patients died during 1st induction chemotherapy, and 16(8%) during the post-induction period, with overall treatment-related mortality being 65(31.5%). The main cause of death during the first two weeks of induction was infection, while infection followed by multi-organ failure was the main cause of mortality in the second phase. A total of 130(63%) patients completed the treatment. Overall survival was 81(62.3%) while disease-free survival was 77 (59.2%).

Conclusions: Overall treatment-related mortality rate in paediatric acute myeloid leukaemia cases was found to be high.

Keywords: Paediatric acute myeloid leukaemia, Mortality, Infection, Bleeding, Pakistan.

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Introduction

Acute myeloid leukaemia (AML) in children is rare, accounting for 15–25% of childhood leukaemia with a yearly incidence rate of 5–7/million. In high-income countries (HICs), five-year survival rates of paediatric AML now approach 70% due to recent advances in chemotherapy, risk-based intensive treatment and better supportive care.[1-3] Despite the best possible supportive care, treatment-related mortality (TRM) rates of 7.6 -13.8% have been reported from HICs.[4] However, most children live in low-income countries (LICs) where survival is still very low. The contributing factors to this survival differences are delay in diagnosis, abandonment of therapy, comorbid conditions, including malnutrition, suboptimal supportive care and higher TRM.[4-6]

Because of limited treatment facilities, poor socioeconomic conditions and non-affordability of treatment, high TRM and high relapse rate (RR), the majority of children with AML are not treated in Pakistan. Very limited published data is available on mortality of childhood AML from this part of the world. The majority of published data focusses on morphology and refers to both adults and children.[5]

Understanding of the causes and patterns of mortality during the treatment of AML is important to design strategies to decrease TRM. The current study was planned to analyse the common causes of mortality in paediatric AML in a tertiary care setting.

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Patients and Methods

The retrospective study was carried out at the Paediatric Oncology Department of Combined Military Hospital (CMH) and the Armed Forces Bone Marrow Transplant Centre (AFBMTC), Rawalpindi, Pakistan, and comprised newly-registered AML cases aged <18 years from January 1, 2012, onwards and who completed their treatment before January 31, 2019. CMH and AFBMTC are military hospitals primarily responsible for treating army personnel and their dependents, but because of the scarcity of dedicated facilities for haematology and oncology in the country, a large number of civilians, especially from northern Pakistan, are also treated there.

The study was approved by the institutional review board and the hospital ethics committee, and informed consent had been taken from al the subjects. Details that might disclose the identity of the subjects were omitted. Data excluded related to patients having acute promyelocytic leukaemia (APL), prior chemotherapy or having left during the treatment.

Data noted included age, gender, blood counts at presentation, central nervous system (CNS) disease status, French American-British (FAB) classification,[3,7-9] immunophenotype, genetic abnormalities at diagnosis, chemotherapy protocol, treatment outcome, use of haematopoietic stem cell transplantation (HSCT), last

follow-up, and cause of death.

Detailed medical history was taken, and clinical examination was performed on each case. All the patients were weighed at the time of admission before the start of chemotherapy. The weight was recorded in kilograms and plotted on the standard World Health Organisation (WHO) Z-score chart for age and gender.[10] The patients were categorised as adequately nourished, moderately malnourished and severely malnourished if they had Z score >-2, between ≤-2 and >-3 and ≤-3 respectively. Diagnosis of AML was made on bone marrow morphology and flow cytometric immunophenotyping by standard techniques. Initial workup included full blood count, coagulation profile, and biochemical profile, including hepatic and renal function tests, and cardiac function assessment by performing echocardiography.

Treatment was based on AML17 Paediatric version.[11]

During induction therapy, two courses of anthracycline-based chemotherapy were given; either Daunorubicin 50 mg/m^2 daily on days 1, 3 and 5, Cytarabine 100 mg/m^2 12-hourly on days 1-10 and Etoposide 100 mg/m^2 daily on days 1-5 (ADE-1) or Daunorubicin 50 mg/m^2 daily on days 1, 3 and 5 and Cytarabine100 mg/m^2 12-hourly on days 1-10 (D3A10) were used as induction chemotherapy course 1. Second induction chemotherapy (ADE-2 or D3A8) was the same as chemotherapy course 2, but Cytarabine was given for 8 days.

In post-remission therapy, two courses of high-dose Cytarabine-based chemotherapy ([HiDAC]; Cytarabine 3000 mg/m^2 twice daily on days 1, 3 and 5) were used for consolidation. Patients showing a partial response after induction chemotherapy received Fludarabine 30 mg/m^2 daily on days 1-5, Cytosine Arabinoside 2000 mg/m^2 daily on days 1-5 and Idarubicin 10 mg/m^2 on days 4, 5 and 6 (FLA-Ida) as consolidation therapy.

Patients with high-risk disease, having Human leukocyte antigen (HLA)-matched sibling donor available, underwent allogeneic stem cell transplantation (SCT). The conditioning regimen used consisted of Busulfan, Cyclophosphamide, and Melphalan (BuCyMel) with Methotrexate and Cyclosporine for graft-versus-host disease (GVHD) prophylaxis.

All patients were hospitalised for the initiation of the induction chemotherapy. Tumour lysis prophylaxis with hyper-hydration and allopurinol was commenced 24 hours prior to the start of chemotherapy and continued for at least 4 days. Rasburicase and leukapheresis were not used for any case. Intake, output and electrolytes were monitored carefully.

Subsequent chemotherapy was given as inpatient or in day-care as outdoor cases. Outdoor cases were admitted immediately in case of fever or any other problem. Patients not admitted in the hospital were reviewed at least twice weekly in outdoor clinics. No prophylactic antimicrobials and colony stimulating factors were used during the neutropenic period. However, all cases of febrile neutropenia were treated as inpatients with broad-spectrum intravenous (IV) antibiotics. Fever was defined as a single oral temperature of >38^{o}C or two readings >37.5^{o}C at least 2 hours apart. Neutropenia was defined as an absolute neutrophil count (ANC) of <1000. Febrile patients with ANC< 1000 were treated with a combination of Piperacillin-Tazobactam and Amikacin. Vancomycin or Teicoplanin was added if central venous line infection was suspected. Piperacillin-Tazobactam was swapped with Meropenem if fever continued after 48 hours. Anti-fungal Amphotericin B was added empirically if fever continued beyond 96 hours.

Blood and blood product transfusion was given on a regular basis. Haemoglobin (Hb) transfusion threshold was 8.0 g/dl. Thresholds for platelet transfusion were 10x10^9/L for asymptomatic patients and 20x10^9/L for febrile patients.

The definitions were set in the light of literature.[3,7-9] The diagnosis of AML was based upon morphological analysis of bone marrow (BM) aspirates according to the FAB classifications. CNS involvement was defined as more than five leucocytes per microliter in the cerebrospinal fluid (CSF) in combination with detectable leukaemic cells in the cytospin and/or presence of neurological symptoms, such as cranial nerve palsy.

Complete Remission (CR) was defined as <5% blasts in the BM; absence of blasts with Auer rods; absence of extramedullary disease; absolute neutrophil count >1x 10^9/l; platelet count >100 x 10^9/l; independence of red cell transfusions.

CR with incomplete recovery (CRi) meant CR except for residual neutropenia (ANC<1.0x10^9/l) or thrombocytopenia (<100 x10^9/l).

Partial Remission (PR) meant all haematological criteria of CR; a decrease of BM blast percentage to 5–25%; and decrease of pre-treatment BM blast percentage by at least 50%.

Resistant/Refractory Disease (RD) meant failure to achieve CR or CRi; and only included patients surviving ≥7d following completion of the initial treatment, with evidence of persistent leukaemia by blood and/or BM examination. RD was defined as >5% blasts in the BM after two courses of induction treatment.

TRM was defined as any early death (all deaths occurring before or during induction) or any death as a first event that occurred after this period. TRM was further sub-divided into specific causes: infection, bleeding and other causes, including metabolic derangements and organ dysfunction. An additional category of disease-related death (DRD) was included for patients who died during induction therapy. The local site determined the cause. The phase of TRM was categorised as either; Before induction, meaning before the start of chemotherapy; Induction meaning start of chemotherapy to day 42; and Post-induction (after day 42).

Early death (ED) was defined as a fatal event occurring before or within the first 6 weeks (42 days) of treatment. ED was further subdivided into two types: ED0–14 meaning ED before the start of treatment or within the first two weeks (<15 days) of therapy, which mainly reflected lethal events due to leukostasis and bleeding; and ED_{15-42} meaning ED between days 15–42 of treatment, which mainly reflected deaths caused by complications from infections during aplasia after induction therapy.

Relapse was defined as BM blasts ≥5%; or reappearance of blasts in the blood; or development of extra-medullary disease after attaining CR.

Hyperleukocytosis was defined as white blood cell count (WBC) ≥100 $x10^9$/l at diagnosis. Disease-free survival (DFS) was defined as the time from the achievement of CR until relapse. Overall survival (OS) was defined as the time from the date of diagnosis till last follow-up or death from any cause.

Data was analysed using SPSS 23, and $p<0.05$ was considered statistically significant.

Results

Of the 255 registered cases, 206(80.78%) met the inclusion criteria. Of them, 130(63.1%) were males and 76(36.9%) were females. Overall mean age at diagnosis was 5.96±3.57 years (range: 9 months to 15 years). The mean duration of symptoms before presenting to the oncologist was 52.64±57.69 days (range: 01-425 days).

The most common presenting feature was pallor in 172(83.5%), followed by fever 158(76.7%) and bruising/bleeding 105(51%) cases. Physical examination revealed pallor in 172(83.5%) and visceromegaly in 155(75.2%) patients. Unilateral or bilateral proptosis was documented in 31(15%) cases. The mean WBC count at presentation was 55.67± 68.45$x10^9$/l (range: 1.1-408 $x10^9$/l). Initial WBC of >50$x10^9$/L was seen in 77(37.4%) patients. The mean Hb was 7.59±2.53 g/dl, and the mean platelets count was 55.51±78.40$x10^9$/l.

Table-1: Patient characteristics.

	n (%)
Total number	206 100)
Mean Age 5.96 ± 3.57 years (Range; 9 months to 15 years)	
Less than 5 years	89 (43.2)
>5-10 years	79 (38.3)
>10-15 years	38 (18.4)
Gender	
Male	130 (63.1)
Female	76 (36.9)
Duration of symptoms; Mean 52.64 ± 57.69 days (Range; 1-425 days)	
Presentation	
Pallor	172 (83.5)
Fever	158 (76.7)
Visceromegaly	155 (75.2)
Bruising & Bleeding	105 (51.0)
Bone Pains	30 (14.6)
Proptosis	31 (15.0)
CNS Positive	7 (3.4)
Granulocytic Sarcoma	2 (1.0)
WBC count (x109/L); Mean 55.67 ± 68.45 (Range; 1.1-408)	
(< 50 $x10^9$/L)	129 (62.6)
(> 50 $x10^9$/L)	77 (37.4)
Haemoglobin (g/dl); Mean 7.59± 2.53 (Range; 2.9-15.9)	
Platelets ($x10^9$/L); Mean 55.51± 78.40 (Range; 2-684)	
FAB Classification	
AML-M0	17 (8.3)
AML-M1	22 (10.7)
AML-M2	92 (44.7)
AML-M4	26 (12.6)
AML-M5	11 (5.3)
AML-M6	4 (1.9)
AML-M7	5 (2.4)
Granulocytic Sarcoma	2 (1.0)
AML-DS	4 (1.9)
AML-NOS	23 (11.2)
Cytogenetic Analysis	110 (53.4)
Normal Cytogenetics	53 (48.2)
Favourable	38 (34.5)
AML1-ETO	29 (27.1)
CBFB-MYH11	8 (7.5)
NPM1 Mutation	1 (0.5)
Unfavourable	15 (14.1)
Complex Cytogenetics	12 (12.1)
FUS-ERG	1 (1.0)
Monosomy 7	1 (1.0)
Trisomy 8	1
Trisomy 21	4 (3.6)

Only 7(3.4%) patients had CNS disease. The most common FAB subtype was M-2 in 92(44.7 %), followed by M-4 26(12.6%). Genetic analysis was available in 110(53.4%) cases, and, of them, 53(48.2%) had normal cytogenetics followed by 38(34.5%) favourable and 15(14.1%) unfavourable abnormalities (Table 1).

Six (2.9%) patients died before the start of chemotherapy.

Table-2: Treatment Phases and Causes of death in Acute myeloid leukaemia (AML) (n=125).

Phase of treatment	n (%)	Cause of death							
		Neutropenic Fever	Bleeding	Hyper leukocytosis	Hepatic Failure	Respiratory Failure	MOF	RD	Total
Induction death (day 0-14)	22 (17.6)	7	5	5	1	3	1	0	22
Induction death (day 15-42)	27 (21.6)	11	3	0	1	5	7	0	27
Death in 2nd Induction	11 (8.8)	4	1	0	0	4	2	0	11
Death in Consolidation Phase	5 (4.0)	2	0	0	0	3	0	0	5
Death due to resistant disease	9 (7.2)	0	0	0	0	0	0	9	9
Death due to relapsed disease	51 (40.8)	0	0	0	0	0	0	51	51
Total	125 (100)	24	9	5	2	13	10	60	125

MOF: Multi-Organ Failure; RD: Resistant/Relapsed disease

Of the remaining 200(97%) cases, 114(57%) patients had ADE chemotherapy and 86(43.0 %) had D3A10 chemotherapy. Another 43(21.5%) patients died during first induction chemotherapy, including 27(23.7%) in ADE and 16(18.6%) in D3A10 group. Out of 49(23.78%) cases of ED, 22(45%) were in the first two weeks (ED_{0-14}). The main causes of death during the first two weeks of induction chemotherapy (ED_{0-14}) were infection, bleeding, hyperleukocytosis and respiratory failure. However, infection followed by multi-organ failure (MOF) and respiratory failure were the main causes of mortality in 27(55%) cases, during ED_{15-42}.

Of the 154(77%) patients who received a second chemotherapy course, 11(7.1%) died, including 5(6.4%), 2(3.2%) and 4(30.8%) in ADE, D3A8 and Fla-Ida chemotherapy, respectively. The third course of chemotherapy was given to 138(69%) cases, and 5(3.6%) of them, including 3(2.3%) in HiDAC and 2(25%) in Fla-Ida chemotherapy, expired. Respiratory failure, neutropenic fever and MOF were the main causes of death after induction. Fourth round of chemotherapy was given to 130(65%), including 3(2.3%) patients having BM transplant. There was no death during the 4th course of chemotherapy.

Out of the 157 cases having bone marrow examination after the 1st course of chemotherapy, 117(74.5%) achieved CR, 25(15.9%) had PR and 15(9.6%) had RD. The relapsed rate was 80%, 68% and 43.6% in patients having RD, PR and CR after first round of chemotherapy (p=0.005). In total, 64(32%) patients had resistant or relapsed disease and, of them, 60(93.7%) expired. Bleeding and infection were the main causes of death in relapsed patients (Table 2).

OS and DFS were significantly better in patients with WBC count <50x10^9/l. OS was 58(45%) and 23 (29.9%) (p=0.010) and DFS was 56(43.4%) and 21(27.3%) (p=0.005) in groups having WBC <50x10^9/l and >50x10^9/l respectively.

Discussion

The current study of 206 patients represents the largest cohort of children with AML studied in Pakistan. The TRM in the present study was 31.5%. This includes six cases that died before the start of chemotherapy. Gupta et al.[4] have reported TRM of 23.3% from Central America and Jastaniah et al.[12] have reported 20.8% from Saudi Arabia. The majority of TRM (75.4%) in the present study occurred either before or during induction therapy, resulting in ED rate of 24.1%. This very high ED rate sharply contrasts with the reported ED rates in HICs. The Medical Research Council in the United Kingdom, BFM and Nordic Society of Paediatric Haematology and Oncology (NOPHO) cooperative groups have reported ED rates of 4.1%, 5.4% and 5.9%, respectively.[8,9,13] Two recent studies from the Japanese Childhood AML Cooperative Study Group have reported induction death rates of 0.9% and 1.7%.[14,15] Almost all HICs have shown a decrease in TRM over time. However, despite the use of prophylactic antimicrobials, Gupta et al. found no evidence of a decrease in TRM in paediatric AML treated in LICs of Central America.[4] In the present study, infection, bleeding and hyperleukocytosis were the major causes of early induction deaths in the first 14 days. And neutropenic infection alone and with associated respiratory failure and MOF were the major causes of death during day 15-42 of induction. A similar pattern has been reported by other AML studies, both from HICs and LICs (Table 3).[4,8,9,13,16]

Higher WBC count at presentation, older age and M4 or M5 FAB classification is associated with a higher risk of TRM.[9] In the present study, neutropenic sepsis and hyperleukocytosis were the two leading causes of early induction death. The subgroup having WBC >50x10^9/l at the time of presentation had higher early induction mortality (15.6%) compared to 7.8% in subgroup with WBC

Table-3: Treatment-related mortality (TRM) rates in selected studies in paediatric Acute Myeloid Leukaemia (AML).

Study	Protocol	Treatment era	Death before induction (%)	Death during induction (%)	Death after induction (%)	Total TRM
Molgaard-Hansen[8]	NOPHO AML-84, 88, 93	1984–2003	5.9	7.4	13.3	26.6
Slats[14]	DCOG AML-82, 87, 92/94	1982–1998	4.4	8.7	6.1	19.2
Riley[11]	UK MRC AML 10	1988-1995	0.6	3.5	9.7	13.8
Gupta[4]	AHOPCA AML 1999, 2007	2000-2008	7.5	10.8	5.0	23.3
Ghafoor (Current)	UK MRC AML 17	2012-2018	2.9	20.9	7.8	31.6

<50x10^9/l. OS and DFS were significantly better in patients with WBC count <50x10^9/l. This finding of better CR, OS and DFS with low WBC at presentation is similar to earlier results.[17] In the present study, younger age was associated with a higher mortality rate. Induction mortality was 31.5%, 17.7% and 18.4% in age group <5 years, 5-10 years and >10 years, respectively (p=0.078). FAB AML subtypes have a statistically significant difference in induction mortality rate (p<0.001). The highest early induction death (ED_{0-14}) mortality rate of 45.5% was documented in AML-M5.

An unhealthy body mass index (BMI) is associated with worse survival and high TRM in children with AML.[18,19] Malnutrition is a negative prognostic factor that is often associated with increased morbidity and mortality in paediatric cancer patients.[18] In the present study, TRM was significantly high (p=0.003) in severely malnourished (56.2%) children than well-nourished children (25.5%). OS and DFS were also significantly lower in malnourished children than in well-nourished children. OS was 43.8%, 39.1% and 21.9% (p=0.014) and DFS was 43.0%, 32.6% and 21.9% (p=0.021) in well-nourished, moderately malnourished and severely malnourished children, respectively. This high mortality can be explained on the basis of the fact that malnutrition worsens in cancer patients because of an increased metabolic rate due to disease and neutropenic fever.[20] Moreover, anorexia secondary to chemotherapy-induced nausea and vomiting, and mucositis results in decreased oral intake. Decreased availability of the food of choice in the hospital also results in decreased oral intake. Targeted nutritional interventions for high-risk groups can improve morbidity and mortality as demonstrated in other LICs.[21] Parenteral nutrition for paediatric patients was not available in our hospital. Though commercially available nutritional supplements were advised to children, many of them were not very eager to take them.

Relapsed or refractory disease is the major cause of mortality in AML.[4,5,8] Childhood AML is resistant to therapy in 5–10% or relapses in 30–40% of patients.[22,23]

In the present study, remission status was documented on the basis of the presence of fewer than 5 blasts, and 40(20%) patients did not achieve haematological CR after the first round of chemotherapy. Facilities for minimal residual disease (MRD) detection are not available at our centre. Further, 55(42.3%) cases relapsed post-treatment. This high relapse rate may be associated with MRD positivity after induction chemotherapy. Several studies have demonstrated that children with AML who have residual MRD after induction therapy have a worse prognosis compared to those who are MRD-negative.[13,22] It has been established that allogeneic HSCT is of benefit for all patients in CR2. In the present study, only three patients could have allogeneic HSCT, mainly because of the very limited facilities at our setup. All three of them are surviving without any complication. Majority of relapsed/refractory disease cases died because they were offered only palliative care. Availability of HSCT for high-risk patients on the basis of residual disease and high-risk cytogenetics can improve DFS in AML patients.

Conclusion

Neutropenic fever, bleeding and hyperleukocytosis were the main causes of early induction death, and neutropenic fever with associated MOF was the major cause of mortality in late induction and post-induction TRM. Younger age, lower body weight for age, malnutrition, higher WBC count at presentation and AML-M5 subtype were associated with higher risk of early induction death.

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