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Original Article

Treatment Outcome of Paediatric Acute Myeloid Leukemia: An Experience at Tertiary Care Oncology Unit

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ABSTRACT

Objective: To determine the clinical characteristics and treatment outcome of Acute Myeloid Leukaemia (AML) inPaediatric population in a tertiary care hospital.
Study Design: Prospective longitudinal study
Place and Duration of Study: Pediatric Oncology Ward, Combined Military Hospital, Rawalpindi Pakistan, from Sep 2018 to Aug 2019.
Methodology: **Inclusion criteria**: Newly diagnosed patients of Acute myeloid leukemia under 18 years, admitted to paediatric oncology ward in CMH, from 1st September 2018 to 31st August 2019.
Exclusion criteria: Children above 18 years, those getting treatment from other hospitals and who left treatment.
Results: Data of 33 patients with Acute myeloid leukemia including 24(72.7%) males and 9(27.3%) females was analysed. Majority of children (39.4%)were less than 5 years of age. The most common presenting feature was fever in 27(81.8%) followed by pallor in 25(75.8%) cases. High WBC(>50x109/l) count was observed in 8(24.2%) patients. The most common French-American-British Acute myeloid leukemia Subtype M2 was seen in 16(48.5%).
Treatment-related mortality (TRM) was 7(21.2%) with neutropenic sepsis as the major cause. After a median follow-up of 9 months, OS was 18(54.5%) and DFS was 17(51.5%).
Conclusion: High Treatment related mortality was observed during induction chemotherapy and maximum remission was seen in patients with AML-M2 subtypes and favourable cytogenetics. Malnutrition and high WBC count at presentation were poor prognostic factors.

Keywords: Acute Myeloid Leukemia (AML), Clinical Features, Pediatrics.

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INTRODUCTION

Acute myeloid leukaemia (AML) is a clonal disease of the haematopoietic tissue, characterized by abnormal proliferation of myeloid progenitor cells, resulting in the insufficient generation of normal mature blood cells.[1] AML accounts for approximately 15-25% of paediatric leukaemia worldwide.

Several chromosomal abnormalities and mutations have been detected in AML that are associated with the pathogenesis, diagnosis, and prognosis of the disease.[2] The rapid expansion of malignant cells suppresses normal haematopoiesis and can cause life-threatening thrombocytopenia, anaemia, and immunodeficiency.[3] The core of most AML chemotherapy regimens consists of continuously infused cytarabine with anthracyclines such as daunorubicin.[4] More intense combination regimens, such as FLAG-Ida (Fludarabine, Cytarabine, Idarubicin, and Filgrastim), have higher rates of CR but are associated with increased toxicity, resulting in no improvement in overall survival.[5] Finally, it has been well established that allogeneic HSCT is the post-remission treatment of choice in eligible patients with intermediate or high-risk AML.[6] Resistant disease and relapse are the major causes of treatment failure and mortality in AML.[7]

Prognostic factors predicting treatment outcome include age, sex, performance status, white blood cell count, splenomegaly, presence or absence of bleeding or infection, time to achieve CR and AML subtypes.[8]

In developed countries, due to new developments and advances in chemotherapy five years survival rate of paediatric AML has increased to about 70%.[9,10] Paediatric oncology department at Combined Military Hospital Rawalpindi is treating all types of Paediatric AML coming from all over the country. This study describes the clinical

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characteristics and treatment outcome of childhood AML in Pakistan.

METHODOLOGY

This Prospective longitudinal studywas conducted at Paediatrics oncology ward of the combined military hospital Ethical approval from IREB committee (via letter no: A/28/EC/206/2020) and informed consent from the parents of the children was taken before the start of study. (CMH) Rawalpindi from 1st September 2018 to 31st August 2019. CMH is a tertiary care hospital and provides all type of medical services to military personnel and their families as well as to civilian patients. Paediatric oncology unit is a 40 bedded ward and has all types of oncology facilities including ICU, isolation rooms, inpatient and outpatient care with separate chemotherapy unit and procedure rooms. Sample size was calculated by WHO sample size calculator by using population prevalence proportion of response rate in Acute myeloid leukemia as 50%.[11]

Inclusion Criteria: All the patients admitted in Paediatric oncology ward under 18 years of age with denovo AML were included in the study using non-probability consecutive sampling technique.

Exclusion Criteria: Patients with Down syndrome, APML, Secondary AML, getting treatment from other hospitals and those who left treatment were excluded from the study.

Detailed medical history and clinical examination of each patient was performed. Diagnosis of AML was confirmed on the findings of peripheral blood, bone marrow morphology, flow cytometric immuno-phenotyping, molecular and cytogenetic analysis by standard techniques. Karyotypes were described according to the International System for Human Cytogenetic Nomenclature (ISCN) 2009. Complex karyotypes were defined as those with at least three acquired chromosomal aberrations in the absence of cytogenetic abnormalities listed under the WHO category of AML with recurrent genetic abnormalities. Cytogenetic abnormalities were divided into favourable, intermediate and unfavourable risk groups according to WHO 2016 update. All the patients were admitted for chemotherapy and initially supported with intravenous hydration and allopurinol at least 24 hours before starting chemotherapy to prevent tumour lysis syndrome. Supportive transfusions were given if haemoglobin was less than 8.0 g/dl and platelets less than 20×109 /L.

Treatment was based on the AML 17 Paediatric version. During induction chemotherapy, two courses of chemotherapy containing 3 doses of daunorubicin (50mg/m2) once daily on day 1, 3 and 5 and 20 doses of cytarabine (100mg/m2) twice daily for 10 days in course 1 and 8 days in course 2 (D3A10 and D3A8) were given. After induction chemotherapy remission status was assessed by repeating bone marrow aspiration when peripheral counts were recovered that is absolute neutrophil count (ANC) was >1.0109/L and platelets were >100×109/L. Post remission treatment was followed by 2 courses of high dose cytarabine(HiDAC; Cytarabine 3000mg/m2 twice daily on day 1, 3 and 5) as consolidation therapy. Patients showing partial response (BM Blasts 5-25% and 50% decrease of pre-treatment BM blasts) after induction chemotherapy received FLA-Ida chemotherapy(Fludarabine 30mg/m2 daily on day 1-5, cytosine arabinoside 2000mg/m2 daily on day 1-5 and Idarubicin 10mg/m2 on day 4, 5 and 6) as consolidation therapy.

Post chemotherapy febrile neutropenia was managed with broad-spectrum intravenous antibiotics and supportive transfusions if required. Treatment-related mortality (TRM) was defined as any death occurring within 42 days of starting chemotherapy or any death after this period, which is not due to relapsed or refractory disease while the patient is still on treatment.

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 the last follow-up or death from any cause. Complete remission (CR) was defined as bone marrow blasts less than 5% and evidence of regenerating normal hematopoietic cells. Disease relapse was defined as >5% blasts in Bone marrow after achieving complete remission.

Data was collected regarding demographic characteristics like age, sex and weight, clinical presentation, examination findings, haematological features like complete blood counts, BMA findings, immunophenotyping, cytogenetic analysis, course of the disease, febrile neutropenia, treatment and follow up details, treatment outcome in terms of remission, survival, relapse and mortality. Data obtained was recorded on the preformed questionnaire, electronically formalized, entered into excel spreadsheets and then analysed with SPSS (IBM SPSS version 23). Descr/iptive statistics were applied.

Mean, the standard deviation was used for numerical variables and percentages, frequencies for all categorical variables.

RESULTS

During the study period, 33 newly diagnosed cases of acute myeloid leukaemia were registered at the paediatric oncology department of CMH Rawalpindi. Out of them, 24(72.7%) were males and 9(27.3%) were females. The mean age of presentation was 7.29+4.31 years and 13(39.4%) patients were less than 5 years of age.

Table: Clinical characteristics and outcome of AML patients

	n(%)
Age	
Less than 5 years	13(39.4%)
>5-10 years	8(24.2%)
>10-15 years	12(36.4%)
Gender	
Male	24(72.7%)
Female	9(27.3%)
Presentation	
Pallor	25(75.7%)
Fever	27(81.8%)
Visceromegaly	23(69.7%)
Bruising and lymphadenopathy	13(39.4%)
Bone pains	5(15.2%)
Proptosis	3(9.1%)
CNS positive	3(9.1%)
WBC Count (×109 /L)	49.48+70.63(SD)
(< 50 ×109 /L)	25(75.7%)
(> 50 ×109 /L)	8(24.2%)
Haemoglobin (g/dl)	8.1+2.79
Platelets (×109 /L)	70+85.8
French-American-British classification	
AML-M0	2(6.0%)
AML-M1	3(9.1%)
AML-M2	16(48.5%)
AML-M4	2(6.0%)
AML-M5	4(12.12%)
AML-M6	1(3.0%)
AML-M7	1(3.0%)
AML-NOS	1(3.0%)
Cytogenic Analysis	
Normal Cytogenetics	15(45.5%)
Favourable	8(24.2%)
T(8,21)/AML-ETO	7(21.2%)
inv 16,t(16,16)/CBFB-MYH11	(3.0%)

The most common presenting feature was fever in 27(81.8%) followed by pallor in 25(75.8%) and bruises in 13(39.4%) patients. Only 4(12.1%) patients had CNS disease at presentation. The mean WBC (White blood cell) count at presentation was 49.48+70.63x109/l and hyperleukocytosis was observed in 8(24.2%) patients. Most common FAB AML Subtype was AMLM2 seen in 16(48.5%) patients followed by AMLM5 and AMLNOS in 4(12.1%) and AMLM1 in 3(9.1%) patients. Cytogenetic analysis was performed in all patients, 10(30.3%) patients had culture failure, 15(45.5%) patients had normal cytogenetics and 8(24.2%) patients had favourable cytogenetics. AML1-ETO was documented in 7(21.2%) patients and none of the patients showed an unfavourable cytogenetic abnormality. Assessment of nutritional status revealed 18(54.54%) patients were malnourished.

All the patients received induction chemotherapy with 2 courses, D3A10 and D3A8. At the end of induction chemotherapy, 24(72.7%) patients achieved CR, 3(9.1%) patients had the resistant disease and 6(18.2%) patients had TRM. After 2 courses of induction, 2 patients having resistant disease opted for no more chemotherapy and remaining 25 cases received a third course of chemotherapy including 24 cases having HiDAC and 1 case having FLA-Ida chemotherapy. One patient died during the third course of chemotherapy and the remaining 24 cases had the fourth course of chemotherapy. At the end of treatment, TRM was 7(69.7%), CR was 23(69.7%) and 3(9.0%) had refractory disease. Six patients relapsed after finishing chemotherapy. Out of 9 cases of resistant and relapsed disease, 8 patient died. After a median follow-up of 9 months, OS was 18(54.5%) and DFS was 17(51.5%).

DISCUSSION

Clinical outcome of Paediatric AML has improved over the past few decades. The present study is done to determine the outcome of AML in Pakistan. This study presents an increased occurrence of AML in males as almost 3/4th of our patients were males. Previous studies have also reported the increased incidence of AML in males as compared to females.[12] Age group more commonly affected was below 5 years of age i.e. 13(39.4%) patients were less than 5 years. These findings are similar to other studies. Age of presentation is considered to be another prognostic factor in AML and children less than 10 years of age have better disease outcome as compared to older children.[13,14]

The clinical manifestation of AML is a result of the replacement of bone marrow by myeloblast cells resulting in ineffective haematopoiesis and secondary bone marrow failure. Common presenting symptoms in this study were fever, pallor, visceromegaly, bruising and lymphadenopathy. The presentation with the same signs and symptoms has been reported

in previous studies. Gingival hyperplasia and chloromas which are solid tumour masses of myeloblasts may occur anywhere in the body have also been reported. These cholromas are most commonly associated with AML M2 subtype.[15,16]

Most common FAB AML Subtype was M2 seen in around fifty percent patients in the present study. AMLM2 subtype is considered to have a good prognosis and is associated with better survival in children with AML. Another local study from Pakistan reported AML M4 as the commonest subtype while a study from Saudi Arabia described AMLM1 as the most common subtype.[15,17]

Previous studies have reported that a higher WBC count at presentation had lower OS as compared to the patient with lower WBC count at presentation. Hyperleukocytosis is associated with the development of complications like tumour lysis syndrome, pulmonary and cerebral infarcts etc. Hyper-leukocytosis is commonly associated with monocytic variants and is a medical emergency.[18] In the present study, one-quarter of patients had hyperleukocytosis and survival in these patients was lower as compared to the patients having low WBC count.

Certain genetic changes in haematopoietic precursor cells and specific genetic abnormalities are responsible for developmental of AML. Cytogenetics affect the prognosis and treatment planning of AML. Patients with favourable cytogenetics such as t(8:21), inv(16) and t(15:17) have high OS while patients with adverse cytogenetics like complex cytogenetics, trisomies, monosomies and deletions have poor outcomes.[19] Patients with normal cytogenetics have intermediate prognostic risk.[20] Similarly, in our study maximum remission rate was observed in patients with favourable cytogenetics.Results of the current study show that 27.3% were severely malnourished however, other studies also reported that nutritional status is an important factor influencing survival and TRM in children with AML.[21] Meticulous supportive care with nutritional rehabilitation is necessary to improve survival in this subgroup of patients.

Treatment-related mortality and relapsed related mortality remains a major cause of reduced OS and DFS in AML.[22] Unavailability of supportive and intensive care in under developing countries is the main cause of very high TRM. In our study, TRM was 21.2% of patients. Another study from Pakistan has reported 17.4% TRMin AML. This study was also done in small cohort and results were comparable to our study.[13] TRM reported in developed countries is lower than the findings observed in our study and is reported in the range of 7.6-13.8%. In MRC AML 10 trial TRM was reported to be 14%. The major cause of TRM in our study and in the literatureis neutropenic sepsis.[23]

Maximum remission rate was seen in patients with AMLM2 subtype (91.6%) and favourable risk cytogenetics (100%) but this was not found to be statistically significant (p=0.2 and 0.6). AML M2 subtype and favourable cytogenetics are both associated with a favourable outcome.[24]

Over the past few years, survival for childhood AML has improved due to better understanding of disease biology, improved diagnostic facilities, risk group stratification, better supportive care combined with chemotherapy and stem cell transplantation. Recent studies have reported better survival rates in developed countries where OS is reported as 60-70%.[9] In developing countries like Pakistan, survival rates are still low. In our study, OS was 54.5% and DFS was 51.5 % over a median follow-up of 9 months. Other centres from Pakistan has reported OS of 50%.[14]

LIMITATION OF STUDY

This study has some limitations, due to time constraint; fewer numbers of patients are included. It is a single centre-based study so the results of the current study could not be generalized. Further studies from other centres are required to see the outcome of disease in Pakistan.

CONCLUSION

High TRM was observed during induction chemotherapy and maximum remission was seen in patients with AML-M2 subtypes and favourable cytogenetics. Malnutrition and high WBC count at presentation were poor prognostic factors.

LMIC countries like Pakistan, clinical outcome and survival rate is still not comparable to developed countries. Efforts are required to identify the high-risk patients, modifiable risk factors and improve supportive care to ameliorate the disease outcome and reduce treatment-related toxicities.

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Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

SN & TG: Data acquisition, data analysis, critical review, approval of the final version to be published.

SK & QM: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

FB & FI: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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