ORIGINAL ARTICLE

TREATMENT OUTCOMES OF PATIENTS WITH NEWLY DIAGNOSED ACUTE PROMYELOCYTIC LEUKEMIA; EXPERIENCE FROM A DEVELOPING COUNTRY

Hammad Javed, Qamar-un-Nisa Chudary, Raheel Iftikhar, Nighat Shahbaz, Mehreen Ali, Saima Hamayun

Armed Forces Bone Marrow Transplant Center, Rawalpindi-Pakistan

Background: Acute promyelocytic leukaemia (APL) characterized by t (15;17) leading to formation of fusion protein PML-RARA is an acute leukaemia with highest mortality. A remarkable improvement in the outcomes has been witnessed due to evolution of highly effective targeted therapies replacing the traditional chemotherapy is most patients. However limited data is available regarding treatment outcomes of APL using various novel regimens from developing countries like Pakistan. **Methods:** This was a retrospective descriptive study which included APL patients treated at AFBMTC Rawalpindi from 2005 to 2020. It included a total of 51 eligible patients with a diagnosis of de novo APL confirmed by the presence of PML-RARA transcript or presence of t (15;17) by cytogenetics or FISH analysis. The protocols used for treatment included the UKAML MRC 12, the LPA-99/LPA-2005 PETHEMA, the APML4 and non-chemotherapy based ATO-ATRA protocol. **Results:** The study included 51 patients in which 31 (60.78%) were male and 20 (39.2%) were female. The median age at diagnosis was 30 years (range 5–70). The commonest symptom was fever seen in 43 (84.3%) patients and bruising was the commonest physical finding present in 44 (86.3%) patients. High-risk patients were 23 (46.1%), 18 (35.3%) were intermediate risk and 10 (19.6%) were low risk. The LPA99/LPA2005 was most frequently employed protocol being used in 36 (72%) patients. There were 2 deaths during induction and 44 (86.3%) achieved CR post induction. The median follow up time was 32 months (range 1 to 190 months) with an overall survival (OS) of 76.5% and a relapse free survival (RFS) of 66.7%. **Conclusion:** Our study shows APL is a highly curable malignancy and outcomes have improved with newer non-chemotherapy based therapies. It can also be concluded that outcomes of APL gradually improved over the past 2 decades due to improvement in supportive care, provision of blood products and use of newer protocols. The prognosis remains less favourable in high risk patients.

Keywords: Acute promyelocytic leukaemia (APL); All trans retinoic acid (ATRA); Arsenic trioxide (ATO)

Citation: Javed H, Treatment outcomes of patients with newly diagnosed acute promyelocytic leukaemia; Experience from a developing country. J Ayub Med Coll Abbottabad 2022;34(4):791–6.

DOI: 10.55519/JAMC-04-10127

INTRODUCTION

Acute promyelocytic leukaemia (APL) first described by Hillestad in 1957[1], is a peculiar subtype of acute myeloid leukaemia (AML) characterized by a specific cytogenetic abnormality, i.e., t (15;17) and a high induction mortality[2]. The cytogenetic abnormality leads to fusion of PML and RARA genes and production of an abnormal fusion transcript called PML-RARA. The PML-RARA fusion transcript causes maturation arrest and excessive proliferation of myeloid precursors at promyelocytes stage. These abnormal promyelocytes cause a coagulopathy which is the cause of high rate of early deaths in this leukaemia.[3] Nevertheless, with recent advances in molecular diagnosis and advent of differentiation-based therapies, APL has become one of the most curable haematological malignancies.[4] The use of ATRA with chemotherapy has resulted in the improvement in survival with long term survival now exceeding 80%.[5–7] This has been further improved by incorporation of arsenic trioxide in the treatment regimen. Arsenic trioxide in combination with ATRA, overcomes the maturation arrest, induces differentiation as well as apoptosis leading to disease eradication.[8,9] The role of supportive care is also vital in preventing early mortality as shown in studies incorporating early administration of steroids for prevention of

ATRA syndrome.[10,11] However, the relapse rate is still in the range of 20–30% and salvage therapy is required in these cases.[12]

There have been numerous landmark studies delineating the evolution of this disease most notably by the GIMEMA and PETHEMA groups but data from developing countries is not available to an appreciable extent. Likewise, there is paucity of published data of treatment outcomes of APL patients from Pakistan. In this study we aim to describe treatment outcomes of APL patients in terms of complete remission (CR), overall survival (OS) and event free survival (EFS)

MATERIAL AND METHODS

This was a retrospective descriptive study in which APL patients treated at Armed Forces Bone Marrow Transplant Center/National Institute of Bone Marrow Transplant (AFBMTC/NIBMT) from 2001 to 2020 were included. The study was approved by the institutional review board of AFBMTC/NIBMT. All the patients with a diagnosis of de novo APL based on bone marrow biopsy and/or molecular/cytogenetic evidence of t (15;17) were included in the study. Other inclusion criteria included age >1 year with no upper limit, Eastern Cooperative Oncology Group (ECOG) performance status 2 or less, ejection fraction (EF) > 60% and corrected QT (cQT) <500 milliseconds, normal renal and hepatic function. All those with relapsed APL, history of prior malignancy and cardiac disease were excluded from the study.

The primary endpoint was overall survival (OS) defined as time from diagnosis till death. Secondary outcome measures which were included in the study were complete remission

There were four protocols used for the treatment of APL patients at our center as shown in table 1. The choice of protocols underwent a transition from anthracycline based multi-agent chemotherapy to a combination of ATRA with chemotherapy to chemo-free ATO-ATRA based therapies. Patients were stratified in low, intermediate and high-risk groups as per Sanz classification (12). High risk patients were treated with ATRA based chemotherapy whereas non-chemo based ATRA-ATO regimen was used for non-high risk patients only. The risk class was not switched after increase of WBC count in response to ATRA and/or ATO therapy.

During induction all the patients were treated indoor and closely monitored for development of disease and treatment related complications including infections, differentiation syndrome (DS), and disseminated intravascular coagulation (DIC). Prednisone at 1 mg/kg/d for 10 days was given to all patients to prevent differentiation syndrome. Coagulation profile was monitored daily until the resolution of coagulopathy. Blood counts and cultures, CRP, serum beta D Glucan and serum galactomannan were monitored for suspected infection. Empirical antimicrobial therapy was started based on hospital guidelines and modified in the light of clinical response and culture results. Blood component support was provided to keep Hb >8 gm/dL, platelets >30 $x10^9$/L, INR <1.5 and fibrinogen >150 gm/dL. Those with hyperleukocytosis were given cytoreductive therapy in the form of idarubicin or cytarabine on a case-to-case basis.[12] ECG was done daily to monitor QTc interval and electrolytes were monitored thrice weekly to look for ATO-induced arrhythmias. For non-haematological toxicity grade 3 or higher, treatment with ATRA or ATO was withheld or lowered to minimal effective doses (25 mg/m2/d for ATRA and 0.08mg/kg/d for ATO)

Bone marrow assessment was done at the diagnosis and at the end of induction to document haematological remission. The timing of bone marrow exam was at the achievement of complete haematological response and not before a minimum of 35 days. Complete remission was defined as a normocellular bone marrow with <5% blasts and abnormal promyelocytes, no circulating blasts and no blasts with Auer rods along with ANC >1.0 $x10^9$/L and platelets >100 $x10^9$/L. Presence of dysplastic features did not exclude a diagnosis of morphological remission. Molecular remission was defined as negative molecular markers, i.e., cytogenetic or FISH for t (15;17) or PCR for PML-RARA fusion transcript. PCR for PML-RARA was done at the end of induction therapy, then at end of consolidation and 3 monthly thereafter during follow up period.

RESULTS

The initial data revealed 58 patients of APL treated at our center out of which 7 were excluded due to incomplete data or as per the exclusion criteria. Majority of the patients were male 31 (60.8%) and females were 20 (39.2%). Median age at diagnosis was 30 years (range 12-58). Majority had an ECOG performance score of 1 or 0 (40%). The morphological diagnosis was hyper granular in 42 (82.35%) and microgranular in 9 (17.65%) patients. Molecular studies revealed abnormal cytogenetics in 11.1%, abnormal FISH findings in 21.40% and PML-RARA was positive

in 100% cases. The clinical characteristics are summarized in table-2.

Fifty-one patients received induction therapy according to the Sanz risk classification. From 2001 to 2004 the regimen solely used was UKAML12 chemotherapy-based protocol. Later on, AIDA protocol was the most commonly used one and employed for all risk groups. APML4 was used for high risk and ATO-ATRA protocol for non-high risk cases (Table-3).

As many as 73% of patients suffered some degree of adverse effects during therapy yet only 15% had grade III/IV adverse events. Febrile neutropenia was the commonest complication which was managed with use of antibiotics as per the institutional guidelines. Differentiation syndrome was the 2nd commonest adverse effect and led to temporary cessation of therapy in 3 patients only. Other common adverse events included transaminitis, DIC, electrolyte disturbances, benign intracranial hypertension and azotaemia. There were 2 deaths during the induction phase due to sepsis and differentiation syndrome respectively. The CR rate was 89.79% post induction. PCR for PML-RARA was negative in 94.87% post induction.

Forty-nine patients went on to receive consolidation therapy of which 45 patients completed and there were 4 deaths during consolidation therapy. A total of 36 patients were eligible for maintenance therapy (13 did not receive maintenance due to either death during treatment or as per the protocol). There were 4 deaths during maintenance and 32 were able to complete maintenance therapy.

There was a median follow up of 70 months and overall survival at 2, 3 and 5 years was 83%, 70% and 66.6% respectively. The survival in low risk group was 90%, in intermediate risk group was 88% and in high risk group was 73.9 % (p=0.54). The overall survival rate as per protocol was 85.7% for UKAML12, 76.4% for AIDA/LPA2005 and 100% for both APML4 and ATO-ATRA protocol (p=0.55). The overall survival for non-ATRA based regimens was 85.7% compared with 92.1% for ATRA based regimens. The survival curve showed a significant survival benefit for those patients who were able to complete the treatment protocol (p< 0.001).

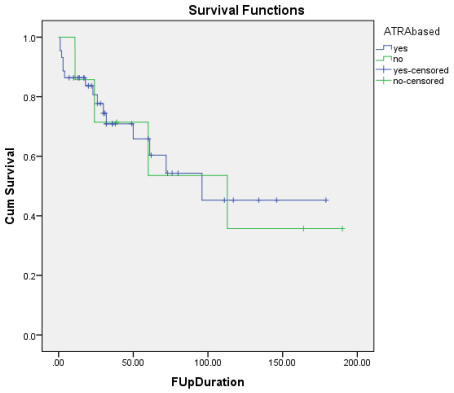

Figure-1: Survival curve of patients receiving ATRA vs non-ATRA based therapy

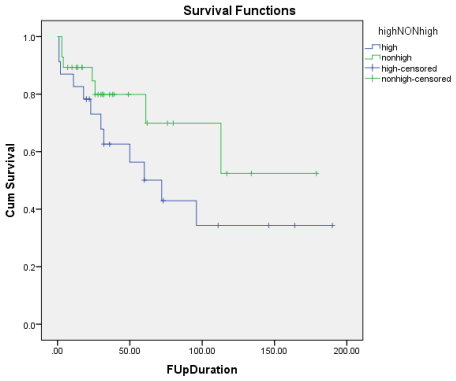

Figure-2: Survival curve of High vs non-high risk patients

Table-1: Regimens used in the current study

Phase / Protocol	Induction		Consolidation		Maintenance	
	Drugs	Duration / Courses	Drugs	Duration / Courses	Drugs	Courses
ADE	Ara-C+ Daunorubicin+ etoposide	1x course	Ara-C+ Daunorubicin+ Etoposide	2x course	Nil	Nil
AIDA (19)	Ida+ATRA	1x course	ATRA with Chemotherapy	3x course	ATRA with low dose chemo	8x 3montyly courses for 2 years
APML4 (17)	Ida+ATRA+ ATO	1x course	ATRA+ATO (Chemo-free)	2x course	ATRA with low dose chemo	8x 3montyly courses for 2 years
ATO-ATRA(18)	ATO + ATRA	1x course	ATO-ATRA (Chemo free)		Nil	Nil

Table-2: Clinical characteristics of patients

Characteristics	No (%)	Median (range)
Total patients	51	
Age		30 years (12-58)
Age subgroups		
<20 years	7 (13.7)	
20-40 years	33 (65.7)	
>40 years	11 (21.5)	
Gender		
Male	31 (60.78)	
Female	20(39.22)	
ECOG Status		
0	25 (49.01)	
1	15 (29.41)	
2	11 (21.56)	
Morphological subtype		
M3	42 (82.35)	
M3v	9 (17.64)	
WBC Count $x10^9$/L		7.0 (0.4 to 245)
Platelet count $x10^9$/L		32 (6-238)
Haemoglobin gm/dL		9 (4.4-16.3)
Sanz Risk		
Low	10 (19.1)	
Intermediate	19 (37.2)	
High	22 (43.1)	

Table-3: Treatment Details

Characteristics	No (%)
Induction regimen	
UKAML-12	7 (13.7%)
LPA-99/2005	34 (66.66%)
APML4	7 (7.28%)
ATO-ATRA	3 (5.8%)
Complications	
Febrile Neutropenia	37 (72.5%)
Differentiation Syndrome	23 (45.01%)
DIC	18 (35.29%)
Transaminitis	13 (25.4%)
Hypokalemia	11 (21.5%)
BIH	6 (11.7%)
Azotemia	5 (9.8%)
Early Death rate	2 (3.9%)
Overall	2 (3.9%)
ATO based regimen	0
Post induction Remission status	
CR	44 (86.2%)
Not in remission	5 (5.8%)
Post induction PCR	
Positive	5.1%
Negative	94.9%

DISCUSSION

This is the largest study to date from Pakistan showing treatment outcomes for acute promyelocytic leukaemia (APL). In 2 studies from AKU hospital Karachi the sample size was 26 patients[13] and 40 patients respectively[14]. Also, this is the first study to incorporate novel, non-chemotherapy based regimens for the treatment of APL patients.

The early induction mortality is a major problem in APL and has been quoted as high as 30% in certain population based studies.[15] In a study from Pakistan, induction mortality was 62% which decreased to 30% in a follow up study where improved supportive care, coagulation support and dexamethasone were added.[14] In a study from Turkey, the early death rate was 5%.[16] The induction mortality in our study was 3.9% as compared with 3.2% in APML4, 7.5% in LPA2005 and 0% in LPA99. It is interesting to note that in our study, the rate of early deaths in patients given ATO-based protocols (APML4 and ATO-ATRA) was zero which is comparable to the international studies. The low induction mortality in our study can be attributed to

pre-emptive use of steroids to prevent differentiation syndromes. DIC, which is a major cause of mortality, was managed with close monitoring of coagulation profile and maintaining fibrinogen levels above 150 mg/dl using cryoprecipitate.

The rate of complete remission (CR) at the end of induction was 89.8% in our study compared with 85% in the Turkish study[16] and 84% in an Indian study. The CR rate for AIDA/LPA protocol was 75.3% in our study compared with 92% in LPA2005. The rate of haematological remission for regimens incorporating ATO (APML4 and ATO-ATRA) was 100% in our study which is comparable to the international trials, i.e., APML4[17] and ATO-ATRA by Lo Coco *et al*.[18]

The incidence of relapse at 3 years was 17.1% in our study. This is comparable to 30% in a Pakistani study[13] and 27% in a Turkish study[16]. The 3-year incidence of relapse for LPA/AIDA protocol was 31.2% in our study compared with 7% in LPA2005.[19] The 2-year incidence of relapse for APML4 protocol was zero compared with 3.5% in the APML4 study by the Australian group.[17] There was a significant relationship between the incidence of relapse and age group with younger patients having more risk (p=0.037) and in those unable to complete the treatment protocol (p=0.005). There was no significant difference in relapse risk with respect to treatment protocol and differentiation-agents based therapy (p=0.47 and p=0.913 respectively).

The 3-years overall survival was 70% in our study compared with 27%[13] and 65%[14] in two Pakistani studies and 75% in an Indian study. In another study from Pakistan, the overall survival for non-ATRA based therapy was 29.4% whereas it was 71.4% for ATRA-based therapy.[20] However, our results are inferior to the reported rates of 94% (APL2000) and 88% (MDACC) reported in international studies. This can be due to the fact that majority (n=22, 43.1%) of our patients belonged to Sanz high risk group. Survival rate in low risk population was 90% which is comparable with international studies.[21] However, survival was lower (74%) in high risk patients which can be attributed to late presentation and higher incidence of induction deaths in high risk group. Lack of early diagnosis is due to fewer diagnostic facilities with molecular methods for detecting PML-RARA by PCR and thus delays in initiating ATRA therapy.

There is a gradual shift in the treatment of APL towards chemotherapy-free regimens as has been in our study as well. This has resulted in better remission induction as well as long term disease control. However, the most important contributor to improved outcomes has been provision of better supportive care. This can be appreciated in the study by Raza *et al*. which showed a mortality rate of 70.6% for non-ATRA based therapy and 28.6% for ATRA based therapy. This is in contrast to our current study which has shown the early death rate of 3.9% only. Frequent monitoring of coagulation parameters with pre-emptive replacement of fibrinogen using cryoprecipitate is vital to prevent DIC and thus improve survival.

Although a small number of patients received ATO-ATRA based regimens, the overall survival of 100% shows that these agents are highly effective in achieving long term remission and lead to cure in majority of cases. This has been shown in recent studies that ATO-ATRA combination is an effective treatment regimen for both high risk and non-high risk patients.[22]

Our study is based on real-world experience of APL patients with a paradigm shift in the treatment strategies as well as outcomes. This is based on scientific evidence and targeted therapies which have enabled improved outcomes with minimal toxicities and better long term survival. There is a need to incorporate ATO-ATRA based therapy at the time of diagnosis based on appropriate risk stratification.

CONCLUSION

Our study shows APL is a highly curable malignancy with an OS rate of 76.5% and induction mortality of 4%. It can also be concluded that outcomes of APL gradually improved over the past 2 decades due to improvement in supportive care, provision of blood products and use of newer protocols. The prognosis remains less favourable in high risk patients as OS in high risk was 74% compared with 90% in low risk group.

Conflict of interest: None
Disclosure: None
Funding: None

AUTHORS' CONTRIBUTION

HJ: Writing the manuscript, data collection and analysis. QN: Overall supervision and final approval of draft. RI: Review of manuscript and statistical analysis. NS; Review of biostatistics and analysis. MA: Review of manuscript and data analysis. SH: Data collection and analysis.

REFERENCES

1. Thomas X. Acute Promyelocytic Leukemia: A History over 60 Years—From the Most Malignant to the most Curable Form of Acute Leukemia. Oncol Ther 2019;7(1):33–65.
2. de Thé H, Pandolfi PP, Chen Z. Acute Promyelocytic Leukemia: A Paradigm for Oncoprotein-Targeted Cure. Cancer Cell 2017;32(5):552–60.
3. Cao M, Li T, He Z, Wang L, Yang X, Kou Y, *et al*. Promyelocytic extracellular chromatin exacerbates

coagulation and fibrinolysis in acute promyelocytic leukemia. Blood 2017;129(13):1855–64.
4. Jimenez JJ, Chale RS, Abad AC, Schally AV. Acute promyelocytic leukemia (APL): a review of the literature. Oncotarget 2020;11(11):992–1003.
5. Osman AEG, Anderson J, Churpek JE, Christ TN, Curran E, Godley LA, *et al*. Treatment of Acute Promyelocytic Leukemia in Adults. J Oncol Pract 2018;14(11):649–57.
6. Yilmaz M, Kantarjian H, Ravandi F. Acute promyelocytic leukemia current treatment algorithms. Blood Cancer J 2021;11(6):123.
7. Zhang X, Liu L, Yao Y, Gong S, Wang M, Xi J, *et al*. Treatment of non-high-risk acute promyelocytic leukemia with realgar-indigo naturalis formula (RIF) and all-trans retinoid acid (ATRA): study protocol for a randomized controlled trial. Trials 2020;21(1):7.
8. Noguera NI, Pelosi E, Angelini DF, Piredda ML, Guerrera G, Piras E, *et al*. High-dose ascorbate and arsenic trioxide selectively kill acute myeloid leukemia and acute promyelocytic leukemia blasts in vitro. Oncotarget 2017;8(20):32550–65.
9. Gurnari C, De Bellis E, Divona M, Ottone T, Lavorgna S, Voso MT. When Poisons Cure: The Case of Arsenic in Acute Promyelocytic Leukemia. Chemotherapy 2019;64(5-6):238–47.
10. Stahl M, Tallman MS. Differentiation syndrome in acute promyelocytic leukaemia. Br J Haematol 2019;187(2):157–62.
11. Abedin S, Altman JK. Acute promyelocytic leukemia: preventing early complications and late toxicities. Hematology Am Soc Hematol Educ Program 2016;2016(1):10–5.
12. Sanz MA, Fenaux P, Tallman MS, Estey EH, Löwenberg B, Naoe T, *et al*. Management of acute promyelocytic leukemia: updated recommendations from an expert panel of the European LeukemiaNet. Blood 2019;133(15):1630–43.
13. Karim F, Shaikh U, Adil SN, Khurshid M. Clinical characteristics, outcome and early induction deaths in patients with acute promyelocytic leukaemia: a five-year experience at a tertiary care centre. Singapore Med J 2014;55(8):443–7.
14. Shaikh MU, Ali N, Karim F, Raheem A, Sarwar S. Improved outcome in early induction deaths in patients with acute promyelocytic leukemia after therapeutic and supportive interventions: a follow up study of seven-years' experience at a tertiary care center. Am J Blood Res 2020;10(4):82–9.
15. Jillella AP, Kota VK. The global problem of early deaths in acute promyelocytic leukemia: A strategy to decrease induction mortality in the most curable leukemia. Blood Rev 2018;32(2):89–95.
16. Yildirim R, Gundogdu M, Ozbıcer A, Kiki I, Erdem F, Dogan H. Acute promyelocytic leukemia, centre, experience, Turkey. Transfus Apher Sci 2013;48(1):45–9.
17. Iland HJ, Bradstock K, Supple SG, Catalano A, Collins M, Hertzberg M, *et al*. All-trans-retinoic acid, idarubicin, and IV arsenic trioxide as initial therapy in acute promyelocytic leukemia (APML4). Blood 2012;120(8):1570–80.
18. Lo-Coco F, Avvisati G, Vignetti M, Thiede C, Orlando SM, Iacobelli S, *et al*. Retinoic acid and arsenic trioxide for acute promyelocytic leukemia. N Engl J Med 2013;369(2):111–21.
19. Sanz MA, Montesinos P, Rayón C, Holowiecka A, de la Serna J, Milone G, *et al*. Risk-adapted treatment of acute promyelocytic leukemia based on all-trans retinoic acid and anthracycline with addition of cytarabine in consolidation therapy for high-risk patients: further improvements in treatment outcome. Blood 2010;115(25):5137–46.
20. Raza S, Ullah K, Ahmed P, Khan B. Comparison of anthracycline-based combination chemotherapy with or without all-trans retinoic acid in acute promyelocytic leukemia. J Coll Physicians Surg Pak 2008;18(9):546–50.
21. Kayser S, Schlenk RF, Lebon D, Carre M, Götze KS, Stölzel F, *et al*. Characteristics and outcome of patients with low-/intermediate-risk acute promyelocytic leukemia treated with arsenic trioxide: an international collaborative study. Haematologica 2021;106(12):3100–6.
22. Zhang X, Zhang H, Chen L, Wang M, Xi J, Liu X, *et al*. Arsenic trioxide and all-trans retinoic acid (ATRA) treatment for acute promyelocytic leukemia in all risk groups: study protocol for a randomized controlled trial. Trials 2018;19(1):476.

Submitted: September 13, 2021	*Revised: June 14, 2022*	*Accepted: June 21, 2022*

Address for Correspondence:

Dr Hammad Javed, Consultant Medical Specialist, Resident Clinical Haematology, Armed Forces Bone Marrow Transplant Centre, Rawalpindi-Pakistan
Cell: +92 334 529 4940
Email: hammad2286@gmail.com