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Original Research Article

Clinical Profile and Induction Outcome in Adult and Pediatric Acute Promyelocytic Leukemia

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Abstract: Acute Promyelocytic Leukemia (APL) is a curable malignancy, but it carries a high early mortality rate of around 10-20% in various studies. As data from India regarding APL is scarce, we have undertaken a single centre study on the mortality and induction morbidities on patients with APL. This was a descriptive study conducted in a tertiary cancer centre on all adult and pediatric patients with confirmed APL from May 2018 to May 2019. Patients were treated as per protocol with all-trans retinoic acid (ATRA) along with arsenic trioxide in low risk and daunorubicin in high risk patients. A total of 57 patients were included, of which 51 patients were adults and six were pediatric patients. Among these, 26 adults and 4 children were high risk and 25 adults and 2 children were low risk APL. The median age of the adult patients was 29 years. The most common presenting complaint was fever (n=50) and bleeding manifestation (n=41). Six patients had intracranial hemorrhage at presentation. The median hemoglobin, total count and platelet count were 7g/dL, 14000/cmm and 20000/cmm respectively. The overall CR rate is 56.5%, with a median time to remission of 40 days (IQR 33 – 45 days). The median EFS is 18 days (IQR 9 – 39 days). The overall mortality rate is 43%, with 35% deaths in first week due to intracranial hemorrhage. The outcome of APL when compared to literature is very poor and further studies on how to improve outcomes are the need of the hour.

Keywords: Acute promyelocytic leukemia, induction, morbidity, mortality, complete remission.

INTRODUCTION

Acute promyelocytic leukemia (APL) is rare and constitutes about 7-8% of all acute myeloid leukemias. APL is a paradigm of a highly lethal disease for which a cure is possible in the form of all-trans-retinoic acid. But, despite the major strides achieved in the treatment and outcome, early death in APL is still significant enough to impact the treatment outcomes. In clinical trials, the incidence of early hemorrhagic death is around 3.7 percent, but as many patients die before reaching the hemato-oncologist, the early death rate in population-based surveys is higher, around 17 to 29%.There have been a few studies on the factors that lead to increased early deaths and the consistent prognostic indicator has been the peripheral white blood cell counts. Some studies have also pointed out that delay in administration of ATRA can affect the mortality rates. The 2 year disease-free survival rates in APL is now 90-97%.(Lo-Coco *et al*., 2010).

As data on outcome of APL patients from India is very limited, we have undertaken a single centre institutional study on adult and pediatric patients. Ours is a tertiary care centre where the treatment is either free or subsidized due to various government schemes. We studied the clinical characteristics and induction outcomes, including mortality and morbidity.

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MATERIALS AND METHODS

This was a retrospective study on all confirmed and diagnosed cases of APL, both adult and pediatric, who presented to our institute between May 2018 and May 2019. The study was conducted after approval from the Institutional ethics committee and Institutional Review Board. All consecutive patients with confirmed diagnosis of APL were included in the study. The diagnosis of APL in all the patients had been done by bone marrow examination and immunophenotyping and confirmed by FISH for t(15;17) or if FISH was negative, by RT-PCR for PML-RARA. If patients had bone marrow study done in another centre, they were reviewed by the pathologist in addition to confirmatory testing by FISH. If patients were referred with a positive report ofRT-PCR for PML-RARA from an approved laboratory, they were included in the study.

Patients were started on all-trans retinoic acid (ATRA) 45mg/m^2/day (or 25mg/m^2/day in those less than 14 years of age) immediately if clinical features were suspicious of APL, like bleeding manifestations or if promyelocytes were seen on peripheral smear, without waiting for the confirmatory reports. Once the diagnosis of APL was confirmed, patients were shifted to the leukemia wards where they were isolated from other patients until complete hematological remission. Patients were risk stratified according to the peripheral white blood cell counts (TC) at presentation, as per NCCN guidelines. Low-risk APL (TC≤10,000/µL) was treated withATRAand arsenic trioxide (ATO) 0.15mg/kg/day from day 8 and continued until hematological remission (Lo-Coco protocol). High-risk APL was treated with ATRA and Daunorubicin 50 mg/m^2/day from D1 to D4 (or 45mg/m^2/day from D1 to D3 in pediatric patients) as per IC APL 2006 protocol. In patients who were in altered sensorium at presentation, precluding oral intake, ATRA was replaced by ATO.

In all patients, supportive care in the form of blood transfusions (to keep hemoglobin above 8g/dL, platelet count above 30,000/µL and serum fibrinogen levels above 150 mg/dL), management of infections and neutropenic care were given. Blood counts were monitored every alternate day in low-risk or daily in case of high-risk patients and coagulation parameters twice weekly. Patients found to have any features of differentiation syndrome were managed with high dose steroids and temporary withdrawal of differentiating agent. Cytoreductive anthracycline, hydroxyurea or cytarabine were given to those who, either did not respond, or had a rapidly deteriorating course of differentiation. Antibiotics were also addedin those who had high-grade fever. Once the peripheral blood counts normalized, after day 28, bone marrow aspiration was done to document remission.

Complete morphological or hematological remission was defined as bone marrow aspirate with spicules showing <5% blasts and no blasts with Auer rods, with blood counts of absolute neutrophil count (ANC) >1000/µL and platelet count of ≥1,00,000/µL independent of transfusions and no evidence of extra-medullary disease.

Differentiation syndrome was diagnosed if there were 2 of the following: unexplained fever, weight gain greater than 5 kg, acute respiratory distress with interstitial pulmonary infiltrates, acute renal failure, unexplained hypotension, and pleuropericardial effusion.

Event free survival (EFS) was defined as the time to any event – relapse, death or lost to follow up – from the time of presentation.

Statistical analysis of the data collected was done using IBM SPSS software v23.0. Descriptive analysis involved computation of mean with standard deviation for normally distributed data and median and interquartile ranges for non-Gaussian data. All categorical data were represented as frequencies and percentages. Univariate analysis was done using Chi square test and $p<0.05$ was considered significant. Multivariate analysis was done by logistic regression on those variables which were found to be significant.

RESULTS

There were 57 patients who were diagnosed between May 2018 and May 2019 and were included in the study. Among these, six (10.5%) were children below the age of 14 years. The median age was 29 years (IQR 24 - 45). There were 27 (47.4%) males. The baseline characteristics have been shown in Table 1.

Table-1: Baseline characteristics of the patients

Characteristics	Low risk APL (N=27)	High-risk APL (N=30)	Total (N=57)
Number of adults	25	26	51
Number of children	2	4	6
Gender, Female:Male	16:11	14:16	30:27
Patients with comorbidities	7	7	14
Performance status (ECOG)*			
1	2	1	3
2	3	2	5
3	4	5	9
4	1	4	5
Clinical features at presentation:			
Bleeding manifestations			
Intracranial bleeding	16	25	41
Fever	4	2	6
Spontaneous differentiation	21	29	50
Severe anemia (Hemoglobin<8g/dL)	0	2	2
	18	19	37

* Missing data

The most common comorbidities were diabetes (n = 9, 16%) and hypertension (n = 4, 7%). There was one patient who was hypothyroid. There were two patients who were in gestation, one was in the first trimester, who had low risk APL and the other in the second trimester with high risk APL. Both these ladies succumbed during therapy. There were two patientswho presented in the fourth month postpartum, one of whom was in the high-risk category and she attained remission. There were two patients who were diagnosed with APL while on treatment for Plasmodium vivax malaria. One patient was incidentally detected to be HBsAg positive.

Clinical Features

The most common symptom at presentation was fever (n = 50, 88%) and bleeding manifestations (n = 41, 72%), both these symptoms being more common in the high-risk APL patients. Bleeding manifestations included both mucosal and cutaneous bleeding, of which the most common was epistaxis (n = 18, 32%). There was one patient who presented with intramuscular hematoma in the calf. There were six patients who had intracranial hemorrhage at presentation; the most common type was subdural hemorrhage. Paradoxically, it was seen more in the low-risk category. But during induction, five more patients in the high-risk APL developed intracranial hemorrhage (all in the first week) while in the low-risk category, no such further events occurred.

Among the 50 (88%) patients who presented with fever, there was one patient in the high-risk category who had been started on induction therapy and had presented to us with febrile neutropenia and hepatic mucormycosis proven by cytology of the aspirate.

There were two patients who presented with spontaneous differentiation, both of whom did not complete induction and succumbed.

There was one patient who presented with gingival and buccal mucosal swelling, which was proven by cytology to be leukemic infiltrates, a rare presentation.

There were 37 patients (65%) with severe anemia (hemoglobin <8 g/dL) and 32 patients (56%) with coagulation profile abnormalities. The serum LDH was abnormal in 43 patients (75%). The median values and the interquartile ranges according to the risk category are represented in table 2.

Diagnosis

Bone marrow study was done in all the patients, where the median blast percentage was 88%.(Table 2) Those who had negative FISH for t(15;17) were screened out (n=10). Two patients, who presented with intracranial hemorrhage, succumbed before bone marrow or FISH could be done. In the immunophenotyping, besides the typical profile of CD 13, 33, 117, MPO positive and negative CD 34 and HLA-DR, CD 15 was additionally positive in 24 patients (42%). CD 14 was positive in 5 patients (9%), while CD 34 was positive in 6 (10%) and HLA-DR was positive in 2 (3%) patients.

Table-2: Lab investigations and time to initiation of ATRA in each risk category

Investigations and diagnosis - Median (interquartile range)	Low risk APL (N=27)	High-risk APL (N=30)	Total (N=57)
Hemoglobin (gm/dL)	7.0 (5.7 – 8.4)	7.05 (6 – 8.6)	7.0 (6 – 8.5)
Total leukocyte count x 10^9/µL	2.6 (1.1 – 7.0)	34 (18 – 50)	14 (2.6 – 37.5)
Platelet count x 10^9/µL	15 (11 – 25)	23 (14 – 50)	20 (12 – 32.5)
Serum LDH	284 (187 – 387)	399 (193 – 607)	330 (192 – 492)
Plasma Fibrinogen	195 (165 – 289)	135 (122 – 168)	159 (138 – 220)
Bone marrow blasts (%)	78 (60 – 91)	90 (83.2 – 92)	88 (71 – 91)
Time to initiation of ATRA after first hospital contact	4 (3 – 7)	3 (2 – 5)	4 (3 -6)

Treatment outcomes and complications

All the patients who were suspected of having APL were started on ATRA immediately. The time to start differentiating agent after the first hospital contact was also studied and the median was 4 days (IQR 3 – 6) as in Table 2. Of the 68 patients who were suspected of APL and started on ATRA, 9 patients were t (15;17) negative, and two patients died before any confirmatory tests could be done. The remaining 57 patients were confirmed to be APL, and among these patients, 27 were low-risk and 30 were high-risk patients. Among them, 11 patients (6 in the low-risk and 5 in the high-risk category) opted to go to another hospital or left against medical advice due to social and financial reasons. 13 patients in each category completed induction therapy and all of them attained morphological remission. The flowchart is as given below in Figure 1.

Among patients who remained on treatment, 13 out of 21 (62%) of the low-risk patients and 13 out of 25 (52%) of the high-risk patients attained CR at the end of induction. The overall CR rate is 56.5%, with a median time to remission of 40 days (IQR 33 – 45 days).

The median EFS is 18 days (IQR 9 – 39 days).

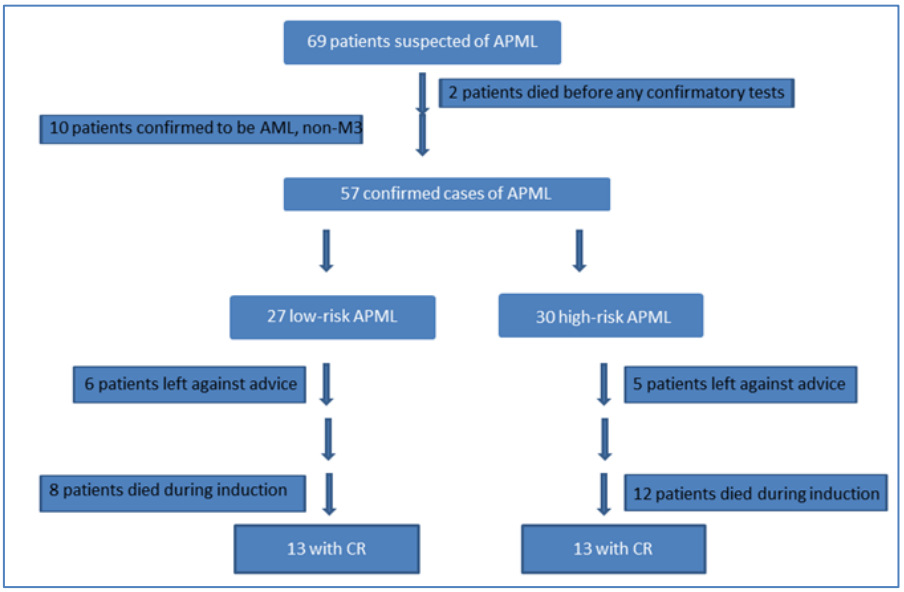

Fig-1: Flowchart depicting the number of patients who completed the treatment

All patients were given supportive treatment to control infections and bleeding. All infections were treated initially with empirical broad-spectrum antibiotics with third generation cephalosporins or carbapenems and later changed to specific antibiotics according to the culture and sensitivity reports. Infections were seen in 30% (n=14), differentiation syndrome in 52% (n=24) and bleeding manifestations in 89% (n=41) of the patients during treatment.

Infections were seen in 4 patients of the low-risk category amongst whom one patient succumbed to pneumonia and septic shock. Infections in the others were cellulitis, pneumonia and diarrhea. The common organisms isolated were Staphylococcus hemolyticus, multidrug-resistant (MDR) Klebsiella and MDR E.coli. None of these infections were associated with neutropenia.

Among the high-risk patients, all infections were seen in the second and third weeks and were due to neutropenia, except in one patient who presented with pneumonia. 10 patients had sepsis, of which 3 succumbed. One of these patients was in the first trimester of pregnancy at presentation and developed intrauterine death (IUD) on the second day. She

developed IUD related sepsis which was fatal. The most common infections seen were pneumonia and colitis, due to MDR Klebsiella, Acinetobacter, Enterobacter, MDR E.coli and Staphylococcus.

There were nine patients (43%) who had features of differentiation syndrome among the low-risk category, of whom two patients succumbed. Among the high-risk patients, 15 (60%) developed features of differentiation, of whom two had presented with spontaneous differentiation. Three patients succumbed to it. The death rate due to differentiation was 21%. Differentiation syndrome was predominantly seen during the first week and the third week. The median day of differentiation is 4 days.

Forty one patients had bleeding manifestations at presentation, of which six had intracranial hemorrhage. During treatment, 5 more patients developed the same, all in the high-risk category. Among the 11 patients with intracranial bleed, 9 patients succumbed, while one patient left against advice and one patient completed induction and remains in remission. Two patients developed massive hemoptysis, possibly due to pulmonary hemorrhage, in the third week which was fatal. Both these patients were in the low-risk category.

Among the pediatric group with APL, three were low-risk and three were high-risk. Four children out of six (67%) achieved remission and two (33%) died. Both were high-risk APL and the causes were differentiation and sepsis – colitis with MDR E.coli.

The overall mortality rate is 43%. Deaths occurred up to the 19th day of therapy, with 35% deaths in first week (all due to intracranial hemorrhage) and 30% in the second week.

The causes of mortality have been summarized in Table 3. 55% of the deaths were due to hemorrhage, 25% due to differentiation and 20% due to infection.

Table-3: Causes of mortality among those who remained on treatment

Causes	Low-Risk (n = 21)	High-Risk (n = 25)	Total (n = 46)
Hemorrhagic death:			
Intracranial bleeding	3	6	9
Pulmonary hemorrhage	2	0	2
Sepsis	1	3	4
Differentiation	2	3	5
Total deaths (mortality rate)	8 (38%)	12 (48%)	20 (43%)

Univariate analysis was carried out to find out the correlation between some of the variables and death and the results are as shown in Table 4.

Table-4: Correlation between some of the clinical variables and death

Factor	Patients who survived	Patients who died	P value
Male sex	17	10	0.77
Age >50 years	18	10	0.922
Presence of comorbidities	9	5	0.955
Hemoglobin<8g/dL	23	14	0.554
Total Count > $10x10^9/\mu L$	18	12	0.413
Platelet Count <$30x10^9/\mu L$	25	15	0.558
Presence of coagulopathy	17	15	0.035
S LDH > ULN	30	15	0.591
Marrow blasts >90%	8	8	0.141
Time to ATRA >4 days	21	12	0.813

Among these factors, only presence of coagulopathy had a significant correlation with death. (p =0.035).

Toxicities

The treatment was generally tolerated well by the patients. Pseudotumorcerebri due to ATRA was seen in 4 of the 27 low-risk patients and 4 of the high-risk patients. This resolved with supportive treatment. One of the patients developed daunorubicin-induced acute cardiomyopathy and severe left ventricular dysfunction which recovered after two months. Another patient developed hypokalemia and QT prolongation due to ATO on the 20th day. She also responded to supportive care.

DISCUSSION

The study elucidates the clinical presentation and the outcomes of APL patients who were admitted at a tertiary cancer care centre in North India.

The median age of the patient cohort was 29 years (IQR 24 - 45). This is similar to the other studies reported from India, where the median age was 30 years (Bajpai *et al*., 2011; Dayama *et al*., 2015) and 31 years (Yedla *et al*., 2020). This is much lesser than what is

reported in the international studies – 45years*(Adès et al*., 2018).

There was slightly more females than males, in contrast to the other studies where males are predominant.(Bajpai et al., 2011; Dayama *et al*., 2015)There is a single centre retrospective study from Stanford hospital, USA where there is female preponderance of 63%.(Mcclellan *et al*., 2012).

The proportion of high-risk patients in our study was 52.6%, which is much higher than reported by Bajpai *et al*. – 23%, (Bajpai *et al*., 2011) and the other Indian single centre studies - 41% (Dayama et al., 2015) and 43% (Yedla *et al*., 2020). In international studies, high-risk patients constituted about 22.9% in the PETHEMA and 22.2% in the GIMEMA groups.(Sanz *et al*., 2000) The difference might be due to late presentation to the hospital because of financial or social reasons or difficulty in healthcare access.

The CR rate in this patient population is 56.5%,with 43% mortality. The CR rate is much lesser than other studies where it is 79% (Yedla *et al*., 2020), 82% (Bajpai *et al*., 2011), 86% (Mathews et al., 2010) and 88% (Dayama *et al*., 2015). In multicenter clinical trials, the CR rates are close to 90%.(Lo-Coco *et al*., 2010; Powell *et al*., 2010). This is because of a highly selected population that undergoes the treatment in such trials. The median time to CR is 40 days which is similar to the study by Yedla et al. -30 days. *(Yedla et al*., 2020)The mortality during induction was 43%, which is higher than those reported by retrospective, single centre studies – 14.7% (Dayama *et al*., 2015), 18% (Bajpai *et al*., 2011) and 21% (Yedla *et al*., 2020). But there are a few studies reporting high mortality rates during induction – 43.9% in a retrospective, population-based study on 963 APL patients in California(Ho *et al*., 2019) and 85% in a single centre study from India.(Jacob *et al*., 2019) The mortality rates as reported in clinical trials are usually not a true reflection of the real scenario as the early deaths, before the start of definitive therapy, when the majority of deaths occur, are not accounted for. So comparison has been carried out between retrospective studies only. The causes of mortality were similar across studies, but in this study the proportion of deaths due to hemorrhage is high – 55%, while in other studies, the most common cause of death is infection.(Bajpai *et al*., 2011; Dayama *et al*., 2015) This probably reflects the higher proportion of high-risk patients in our cohort due to delay in seeking treatment and the need for more intensive support during induction to prevent hemorrhagic deaths.

On studying the various factors responsible for induction mortality, only coagulopathy showed a significant association. Several factors like advanced age, male sex, high WBC count, serum creatinine and serum fibrinogen levels have been shown to be risk factors for mortality.(De La Serna *et al*., 2008; Sanz *et al*., 2008) But in our study, only coagulopathy was associated. This is similar to another single centre study from India.(Dayama *et al*., 2015) There was no association with the median time to initiationof ATRA after first hospital contact which is 4 days. The lack of association is probably because this does not take into account the total symptomatic period this was not available from records. Further, we have not studied the performance status as a risk factor, due to missing data.

CONCLUSION

This study shows that there is higher proportion of high-risk patients likely due to delay in seeking treatment. Improvement of outcomes can only occur with better health awareness programmes so that patients present without delay and sensitization of healthcare personnel to initiate ATRA without delay in cases of suspicion. In addition, aggressive blood transfusion and supportive care during induction therapy is also mandatory for better outcomes.

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