Outcomes of Acute Promyelocytic Leukaemia in Paediatric Patients: Insights from a Low-Middle-Income Country

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ABSTRACT

Objective: To describe the prognostic variables and course of paediatric acute promyelocytic leukaemia (APL) in Pakistan.

Study Design: Cohort study.

Place and Duration of the Study: Department of Paediatric Oncology, Combined Military Hospital, Rawalpindi, Pakistan, from January 2012 to December 2022.

Methodology: Patients aged 1-15 years, clinically confirmed APL with promyelocytic leukaemia- retinoic acid receptor alpha (PML-RARA) were enrolled. Initial admission included a thorough examination, recording demographic and clinical data, reporting time, prior treatment, and socioeconomic status. Statistical analysis used SPSS 25.0, with significance at $p < 0.05$.

Results: This study included 50 cases of APL. Out of which, 32 (64%) were males and 18 (34%) were females. The mean age at diagnosis was 7.02 ± 3.86 years. Pallor (96%) and fever (88%) were common presentations. The average white blood cell count was 28.70 ± 35.39 x10^9/L. Treatment protocols include 48% International Consortium for Childhood (ICC)-APL, and 52% arsenic trioxide (ATO). High-risk cases were 54%. Neutropenic fever and differentiation syndrome were common induction complications. Delays over one month increased induction deaths (6.7 to 35%, $p = 0.011$), reducing disease-free survival (DFS), (76.7 to 35%, $p = 0.001$), and overall survival (OS), (80 to 45%, $p = 0.007$). After 40.90 ± 45.19 months' follow-up, 10-year OS and DFS were 66.0% and 60.0%, respectively. The best OS and DFS, at 80%, were observed in standard-risk cases treated with ATO.

Conclusion: Neutropenic fever and bleeding were the primary causes of mortality in paediatric APL induction. Treatment delay was a key prognostic factor. ATO-based therapy offered safer, improved DFS, and OS suitable for primary healthcare settings.

Key Words: *Acute promyelocytic leukaemia, Chemotherapy, Neutropenic fever.*

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INTRODUCTION

Acute promyelocytic leukaemia (APL) is a rare disease accounting for only 5-10% of paediatric acute myeloid leukaemia (AML).[1] Since the introduction of all-trans-retinoic acid (ATRA) therapy, the prognosis of APL in adults and children has significantly improved. With modifications, paediatric APL has always been treated with adult methodologies.[2] The combination of ATRA and chemotherapy has resulted in exceptional cure rates for both infants and adults over the past few decades.[3] In the 1990s, arsenic trioxide (ATO) was developed, and the treatment strategy for acute lymphoblastic leukaemia (ALL) shifted from standard chemotherapy to cancer cell differentiation and cancer-targeted therapy.[4] Due to the acute and long-term effects of anthracycline chemotherapy, attempts have been made to reduce or eliminate anthracycline from paediatric protocols.[5]

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The standard of care for individuals with APL and at standard risk is a combination of ATRA and ATO without chemotherapy in the induction phase and maintenance therapy. However, it is uncertain whether such regimens are safe and effective for the treatment of high-risk APL or standard-risk APL in adolescents.[3,5] In Pakistan, due to a paucity of medical facilities, high treatment costs, and mortality (TRM), many children with AML are not treated. In addition, there are no national uniform treatment protocols for paediatric AML/APL patients.[6]

This study aimed to evaluate the clinical characteristics and treatment outcomes of paediatric APL patients treated with the International Consortium for Childhood (ICC) APL-01 trial protocol and an ATO-based technique.

METHODOLOGY

This cohort study was conducted in the Paediatric Oncology Department of the Combined Military Hospital (CMH) in Rawalpindi, Pakistan. The study included all participants registered between January 2012 and December 2022, who were initially diagnosed with APL and later found to have promyelocytic leukaemia-retinoic acid receptor alpha (PML-RARA). The patients clinically diagnosed with APL who subsequently tested negative for PML-RARA were excluded from the study. Patients who received alternative chemotherapy for 7 days or longer

without ATRA for any reason (either because APL was not initially suspected or ATRA was unavailable) and those who refused to participate were excluded from the study. The final follow-up to the study was conducted on 30th June 2023. Approval from the Institutional Review Board (Serial No. 438) was acquired and informed consent of the parents / guardians of the patients was obtained.

On admission, a comprehensive clinical examination and medical history were conducted. Data were collected on an Excel sheet and then transferred to SPSS software. The baseline demographic and clinical data collected included age, gender, weight, pallor, fever, bruising, bleeding, bone aches, respiratory symptoms, lymphadenopathy, and visceromegaly. Other essential criteria, such as reporting time, prior treatment information, and socioeconomic status, were also recorded. Bone marrow (BM) morphology and flow cytometric immunophenotyping were used to establish the diagnosis of APL. By demonstrating t (15;17) and / or positive results from reverse transcription polymerase chain reaction (RT-PCR) assays or fluorescence *in situ* hybridisation (FISH) tests for PML/RARA fusion, conventional cytogenetics confirmed the diagnosis. The initial evaluation included a complete blood count, coagulation profile, and biochemical profile, in addition to hepatic and renal function tests and echocardiography to evaluate the cardiac function. Patients were divided into two categories based on baseline white blood cell counts of 10 109/L and 10 109/L: Standard-risk (SR) and high-risk (HR). During the research, two treatments were utilised. During the first five years of the study, from January 2012 to December 2016, the ICC-APL-01 trial protocol was the primary treatment protocol. The SR and HR groups received identical ATRA and idarubicin induction treatments. The SR and HR patients received two or three cycles of consolidation therapy, while rest of the patients received two years of maintenance therapy with low-dose chemotherapy and ATRA cycles.[7] In 2017, an ATO-based approach was adopted as the primary therapy plan for paediatric APL following an interim analysis of treatment outcomes using the ICC-APL-01 trial protocol, input from haematologists treating adult APL patients, and a literature review. SR patients received ATO and ATRA for induction, while HR patients received ATO, ATRA, and Daunorubicin.[4,8,9]

To ascertain response to chemotherapy following induction, BM aspiration was performed no sooner than 7 days after the administration of ATRA. According to the European Leukaemia Network, cases in complete remission and resistant / refractory illness were identified.[10] Morphological complete remission (CR) was defined as <5% blast cells and promyelocytes in the BM. Partial response (PR) and no response (NR) were defined when BM morphology showed more than 5% but less than 25% blasts and 25% or more blasts, respectively. Molecular CR and relapse were defined as the disappearance and reappearance of RT-PCR positivity for the PML-RARA fusion transcript in the BM. Resistant / refractory disease (RD) was defined as the persistent detection of morphological, cytogenetic, and / or molecular evidence of APL after consolidation therapy.[10]

At the time of diagnosis, all patients were hospitalised for APL therapy, hyperhydration, monitoring, and management of any complications. The electrolytes were monitored to keep them within the normal range; specifically, the potassium level was kept above 4 mmol/L, the magnesium level was kept above 0.75 mmol/L, and the serum calcium level was kept within the normal range (2.25-2.74 mmol/L). Following the induction phase of treatment, liver function, renal function, and electrolytes were assessed twice weekly. Monitoring of the QTc interval required electrocardiograms every week. If a patient displayed APL differentiation-like syndrome, dexamethasone (5 mg twice daily) was administered for at least three days, and ATRA/ATO was temporarily discontinued.[11-13]

Statistical analysis was conducted using SPSS 25.0 software. The One-way ANOVA was employed to compare continuous variables as mean, median, and standard deviation, while categorical variables were analysed by Chi-squared tests. Categorical variables were subjected to calculations of frequencies and percentages. A p-value <0.05 was considered as statistically significant. Disease-free survival (DFS) pertains to the duration from CR until the occurrence of recurrence or mortality. The overall survival (OS) encompassed the duration from the date of diagnosis to the last follow-up examination or occurrence of mortality. Censorship was implemented during the period of the preceding correspondence, which occurred on the 30th of June 2023. The interquartile range of the median follow-up time ranged from 10.40 to 90.57 months, equivalent to a total of 40.90 to 45.19 months.

RESULTS

During the 11 years of the study period, a total of 389 patients of paediatric AML were registered at the study centre. Among them, 56 (14.4%) were diagnosed with APL. The initial diagnosis of APL was based on the morphology of the blast cells from bone marrow aspiration and / or peripheral blood sample. One case abandoned the treatment during the induction phase. Out of the remaining 55 cases, 5 cases were excluded from the study due to the unavailability of PML-RARA. Data of 50 cases including 32 males (64%) and 18 females (36%) were analysed. Only 7 (14%) cases were children of army personnel. The mean age at diagnosis was 7.02 ± 3.86 years (ranging from 1.25 to 15 years). The mean time to reach the paediatric oncologist was 30.20 ± 22.15 days (ranging from 2 to 92 days). The most common presenting symptom was pallor in 48 (96%) cases followed by fever in 44 (88%) cases and bruising / bleeding in 37 (74%) cases. Physical examination revealed pallor in 48 (96%) and visceromegaly in 30 (60%) cases. The mean white blood cell count was 28.70 ± 35.39 x10^9/L (ranging from 1.0 to 145 x 10^9/L). Initial WBC of >10x10^9/L was documented in 27 (54%) cases. The mean haemoglobin was 7.36 ± 2.66 g/dl and the mean platelets count was 33.58 ± 37.64x10^9/L. Coagulation was deranged in 29 (58%) cases and hyperfibrinogenaemia was documented in 8 (16%) cases only (Table I).

Table I: Clinical and laboratory characteristics of paediatric APL cases (n = 50), Chi-squared and One-way ANOVA tests were used.

Variable	ICC-APL-01 protocol		ATO protocol		Total		p-value
	Number (%)	95% CI	Number (%)	95% CI	Number (%)	95% CI	
Total number	24 (48%)		26 (52%)		50 (100%)		
Age (years)	5.63 ± 3.89	3.98-7.28	8.30 ± 3.43	6.92-9.69	7.02 ± 3.86	5.92-8.12	0.013
Age groups							0.002
Less than 5 years	16 (66.7)		6 (23.1)		22 (44)		
More than 5 years	8 (33.3)		20 (76.9)		28 (56)		
Gender							0.832
Male	15 (62.5)		17 (65.4)		32 (64)		
Female	9 (37.5)		9 (34.6)		18 (36)		
Clinical features							
Fever	20 (83.3)		24 (92.3)		44 (88)		0.329
Pallor	23 (95.8)		25 (96.2)		48 (96)		0.954
Bleeding	18 (75)		19 (73)		37 (74)		0.877
Visceromegaly	14 (58.3)		16 (61.50		30 (60)		0.817
Laboratory features							
WBC count ($x10^9$/L)	32.10 ± 34.51	17.53 - 46.68	25.56 ± 36.57	10.79 - 40.33	28.70 ± 35.39	18.64 - 38.76	0.519
Haemoglobin (g/dl)	7.52 ± 2.29	6.54 - 8.49	7.21 ± 2.99	6.00 - 8.42	7.36 ± 2.66	6.60 - 8.11	0.690
Platelets ($x10^9$/L)	37.16 ± 41.30	19.72 - 54.60	30.26 ± 34.41	16.36 - 44.17	33.58 ± 37.64	22.88 - 44.27	0.523
Deranged coagulation	12 (50)		17 (65.4)		29 (58)		0.708

Table II: Treatment outcomes of paediatric APL cases (n = 50), Chi-squared test was used.

Variable	ICC-APL-01 protocol (n = 24) Number (%)	ATO protocol (n = 26) Number (%)	Total (n = 50) Number (%)	p-value
Risk group				0.084
Standard	8 (33.3)	15 (57.7)	23 (46.0)	
High-risk	16 (66.7)	11 (42.3)	27 (54.0)	
Induction complications				
Neutropenic fever	19 (79.2)	20 (76.9)	39 (78%)	0.848
Differentiation syndrome	2 (8.3)	5 (19.2)	7 (14)	0.267
Benign intracranial hypertension	2 (8.3)	4 (15.4)	6 (12.0)	0.443
Induction mortality	6 (25)	3 (11.5)	9 (18)	0.216
Remission status after induction chemotherapy (41 cases after excluding induction deaths)				
Complete remission (CR)	13 (72.2)	23 (100)	36 (87.8)	0.026
Partial remission (PR)	3 (16.7)	0 (0.0)	3 (7.3)	
No response (NR)	2 (11.1)	0 (0.0)	2 (4.9)	
Total number	18 (100)	23 (100)	41 (100)	
Death after induction	0 (0.0)	0 (0.0)	0 (0.0)	
Relapse	10 (55.6)	4 (17.4)	14 (34.1)	0.039
Disease free survival	11 (45.8)	19 (73.1)	30 (60)	0.049
Overall survival	13 (54.2)	20 (76.9)	33 (66)	0.090

Table III: Results of statistical tests of association between OS and DFS and study variables in acute promyelocytic leukaemia cases (n = 50), binary logistic regression test used.

Variable (n)	OS				DFS			
	Value	95% CI	Log-rank	p-value	Value	95% CI	Log-rank	p-value
Age								
<5 years (22)	63.6%	60.75-115.14			50.0%	34.18-81.69		
≥5 years (28)	67.9%	69.94-112.76	0.193	0.661	67.9%	67.69-111.28	1.99	0.158
Gender								
Male (32)	65.6%	71.78-114.02	0.003	0.960	56.3%	53.37-97.76	0.446	0.504
Female (18)	66.7%	59.07-112.77			66.7%	57.61-111.36		
Reporting time to oncologist								
<1 month (30)	80.0%	92.26-129.30	7.294	0.007	76.7%	77.36-112.83	10.153	0.001
>1 month (20)	45.0%	36.01-93.46			35.0%	21.37-74.72		
WBC count at presentation								
<10x10^9/L (23)	78.3%	87.39-130.99	3.397	0.065	73.9%	72.83-115.83	3.584	0.058
>10x10^9/L (27)	55.6%	52.64-102.40			48.1%	40.17-88.27		
PLTs count at presentation								
<50x10^9/L (41)	68.3%	77.99-114.60	0.967	0.325	63.4%	65.84-103.03	1.818	0.178
>50x10^9/L (9)	55.6%	21.62-83.97			44.4%	10.23-71.85		
Hb at presentation								
<7 g/dl (23)	60.9%	58.00-110.63	0.493	0.483	56.5%	46.19-96.09		
>7g/dl (27)	70.4%	75.60-120.82			63.0%	59.52-106.32	0.197	0.657
Treatment Group								
ICC APL (24)	54.2%	56.89-107.16			45.8%	41.98-91.34		
ATO (26)	76.9%	70.99-112.25	1.338	0.247	73.1%	65.41-107.61	2.416	0.120
Remission after induction								
CR (36)	83.3%	98.31-131.02			75.0%	79.79-116.61		
No CR (5)	60.0%	76.61-99.34	0.488	0.485	60.0%	74.21-96.66	0.041	0.840

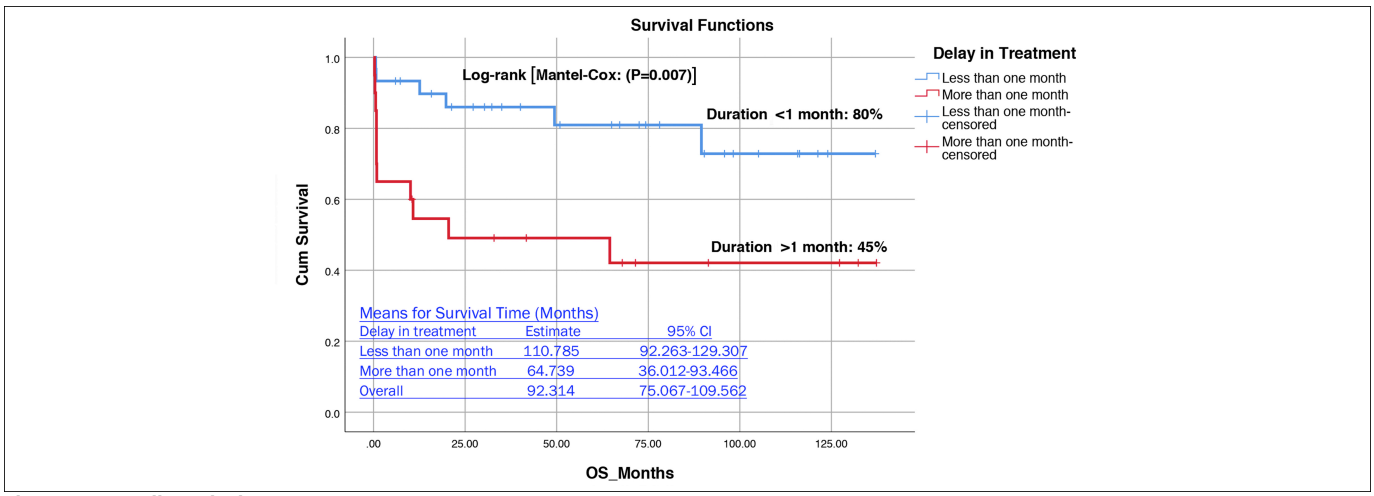

Figure 1: Overall survival.

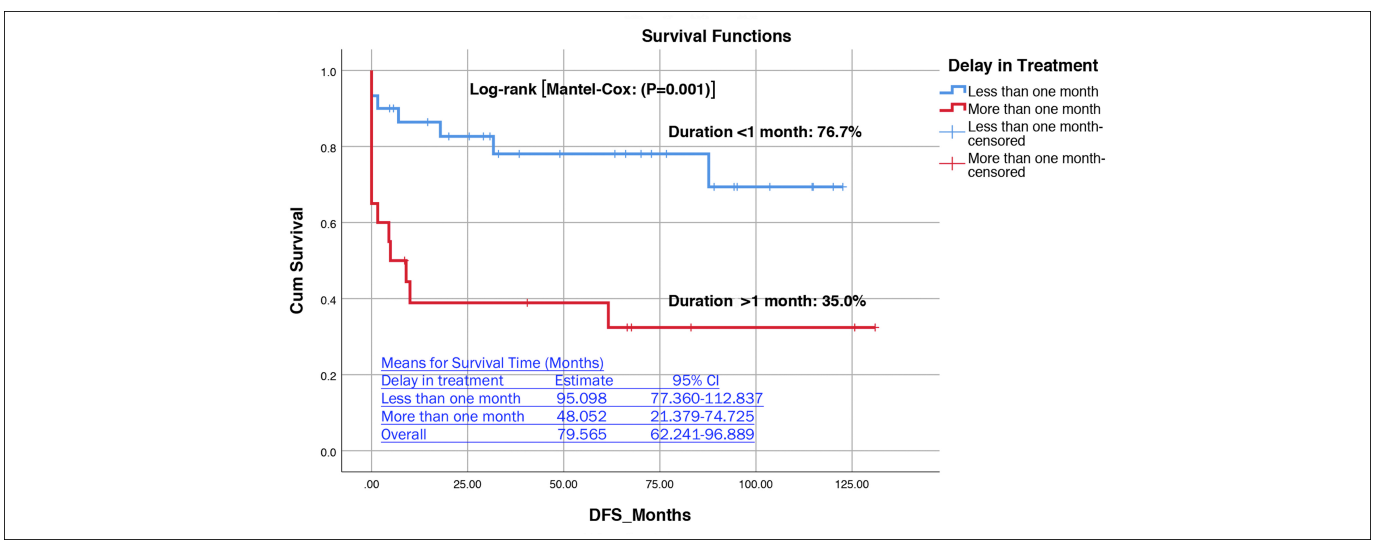

Figure 2: Disease free survival.

Twenty-four (48%) cases were treated on ICC-APL protocol, out of these 24 cases, 8 (33.3%) were SR and 16 (66.7%) were HR. Twenty-six (52%) were treated on ATO-based protocol, including 15 (57.7%) in SR and 11 (42.3%) in the HR group. Neutropenic fever was the most common complication documented in 39 (78%) cases. Seven (14%) cases developed differentiation syndrome (DS) and 6 (12%) cases had benign intracranial hypertension (BIH). Nine (18%) cases including 6/24 (25%) on ICC-APL 01 protocol and 3/26 (11.5%) on ATO-based protocol, expired the during the induction (p = 0.216). Response to induction treatment was documented by performing BM aspiration in the remaining 41 cases. Thirty-six (87.8%) cases including 13 (72.2%) on ICC-APL 01 protocol and 23 (100%) on ATO-based protocol achieved CR (p = 0.007). Age, gender, delay in treatment, and risk group had no statistically significant impact on achieving CR after induction (Table II).

All 23 cases of ATO-based protocol continued the same treatment. Five cases of ICC-APL protocol that did not achieve CR after induction received the consolidation phase of the same protocol. Two of them achieved morphological CR after consolidation and continued the same treatment protocol. The remaining three of them and one more case who initially achieved CR after induction but had RD after the consolidation phase of ICC-APL protocol were switched to ATO-based protocol.

During the study period, 16 (32%) cases expired including 9/16 (56.2%) induction deaths (ID) and 7/16 (43.8%) relapse-related mortality (RRM). The induction death rate was 8.7% in the SR group and 25.9% in the HR group (p = 0.114, OR for risk group = high-risk 3.67, CI 0.68-19.85). Delay at the start of treatment was the only statistically significant risk factor associated with ID. ID rate was 6.7% and 35.0%, respectively, in cases presenting before and after one month of symptoms (p = 0.020, OR for delayed presentation = 7.54, CI 1.37-41.41). Age, gender, presenting blood counts, and treatment protocol had no statistically significant effect on ID. Neutropenic fever was the most common cause of death, documented in 7/9 (77.8%) cases. Two (22.2%) cases died of internal bleeding;

one had an intracranial bleed and the other had a massive gastrointestinal bleed. There was no treatment-related death after the induction phase of the treatment.

Out of 24 cases of ICC-APL protocol, six died during induction and 4/18 (22.2%) had the RD and were shifted to ATO-based protocol after the consolidation phase of treatment. Out of the remaining 14 cases, 6 cases relapsed during maintenance therapy, two of them were rescued with ATO-based treatment and the remaining four were expired. Out of 26 cases of ATO protocol, three died during induction and 4/23 (17.4%) encountered relapsed. One of the relapsed cases underwent a haplo-identical bone marrow transplant and the remaining 3 (75%) cases were expired. The relapse / refractory rate was 14/41 (34.1%) of the total cohort, 10/18 (55.6%) in ICC-APL, and 4/23 (17.4%) in ATO protocol ($p = 0.011$). Other factors associated with a high relapse rate were age and remission after induction. The relapse rate was 27.8% in the CR group *vs.* 80% in the no-CR group ($p = 0.021$), 52.9% and 20.8% in age <5 and >5 years, respectively ($p = 0.033$).

The median follow-up time was 40.90 ± 45.19 months, and 10-year OS and DFS rates were 66.0% and 60.0%, respectively. OS at 2 years, 5 years, and 10 years was 72%, 68%, and 66%, respectively. DFS at 2 years, 5 years, and 10 years was 66%, 62%, and 60%, respectively. OS of ICC-APL and ATO protocol was 54.2% and 76.9%, respectively ($p = 0.090$). DFS of ICC-APL and ATO protocol was 45.8% and 73.1%, respectively ($p = 0.049$). OS was 78.3% and 55.6% in the SR and HR group, respectively ($p = 0.065$). DFS was 73.9% and 48.1% in the SR and HR groups, respectively ($p = 0.058$). The best OS and DFS was 80% in SR cases treated on ATO protocol. The worst OS and DFS were 43.8% and 37.5% in HR cases treated on ICC-APL protocol. The authors also looked at various factors influencing OS and DFS. Delay in starting treatment was the only factor having a statistically significant influence on OS and DFS. The OS was 80% and 45% in cases receiving treatment before and after one month of symptoms ($p = 0.007$). Similarly, DFS survival decreased from 76.7 to 35% in cases having a delay in treatment ($p = 0.001$, Table III, Figure 1).

DISCUSSION

To the authors' knowledge, the present study is the largest cohort of childhood APL from Pakistan. Several paediatric APL studies from developed countries have reported induction death rates between 3 to 13%. However, in low-and middle-income countries (LMICs), ID rates as high as 20 to 32% have been reported.[5,14-16] Similarly, a high ID death rate (18%) was documented in the present study. Though the ID rate in the HR group was three times higher as compared to SR, it was not statistically significant ($p = 0.114$). A study from Karachi, Pakistan has reported 23.3% deaths during the induction period.[15] The major reasons for ID in APL are coagulopathy, infection, and DS.[14,17] The present study also documented infection and coagulopathy as major reasons for ID. Two other treatment-related problems during induction, DS and BIH, were managed successfully with dexamethasone and temporary discontinuation of ATRA. Acetazolamide was also used for the management of BIH. ATO was well tolerated during induction and maintenance phases over 3 years and showed no neurological and cardiovascular toxicity including prolongation of QTc interval.

APL is the most curable subtype of AML in children. OS has been reported from 95 to 100% in APL cases treated with ATO and ATRA combination. This high OS is mainly due to very low early deaths during induction mainly achieved with early use of ATRA.[5,18,19] In the present study, the best OS and DFS was 80% in SR cases treated on ATO protocol. This lower survival in the present study is mainly due to high induction deaths. Delay in diagnosis and management is a very common problem in Pakistan and other LMICs.[13,20] In the present study, a delay of more than one month to start the treatment increased induction deaths from 6.7 to 35% ($p = 0.011$), relapse rate from 23.3 to 35% ($p = 0.368$), decreased DFS from 76.7 to 35% ($p = 0.001$), and OS from 80 to 45% ($p = 0.007$). Awareness and education of the healthcare providers, especially primary care paediatricians, is required. They should be sensitised to think about leukaemia as a possible diagnosis. An early referral will improve the outcome of APL in children.

A relapse is a rare event in paediatric APL.[5,21] However, the present study documented a high relapse rate of 34.1% of the total cohort, 55.6% of ICC-APL, and 17.4% of ATO protocol. Six cases (60%) of ICC-APL protocol were rescued with ATO and four cases died of relapsed disease. Only one relapsed case of ATO protocol was treated with a haplo-identical bone marrow transplant and the remaining 3 (75%) cases expired of progressive disease as parents opted for palliation.

After the exclusion of induction mortality, ATO-based protocol attained 100% molecular remission. The DFS and OS were much better than the ICC-APL protocol. There were no hospital admissions, infections, or any other complications after the induction. The most significant finding was the convenience of using ATO in primary healthcare units of their local area. Most of the cases in the present study belonged to rural areas with limited healthcare facilities and inadequate financial resources. The patients were kept on regular OPD visits as per protocol (monthly during 1st year, two-monthly during 2nd year, and three-monthly during 3rd year of ATO therapy. They were provided instructions to prepare and administer ATO and to monitor electrolytes and ECG at the local healthcare unit. This resulted in saving the hospital beds and expenses. Moreover, parents continued their daily routine without interruption. No major complication was documented during their treatment.

CONCLUSION

Neutropenic fever and bleeding are the leading causes of induction mortality in paediatric APL. Delay in treatment is the most significant prognostic factor. ATO-based treatment is safe, has better DFS and OS and can be conveniently administered in primary healthcare facilities. The present study is a single-centre, small-sized cohort. The authors recommend a multicentre, larger-scale study for statistically more significant results.

ETHICAL APPROVAL:
This study was approved by Research Ethics Committee / The Institutional Review Board of Rawalpindi, CMH (Serial no.438).

PATIENTS' CONSENT:
Informed consent of the patients' parents / guardians was obtained.

COMPETING INTEREST:
The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:
SN: Acquisition and drafting of the work.
TG: Critically revision for important intellectual content, conception and design of the work, analysis, and interpretation of the data.
RM, BH: Data collection and statistical analysis of the data.
SA: Analysis or interpretation of data for the work.
AA: Final approval of the manuscript to be published.
All authors approved the final version of the manuscript to be published.

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