Early response to treatment and adverse events in pediatric acute promyelocytic leukemia: a single center observational study in Bangladesh

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Abstract

Abstract: Objective: Pediatric acute promyelocytic leukemia (APL) is one of the most curable subtypes of acute myeloid leukemia of childhood. But it may have many early complications, especially in developing countries. This study aims to describe the early course of disease and adverse events in the management of pediatric APL cases in Bangladesh. Method: This prospective observational study was conducted in the Department of Pediatric Hematology and Oncology, Bangabandhu Sheikh Mujib Medical University, Dhaka from September 2017 to March 2019. The study included twenty PML:RAR-α (ProMyelocytic Leukemia-Retinoic Acid Receptor-α) positive APL cases. After taking informed written consent from the parents, patients were treated with risk directed ATRA (All-trans-retinoic acid) based chemotherapy. Results: The mean age was 6.8 years with male-female ratio of 1:1.2. Hemorrhagic manifestations were observed in 95% of patients, with mucosal bleeding in 55% and CNS hemorrhage in one patient. Fever was the present in 95% of children. Most of the children (65%) were in the high risk group. DIC was present in 90% cases and mean D-Dimer was 4.1 µg /ml. Overall 90% (18/20) patients achieved clinical and peripheral remission with resolution of coagulopathy. But only 75% patients (15/20) reached maintenance therapy in bone marrow remission. Causes of deaths were neutropenic sepsis, intracranial hemorrhage, complicated differentiation syndrome and stroke. Neutropenic sepsis was the most common adverse event. Conclusion: In Bangladeshi pediatric APL patients, neutropenic sepsis is the most common and also the most severe adverse event. Key words: acute promyelocytic leukemia, children, response to treatment

Abbreviation	Full term
APL	Acute promyelocytic leukemia
ATRA	All-*trans*-retinoic acid
DIC	Disseminated intravascular coagulation
PML:RAR-α	Promyelocytic Leukemia : Retinoic acid receptor-α

Introduction:

Pediatric Acute Promyelocytic leukemia (APL) is the most curable subtype of acute myeloid leukemia (AML) of childhood, due to its unique responsiveness to the All-*Trans*-Retinoic-Acid (ATRA), a vitamin

A derivative[1]. Currently, APL is classified by World Health Organization (WHO) as AML with recurrent genetic abnormality, a reciprocal balanced translocation involving Retinoic acid Receptor-α (RAR-α) gene at chromosome 17q21 and usually associated with features of disseminated intravascular coagulation (DIC)[2]. Malignant promyelocytes release tissue factor, cancer procoagulant and microparticles causing abnormal, excessive activation of coagulation cascade. Also, there is excessive fibrinolysis due to release of plasminogen activators, Annexin II and proteases; and endothelial damage due to release of interleukin 1β, tumor necrosis factor α and vascular endothelial growth factor, leading to characteristic DIC[3,4,5,6]. When ATRA is administered, it causes conformational change in malignant RAR-α gene and removes the blockage in promyelocyte differentiation[7,8]. Although ATRA decreases the inappropriate activation of coagulation cascade, low level of fibrinolysis and expression of cytokines may continue for some period[9]. APL should be considered as a medical emergency, because hemorrhagic complications within the first hours and days are frequent and can be lethal. The treatment must be started immediately with ATRA, even before confirmation of the diagnosis has been made[1]. With current treatment protocols consisting of ATRA and anthracyclines, clinical remission rate in pediatric APL is 85-95%, 5 year overall survivals rate is 75-90% and 5 year event-free-survivals rate is 72-83%[10-17]. Most of the studies suggest that higher leukocyte count is the single most significant predictor of poor outcome[18,19]. In most of the current management protocols, the patients are categorized into standard and high risk groups based on total leukocyte count, which is known as Sanz criteria[20]. Despite excellent long term outcome, early deaths (ED), defined as deaths within 30 days of diagnosis, were found to occur at high rates in adult APL patients, usually from severe hemorrhages, which were 26% in USA and 30% in Bangladesh[21,22]. Early death rate is also high in pediatric APL patients of India (39%) and is found to be the major impediment to excellent long term outcome[23]. Post-chemotherapy neutropenic sepsis may occur in APL. Its incidence is 30% in a Canadian study and 33% In an Indian study[24,25]. Differentiation syndrome or Retinoic acid syndrome, a unique treatment related complication of APL, occurs in 8- 29%of cases[10-13,23]. It is a clinico-pathological syndrome characterized by any 3 of the 7 features: unexplained fever, unusual weight gain, dyspnea, pulmonary infiltrates and pleuro-pericardial effusion, episodic hypotension and renal insufficiency. It may be also associated with peripheral edema or hyperbilirubinemia[26,27]. Severe headache (isolated or associated with pseudotumor cerebri), an adverse effect of ATRA, may occur in 8- 39% cases[10-12]. Patients with APL may also develop thrombotic complications. A pediatric study in Turkey reported thrombotic stroke in one patient out of a total of 17 patients[16]. In adult studies, thrombotic complications occur in 5.1% cases[28]. Thrombosis in APL may be attributable to hypercoagulability caused by malignant promyelocytes and circulating cytokines[29,30]. As far as known, there is no published study on pediatric APL in Bangladesh. This prospective observational study aims to describe the clinical manifestations, hematological profile, response to treatment and adverse events in pediatric APL in a tertiary care hospital in Bangladesh.

Materials and Method

Study population: All pediatric (<15 years) cases of APL, admitted in Pediatric Hematology and Oncology ward, Bangabandhu Sheikh Mujib Medial University (BSMMU), Dhaka, Bangladesh, from September 2017 to March 2019 were included in the study. The patients were tested for Promyelocytic Leukemia:Retinoic acid receptor-α (PML:RAR-α) transcript assay through Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR) technique of bone marrow aspiration sample. PML:RAR-α negative cases were excluded from the study. Another exclusion criterion was presence of cardiac contraindication of anthracycline therapy.

Study procedure: Ethical clearance of the study protocol (No.BSMMU/2017/8715-23.08.2017) was obtained from Institutional Review Board (IRB) of Bangabandhu Sheikh Mujib Medial University. Informed written consent from the parents was obtained at the time of study enrollment. All features from detailed clinical history, physical findings and laboratory investigations were documented in the clinical data collection sheet.

Treatment protocol and supportive care: The treatment was started according to modified protocol of International Consortium for Childhood (ICC) APL, sponsored by AIEOP (Associazione Italiana di Ematologiaed Oncologia Pediatrica) which has been shown in figure 1. The result of ICC-APL clinical trial

has been published recently with 5 year overall survival of 94.6%[17]. After confirmation of diagnosis, the patients were categorized into risk groups based on total leukocyte count, the patients with total leukocyte count $10x10^9$/L or more were categorized in the high risk group and those having the lower count were assigned to standard risk group. ATRA was included in all phases: induction, consolidation and maintenance. Induction consisted of oral ATRA (25 mg/m^2/day) for 30 consecutive days and 3 doses of Idarubicin. In high risk patients, dexamethasone (5mg/m^2/day) was given during the first 5 days as differentiation syndrome prophylaxis. Then, standard risk and high risk patients received 2 or 3 consolidation blocks, respectively, after peripheral blood count recovery (neutrophil count [?]$1.0x10^9$/L and platelet count [?]$100x10^9$/L). A 14 day course of ATRA was associated with cytarabine and mitoxantrone in the first block, with idarubicin in the second block and with cytarabine and idarubicin in the third block. Intrathecal cytarabine (age adjusted dose) was administered at the start of each consolidation therapy. Standard risk patients, still PML:RAR-α positive at the end of the 2nd consolidation block, would receive a 3rd consolidation block. All patients who were PML:RARα negative at the end of consolidation therapy would receive low-dose maintenance chemotherapy for 2 years. Patients who were PCR-positive after third consolidation therapy would be considered as refractory disease and would receive salvage therapy, including ArsenicTrioxide + Gemtuzumab-Ozogamycin+/-ATRA. Platelets and fresh frozen plasma were transfused to maintain the platelet count $>50x10^9$/L and the fibrinogen level >1.5g/dl, respectively during the first 10 days of induction or longer in the presence of coagulopathy. As APL is a medical emergency, ATRA was started as soon as possible after diagnosis was confirmed or strongly suspected. The end point of the study was the beginning of maintenance phase of chemotherapy.

Operational definitions: Coagulopathy/DIC: It is based on the diagnostic criteria for DIC in hematologic disorders from the Japanese Society on Thrombosis and Hemostasis (JSTH), which includes platelet count, prothrombin time: INR, fibrinogen level, fibrin related markers- Fibrin Degradation Product (FDP) or D-Dimer; and absence of liver dysfunction. A score [?] 4/13 was considered as DIC[31].

Response to treatment: Response to treatment includes achievement of clinical remission and peripheral remission, resolution of coagulopathy and bone marrow remission (morphological and molecular) at the end of consolidation phase of chemotherapy.

Early Death: Early death includes deaths that occurred within 30 days of diagnosis.

Clinical remission: Clinical remission is defined as a patient becoming afebrile with absence of pallor, hemorrhagic manifestations or organomegaly after initiation of chemotherapy.

Peripheral remission: Peripheral remission is defined as absence of blast/promyelocyte in peripheral blood smear after initiation of chemotherapy.

Bone marrow remission: Bone marrow remission is defined as absence of blast/malignant promyelocyte with negative RT-PCR for PML:RAR-α in bone marrow sample at the end of consolidation phase of chemotherapy.

Resolution of coagulopathy: Normalization of PT and APTT, platelet count > 50,000/cumm and plasma fibrinogen >150 mg/dl. Isolated raised D-Dimer or FDP was not considered to be a sign of non-resolution of coagulopathy as low grade fibrinolysis may persist for prolong period in a compensated manner[9].

Differentiation syndrome: Any 3 of the following features after initiation of ATRA: Unexplained fever, dyspnea, pulmonary infiltrates, pleuro/pericardial effusion, weight gain, peripheral edema, episodic hypotension, renal function impairment, hyperbilirubinemia.

Pseudotumor cerebri: Patients having severe headache, vomiting, visual disturbance and response to withholding ATRA were designated as suspected pseudotumor cerebri. If they also have papilledema and/or suggestive neuro-imaging, they were assigned as definitive pseudotumor cerebri.

Refractory disease: Refractory disease is defined as patients having PML:RAR-α positive post-consolidation bone marrow sample.

Data analysis: All data were documented in preformed data collection form. Statistical analysis was performed by using SPSS (Statistical Package for the Social Sciences) for windows version 23. Quantitative data were presented as mean, standard deviation and range. Qualitative data were expressed as total numbers and percentages.

Results:

Clinical and hematological characteristics: The total number of patients of APL (PML:RAR-α positive) in this study was 20. Among the study population, 7 patients were in the standard risk group and 13 patients were in the high risk group. Mean age was 6.8 years and 30% of patients were below 5 years of age. Male: female ratio was 1:1.2. The commonest clinical features were fever (95%) and hemorrhage (95%). Mucosal bleeding was observed in 55% patients and one patient had fatal CNS hemorrhage. Hepatomegaly was present in 70% cases and 40% had splenomegaly. Among hematological parameters, mean hemoglobin was 6.28 gm/dl, mean total leukocyte count was 56.8 x 10^9/L, and mean platelet count was 16.6 x10^9/L. Total leukocyte count was > 100 x10^9/L in 25% of patients. DIC was present in 90% of patients, mean plasma fibrinogen was 232.6 mg/dl and mean plasma D-Dimer was 4.1 µg /ml. (Table 1).

Response to therapy: Clinical and peripheral remission was achieved in 90% patients (18/20) during induction chemotherapy. Failure to achieve remission was due to early hemorrhagic death (intracranial hemorrhage) on 1st day of admission before initiation of ATRA in one patient. Another patient who failed to achieve remission developed hyperleukocytosis (despite getting ATRA, steroid and later hydroxyuia), differentiation syndrome, severe sepsis and profuse gastro-intestinal hemorrhage leading to death. One patient died from massive ischemic stroke on 26th day of induction after achieving clinical and peripheral remission. Two patients died from septic shock due to neutropenic sepsis after completion of consolidation chemotherapy. Finally, 15 patients (75%) successfully reached maintenance therapy and are currently in clinical, peripheral and bone marrow remission. The commonest cause of death was post-chemotherapy neutropenic sepsis (Table 2).

Adverse events: Incidence of post-chemotherapy sepsis was 58% which most frequent after induction and consolidation III (84% and 70% respectively). Among the neutropenic sepsis events, the commonest causes were febrile neutropenia with no specific focus and respiratory tract infection (Table 3).

Differentiation syndrome was found to occur in 4 patients (20%). All four patients developing differentiation syndrome were in the high risk group, having cough, tachypnea, pulmonary infiltrates and associated infection. Unexplained fever was observed in 3 patients (75%), pleural effusion, ascitis, abnormal weight gain, hyperbilirubinemia were observed in 2 patients each (50%). No patient had renal impairment. One patient did not respond to steroid and died from progressive hyperleukocytosis, severe sepsis, gastrointestinal hemorrhage and multiorgan failure. Pseudotumor cerebri was observed in 3 patients during induction therapy. All patients had intense headache with vomiting which were improved after transient dose reduction of ATRA and steroid. One patient also had papiloedema, bradycardia and generalized seizure, which responded to intravenous midazolam, mannitol and dexamethasone. Other adverse events were hyperpigmentation of skin, cheilitis, visual disturbance due to retinal hemorrhage, elevated liver enzymes (>4 folds of upper limit) and ischemic stroke (Table 4).

Discussion

This prospective observational study, total number of PML:RAR-α positive APL patients was 20. The mean age was 6.8 years (ranging from 3-13 years). There was slight female predominance with male-female ratio of 1:1.2 which is consistent with previous European studies[10,11].

In this study, mean duration of illness was 31 days (7-90 days). Hemorrhagic manifestations were observed in 95% of patients, with mucosal bleeding in 55% cases. These features are also consistent with previous European studies which found hemorrhagic manifestations in 80% of children with mucosal bleeding in 59% cases[10]. Fever was present in 95% of patients which is higher than previous studies in Italy (42%), Korea (62%) or in Turkey (59%)[12,13,16] . Hepatomegaly was present in 70% of cases, also higher previous studies

in Europe (19%) and in Korea (32%)[10,13] .

In this study, most of the patients (63%) were in the high risk group, which is also higher than studies in Europe (48%), Spain (39%), Italy (38%), Korea (35%), China (26%) and India (46%)[10-13,15,23]. Mean plasma fibrinogen in this study was 232 mg/dl and mean D-Dimer was 4.1 µg /ml. Mean plasma fibrinogen level is found to be higher than the previously published data, as it was 140 mg/dl in both of the two European studies and 149.5 mg/dl in a Turkish study[10,14,16]. This may be due to the fact that, in this study, most of the patients (75%) received prior blood or blood product transfusion.

Early death occurred in three patients (15%). This incidence is higher than a previous multinational pediatric APL study, which documented 5.6% of early death, but lower than early death rate in another previous pediatric study in India[18,23]. Early hemorrhagic death occurred in one patient (5%) in this study, which was 3.1- 3.8% in Europe, 2.8% in Italy, 7.5% in Spain, 13% in Korea, 11.7% in Turkey and 30% in India[10-14, 16,23].

The frequency of post-chemotherapy neutropenic sepsis was 58%. The rate of infection is much higher than the study performed in Canada (30%) and India (33%)[24,25]. This difference may be due to poor adherence to infection control measures. Neutropenic sepsis was the cause of death in two patients.

The incidence of differentiation syndrome was 20%. In previous studies its incidences were 13-16% in Europe, 20% in Spain, 6% in Italy, 17% in Korea and 29% in India[10-14,16,23]. Differentiation syndrome was the cause of death in one patient. This patient had progressive leukocytosis after initiation of ATRA, which is thought to be a predictor of differentiation syndrome and early death in adult cases[32].

Incidence of pseudotumor cerebri (suspected and definitive) was 15%. In previous studies its incidences were 14% in Europe, 6% in Spain and 8% in Italy [10-12, 14].

One patient died from ischemic stroke during later period of induction therapy. This thrombotic event in pediatric APL was also documented in a previous study in Turkey[16].

All five deaths occurred in the high risk group. This finding is consistent with the most of the studies which suggest that higher leukocyte count is the single most significant predictor of poor outcome[18,19]. In this developing country, delayed presentation is very common which leads to more aggressive disease presentations. Here, crowded hospital settings and rapid turnover of patients make infection control measures difficult. These challenges still creates barrier to achieve greater outcome in this highly curable malignancy.

Limitation of the study: This is a relatively small study involving only 20 cases. The patients were followed up only till the beginning of maintenance therapy.

Conclusion

In Bangladesh, clinical and peripheral remission rate of pediatric APL after induction chemotherapy is 90%, but post-consolidation bone marrow remission rate is only 75%. Causes of deaths are neutropenic sepsis, severe hemorrhage, differentiation syndrome and stroke. Neutropenic sepsis is the most common adverse event.

Recommendations

Large, multi-center studies with long term follow up plan should be performed in developing countries.

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Conflicts of interest Authors declare no conflicts of interests.

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Legends:

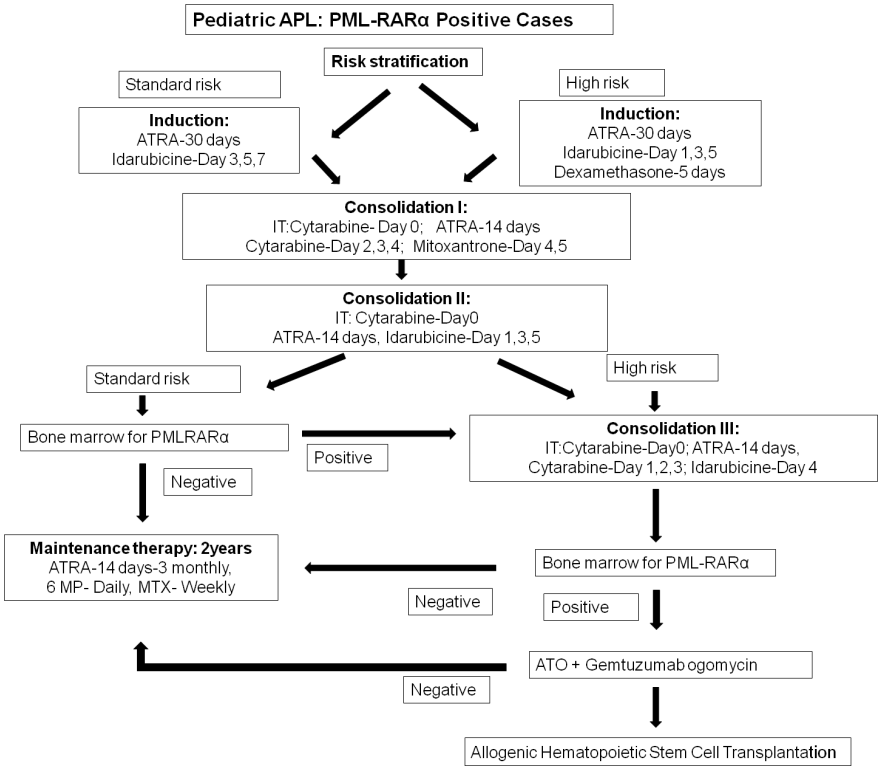
Figure 1: Chemotherapy protocol for pediatric APL patients

TABLE 1: Clinico-hematological profile of pediatric APL cases

TABLE 2 Response to treatment of pediatric APL cases

TABLE 3 Adverse events: neutropenic sepsis in pediatric APL cases

TABLE 4 Adverse events (other than sepsis) in pediatric APL cases



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