Leukemia - Original Article

Acute promyelocytic leukemia: An experience from a tertiary care centre in north India

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Abstract

BACKGROUND: There are very limited data reported about acute promyelocytic leukemia (APL) from developing countries. We reviewed the clinical course and treatment outcome of APL patients treated at our center. **MATERIALS AND METHODS:** Between January 1997 and December 2007, 33 patients with APL received induction therapy using ATRA + daunorubicin ($n = 26$), As_2O_3 ($n = 4$) or daunorubicin + cytosar ($n = 3$). **RESULTS:** Median age was 30 years with a male to female ratio of 1.68. Twenty seven patients (82%) achieved CR. Complications during induction therapy were febrile neutropenia (33%), ATRA syndrome (30%), bleeding (58%), and diarrhea in (6%) patients. During induction and follow up, 8 (24.24%) patients died, 6 (18.18%) during induction, 1 (3%) during maintenance, and 1 (3%) after relapse. Median OS is 128 months while median EFS is 61 months. Four patients relapsed at a median time of 61 months. At the time of censoring, 25 patients were alive at a median follow up of 13 months (range 0.6 -127 months); 21 in CR1, 3 in CR2, 1 in CR3. Comparisons among the risk groups (CR and relapse rate and survival statistics) were not statistically significant. **CONCLUSIONS:** APL is a highly curable malignancy. Our results confirm the findings of the published literature from larger cooperative studies from the West. We may further improve outcome with quicker diagnosis and more efficient supportive care system.

Key words: Acute promyelocytic leukemia, all-trans-retinoic acid, arsenic trioxide

Introduction

Acute promyelocytic leukemia (APL) accounts for approximately 10% of AML cases in adults, and is regarded as the most curable subtype of AML.[1] There are a variety of unique features of this disease including the potential for chemotherapy-induced complete remission without marrow aplasia, the potentially life-threatening coagulopathy, the characteristic $t(15;17)$ translocation resulting in the PML-RAR α´ gene, and the unique sensitivity to all-trans-retinoic acid (ATRA) and arsenicals.[2-8] Combination of ATRA and daunomycin (an anthracyclin) has resulted in the CR rates of 90% to 95% with a 6-year disease-free survival (DFS) of 86% (+/− 10%) in low-risk patients.[9] Phase III trials from Europe and North America have established the combination of ATRA and daunomycin as the current standard of care.[10-15] Arsenic trioxide (As_2O_3) was introduced in early 1990s for the treatment of refractory or relapsed APL. Recently, this has also been used in the treatment of newly diagnosed APL.[16]

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Data on the outcome of APL patients from India is limited. We have reviewed records of the patients diagnosed and treated at our centre during the past 11 years. This report describes the results.

Materials and Methods

A total of 43 patients were diagnosed to have APL from January 1997 to December 2007. All

patients underwent detailed physical examination and investigations including hemogram, liver and renal function tests, bone marrow studies.

The diagnosis was based on either morphology (promyelocytes on peripheral smear and/or bone marrow) or cytogenetics (detection of the *t*(15; 17) chromosomal translocation by cytogenetic analysis or FISH or of PML/RAR α´ rearrangement by RT-PCR analysis) and flow cytometry (CD13, CD 33 positive, HLADR negative). Cytogenetics and flow cytometry were done whenever possible. Coagulation profile was done at baseline in all patients. Laboratory diagnosis of Disseminated Intravascular Coagulation (DIC) was based on changes in activated partial thromboplastin time, prothrombin time, fibrinogen degradation products (FDPs), and/or D-dimers. Patients were classified according to the risk of relapse on the basis of WBC and platelet counts (PLT) at diagnosis.[14]

1. Low risk, WBC<10 × 10^9/L and PLT >40 × 10^9/L;
2. Intermediate risk, WBC<10 × 10^9/L and PLT < 40 × 10^9/L;
3. High risk, WBC>10 × 10^9/L. [Table 1]

Various treatment protocols used in this study are as follows: Table 2

ATRA + Anthracyclins

In induction, ATRA 45 mg/m^2/day, divided into 2 doses until CR (no longer than 90 days) + daunorubicin (45-60 mg /m^2 × 3 days) and in consolidation, Daunorubicin 60 mg/m^2 × 3 days + ATRA (45 mg/m^2/Day, divided into two doses for 3 weeks) were used.

For maintenance, ATRA 45 mg/m^2/day, divided into two doses for 7 days every month plus 6 –mercaptopurine (6-MP) 90 mg/m^2/day plus methotrexate (MTX) 15 mg/m^2/week all for 1.5 years) were used.

As_2O_3

For induction therapy, As_2O_3 was administered once daily until hematologic CR or for a maximum of 60 days at a fixed dose of 10 mg/day for adults and 0.15 mg/kg/day for children; in consolidation, As_2O_3 was administered once daily for 28 days. For maintenance therapy (after a 4 week interval) As_2O_3 was administered once daily for 10 days, every month for 6-12 months.

Patients were hospitalized for induction therapy under closed supervision and monitoring. Complete blood counts (CBCs) were done daily for the first 2 weeks

Table 1: Patients characteristics (*N* = 43)

Gender		**Male**	**Female**	**Ratio**
		27 (62.8%)	16 (37.20%)	1.68
Median age (30, range 2-75)years]		31.5(2-75)	27(18-45)	
Risk category		**Low**	**Intermediate**	**High**
No of patients (%)		13 (30.23)	20 (46.51)	10 (23.25)
PS(ECOG)*	**I**	**II**	**III**	**IV**
No of patients (%)	8(18.60)	20 (46.51)	3(6.9)	4(9.3)
Symptoms	**Patient no (%)**	**Signs**	**Patient no (%)**	
Fever	31 (72)	Pallor	40 (93)	
Bleeding	30 (69.76)	Lymphadenopathy	8 (18.60)	
Weakness	15 (34.88)	Edema	5 (11.62)	
Bone pains	7 (16.27)	Gum hypertrophy	5 (11.62)	
Breathlessness	3 (6.97)	Sternal tenderness	2 (4.65)	
		Icterus	1 (2.32)	
Lab parameters				
****CBC**			**Mean**	
Hemoglobin (range) gm%			6.67 (3.5-12.5)	
TLC (range)per cm			9183 (700-54,400)	
Platelets (range)per cm			51,900 (8000-2,80,000)	
Lab parameters			**Number of patients (%)**	
***PML in peripheral smear			29.45 %	
PML in bone marrow			83.21 %	
DIC positivity			5 (11.62)	
Abnormal renal functions			5 (11.62)	
Abnormal chest X-ray			6 (13.95)	

*PS= Performance; **CBC= Complete blood; ***PML= Promyelocytes

Table 2: Treatment regimens and response

Induction (N = 33)	No of pts (%)	CR (%)	Induction deaths (%)
D + ATRA	26 (78.78)*	21 (80.76)	4 (15.38)
AS203	4 (12.12)	2 (50)	2 (50)
D + ARAC	3 (9)	3 (100)	0
Risk category			
Low	13	12 (92.30)	0
Intermediate	20	16 (80)	4(20)
High	10	8 (80)	2(20)

D= Daunorubicin; *One patient failed D + ATRA induction but subsequently attain CR with high dose ARAC

or until the patient was clinically stable, whichever occurred earlier. The CBCs were subsequently done on alternate days in induction, weekly in consolidation, and at each subsequent visit in maintenance and follow-up. Bone marrow analysis was done at the end of induction when two sequential CBCs were consistent with complete remission (CR). If the bone marrow analysis showed evidence of persistent disease, then therapy was continued and the bone marrow analysis was repeated at weekly intervals until CR was achieved or until the maximum duration of the induction period.

Coagulation parameters were monitored on weekly basis (every alternate days or earlier if deranged and / or bleeding manifestations present) and included a prothrombin time (PT), activated partial thromboplastin time (aPTT), and thrombin time (TT) performed by standard methods. Fibrinogen level was assayed if deranged coagulation parameters persisted in spite of attempted correction by fresh-frozen plasma (FFP). Unless clinically indicated, these tests were not regularly done during consolidation or maintenance phases.

Liver function tests, renal function tests, and electrolytes were done twice a week in induction, once a week in consolidation, and at each visit in maintenance and subsequent follow-up. Electrocardiogram (ECG) was done only if clinically indicated.

Platelet concentrates were transfused to maintain a platelet count higher than 45×10^9/L. Fresh-frozen plasma was infused (15 mL/kg) if the PT or a PTT was deranged. Packed red cell transfusions were infused to maintain a hemoglobin level higher than 80 g/L (8 g%). Patients received antifungal prophylaxis during induction chemotherapy and those with neutropenic fever were managed as per the standard departmental policy.

Toxicities were documented using the National Cancer Institute–Common Toxicity Criteria version 2.0 (NCI-CTC v 2.0; Bethesda, MD). Therapy was withheld for any grade 3/4 non-hematological toxicity and the patient rechallenged once the abnormality was corrected or if the grade reduced to less than 3. If grade 3/4 toxicity persisted after discontinuation of therapy or recurred on rechallenging the individual, the drug was planned for discontinuation, though none of the patient required the same.

Criteria for diagnosis of a differentiation syndrome were those defined in earlier studies.[17]

Definition of outcomes

Achievement of CR required patients to have no clinical evidence of APL, an ANC higher than 1.5×10^9/L, an unsupported platelet count of more than 100×10^9/L, and a bone marrow analysis showing normocellularity to moderate hypocellularity with less than 5% blasts plus promyelocytes. Overall survival (OS) was defined as time from initiating treatment to last follow-up or death. Event-free survival (EFS) was calculated from time of initiating therapy to last follow-up or an event (relapse or death). Relapse-free survival (RFS) was calculated from time of achieving CR to last follow-up or an event (relapse).

Statistical analysis

Analysis was done on the patients who were treated. Fisher's exact test was used to compare differences between groups with respect to number of patients in each group, frequencies of bleeding and DIC at diagnosis and response to therapy. The probability of survival was estimated with the use of the Kaplan and Meier method for overall survival, event-free surviva,l and disease-free survival and compared by the log-rank test among the three risk groups. All survival estimates are reported ± 1 SE. All *P* values were two-sided, with values of 0.05 or less indicating a statistical significance. Statistical analysis was performed using STATA 9.1 software.

Results

Patient accrual and baseline characteristics

A total of 43 patients were registered from January 1997 to December 2007; 33 of 43 patients received treatment; 2 died of bleeding and sepsis within 24 hours of admission; and 8 patients received treatment elsewhere.

Patient's characteristics are shown in Table 1.

Thirty-three patients received induction therapy using either ATRA + daunorubicin, $n = 26$ (78.78%) or AS_2O_3, $n = 4$ (12.12%) or daunorubicin (45 mg/m^2

days 1-3 and cytosine arabinoside (100 mg/m^2 continuous IV infusion days 1-7), n = 3(9%). Later cases were treated before year 2000 when ATRA was not easily available in India. Following induction therapy, 26 patients achieved CR. Out of remaining 7 patients, 6 (18.18%) died during induction, 4 (12.12%) within 14 days of induction, (early mortality) while 2 after 14 days, due to bleeding and sepsis. One patient did not achieve CR and required reinduction with high dose cytosar to achieve CR. Thus, the CR rate for all 33 patients was 27/33 = 81.81%.

All the 27 patients who achieved CR received consolidation chemotherapy using ATRA + daunorubicin, n = 23 (85%), arsenic trioxide, n = 2 (7.4%) or daunorubicin + cytosar, n = 3 (11.11 %), high dose ARAC, 1(3.7%). Twenty-four patients received maintenance chemotherapy; ATRA+MTX+6MP, n = 21 (87.5%), As_2O_3 alone, n = 2 (8.33 %), and ATRA alone, n = 1(4.17 %).

Complications during induction therapy with ATRA were febrile neutropenia (FN), n = 21(64%), ATRA syndrome, n=10 (33%), bleeding, n = 19 (58%), and diarrhea, n = 2 (6%) patients.

Of 33 patients, 21 developed febrile neutropenia. Clinical sites of infection (n = 19) were chest 4(12.12%), genito-urinary 7(21.21%), skin and soft tissue 5(15.15%), oral cavity 2(6%) and central line 1(3%). Radiological abnormality was identified in 7 patients (21.21%) mainly being chest 6(18.18%), and sinusitis in 1 patient. The microbiological source could be identified in 7 patients, blood culture (5) and wound swab culture (2).

Ten of 33 patients developed ATRA syndrome. Most common features were dyspnea in 9, weight gain in 8, pulmonary infiltrates in 4, skin rash in 1 and tachycardia in 3 patients. The mean time for ATRA syndrome was 7.5 days with a range of 1-22 days. All patients responded to temporary discontinuation of ATRA and treatment with dexamethasone. This is conceivable that this policy along with early institution of chemotherapy prevent the development of life-threatening manifestations of ATRA syndrome. All These patients were successfully rechallenged with ATRA and completed the remainder of their induction regimen uneventfully. There were no cases of a differentiation syndrome documented either in consolidation or in maintenance with AS_2O_3 therapy.

Bleeding episodes occurred in 19 (58%) patients. Two patients had intracranial bleed and then succumb to their illness. Other sites were oral cavity, nasal, pulmonary, gastrointestinal, retinal, vaginal, and hematuria. Among these, five had a deranged coagulation profile.

Previous studies have raised concerns for the cardiac[18,19] and hepatic[20] toxicity with the use of As_2O_3. We documented asymptomatic QTc prolongation in one patient; no other event was recorded. In this series, grade III transaminitis was recorded in two patients; it reverted to normal on temporary discontinuation of therapy and on rechallenge, patients did not manifest it again.

Four patients relapsed at a median time of 63 months. These patients received re-induction therapy [Daunomycin and ATRA (2), As_2O_3 (1), ATRA (1)]. Three patients achieved second CR and were given consolidation and maintenance therapy. One patient expired during induction therapy, other one developed second malignancy (Base of tongue) 6 years after completion of treatment.

Of 33 patients, 25 are alive till the time of censoring with a median follow up of 13 months (range 0.6-127 months); 21 patients are in first CR, 3 in second CR and 1 in third CR. Eight patients (24.24%) died; 6(18.18%) during induction, 1(3%) during maintenance, and another during re-induction (after relapse). Among these, six patients were of intermediate risk and two were of high risk category. Median OS for all patients is 128 months [Figure 1]. Median EFS is 61 months and median RFS is 61 months. In this cohort, the 2-year Kaplan-Meier estimates of OS, DFS, and EFS were 75.13% ± 8.51%, 83.08% ± 1.1%, and 62.15% ± 1.08%, respectively [Figures 1a, b and 2a, b].

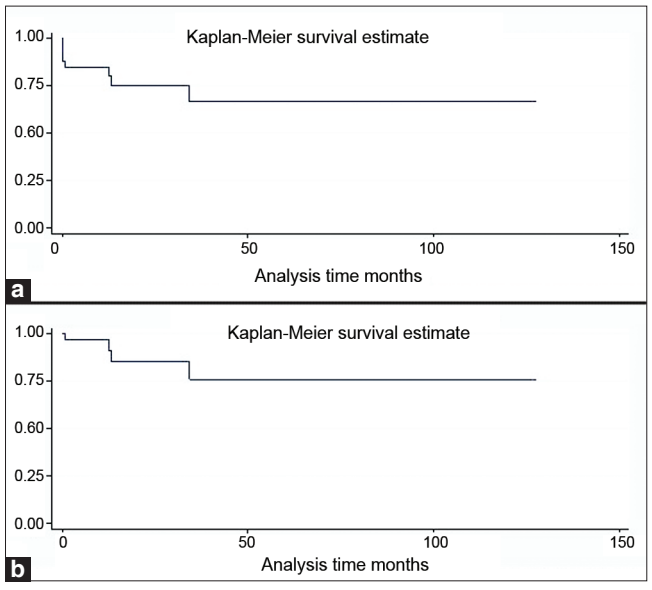

Figure 1: The overall survival curves of all patients by risk group (a) and of those who survived first 14 days of induction (b)

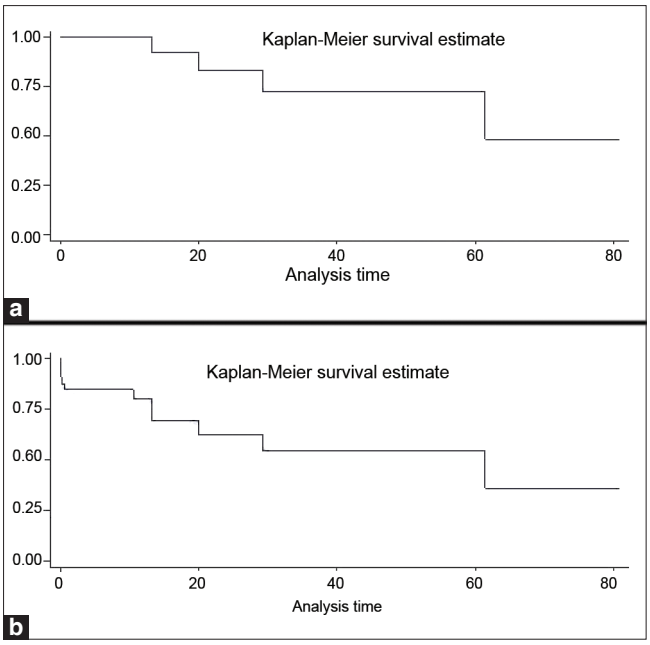

Figure 2: Relapse free survival (a), event free survival (b). Median OS for all patients is 128 months. Median EFS is 61 months and median RFS is 61 months. In this cohort, the 2-year Kaplan-Meier estimates of OS, DFS and EFS were 75.13% ± 8.51%, 83.08% ± 1.1%, and 62.15% ± 1.08%, respectively

Discussion

In present study, we performed in depth analysis on 33 patients with APL treated at our centre. Base line characteristics of these patients are similar to earlier reports.[4,5]

Based on the risk score, about 23% of patient had high risk disease, almost similar to earlier studies by PETHEMA and GIMEMA group (23.25 vs. 22.6%).[14] The CR rate of 81.81% in our series is similar to earlier studies but is slightly lower than that reported in multicentric studies from Italy and Spain.[21,22] Higher induction mortality is possibly due to delay in referral of these patients when they already have coagulopathy/bleeding ± infection. Although the time taken to reach specialized care was not accessed, studies on other hematological malignances suggest that this factor may be associated with the frequency of high tumor burden.[23] Because of rarity of this condition, diagnosis may not be suspected by a referring physician, leading to delay in referral. Therefore, an early diagnosis and prompt referral to a specialized centre may help to salvage some of patients in this highly curable disease.

We have used ATRA and daunomycin-based therapy for induction and consolidation followed by maintenance therapy. Recently, we have also used As_2O_3 as induction therapy based on earlier reports and experience from South India that As_2O_3 may be associated with similar CR rates with less morbidity.[24-26]

In a recent Indian study it was found that single-agent ATO in the management of newly diagnosed cases of APL is safe and is associated with durable responses.[27]

Relapse of APML still remains a problem in 10-15% of patients. In the present study, the relapse rate was 12% (4/33), which is similar to those of large international studies (PETHEMA and GIMEMA groups) (12.4 %).[14] In our study, the median time to relapse was 61 months; all relapses were hematological (medullary). Slightly higher incidence of extramedullary relapse particularly in CNS has been reported in earlier studies.[21,22] It is possible that with more number of cases and with longer follow up we may also see some extramedullary relapses.

Eight of 33 patients died (24.2%); 6 (18.2%) during induction. Four patients (12.12%) died within 14 days of diagnosis (early mortality), while 2 patients died after that mainly due to bleeding and sepsis. One patient (3%) died during maintenance and 1(3%) died during re-induction therapy (after relapse). The overall survival curves of all patients of the risk group and of those who survived first 14 days of induction respectively are shown in Figure 1. The comparative analysis of these two curves reinforces the hypothesis that support during induction is the major issue to be addressed in developing countries. Patients with intermediate and high risk disease (based on WBC and platelet counts at initial presentation) have higher risk of mortality and relapse as seen in previous studies, though observed difference was not statistically significant in the present study (possibly due to small numbers). Such patients can be benefited with more intensive supportive care during induction.

Our experience in relatively small number of patients support and confirm earlier reports that both ATRA and arsenic trioxide are effective in treatment of APL with achievement of high CR rates. But, in spite of tremendous progress in management of APL a sizable proportion of patients will eventually die of early complications during induction or of disease relapse after standard treatment. Therefore, therapeutic approaches should target two minor, but sizable, subsets individually. Identification of patients at highest risk of early death at diagnosis and taking more intensive supportive measures and, perhaps, less intensive induction treatment may help to reduce the induction mortality. Identification of patients at high risk of relapse (by molecular monitoring and /or based on WBC and platelet

Table 3: Review of the literature

Year	Country	Author and reference no	*n*	CR, %	DFS (%)	OS (%)
1997	Italy	Mandelli *et al.*[21]	108	95	79 ± 3.2 (2 y)	87 ± 2 (2 y)
1999	Spain	Sanz *et al.*[22]	109	89	92 ± 3 (2 y)	82 ± 4 (2 y)
1999	India	Advani *et al.*[30]	43	ATRA 72; ATRA+CT76	42 (4 y)	
2002	United States	Tallman *et al.*[31]	350	ATRA70; DA73	69 (5 y) 29 (5 y)	69 (5 y) 45(5 y)
2003	France	Bourgeois *et al.*[32]	576	92.5		77-84 (5 y)
2003	Italy	Avvisati *et al.*[33]	807	94.3	EFS (n=268):70 (5 y)	
2003	Australia	Iland [34]	101	90		88 (5.7 y)
2004	Spain	Sanz *et al.*[9]	426 (79)*	90	81 (3y, LPA96), 90 (3y, LPA99)	
2006	Brazil	Jacomo *et al.* and Ribeiro *et al.*[35,36]	148			133 pts: 1.7 y, excluding early mortality 2.3 y
2006	India	Mathews *et al.*[16]	72	86.1	87.21± 4.93 (3 y)	86.11± 4.08 (3 y)
2007	Japan	Asou *et al.*[37]	283	94	68.5 (6 y)	83.9 (6 y)
2007	Brazil	Rafael *et al.*[23]	157	72.85		23.5 months
2010	India	Mathews *et al.*[27]	72	86%	80% ± 5.2% (5 y)	74.2% ± 5.2% (5 y)
2008	India	Present study	43 (33 treated)	81.81	83.08 ± 1.1	75.13 ± 8.51

DFS= Disease-free survival; OS= Overall survival; EFS= Event-free survival; DA, Daunorubicin and cytarabine; pts= Patients; *Low risk (WBC count <10 × 10^9/L; platelet count <40 × 10^9/L). LPA96, CT in consolidation therapy. LPA99, CT+ATRA in consolidation therapy

counts) can help to take appropriate measures (e.g. post remission intensification with anthracyclines, and/or hematopoietic stem cell transplantation) to reduce further late mortality in this otherwise a highly curable disease. Whether patients with low risk disease can be given less aggressive induction and shorter maintenance therapy need to be defined in future studies.

Table 3 is showing summary of the results of present and previous studies.

In addition to that, in a study it was demonstrated that although efficacy of ATRA combined with chemotherapy in elderly APL was similar to younger APL, elderly patients had lower overall survival at 10 years and reduction of intensity of post-remission chemotherapy along with non-myelosuppressive agents such as arsenic trioxide and/or tamibarotene should be considered in elderly patients.[36] In another study, the risk-adapted strategy was used and it was shown that for low/intermediate risk children, the anthracycline-based plus ATRA consolidation is equally effective as the previous cytarabine-containing regimen and resulted into a significant improvement in OS for all children. Further, it was demonstrated that cytarabine coupled to anthracyclines and ATRA during consolidation is having role in the high-risk group of APL patients.[37]

Although we have a limitation of small sample size we may conclude that APL is predominantly a disease of younger age and is highly curable. Our results confirm the published literature from larger cooperative studies from the West as well as from other parts of India. We may further improve outcome with quicker diagnosis and more efficient supportive care system. The major challenges for future clinical trials are to better define the two risk groups (for death and for relapse) and to target these subsets individually to achieve long-term meaningful survival.

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