Clinical Features and Treatment Outcome of Pediatric Acute Promyelocytic Leukemia in Combined Military Hospital, Dhaka

Islam MA[1], Nahar K[2]

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ABSTRACT

Background: Acute promyelocytic leukemia (APML) is a relatively rare blood disease in children that is highly curable with current treatment strategies. It is a distinct type of AML characterized by chromosomal translocations involving the retinoid acid receptor (RAR-A) gene on chromosome 17. It accounts for 20-25% of all AML cases. The aim of this study was to describe the diagnostic features of pediatric APL and the result with ATRA and ATO based protocol.

Methods: It was a descriptive type of cross-sectional study with purposively selected 10 newly diagnosed APML patients treated in the Pediatric Oncology unit of the Department of Pediatrics in CMH Dhaka during the period of 2018 to 2022. Diagnosis of all patients were done by aspirating bone marrow morphology and cytogenetic t(15:17) or t(11:17) transcript. Informed written consent was taken from parents. Data were collected by semi-structured questionnaire and analyzed by Statistical Package for Social Sciences (SPSS version 25).

Results: Among 10 respondents median age was 4.2 years with female predominant (60%). Most common clinical presentations at diagnosis were fever (100%), bleeding manifestations (100%), Hepatomegaly (90%) bony tenderness (90%), splenomegaly (70%), and lymphadenopathy (70%). Almost all the patients had low Hb & low platelet count & WBC were variable. Cytogenetic analysis revealed 90% had PML/RARA positive & 30% had FLT3/ITD positive. All of these patients were treated with trans-retinoic acid (ATRA) based treatment, which led to 80% cases ATRA syndrome. Other common toxicities noticed febrile neutropenia (50%), severe headache (30%), hyperpigmented skin (10%), pseudotumor cerebri (10%) and others. There were 10% relapse cases, which later proceeded to relapse protocol and were in remission. The remaining 90% of patients were alive and in remission until the last day of follow-up.

Conclusion: With ATRA-based treatment overall survival is good achieved remission and only 10% of patients developed relapse.

Keywords: Acute promyelocytic leukemia (APML/APL), Pediatric, Arsenic trioxide (ATO), ATRA, Outcome

1. Maj Gen Md Azizul Islam, FCPS, MACP, FRCP(LPR) 2. Lt Col Kamrun Nahar, FCPS.

INTRODUCTION

Acute myeloid leukemia (AML) is a heterogenous hematological malignancy involving the clonal expansion of myeloid blasts in the bone marrow and peripheral blood with possible spread to liver and spleen.[1] Approximately 20-25% of childhood leukemias are of myeloid origin and they represent a spectrum of hematopoietic malignancies.[2] Acute promyelocytic leukemia (APL or APML) is a distinct type of AML that is characterized by chromosomal translocations involving the retinoid acid receptor á (RARA) gene on chromosome 17.[3] It is considered as a distinct subtype because of several factors, including clinical presentation of coagulopathy and unique morphological characteristics (French-American-British [FAB] M3 or its variants), unique molecular etiology as a result of the involvement of the RARA oncogene and unique sensitivity to the differentiating agent tretinoin (ATRA) and to the proapoptotic agent arsenic trioxide (ATO).[1]

APL itself covers about 4-8% of all childhood AML.4 There are many variants, most commonly APL hyper-granular (M3) and APL microgranular variant (M3v). Their cytoplasm of promyelocytes demonstrates a fine granularity, and nuclei are often folded. M3v has the same clinical, cytogenetic, and therapeutic implications as FAB-M3.[2] Immunophenotype characteristics of APL cells show CD13 and CD33 expression and also rarely express HLA-DR, CD34, CD10, CD7, CD11b, and CD14.5 Chromosomal abnormalities like gene fusion product PML-RARA t(15;17)(q24;q21) is found in 90% of cases. Quantitative RT-PCR allows identification and is used for monitoring treatment response and early detection of molecular relapse.6 Other much less common translocations involving the retinoic acid receptor alpha can also result in APL (e.g., t(11;17)(q23;q21) involving the PLZF gene)[7,8] in 5% of patients.9 Identification of cases with the t(11;17) (q23;q21) is important because of their decreased sensitivity to tretinoin.[7] For APL, FLT3 ITD and point mutations occur in 30% to 40% of children and adults.[10-13] Presence of the FLT3 ITD mutation is strongly associated with the microgranular variant (M3v) of APL and with hyperleukocytosis.[12,14-16] This mutation portends a high risk of relapse and may allow for targeted therapy.[17-20] Based on an assessment of prognostic factors; patients were grouped into low-risk & high-risk.[21]

Pediatric APL is one of the most curable subtypes of AML in childhood.[22] The unique features of APL require a high index of suspicion at the time of diagnosis to initiate proper supportive care and to avoid coagulopathic complications during the first days of therapy.[23] APL treatment differs from the other AML subtypes.[22] With current treatment protocols consisting of ATRA and anthracyclines along with ATO-based therapy made childhood APL a highly curable disease with overall remission rates is 85-95%, 5 year overall survivals (OS) is 75-90% and 5-year event-free-survivals (EFS) is 72-83%.[21]

MATERIALS AND METHODS

This descriptive type of cross-sectional study was conducted in the Paediatric Oncology Unit of the Department of Paediatric in Combined Military Hospital (CMH), Dhaka, Bangladesh. 10 diagnosed cases of childhood APML below 12 years of age during the period of 2018 to 2022 from hospital-based cancer registry were enrolled purposively and analyzed them. The data were collected after obtaining informed consent from parents. The data were collected and analyzed according to the study objective through Statistical Package for Social Sciences

(SPSS version 25). It is to be mentioned that, paediatric data set included data from the paediatric cancer registries collecting data in children below 15 years but here in this study data were collected for children who have completed 12 years because pediatric department of CMH Dhaka is designated for the 0 to 12 years age group. Here inclusion criteria were a) all newly diagnosed APML patients b) age completed 12 years and exclusion criteria were a) age above 12 years and b) patient with other sub types of AML c) presence of serious cardiac, hepatic, pulmonary or hepatic disease.

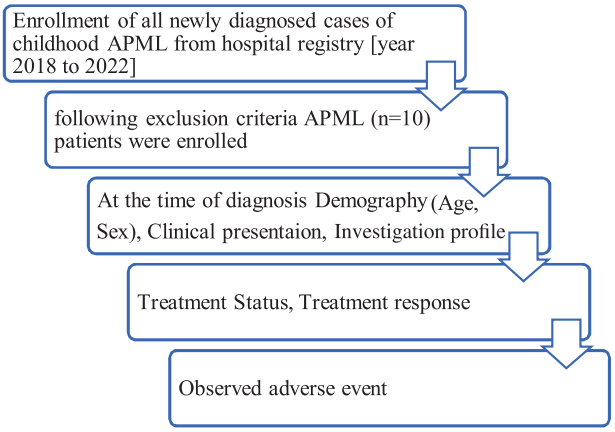

Fig-1: Study flow chart

The morphological criteria defining APL are: >20% promyelocytes are hyper granular in bone marrow aspirate and presence of auer rods. PML-RAR-α rearrangement also seen in bone marrow aspirate using reverse RT-PCR at the time of diagnosis, after induction. Immunophenotypic and cytogenetics data analyses were performed at the time of diagnosis. After confirmation of diagnosis, the patients were categorized into risk groups based on total leukocyte count (TLC). Patients with TLC 10x109/L or more were categorized in high-risk group and those having a lower count were assigned to standard risk group.

All patients were treated with ATRA & ATO based therapy. As it is a medical emergency, all patients were admitted in the hospital during diagnosis. All events were recorded retrospectively observing hospital records. Toxicities were graded according to the National Cancer Institute's Common Toxicity Criteria, version 2.14. Treatment protocol and supportive care were started according to modified protocol of the International Consortium for Childhood (ICC) APL, sponsored by AIEOP (Associazione Italiana di Ematologiaed Oncologia Pediatrica). The aim of this study was to describe the diagnostic features of pediatric APL and the result with ATRA and ATO based protocol.

RESULTS

In this study 10 cases were enrolled and analyzed. Demographic characteristics of all patients (n=10) has been plotted in Table-I where female was found predominant and male female ratio 0.66:1. Age distribution revealed '5-9 years age group' are most common group. Risk group distribution revealed standard risk 60% and high risk 40%.

Table-I: Demographic features of APML patients (n=10)

Trait	Frequency	Percent
Gender		
Male	4	40
Female	6	60
M: F	0.66:1	
Age Group		
0-4 years	3	30
5-9 years	6	60
>10 years	1	10
Risk Group		
Standard (WBC ≤10,000 cells/μL)	6	60
High (WBC ≥10,000 cells/μL)	4	40

Table-II: Distribution of patients by clinical features of APML (n=10)

Name of presenting features	Frequency	Percent
Fever	10	100
Hemorrhagic manifestation	10	100
Mucosal hemorrhage	8	80
CNS hemorrhage	0	0
H/O blood transfusion	2	20
Bony tenderness	9	90
Hepatomegaly	9	90
Splenomegaly	7	70
Lymphadenopathy	7	70
Hypertension	4	40
Gum hypertrophy	2	20
Arthralgia	3	30

*Multiple responses

Table-II reveals clinical features of these patients which include fever in most cases (100%), bleeding/coagulopathy (100%) & Organomegaly like hepatomegaly (90%), splenomegaly (70%) and lymphadenopathy (70%) patient. Bony tenderness was seen in 90% patients. Investigation findings have been narrated in Table-III.

Table-III: Distribution of patients by investigation profile of APML (n=10)

Variables	Frequency	Percent
CBC		
• Anemia (Hb <10 gm/dl)	10	100
• Thrombocytopenia (<150X10^9/L)	10	100
• Leukocytosis	10	100
➢ ≤10 x 10^9/L	4	40
➢ >10-20 x 10^9/L	4	40
➢ >20 x 10^9/L	2	20
Blast in peripheral blood	10	100
<1-20%	3	30
21-40%	3	30
41-60%	2	20
> 61%	2	20
Bone marrow morphology		
• Blast >25-50%	3	30
• Blast >50%	7	70
Bone marrow immunophenotyping		
CD13 +ve	7	70
CD33 +ve	5	50
CD 117 +ve	9	90
HLA DR -ve	9	90
Cytogenetic findings		
PML/RARA Negative or not Evaluated	1	10
PML/RARA +ve with t(15;17), (q21;q22)	9	90
FLT3/ITD +ve	3	30

On average, at diagnosis WBC counts were ≤ 10x109/L for 40%, 10-20X109/L in 40% patients and >20x109/L in 20%. All of the patients had platelet counts <150x109/L. In all cases, the bone marrow aspirate underwent morphological analysis, and the median percentage of abnormal promyelocytes at diagnosis was 68% with a range between 27-87.5%. The test for the PML-RAR-α transcript was positive in 90% of cases, one patient failed to give a proper result due to sample loss. But this patient responded to the ATRA treatment and showed morphological remission.

Table-IV: Distribution of patients by adverse events in APML (n=10)

Trait	Frequency	Percent
Differentiation (ATRA) syndrome	8	80
Febrile neutropenia	5	50
Severe headache	3	30
Severe pain	2	20
Pseudotumor cerebri	1	10
Hyperpigmented skin	2	20
Cheilitis	2	20
Visual disturbance due to retinal hemorrhage	1	10
Elevated liver enzymes (>4 folds of upper normal limit)	5	50
Ischemic stroke	1	10

*Multiple responses

ATRA syndrome was identified in 80% patients; 10% reported severe headache and severe bone pain. Febrile neutropenia, an elevated liver enzyme found in 50% approximately. ATRA syndrome seen mostly in induction phase. Febrile neutropenia occurred in 100% children after first chemotherapy cycle, 60% after the second cycle & 50% after the third cycle (Table-IV).

Table-V: Distribution of patients by treatment outcome of childhood APML (n=10)

Treatment Evaluation	Frequency	Percent
Rx receive	10	100
Remission	10	100
- Clinical remission at induction	10	100
- Peripheral remission at induction	9	90
- Peripheral remission after consolidation 1	1	10
- Bone marrow remission (<5% blast in morphology)	10	100
Minimal Residual Disease (MRD) at end of induction therapy		
- Positive	0	0
- Negative	3	30
- Not done/ Not available	7	70
Resolution of coagulopathy at induction	9	90
Relapse	1	10
Deaths	0	0
Overall survival	10	100
Refused treatment	0	0
Alive	10	100
Lost to follow up	1	10

In Table-V treatment outcome of all 10 patients were described. All of the patients achieved complete remission and proceeded to consolidation therapy followed by maintenance therapy. One patient relapsed and no deaths occurred. The average follow-up period for this study was 12 months.

DISCUSSION

Every year new cases of childhood cancer exceed 2 million globally and the majority of them (>80%) belong to the developing world.[24,25] In developing countries every year childhood cancer happens to be increased by 30%.[26] The situation of our country's children with cancer is similar to other developing countries.[27] Still now no national population-based childhood cancer registry is available for us.[28,29]According to World Child Cancer Report 2005, Bangladesh has some 1.3 to 1.5 million childhood cancer patients.[30,31] Available scenario in nearby countries like Pakistan incidence is 100 per million and in India, it is 64 per million in <15 years of age.[32,33] In India, cancer is the 8th most common cause of death among children between 5 and 14 years of age, covering 2.9%.[34] In 2010, the national pediatric cancer death rate was 39 for children aged 0 to 14 years.[34]

Ferdousi et al reported, per year average of 17 malignant cases came to the pediatric oncology unit of CMH Dhaka. The overall incidence rate is about 3.6 per ten thousand per year, among them ALL 8 patients per year (1.7 per ten thousand per year), CNS tumors 1.4 patients per year (0.29 per ten thousand per year) and other solid tumors were 6.6 patients/year (1.4 per ten thousand per year).[35] Worldwide acute leukemia (32.5%) appears to be the most common cancer in children aged 0-14 years. The highest incidence was recorded in Asia (62.6%).[36] The next common cancer was CNS tumor and Lymphoma. In pediatric oncology unit of CMH Dhaka incidence of acute leukemia cases were 89(52.4%) patients.[35] These results are quite similar to the results from BSMMU30 and NICRH.[37]

In this study analyses were limited only with diagnosed case of APML. In pediatric oncology unit of CMH Dhaka only 10 patients were treated. Gender distribution revealed, male 40%, female 60%; male-female ratio 0.66:1. Dorantes-Acosta et al found equal distribution in both gender.[3] Age group distribution showed 60% children belongs to 5-9 years age group; 30% of 0-4 years and 10% of >10 years. Dorantes-Acosta et al reported mean age 6.7 in their study.[3] Eshita et al found similar findings in this country.[38] Testi et al reported 10.3 years was median age group. In the present study

median age was 5.6 years.[21] Risk group distribution showed 60% of standard risk group and 40% belongs to high-risk group. Risk group stratification was based from National Cancer Institutes.[39] Dorantes-Acosta et al also found high risk group higher (63%).[3] All studied patients presented with thrombocytopenia (<150x109/L) similar to other researchers findings.[3,38] Almost all (90%) the patients had PML/RARA positive with t(15;17), (q21;q22) transcript but no (11:17) transcript was found. FLT3/ITD abnormalities were seen in 30% patients.

Toxicity mostly occurred during the induction. Most common features found ATRA syndrome (80%), febrile neutropenia (50%), severe headache (30%), elevated liver enzyme (50%). Incidence of differentiation/ATRA syndrome are commonest findings by other studies too reported 13-16% in Europe, 20% in Spain, 6% in Italy, and 29% in India.[40-43] Eshita et al also found 58% patients having febrile neutropenia with sepsis.[38] The rate is much higher than study done in Canada (30%),[44] India (33%).[45]

Complete remission was achieved in 100% of patients but later 1 patient relapsed and with relapse protocol, he is now in remission. Overall survival (OS) was 100%. Eshita et al[38] found remission after induction was 90% & Testi et al[21] found OS 95%. In the present study, only 30% patients underwent minimal residual disease evaluation and found negative for malignant cells. PML/RARA transcript was done only in 2 patients after induction phase and found negative.

It is important to emphasize that these patients should not be treated similarly to other AML patients and it presented with medical emergency features because of the biology of the disease. 2 Data demonstrate that intensified ATRA & ATO based chemotherapy is effective for pediatric APL including very young patients. The results have been favorable and also demonstrated that this subtype of AML is highly curable and even in developing and resource limited countries like Bangladesh.

CONCLUSION

Present study demonstrates that with current treatment approach curability of pediatric APML patients are high. Hundred percent patients achieved remission and ninety nine percent patients maintained this status. Only ten percent patients relapsed. No death occurred. Common toxicities were observed like neutropenic sepsis, severe hemorrhage, differentiation syndrome, pseudotumor cerebri.

LIMITATION OF THE STUDY

The sample size was small, has been collected retrospectively and only observed in a single hospital and follow up period was short. It needed long-term evaluation to report five-year survival rates.

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