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Clinical characteristics and induction outcome of pediatric acute myeloid leukemia (AML) patients treated at Tertiary Referral Hospital, Addis Ababa,Ethiopia: a retrospective cross-sectional study

Dinberu Oyamo[1]* and Gashaw Arega[2]

[1]Department of Pediatrics and Child Health, Faculty of Medicine, Dilla University, Ethiopia.
[2]Department of Pediatric and Child Health, Faculty of Medicine, Addis Ababa University, Ethiopia.

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The outcome of acute myeloid leukemia (AML) has remained a major concern in low- and middle-income countries. It is envisaged that the outcome will be far worse in resource limited settings. However, studies are lacking and many of these low-income countries lack an effective cancer registry. The study was conducted to assess the socio-demographics, clinical patterns and induction outcomes of children with AML. All bone marrow confirmed pediatric AML patients less than 15 years old who took induction chemotherapy was recruited and data was collected in a cross-sectional method. Among the 38-bone marrow confirmed pediatric AML patients, 33 patients took induction chemotherapy and 22 (66.7%) achieved complete remission (CR). Infectious morbidity occurred in 60.6% followed by tumor lysis syndrome in 6.1% and induction mortality occurred in 30.3%. The study found a slight male predominance with the mean age of patients being 8.003 ±3.76 SD years and with a range of 5months-15 years. Fatigue was the most common presenting symptom. The median white blood cell, hemoglobin and platelet count were 39.2 ×103 /mm3, 6.65 g/dl and 25.5× 103/mm3 respectively. A positive correlation between platelet count, FAB classification, nutritional status, age, hemoglobin concentration and induction outcome were found. Late presentation to the haemato-oncologist was observed in our study. Health care professionals should suspect acute leukemia and refer them early for appropriate level of care. Most children achieved complete remission, but it was complicated by high induction mortality and infectious morbidity. Induction and post-induction supportive care is highly recommended for better outcome.

Key words: Pediatric AML, Child, Ethiopia, Induction outcome, Clinical characteristics

INTRODUCTION

Among pediatric acute leukemias, 15 to 20% was acute myeloid leukemias (de Rooij et al., 2015). Reports from cancer registries from African hospitals showed 20 to 25% were acute myeloid leukemias (Molyneux et al.,

*Corresponding author. E-mail: dinbe80@gmail.com.

2017; Kassahun et al., 2020) and in Ethiopia the incidinece in children was not studied. Risk factors for its development are genetic and acquired/environmental. Several risk factors have been described in literature (Pizzo et al., 2016). The approximate age at presentation remains to be determined as data's are pausing on this matter. A single institution study showed the median of age at presentation was 7.4 years (range from 8 months to 15.8 years); and of these 19.3% were greater than 12 years (Viana et al., 2003). Others report the mean and median age at diagnosis of 6.30 ± 3.66 years and 5.5 months to 13 years respectively (Ghafoor et al., 2020; Van Weelderen et al., 2021). Symptoms, signs and laboratory values reported in different studies were also divergent. A 15-years' experience in a single institution in Brazil reports a total of 83 pediatric AML patients with the following clinical characteristics: malnutrition prevalence of 29.4% using Mora method, initial WBC count of $23.3\times10^3/mm^3$ and the most common morphology being M2 FAB class (35%) and M3 FAB class (22%) (Viana et al., 2003). In a children's cancer group study (2013), from a total of 498 patients, splenomegaly, hepatomegaly and chloroma were present in 193 (39%), 190 (38%) and 30 (6%) respectively. The most common FAB morphology was M2 (27%) and M4 (26%); and 84% of patients had WBC $<100,000\times10^3/mm^3$, 48% had Hgb <8g/dl and 82 % had platelet count of $>20,000/mm^3$ (Wells et al., 2002). A report by Tariq et al, found that pallor, fever and bleeding/bruising were the presenting symptoms in descending order of frequency; and similarly on physical examination pallor, organomegaly and proptosis were the most detectable findings in that order of frequency. In the study, mean WBC, Hgb and platelet counts were $53.28\pm68.27\times10^3/mm^3$, 7.66±2.55g/dl, $58.41\pm81.68\times10^3/mm^3$ respectively. The M2 and M4 morphology were the most common FAB sub-types in the study (Ghafoor et al., 2020) Figure 1. The induction outcomes observed, including complications of treatment, across setups were far worse in low and middle income countries (Van Weelderen et al., 2021). According to Nicole A. McNeer et al, induction failure occurred in 10-15% of cases and of whom 33% achieved remission upon re-induction (McNeer et al., 2019). Lower complete remissions were documented in those with platelet count of < 20,000 $/mm^3$, palpable liver, FAB M5 morphology, male gender (Wells et al., 2002). Experience from developing countries showed failed induction was associated with presence of malnutrition, elevated white blood cell count of $>50,000/mm^3$, FAB M0 and adding etoposide in induction regimen, but other variables like platelet count were not associated with failed induction (Viana et al., 2003; Ghafoor et al., 2020). Death during or after induction is the main challenge and it is highly associated with poor supportive care with transfusion, administration of anti-infective medications, and lack of ICU care. Such practices are widely and specifically available in high income countries and have profound effect on induction mortality (Gupta et al., 2012). For many reasons low-income countries have a high rate of induction mortality (Van Weelderen et al., 2021).

METHODOLOGY

Study area

The study was conducted at Tikur Anbessa Specialized Hospital, School of Medicine, College of Health Sciences, Addis Ababa University and is the largest referral hospital in Ethiopia. It was established in 1964, and is now the main teaching center for both clinical and preclinical training of most disciplines. It is also an institution where specialized clinical services that are not available in other public or private institutions are rendered to the whole nation. It serves as the only tertiary hospital where pediatric AML patients are being treated with Haemato-oncologist till recently.

Study design and patient selection

A retrospective study was conducted from July 2016 to August 2020 and data was collected cross-sectionally from June to September 2021. A total of 38 pediatric AML patients were included in this study and the included patients were bone marrow-confirmed pediatric AML patients aged 0 to 15 years who took induction chemotherapy and had post induction bone marrow aspiration results. Patients who were not commenced on induction chemotherapy were excluded from the study. Bone marrow aspirations were done to examine the presence of myeloblasts and myeloblasts with Auer rods and azurophilic granules confirming the presence of AML. Patients who had myeloblasts greater than 20% were classified further using FAB morphological classifications. Flow cytometry and cytogenetic studies were not available during the study period. Upon confirmation of the diagnosis, patients were put on induction regimen with: Cytarabine 100 mg/m^2 daily as intravenous infusion for 07 days and Doxorubicin 50 mg/m^2 daily as intravenous infusion for 03 days (7+3 protocol) or Cytarabine 100mg/m2 IV twice daily as intravenous infusion from Days 1 to 10, Doxorubicin 50mg/m2 IV infusion on Days 1, 3 and 5 and Etoposide 100mg/m2 IV infusion from Day1 to 5 (ADE protocol).

For acute promyelocytic (APML) patients: ATRA (All Trans Retinoic Acid) 25 mg/m^2 per day in two divided doses, Doxorubicin 50 mg/m^2 IV push on each of days 3 through 6 (four days) and Cytarabine 200 mg/m^2 daily as a continuous infusion for days 3 through 9 (seven days) was used as induction regimen. Supportive medications given were ciprofloxacin, cotrimoxazole, acyclovir and fluconazole. Transfusion with blood (whole or packed), platelet and fresh frozen plasma were also administered whenever indicated. No separate ICU care was available while induction treatment. Response was assessed after repeat bone marrow done one month after the beginning of the protocol; and if blasts in the bone marrow have decreased by more than 95% or blasts <5%, and for APML: in addition to the above, absence of Auer rods in blasts, then the patient was considered to have complete response (CR).

Data collection

Individual patient charts were retrieved from card room after getting names and medical record numbers from inpatient registry. Data were collected using structured form that contained socio demographic and clinical characteristics, induction chemotherapy outcomes (including remission status, morbidity and mortality). Variables included in the data collection form were obtained after extensive literature search of similar studies. Socio-demographic

Table 1. Socio-demographic characteristics of the patient admitted to TASH Haemato-Oncology unit with AML, 2016 – 2020.

Variables		Frequency	%
Sex	Male	21	55.3
	Female	17	44.7
	Total	38	100
Age (years)	0-2	4	10.5
	2-10	23	60.5
	10-20	11	28.9
	Total	38	100
Region	Oromia	14	36.8
	Amhara	11	28.9
	Addis Ababa	7	18.4
	SNNPR	4	10.5
	Somali	2	5.3
	Total	38	100

and clinical characteristics included were patients age, sex, address, duration of symptom, patient reported symptoms, and physical examination findings with focus on hepatomegaly, splenomegaly and chloromas. Laboratory data collected were leukemic morphology using FAB classification and patients initial white blood cell (WBC), platelet and hemoglobin values. Type of protocol used for induction chemotherapy and co-morbidities (infection and nutritional status) were also extracted. Post induction remission status and post induction mortality and morbidities (like infection and tumor lysis syndrome) were also included in the data collection process.

Data analysis

Data was cleaned and entered into Epi data version 3.1 and exported to SPSS version 25 for analysis. Output data were reported as mean, median standard deviation for continuous data and percentage was used for categorical one. Association between independent and dependent variables was assessed with P-value less than 0.05.

Ethical issue

The research was conducted after obtaining approval from the Ethical Review Board of the Institution. Data was collected from secondary sources which were the patients' charts; and the issue of consent from patients and /or parents was not needed. Data were collected based on declaration of Helsinki excluding patient card number and names and ensuring strict confidentiality.

RESULTS

Socio-demographic characteristic of pediatric AML patients treated at Tikur Anbessa Specialized Hospital

A total 38 pediatrics AML patients were included in this study; 21 (55.3%) were males with a male to female ratio of 1.23:1. The mean age of the patients at diagnosis was 8.003 ±3.76 years with the range of 8 months to -15 years old. Most of the children came from Oromia region, accounted for 36.8% of children and 28.9 % of children were from Amhara region (Table 1).

Clinical Characteristics of pediatrics AML patients

The median duration of illness was 30 days and ranged from 20.75 to 90 days. Majority of patients presented with fatigue, accounted for 29 (76.3%), the other presentations were orbital swelling in 6 (15.8%), abdominal swelling in 2 (5.3%) and nasal bleeding in 1 (2.6%). Physical examination revealed hepatomegaly in 15 (39.5%), splenomegaly in 12 (31.6%) and chloroma in 6 (15.8%) cases. Severe acute malnutrition (SAM) was observed in 5 (13.2%) and Moderate Acute Malnutrition (MAM) in 2(5.3%).The median WBC count was 39.2 $\times 10^3/mm^3$ ranged from 6.05 to 79.7 $\times$ $10^3/mm^3$. White blood cell count above 50,000/mm^3 was observed in 15 (39.5%) patients. The median hemoglobin was 6.65 g/dL, ranging from 4.67-8.82 g/dl. The median platelets count was 25.5$\times$ $10^3/mm^3$, ranging from 16.25 $\times 10^3$ - 66.25$\times 10^3$ /mm^3. Initial platelet count of less than 20×10^3 /mm^3 was observed in 36.8% of patients. Regarding the FAB morphology 12 patients had M2 (31.6%) and M4 (31.6%) morphology, followed by M3 in 5 (13.2%), M1 in 5 (13.2), M5 in 3 (7.9%) and M0 in 1(2.6%) (Table 2).

Induction outcome of children with AML

For all patients, 7+3 protocol chemotherapy was started

Table 2. Clinical characteristics of the patient in admitted to TASH Haemato-Oncology unit with AML 2016 to 2020.

Variables		Frequency	%
WBC count	<10,000	13	34.2
	10,000-99,000	15	39.5
	>100,000	10	26.3
	Total	38	100
Platelet count	<20,000	14	36.8
	>20,000	24	63.2
	Total	38	100
Initial symptoms	Fatigue	29	76.3
	Nasal bleeding	1	2.6
	Orbital swelling	6	15.8
	Abdominal swelling	2	5.3
	Total	38	100
Palpable liver	Yes	15	39.5
	No	23	60.5
	Total	38	100
Palpable spleen	Yea	12	31.6
	No	26	68.4
	Total	38	100
Chloroma	Yea	6	15.8
	No	32	84.2
	Total	38	100
FAB	Mo	1	2.6
	M1	5	13.2
	M2	12	31.6
	M3	5	13.2
	M4	12	31.6
	M5	3	7.9
	Total	38	100
Malnutrition	Normal	31	81.6
	MAM	2	5.3
	SAM	5	13.2
	Total	38	100
Infection or death before induction	Infection	25	65.8
	Dead	5	13.2
	No	8	21.1
	Total	38	100

for 28 (84.8%), Acute promyelocytleukemia protocol to 4 (12.1%) and ADE to 1(3.1%) case. Induction mortality occurred in 10 (30.3%) of pediatrics AML patients (Tables 3 and 4). Bone marrow aspiration done at 1 month of induction showed 22 (66.7%) patients achieved morphological complete remission and 33.3% patients had failed remission. Infection occurred in 20/33(60.6%) of patients, tumor lysis syndrome (clinical and lab) occurred in 2/33 (6.1%) (Figure 1).

Correlation

In this study, we found a weak negative correlation between WBC count, hepatomegaly, splenomegaly and outcome of induction. In subsequent regression model,

Table 3. Pediatric AML induction outcome, Ethiopia, 2016-2020.

Variables		Frequency	%
OUTCOME-Remission	>5%	11	33.3
	<5%	22	66.7
	Total	33	100
Treatment related morbidity or death after induction	Infection	20	60.6
	Died	10	30.3
	TLS	2	6.1
	No	1	3.0
	Total	33	100
PROTOCOL	7+3	28	84.8
	APML	4	12.1
	ADE	1	3.1
	Total	33	100

Table 4. Correlation between various variables and pediatric AML induction outcomes, 2016-2020.

Induction outcome	
AGE	0.10237
WBC	-0.10812
HGB	0.102104
PLT	0.18132574
DUR	0.210793
FAB	0.249149
NUTR	0.170717
LIV	-0.18365
SPL	-0.17148
CHL	0.076932
SEX	0.16855

WBC-white blood cell, PLT-platelet, HGB- hemoglobin, DUR-duration of illness OUT- induction outcome FAB=French American British, NUTR- nutrition, LIV- liver, SPL- spleen, CHL- chloroma.

no variable was statistically significant. Similarly, there was a weak positive correlation between platelet count, FAB morphology, nutritional status, age, hemoglobin concentration, and induction outcome. With multiple logistic regression model, the variables were not statistically significant.

DISCUSSION

Data on pediatric AML is lacking in Ethiopia. Reports from systematic review of literature and Pakistanian study showed median and mean age of 5.5-13 years and 6.3±3.66 years respectively. These reports are consistent with the current study where we found mean age range from 8.003± 3.76 years with the range of 7 months to 15 years with little effect on the outcome of induction chemotherapy as described in their study (Ghafoor et al., 2020; Weelderen et al., 2021). The disease affects more males with no much effect on treatment outcomes like other studies (Viana et al., 2003; Ghafoor et al., 2020; Weelderen et al., 2021). Late presentation to the cancer treatment center was observed in the current study but the effect was not significant in terms of induction outcome or treatment related mortality. The most common presenting symptom reported was fatigue followed by abdominal swelling and bleeding, which was consistent with available literatures (Wells et al., 2002). In the study we have found that the median WBC count was 39.2 x 10^3 /mm^3 with IQR of 6.05 x 10^3-79.7 x 10^3 which was

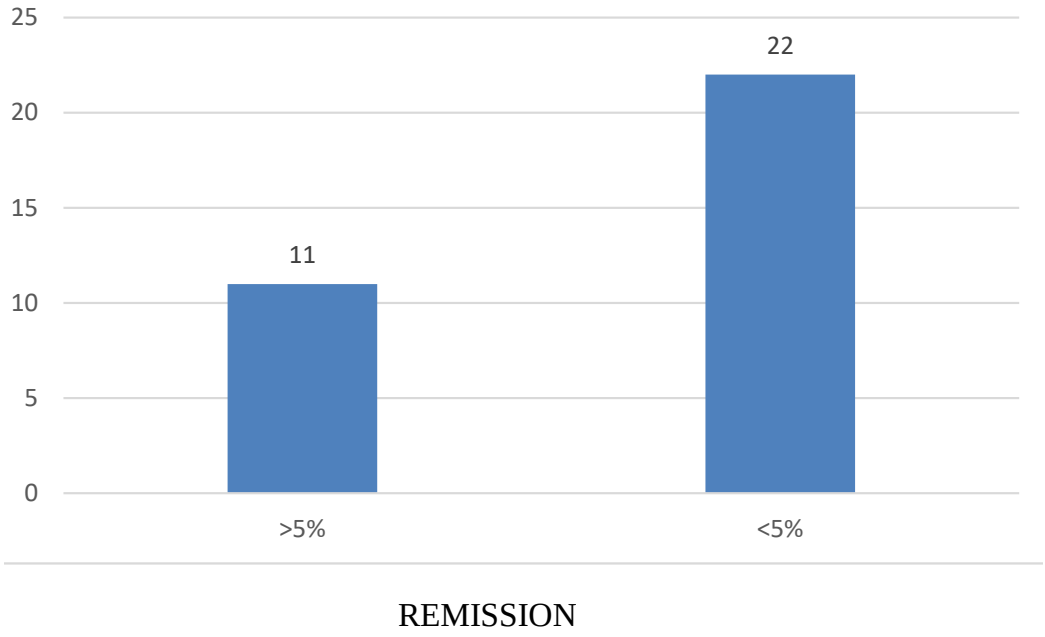

Figure 1. Outcome of AML patients after induction in TASH Haemato-Oncology unit, 2016-2020.

consistent with other studies (Viana et al., 2003; Ghafoor et al., 2020; Gupta et al., 2012; Inaba et al., 2008). Severe anemia is frequently observed (hemoglobin of 3.6g/dl) with median hemoglobin of 6.65g/dl (IQR 4.67-8.82g/dl), which is in line with previously published reports that shows being anemic is not a predictor of induction outcome, rather a predictor of treatment-related mortality and morbidity (Gupta et al., 2012; Inaba et al., 2008).

In our study we have found that 24/38 (63.2%) patients have platelet count of >20x10^3 /ul and 14/38(36.8%) have <20x10^3/ul and most studies report higher platelet count. (Ghafoor et al., 2020; Wells et al., 2002; Gupta et al., 2012) FAB M2 and M4 morphological sub-types were the commonest subtype identified in this study which is similar to other studies (Weelderen et al., 2021; Wells et al., 2002; Gupta et al., 2012; Rasche et al., 2018; Rubnitz et al., 2004; Molgaard-Hansen et al., 2010; Slats et al., 2005; Draga et al., 2006; Testi, 2005; Stéphane et al., 2004; Ortega et al., 2005; Kutny et al., 2017). In our study, complete morphologic remission rate was 66.7%, this is much lower as compared to developed countries (Barbara et al., 2019; Tierens et al., 2016; Rubnitz et al., 2010) owing to the presence of high quality supportive care in these countries,but it is the same as low middle income countries (Van Weelderen et al., 2021) and even higher than sub-saharan African countries (Kersten et al., 2013; Weelderen et al., 2021; Nzamu et al., 2020) which can be explained by the enhanced supportive care given ,though not readily available, with anti-infective medications and transfusion services. Post induction death (30.3%) and Infectious morbidity (60.6%) were very high as compared to other studies (Viana et al., 2003; Wells et al., 2002; Ghafoor et al., 2020; Van Weelderen et al., 2021; McNeer et al., 2019; Gupta et al., 2012.), this is attributed to the lack of isolated ward and unavailability of isolated ICU care. Studies showed high initial WBC count, low platelet count, presence of malnutrition and FAB M5 morphology were associated with failed remission (Viana et al., 2003; Ghafoor et al., 2020; Wells et al., 2002). In our study we found no statistically significant association for the above variables, and this might be due to the small sample size studied and the retrospective nature of the study. Although it was not the scope of the current study, we encourage further prospective cohort studies to explore variables that significantly affect induction outcome.

CONCLUSION AND RECOMMENDATION

The median duration of illness in children with AML was 30 days and presented to haemato-oncology center as late as 90 days. Primary health care professionals should be vigilant of any abnormal blood values and should refer them for appropriate diagnosis and care. The mortality rate in pediatric patients with AML is high and is mainly attributed to infection; hence isolated care is highly recommended and effective interventions have to be practiced to prevent infections and subsequent deaths. Low platelet count at presentation resulted in failed induction. Optimizing blood product transfusion practices is crucial for preventing bleeding outcomes and to achieve a successful remission induction.

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CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

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