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Acute Promyelocytic Leukemia: A Decade Long Experience with Evolving Treatment Strategies

Prakash Singh Shekhawat[1], Prakas Kumar Mandal[1*], Malini Garg[1], Avriti Baveja[1] and Tuphan Kanti Dolai[1]

[1]Department of Hematology, NRS Medical College; Kolkata-700014, India.

Authors' contributions

This work was carried out in collaboration among all authors. Authors PSS, PKM and MG designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors MG and TKD managed the analyses of the study. Authors PSS, MG and AB managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Aims: To study the characteristics and outcome of Acute promyelocytic leukemia (APL) patients.
Study Design: Retrospective analysis of APL patients (n=106) treated at the Department of Hematology, NRS Medical College, Kolkata over a period of more than 10 years from October 2009 to September 2020 was done.
Methodology: Patients were treated with ATO, ATRA+ATO and ATRA+ Anthracycline depending on their Sanz risk stratification. Presenting symptoms, clinical spectrum, events (relapse, death, dropout, and refractory disease), and response to treatment was analyzed. Overall survival (OS), event free survival (EFS) and relapse free survival (RFS) were calculated.
Results: Median age was 26.5 (range, 2-71) years with M:F ratio of 1.7:1. Majority presented with bleeding (91.3%) followed by anaemia (84.4%) and fever (78%). Median hemoglobin, TLC and platelet count were 95gm/L, 6.15 x 10^9/L and 52 x 10^9/L, respectively. As per Sanz risk criteria Low risk (45.3%) was the commonest followed by Intermediate risk (29.2%) and high risk (25.5%). About half of the cases had BCR1, while BCR 3 (41.5%) and BCR 2 (7.55%). ZBTB/RARA t (11;17) was detected in 2 cases (1.9%) and were treated with AML like therapy. Patients with BCR3

**Corresponding author: E-mail: pkm.hem@gmail.com;*

transcript was significantly associated with low platelet count(p=0.009), low Hb (p=0.02) and high TLC (p=0.01) at presentation (p<0.05). Induction mortality was 16.9% and it was significantly associated with low Hb and low platelet count (P<0.05). Most common cause of death was hemorrhagic death. Children (≤18yr) had significantly more differentiation syndrome (DS) than adults (>18yr) (p=0.007). Remission was attained in 83% patients. Median OS, EFS and RFS were not reached. At 10-year OS was 79.1%, EFS was 63.5% and RFS was 78.3%. OS in ATRA+ chemotherapy arm was significantly inferior than ATO (p=0.01) and ATRA+ATO arm (p=0.008), while there was non-significant difference in OS between Vesanoid vs generic ATRA, with or without maintenance.

Conclusion: Bleeding was the commonest presentation. Low risk category was commonest.
Low Hemoglobin and low platelet were significantly associated with Induction mortality and BCR3 transcript. OS in ATRA chemotherapy was significantly inferior to ATO and ATRA+ATO arm ; without any significant difference in OS between original ATRA vs generic ATRA, with or without maintenance, risk categories, or children vs adults.

Keywords: Acute promyelocytic leukemia; sanz criteria; evolving therapy; outcome; decade long experience.

1. INTRODUCTION

Acute promyelocytic leukemia (APL) is a unique and rare subtype of acute myeloid leukemia (AML) due to PML-RARA fusion and high cure rate [1]. Most APL have t(15;17)(q22;q21) translocation causing maturation arrest [2]. About 8% cases lack the typical t(15;17)(q22;q21) on cytogenetics [3]. APL commonly presents with fatigue, epistaxis, gum bleeding, ecchymosis, visual disturbances secondary to retinal/vitreal hemorrhage, and disseminated intravascular coagulopathy (DIC). All trans retinoic acid (ATRA) and supportive care should be started at first suspicion of APL along with intensive monitoring and management to control life-threatening bleeding and DIC. APL field has been moved since the introduction of ATRA in 1988 and arsenic trioxide (ATO) (1996), and recently ATRA+ATO has been strongly supported vs. ATRA+ chemotherapy for the non-high-risk APL [4-6]. Measures to maintain fibrinogen above 100–150 mg/dL, platelets above 30–50×10^9/L, and INR <1.5 should be undertaken to reduce early hemorrhagic and DIC deaths [4]. Most of the early death are due to hemorrhage. Early death (21-26%) was in the pre-ATRA era [7,8], which has significantly reduced to 9-12% after addition of differentiation agents in the ATRA era [9-11] and further reduced to (0-6%) with addition of ATO [5,12,13].

2. MATERIALS AND METHODS

We retrospectively analyzed data of APML patients attending hematology care center. Out of 117 patients, 11 did not get admission due to logistic issues. We analyzed data of 106 cases who were on treatment since 2009. Sanz criteria [11] was used for risk stratification into Low Risk (LR), Intermediate risk (IR), and high risk (HR) based upon presenting TLC and platelet count. Till 2014, we used original ATRA (Vesanoid, Roche pharmaceuticals, Nutley, New Jersy, USA) plus Anthracycline for IR, HR, and ATO for the LR category. From 2015 onwards, patients received generic ATRA as part of Govt. supply, free of cost and started ATRA/ATO for LR and IR. From 2018 onwards, we stopped maintenance for LR and IR patients. Early death was defined as death occurring during induction. Categorical variables were presented in number and percentage (%), and continuous variables were presented as mean ± SD and median (range). Quantitative variables were compared using the unpaired t-test. Correlation was studied using Pearson's correlation coefficient, and the p-value was calculated from the r score. Survival analysis was done using Kaplan Meir curves and survival curves were compared using log-rank test and a p-value of <0.05 was considered statistically significant and data was analyzed using GraphPad Prism version 8 (San Diego, California, USA).

3. RESULTS

The median age of the study cohort was 26.5 years (range, 2 – 71 years) with a male preponderance; male to female ratio was 1.71:1. Baseline CBC parameter revealed median Hb 95g/L (range, 20-166), median TLC 6.15 x 10^9/L (range, 0.8-82) and median platelet was 52 x 10^9/L (range, 2-778). Most common PML-RARA transcript was BCR1 (49.05%; n=52) followed by

BCR3 (41.45%; n=44) and BCR2 (7.55%; n=8) while two patients had t(11:17) as ZBTB/RARA. They were classified as per Sanz criteria into low risk (45.3%; n=48), Intermediate risk (29.2%; n=31) and high risk (25.5%; n=27). Twenty-six (24.5%) patients received single-agent ATO, while ATRA+ATO and ATRA + Chemotherapy were used in 39 (36.8%) and 41 (38.7%), respectively. Two patients were treated with AML like protocols because of ZBTB/RARA. Out of 106 patients, 18 (17%) died in the induction, and four (3.77%) died post-induction. Overall mortality was significantly more in ATRA/chemo (15/41) arm than ATO (2/26) and ATRA/ATO (5/39) groups (p=0.005; chi-square test). All those who survived induction had achieved remission (83%; n=88). Median time to achieve remission was 44 days (range 32-57). Major events were seen in 31 (29.25%) cases. Eleven cases (10.4%) had relapsed after achieving morphological remission. Differentiation syndrome was seen in 12 (11.3%) cases, while six (5.66%) had DIC. Children (≤18yr) had significantly more differentiation syndrome than adults (>18yr) (p=0.007). Febrile neutropenia was seen only in 2 (1.88%) cases. The most common presenting symptom was bleeding (91.3%), followed by anemia (84.4%) and fever (78%). Hepatomegaly was seen in 11% of cases. Most common cause of death was hemorrhagic death. Early hemorrhagic death accounted for 11.32% (12/106). Induction mortality was significantly associated with low Hb and Low platelet count (p<0.05; Pearson correlation). Patients with BCR3 transcript was significantly associated with low platelet (p=0.009; Fisher's exact test), low Hb (p=0.02) and high TLC (p=0.01) at presentation. (p<0.05; Pearson correlation).

3.1 Survival Analysis

Overall Survival was 79.1% at 10 year. Survival outcomes over years were calculated and are represented in Table 1.

Table 1. Survival outcomes (expressed as percentage)

Survival		2 year	5 year	10 year	Median
Overall Survival (79.1% at 10 years)	LR	87.4	87.4	87.4	Not reached (NR)
	IR	70.2	70.2		NR
	HR	74	74	74	NR
	With maintenance	94.2	94.2	94.2	NR
	Without maintenance	100	100	-	NR
	ATO	91.7	91.7	91.7	NR
	ATRA/ATO	88.1	88.1	-	NR
	ATA/Chemo	62.4	62.4	62.4	NR
	Pre 2015	78.57	78.57	78.57	NR
	From 2015 (with generic ATRA)	79.3	79.3	-	NR
	ATRA innovator (Vesanoid)	61.1	61.1	61.1	NR
	ATRA generic	79.3	79.3	-	NR
	Children ≤18yr	75	75	75	
	Adults >18yr	80.6	80.6	80.6	NR
Relapse Free Survival (78.3% at 10 years)	With maintenance	92.5	84.3	77.53	NR
	Without maintenance (LR, IR from 2018)	100	100	-	NR
	Pre 2015	90.7	81.81	74.8	NR
	From 2015 (with generic ATRA)	96	85.6	-	NR
	ATO	90.75	81.81	71.8	NR
	ATRA/ATO	97.36	85.2	-	NR
	ATRA/Chemo	91.4	83.8	83.8	NR
	LR	92.7	83.4	73.9	NR
	IR	94.7	78.9	-	NR
	HR	93.7	93.7	93.7	NR
Event free Survival (63.5% at 10 yrs)	LR	82.9	74.7	66.1	NR
	IR	70.6	58.8	-	NR
	HR	69.4	69.4	69.4	NR

There was no significant difference in OS after switching to ATRA+ATO from year 2015. Although OS in generic ATRA patients was better than innovator ATRA, but it was not significant. There was no OS difference between patients with maintenance or without maintenance for the LR, IR group. Fig. 1 and Fig. 2 shows survival analysis and treatment outcomes.

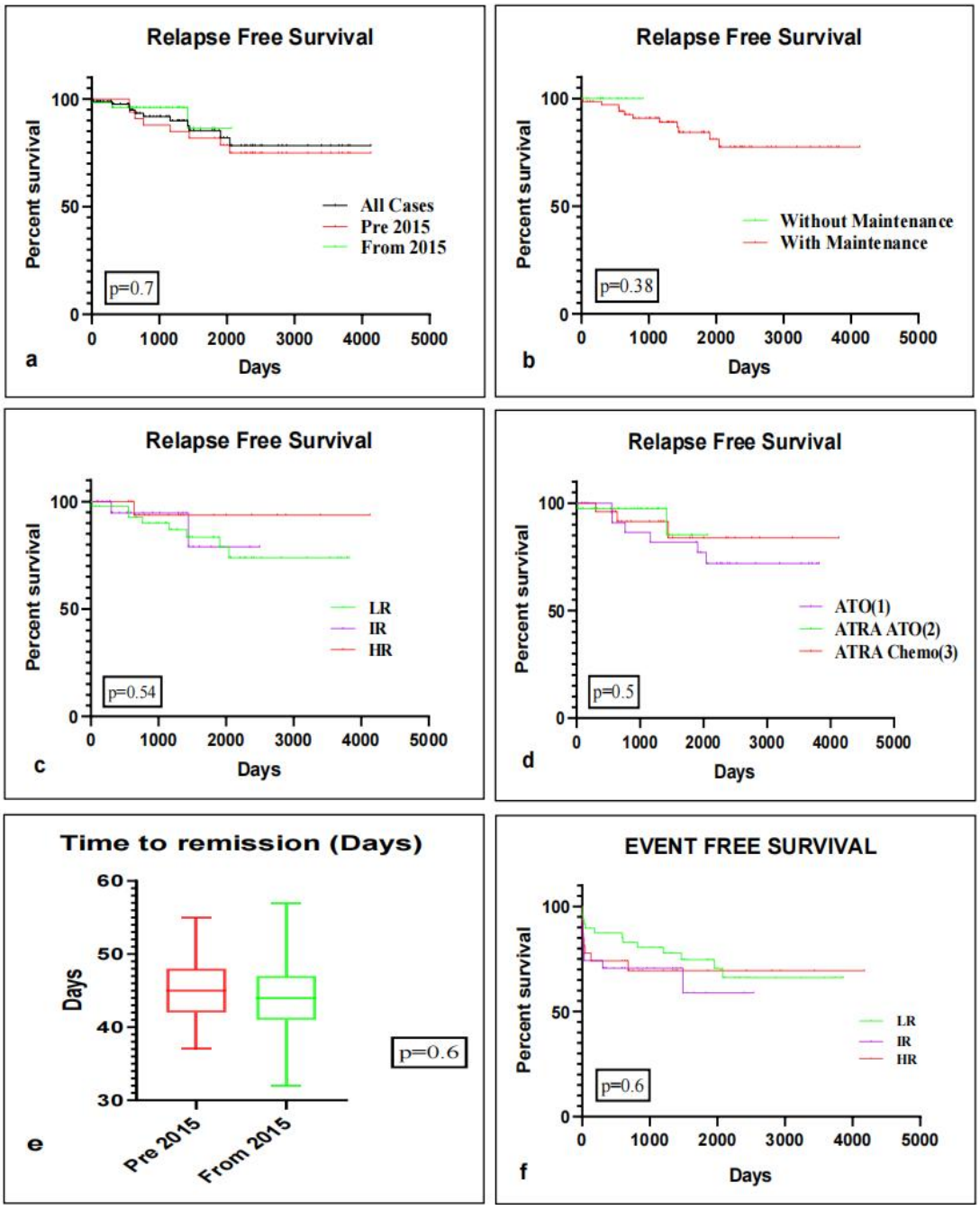

Fig. 1. Treatment outcome including RFS, EFS and Time to remission, (a) shows RFS with pre 2015 vs. from 2015 (b) RFS in respect to with maintenance vs. without maintenance (c) RFS for different risk categories(d) RFS according to type of therapy (e) Time to remission pre 2015 vs. from 2015 (f) EFS according to risk categories

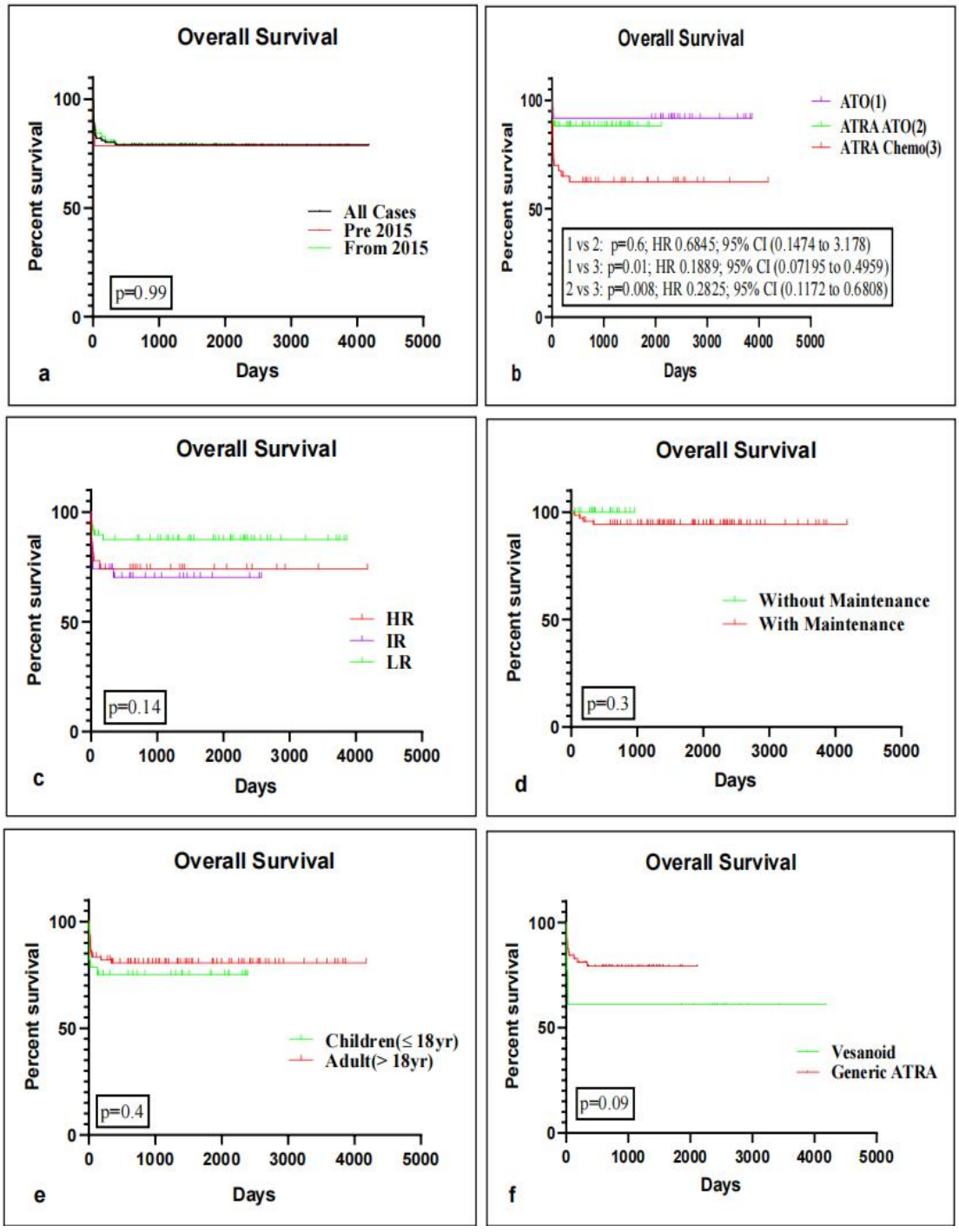

Fig. 2. Shows Overall survival, (a) OS with respect to pre 2015 vs. 2015 (b) OS according to type of therapy(c) OS according to risk categories (d) OS in with maintenance vs. without maintenance arm (e) OS in children vs. adult (f) OS on vesanoid vs. generic ATRA

Patients who received ATRA plus chemotherapy had significantly inferior OS vs ATO alone (p=0.01) and ATRA + ATO group (p=0.008). Relapse-free Survival was not different between cases till 2015 and post 2015 and, also no RFS difference between innovator and generic ATRA.

4. DISCUSSION

Patients' Median age was 26.5 years (Range 2-71yr), which was almost like another Indian study with a male preponderance and M:F ratio of 1.71:1 [14-18]. Median age was higher in GIMEMA and PETHEMA group studies [19,20], whereas Rasekh EO et al, had shown median age similar to the present data [21]. Most of our patients were at low risk, followed by intermediate and high risk. Our study's high risk was comparable to other studies by Bajpai J et al (23%) and by PETHEMA & GIMEMA joint study (23%), while a decade-long experience by Yedla RP et al, had almost 43.3% in high-risk group [14,16,19]. Most common presenting symptom was bleeding followed by anemia. In our study, BCR1 was the commonest transcript (49.05%); which was the same in another study [22]. We found that BCR3 transcript was significantly associated with high TLC at presentation; similar to another Indian study [22] and low Hb and low Platelet count. One of the unique complications with APL treatment is differentiation syndrome, which sometimes warrants temporary therapy cessation. Overall, 11.3% cases had differentiation syndrome, and it was seen significantly more in Children (≤18yr) than adults (>18yr). TLC >10 x 10^9/L and thrombocytopenia <40 x 10^3 /L was more frequent in children than adults, but it was not statistically significant, unlike shown by Rasekh EO et al. [21]. Given lack of consensus and paucity of available resources, we have treated 2 of our ZBTB-RARA patients with AML like 3+7 therapy; of which one died in third cytarabine consolidation.

Early death rate was 17% (18/106); out of these eighteen induction deaths, 12 were hemorrhagic deaths. Thrombotic DIC was seen in three cases, whereas one died due to differentiation. Two out of 18 early deaths were due to sepsis. The early death in APL is well above 20% in the real-world scenario, as opposed to <10% reported in various clinical trials [23,24]. Our induction mortality was comparable to other north Indian studies having mortality of 18.1% and 14.7% [14,17] and it was lower than 23.1% by Xu F et al [25]. All those who survived induction achieved remission. Our remission rate of 83% was similar to earlier Indian data 82% CR1 from AIIMS, New Delhi [14,17]. Relapse was seen in 11(10.4%) cases. Early deaths were significantly associated with lower platelet count [26]. Median OS was not reached (NR). Overall Survival of our patients was 79.1% at 10yr. Ten-year OS was 87.4% for LR, whereas it was 74% for the HR category. From 2015 we have started using ATRA+ATO to LR, IR instead of previous ATO (for LR) and ATRA+ chemotherapy (for IR). We also started using generic ATRA in 2015. Although OS for generic ATRA arm at five years (79.3%) was slightly better than earlier used innovator ATRA (61.1%), but it was not statistically significant (p>0.05). We have found generic ATRA to be effective and it cost saving. Thus, use of generic drugs in APML is effective and of importance in LMIC/resource poor settings where cost is an important issue and using cheaper effective generic ATRA can mitigate the risk of early deaths. Previously, generic ATO has been shown to be effective in APML by CMC Vellore group [27]. OS was significantly inferior in ATRA+ chemotherapy arm (62.4%) compared to 88-91% in non-chemotherapy arm with sustained remission as shown in other study [5]. This finding was like multiple studies proving the efficacy and benefit of ATRA+ATO [5,6,13,19]. APL is one of the most curative hematological malignancies with cure rate already in the range of nineties. However, the use of upfront anthracycline is known to cause increased hemorrhagic deaths, so ATO has been moved in the induction of APL after its promising result in relapsed APL. After the introduction of ATO, early hemorrhagic deaths had been further reduced. In our study, Upfront ATO and ATRA in low-intermediate risk groups had shown significantly better response than the ATRA chemotherapy group (5year OS 88% vs. 62.4% in ATRA + chemotherapy group). Poor outcome in chemotherapy arm is partly contributed by increase in DIC and increased sepsis with anthracyclines [28]. ATO is the most active agent in APL, which has both differentiating and apoptotic activity. Using ATO vs. chemotherapy has shown significant reduction in overall bed admission days, cost, neutropenia, and fungal infections [27]. Single-agent ATO treated patients had an overall molecular remission of 80% from another Indian study suggesting single agent ATO is effective [29].

RFS at 10year was 89%. Relapse frees Survival for the maintenance arm at 10yr was 77.53%. Unlike many other studies, we found that our 10year RFS was best in HR category (93.7%) followed by IR (78.9%) and then LR category (73.9%), although there was no statistical difference (p>0.05).

Maintenance: We have stopped maintenance since 2018 for the LR and IR group, and we did not find any significant difference in RFS and OS.

Although follow-up period was short, there was no statistical difference in OS at two years amongst those who received maintenance (92.5%) vs. those who did not receive maintenance (100%). OS at 2year was 100% without maintenance vs. 94.26% in those who received maintenance. This shows that maintenance can be safely eliminated in the non-high-risk categories, as shown in other studies [30,31].

EFS was 63.5% at ten years. EFS at two years was better in LR than IR and HR, while the gap was reduced as time goes by and EFS at 10yr was best in HR (69.4%) followed by LR (66.1%) and IR (58.8%), but there was no significant difference between EFS in different risk categories.

Thus, the study highlights on: a) Bleeding was commonest presentation in APL, b) Early hemmorhagic death were commonest cause of death, c) Low Hb and Low platelet count was significantly associated with induction mortality, d) ATRA with chemotherapy group had significantly poor OS than non-chemotherapy groups.

The present study has the major limitation of being retrospective and non-randomized one, but it shows promising result in a large number of patients with long term follow up.

5. CONCLUSION

APL being one of the most curable and fatal malignancy needs us to be on the toe and start therapy at slightest doubt. Early hemorrhagic death being the most dreaded, common cause of death. We had male preponderance against almost equal M:F in western countries. BCR1 was commonest transcript, while bcr3 was associated with high TLC. Substitution of chemotherapy by ATO did not have any adverse outcome in terms of RFS. However, OS was improved, better in ATRA+ATO than ATRA+ chemotherapy. Mortality was highest in ATRA+ chemotherapy group. Generic ATRA is a cheaper and equally effective option and a ray of hope for the LMICs. Omitting maintenance in non-high-risk groups did not affect outcomes (OS and RFS) and can safely be omitted in these groups. Variant RARA transcript does poorly to conventional therapy.

CONSENT

As per international standard or university standard and hospital OPD/IPD registry, patients' written consent has been collected and achieved by the Institute.

ETHICAL APPROVAL

The present study is an analysis of retrospective data from the hospital/institute archive. All the patients had given written consent for OPD/IPD attendance that is preserved by the Institute.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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