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Prognostic significance of MRD and its correlation with arsenic concentration in pediatric acute promyelocytic leukemia: a retrospective study by SCCLG-APL group

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Abstract

Background: Treatment outcomes for acute promyelocytic leukemia (APL) have improved with all-trans-retinoic acid and arsenic trioxide, yet relapse remains a concern, especially in pediatric patients. The prognostic value of minimal residual disease (MRD) post-induction and the impact of arsenic levels during induction on MRD are not fully understood.

Objectives: To evaluate the relationship between post-induction MRD levels and relapse-free survival (RFS) in pediatric APL patients, and to investigate the correlation between blood arsenic concentration levels during induction therapy and MRD status.

Design: A retrospective analysis of pediatric APL patients enrolled in a clinical trial from September 2011 to July 2020.

Methods: We assessed the relationship between RFS and post-induction MRD levels using the log-rank test. The optimal MRD cut-off was determined using the "surv_cutpoint" function in the survminer R package. Arsenic concentration levels were monitored in 16 patients on days 7 and 14 of induction therapy, and Spearman correlation was used to analyze the relationship between arsenic concentrations and MRD levels.

Results: Among 176 pediatric APL patients, with a median follow-up of 6 years, 4 relapsed. Patients with MRD $>3.1\%$ had significantly lower RFS compared to those with MRD $\leqslant 3.1\%$ (94.6% vs 100%, $p=0.023$). In addition, a negative correlation was found between blood arsenic concentration levels and post-induction MRD levels. Lower arsenic concentrations were associated with higher MRD levels, with significant correlations observed for trough concentrations ($R=-0.666$, $p=0.005$) and peak concentrations ($R=-0.499$, $p=0.049$) on day 7.

Conclusion: Our study highlights the prognostic significance of post-induction MRD assessment in pediatric APL. We also demonstrate a negative correlation between blood arsenic concentration levels and MRD, suggesting that lower arsenic concentrations during induction therapy may contribute to a higher MRD burden. These findings may inform strategies to optimize treatment and improve outcomes in pediatric APL.

Trial registration: www.clinicaltrials.gov (NCT02200978).

Plain language summary

How residual disease and arsenic levels affect outcomes in children with acute promyelocytic leukemia: a study by the SCCLG-APL group

Background: Treatments for acute promyelocytic leukemia (APL) have improved with the use of all-trans retinoic acid (ATRA) and arsenic trioxide (ATO). However, relapse is still a

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problem, especially for children. We do not fully understand how the amount of residual disease (MRD) after initial treatment or the level of arsenic during treatment affects the risk of relapse. Objectives: We aimed to see how MRD levels after the first phase of treatment relate to the likelihood of staying relapse-free in children with APL. We also wanted to find out if arsenic levels in the blood during the initial treatment phase are linked to MRD levels. Design: We looked back at data from children with APL who were part of a clinical trial from September 2011 to July 2020. Methods: We analyzed how MRD levels after induction relate to relapse-free survival using statistical tests. We also measured arsenic levels in the blood of 16 patients during the induction treatment and examined how these levels were related to MRD levels. Results: Out of 176 children with APL, 4 had a relapse after a median follow-up of 6 years. Children with MRD levels above 3.1% had a lower chance of staying relapse-free compared to those with lower MRD levels (94.6% vs. 100%). We also found that lower arsenic levels were linked to higher MRD levels, meaning that less arsenic in the blood was associated with a greater amount of residual disease. Conclusion: This study shows that MRD levels after induction treatment are important for predicting outcomes in children with APL. Lower levels of arsenic during treatment may lead to higher MRD, suggesting that managing arsenic levels could help improve treatment results for these patients.

Keywords: acute promyelocytic leukemia, arsenic, children, minimal residual disease

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Introduction

Acute promyelocytic leukemia (APL), characterized by the t(15;17) translocation resulting in the promyelocytic leukemia/retinoic acid receptor alpha (PML-RARA) fusion gene, represents a distinct clinical and biological subset of acute myeloid leukemia.[1–3] Historically, APL was associated with a high fatality rate due to severe coagulopathy leading to hemorrhagic complications. However, the introduction of all-trans retinoic acid (ATRA) and arsenic trioxide (ATO) has revolutionized APL treatment, resulting in remarkable improvements in patient outcomes.[4–7] Our multicenter randomized controlled clinical study revealed that oral realgar-indigo naturalis formula (RIF) was not inferior to intravenous ATO in treating pediatric APL. Furthermore, substituting ATO with RIF offers additional benefits, including shorter hospital stays, reduced infection risk, and lower cardiotoxicity. The study reported a 100% 8-year overall survival (OS) rate and a 96.6% 8-year event-free survival (EFS) rate.[8,9] Despite these advances, challenges remain, a minority of patients will relapse, and the risk factors for relapse are largely unclear and controversial. Several retrospective analyses conducted in the context of adding arsenic or ATRA to a chemotherapy backbone have suggested some possible risk factors for relapse, such as the expression of cluster of differentiation (CD)2^+, $CD34^+$ and $CD56^+$, type of PML-RARA transcript, the Sanz risk score, and FMS-like tyrosine kinase 3-internal tandem duplication (FLT3-ITD) mutation.[10–15] However, these high-risk factors have shown varying outcomes in different clinical studies.[8,16,17] In the LoCoco study all these risk factors did not make a difference in OS and EFS when Arsenic and ATRA were used together.[18,19]

The assessment of minimal residual disease (MRD) has emerged as a critical prognostic tool in various hematologic malignancies, including APL.[20] MRD refers to the small number of leukemic cells that persist in the patient after treatment, which can potentially lead to relapse. Techniques such as quantitative reverse transcription-polymerase chain reaction (qRT-PCR) enable sensitive detection of MRD by quantifying the PML-RARA transcript.[21] Previous studies have revealed that after induction therapy, there was no association found between positive PCR results and relapse.[22] Subsequent research further discovered that achieving MRD negativity after

the first consolidation, rather than after induction, was a potential predictor of relapse and disease-free survival in patients treated with ATRA plus chemotherapy.[23] Another study retrospectively analyzed 212 patients diagnosed with non-high-risk APL who received frontline therapy with ATRA plus arsenic. They found that a PML-RARA transcript level of ⩾6.5% at the end of induction therapy was associated with relapse, but positive PML-RARA after consolidation 1 was not related to relapse significantly.[24] However, these study findings are somewhat contradictory and are predominantly based on adult patients or include limited samples of children. The prognostic significance of MRD in pediatric APL remains under investigation. In addition, the relationship between therapeutic drug levels and MRD is an area of active research. Arsenic trioxide's efficacy in APL is dose-dependent, and maintaining appropriate blood arsenic levels during induction therapy is crucial for maximizing treatment benefits.[25]

Given the importance of optimizing therapeutic strategies in pediatric APL, we conducted a retrospective analysis of data from the SCCLG-APL2011 clinical trial. This study aimed to evaluate the prognostic significance of MRD post-induction and explore the correlation between arsenic concentrations during induction therapy and MRD levels. Our findings provide valuable insights into the optimization of pediatric APL treatment, highlighting the potential of MRD and therapeutic drug monitoring to improve patient outcomes.

Methods

Study design and participants

This study is a retrospective analysis of data derived from the SCCLG-APL2011 regimen, a multicenter, randomized controlled trial conducted from September 2011 to July 2020. The trial enrolled a total of 176 newly diagnosed pediatric patients with APL, defined by the presence of the t(15;17) translocation and confirmed by molecular testing for the PML-RARA fusion gene. Patients were treated according to a standardized protocol involving ATRA, arsenic (ATO or RIF), and chemotherapy during the induction phase, followed by consolidation and maintenance therapy. The detailed treatment regimen is provided in Table 1. The study was conducted with institutional review board approval from the first affiliated hospital of Sun Yat-sen University. Informed consent was obtained from patients and/or their families in accordance with the principles outlined in the Declaration of Helsinki. The trial was registered and can be found at www.clinicaltrials.gov (NCT02200978).

Eligible patients were 16 years old or younger with newly diagnosed APL with confirmation of PML-RARa by RT-PCR assay and (or) fluorescence in situ hybridization. Exclusion criteria included any of the following events occurring prior to randomization: death from any cause, or coma, convulsion, paralysis due to intracranial hemorrhage, cerebral thrombosis, or central nervous system leukemia; or who had prolonged QT syndrome because of the risk of QT interval prolongation during arsenic therapy; or who did not accept randomization.

MRD assessment

MRD level monitoring of bone marrow was assessed by using qRT-PCR, targeting the PML-RARA fusion gene transcript at the end of induction, before the beginning of maintenance, and every 24 weeks from the beginning of maintenance to 48 weeks after the end of maintenance. MRD was quantified with a sensitivity threshold of 10^{-4} and evaluated as a prognostic marker for relapse-free survival (RFS). To determine the optimal MRD cut-off value for predicting relapse, the "surv_cutpoint" function in the survminer R package was utilized to identify the best split by verifying all potential cut points. The "surv_cutpoint" function evaluates various thresholds for continuous variables and selects the one that best separates the survival outcomes. This method is widely used for identifying clinically meaningful cut points in survival analysis.[26,27]

Arsenic concentration monitoring

Blood arsenic levels were monitored in a subset of 16 patients who consented to pharmacokinetic studies. Blood samples were collected before and after arsenic administration on days 7 and 14 of the induction phase for the ATO group. For the RIF group, blood samples were collected before the morning oral dose and 2–3 h after the last dose on the same days. Both peak and trough

Table 1. SCCLG-APL protocol.

Induction
ATRA 25 mg/m^2/day, orally 2–3 times daily, d1-HCR (maximum 42 days)
MA 10 mg/m^2/day, intravenously, d3 (low- and intermediated-risk) 7 mg/m^2/day, intravenously, d2–4 (high-risk)
Arsenic: ATO 0.16 mg/kg/day (maximum 10 mg/day), intravenously over 12 h, d5-HCR Or RIF at 135 mg/kg/day (maximum 30 pills/day) orally three times daily
Consolidation 1
ATRA 25 mg/m^2/day, orally 2–3 times daily, d1–15
MA 10 mg/m^2/day, intravenously, d1–2
Consolidation 2[a]
Arsenic: ATO 0.16 mg/kg/day (maximum 10 mg/day), intravenously over 12 h, d1–15 Or RIF at 135 mg/kg/day (maximum 30 pills/day) orally three times daily
AC 1 g/m^2/day, intravenously, d1–2 (high-risk only)
Consolidation 3[a]
ATRA 25 mg/m^2/day, orally 2–3 times daily, d1–15
Arsenic: ATO 0.16 mg/kg/day (≯10 mg/day), intravenously over 12 h, d1–15 Or RIF at 135 mg/kg/day (maximum 30 pills/day) orally three times daily
MA 10 mg/m^2/day, intravenously, d1
AC 1 g/m^2/day, intravenously, d1–2 (high-risk only)
Maintenances (cycle 1)[b]
ATRA 25 mg/m^2/day, orally 2–3 times daily, d1–14
Arsenic: ATO 0.16 mg/kg/day (maximum 10 mg/day), intravenously over 12 h, d1–14 Or RIF at 135 mg/kg/day (maximum 30 pills/day) orally three times daily
MTX 20 mg/m^2/week, d15–63
6MP 50 mg/m^2/day, d15–63
Maintenances (cycle 2)[b]
ATRA 25 mg/m^2/day, orally 2–3 times daily, d1–14
MTX 20 mg/m^2/week, orally, d15–63
6MP 50 mg/m^2/day, orally, d15–63

[a]The interval between consolidations 1, 2, 3, and the beginning of first cycle 1 of maintenance was 28 days.
[b]Repeated cycles 1 and 2 for a total of 8 cycles. Intrathecal injection of cytarabine and dexamethasone was administrated on day 1 of every course of consolidation therapy.
6MP, 6-mercaptopurine; AC, cytarabine; ATO, arsenic trioxide; ATRA, all-trans-retinoic acid; d, day; HCR, hematologic complete remission; MA, mitoxantrone; MTX, methotrexate; RIF, realgar-indigo naturalis formula.

arsenic concentrations were measured using atomic absorption spectroscopy. Plasma samples (1 mL) were processed for total arsenic analysis using PTFE-TFM tubes,[28] which are known for their high thermal stability and chemical inertness. Nitric acid (65%, 3 mL) and hydrogen peroxide (30%, 1 mL) were added to the plasma, followed by heating at 110°C for 2 h. After cooling to room temperature, concentrated hydrochloric acid (1.25 mL) and thiourea-ascorbic acid (5 mL) were added to the products, which were then diluted with water to 25 mL. Arsenic fluorescence intensity was measured using an AFS-9561 double-channel atom fluorophotometer (Beijing Haiguang Instrument Co., LTD, Beijing, China).

Statistical analysis

The relationship between MRD levels and RFS was analyzed using the log-rank test. Kaplan-Meier survival curves were generated to visualize differences in RFS based on MRD status. Spearman correlation was used to assess the relationship between blood arsenic concentrations measured on days 7 and 14 of the induction phase and MRD levels assessed at the end of induction. All statistical analyses were conducted using SPSS25.0 and R software, with a significance level set at $p < 0.05$.

Results

Patient demographics and clinical characteristics

The study cohort included 176 pediatric APL patients with a median age of 8.2 years (range 1.0–15.9 years), including 105 males and 71 females. All of the 176 eligible patients achieved hematological complete remission after induction and achieved molecular complete remission (MCR, qRT-PCR negative for PML-RARa) at the end of consolidation therapy. The median follow-up period was 6 years, during which four patients experienced relapse. The 8-year OS rate and EFS are 100% and 96.6%, respectively. The demographics and clinical characteristics of the patients are summarized in Tables 2 and 3.

MRD as a prognostic marker

Post-induction MRD levels varied among patients, with 30.8% of children ($n = 52$) achieving MRD negativity (defined as MRD $\leqslant 0.01\%$). The "surv_cutpoint" function in the survminer R package was performed to search for the best split of MRD by verifying all potential cut points. Our study found that patients with MRD levels greater than 3.1% post-induction had significantly lower RFS compared to those with MRD levels $\leqslant 3.1\%$ (94.6% vs 100%, $p = 0.023$) (Figure 1). This finding underscores the critical role of MRD as a prognostic marker in pediatric APL, suggesting that higher MRD levels post-induction are associated with an increased risk of relapse.

Correlation between arsenic concentrations and MRD

In the subset of 16 patients monitored for arsenic concentrations, both peak and trough arsenic levels were measured on days 7 and 14 of the induction phase (Table 4). Among these, seven patients received ATO, and nine received RIF. No significant difference in arsenic levels was observed between the two treatment groups (Table 5). The analysis revealed a notable negative correlation between blood arsenic concentrations measured on these days and MRD levels assessed at the end of induction. Lower arsenic concentrations were associated with higher MRD levels, indicating a suboptimal response to therapy. Specifically, arsenic concentration on day 7 showed a significant negative correlation with MRD levels ($R = -0.666$, $p = 0.005$), as did peak concentration ($R = -0.499$, $p = 0.049$) (Figure 2). These results suggest that maintaining adequate blood arsenic levels is crucial for effective disease eradication and optimal therapeutic outcomes.

Discussion

Implications of MRD as a prognostic marker

To our knowledge, this study represents the longest follow-up cohort exploring ATRA plus arsenic as frontline therapy for pediatric APL. Previous studies on MRD-related survival and relapse prognostic factors have mostly been conducted in the context of ATRA plus chemotherapy, or have been limited to adult samples, focusing primarily on the timing of MRD negativity.[11,14,29] Our study, with a long-term follow-up of 6 years, further confirms the high cure rate and low side effects of ATRA combined with oral arsenic as

Table 2. Baseline characteristics of the 176 patients.

Characteristic	Value
Median age, years (range)	8.2 (1.0, 15.9)
Gender, *n* (%)	
Male	105 (59.7%)
Female	71 (40.3%)
Median WBC, $\times 10^9$/L (range)	4.5 (0.3, 228.0)
Median PLT, $\times 10^9$/L (range)	25.5 (4.0, 226.0)
Median Hb, g/L (range)	74.5 (31.0, 141.0)
Sanz risk, *n* (%)	
Low-risk	34 (19.3)
Intermediate-risk	85 (48.3)
high-risk	57 (32.4)
PML-RARA type, *n* (%)	
L	119 (67.6%)
V	22 (12.5%)
S	35 (19.9%)
FLT3-ITD, *n* (%)	
Positive	11 (6.3%)
Negative	165 (93.7%)

FLT3-ITD, FMS-like tyrosine kinase 3-internal tandem duplication; Hb, hemoglobin; PLT, platelet; PML-RARA, promyelocytic leukemia-retinoic acid receptor alpha; WBC, white blood cell.

frontline therapy for pediatric APL.[8] The optimal cut-off value of 3.1% provides a clinically relevant threshold for identifying patients at higher risk of relapse. The identification of MRD as a significant prognostic marker in pediatric APL aligns with findings from adult studies and underscores the importance of MRD monitoring in clinical practice.

In our study, most patients (69.2%) were still PML-RARA positive at the end of induction therapy, a value within the range reported in previous studies (63.82%–90.1%). This may be attributed to different treatment protocols and the use of bone marrow or blood as detection specimens. The RT-PCR positive result at this time point did not predict relapse, consistent with prior findings.[11,24] Our current research indicates that in pediatric APL treated with ATRA plus arsenic as frontline therapy, a PML-RARA transcript level greater than 3.1% at the end of induction therapy is associated with relapse. This is in line with previous reports that induction post-MRD levels greater than 6.5% are associated with relapse.[24] Furthermore, this study found that MRD negativity after the first to fourth consolidation treatments was not associated with relapse. Unfortunately, our study did not measure MRD levels after each consolidation cycle, preventing comparative analysis. Nevertheless, the post-induction PML-RARA transcript level appears to be more significant than conventional relapse risk factors. This information can guide therapeutic decisions, potentially leading to more aggressive treatment strategies or closer monitoring for

Table 3. Characteristics of four relapsed patients.

Case	1	2	3	4
Age of years at diagnosis years	13.2	14.6	4.2	2.8
Gender	Male	Female	Male	Male
WBC, $\times 10^9$/L	13.5	1.3	1.6	53.8
PLT, $\times 10^9$/L	22	34	15	77
Hb, g/L	69	73	78	70
Sanz risk	HR	IR	IR	HR
PML-RARA type	L	L	L	L
FLT3-ITD mutations	Negative	Negative	Negative	Negative

FLT3-ITD, FMS-like tyrosine kinase 3-internal tandem duplication; Hb, hemoglobin; HR, high-risk; IR, intermediate-risk; PLT, platelet; PML-RARA, promyelocytic leukemia-retinoic acid receptor alpha; WBC, white blood cell.

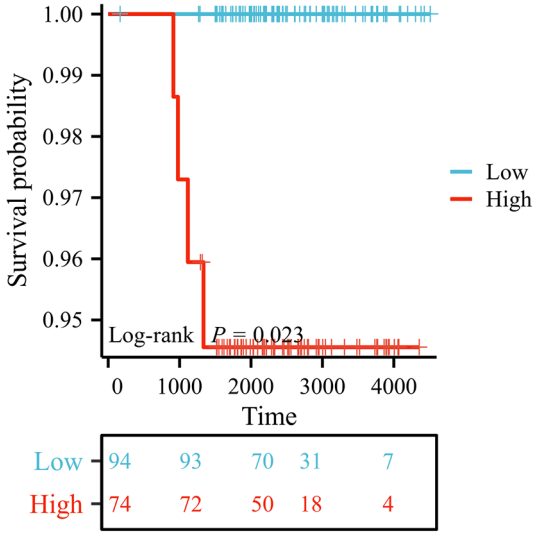

Figure 1. Patients with MRD levels >3.1% showed lower RFS than those ⩽3.1%.
MRD, minimal residual disease; RFS, relapse-free survival.

patients with higher MRD levels post-induction. Our findings support the integration of MRD assessment into standard clinical protocols for pediatric APL, emphasizing its role in predicting long-term outcomes and guiding individualized treatment plans.

In addition, in another multicenter randomized controlled clinical study under the SCCCG-APL2020 protocol, the interim analysis showed that adding one dose of anthracycline chemotherapy during induction could increase the MRD negativity rate after induction compared to the non-chemotherapy group. This suggests that combining ATRA and arsenic with chemotherapy may help reduce post-induction PML-RARA transcript levels and lower the relapse risk in pediatric APL patients. Definitive conclusions will be drawn upon the completion of the SCCCG-APL2020 study (ChiCTR2000038877).

Table 4. Arsenic concentration (μmol/L) before and after medication at D7 and D14.

Patients	D7		D14		MRD
	Medication		Medication		
	Before	After	Before	After	
1	0.47	0.75	0.65	0.53	0
2	0.77	0.62	0.38	1.28	0.0160
3	0.37	0.46	0.27	0.35	0.0844
4	0.71	0.9	0.51	0.51	0.0375
5	0.25	0.54	0.43	0.96	0.4937
6	0.61	0.69	0.39	0.57	0.0314
7	0.47	0.48	0.48	0.91	0.0268
8	0.14	0.3	0.35	0.35	0.5630
9	0.78	0.82	0.69	0.75	0
10	0.86	0.74	0.96	1.01	0
11	0.43	0.87	0.49	0.54	0.2924
12	0.62	0.61	0.74	0.75	0.4107
13	0.6	0.57	1.02	1.07	0.0011
14	0.39	0.47	0.33	0.37	0.0068
15	0.31	0.2	0.43	0.4	1.357
16	0.22	0.24	0.24	0.27	0.1079

MRD, minimal residual disease.

Table 5. Comparison of arsenic levels and risk stratification between ATO and RIF groups.

Characteristics	ATO ($n=7$)	RIF ($n=9$)	p value
RISK, *n* (%)			1.000
Low-risk	3 (42.9%)	4 (44.4%)	
Intermediate-risk	2 (28.6%)	3 (33.3%)	
High-risk	2 (28.6%)	2 (22.2%)	
D7 before medication	0.52 ± 0.19	0.48 ± 0.25	0.740
D7 after medication	0.63 ± 0.16	0.54 ± 0.25	0.379
D14 before medication	0.44 ± 0.12	0.58 ± 0.28	0.209
D14 after medication	0.73 ± 0.33	0.61 ± 0.30	0.464

ATO, arsenic trioxide; RIF, realgar-indigo naturalis formula.

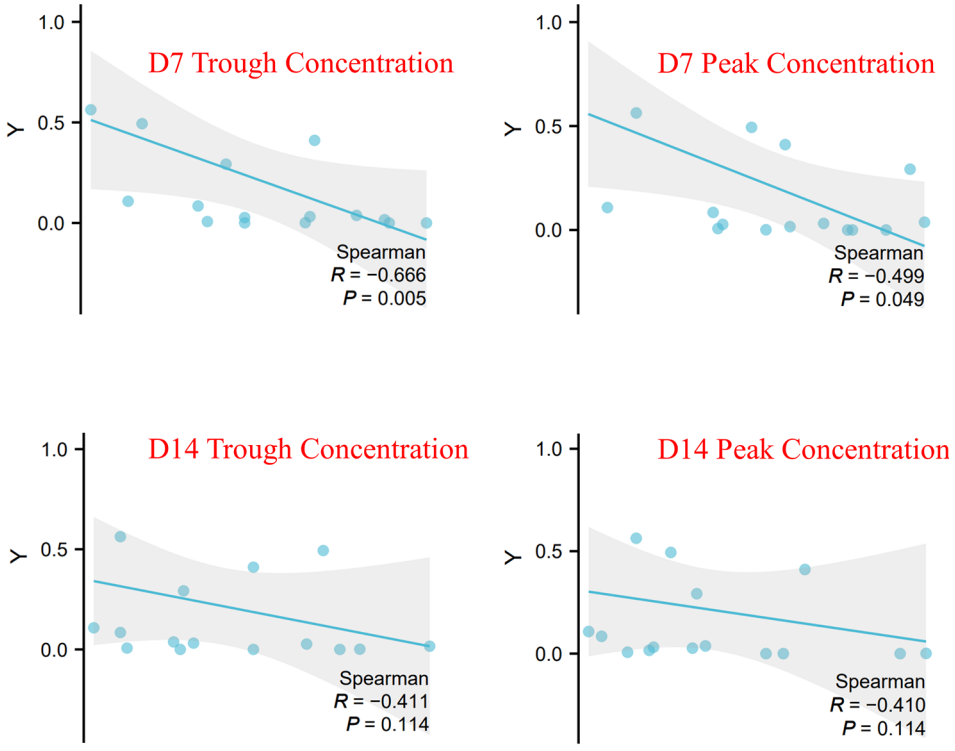

Figure 2. Blood arsenic concentrations during induction were inversely correlated with MRD after induction. *Y* axis: MRD after induction.
MRD, minimal residual disease.

Arsenic concentration monitoring and treatment optimization

ATO exhibits dose-dependent dual effects on APL cells in vitro: Inducing preferential apoptosis at relatively high concentrations (0.5–2 μmol/L) or partial differentiation at lower concentrations (0.1–0.5 μmol/L).[25] A study in adult patients demonstrated that an ATO dose of 0.16 mg/kg/day achieved apoptosis-inducing plasma arsenic concentrations (median 0.75 μmol/L) by day 8.[30] Zhu et al. recommended a RIF dose of 60 mg/kg/day for adult patients.[30] The results showed that the median plasma arsenic concentration on day 8 was lower in the RIF group than in the ATO group (0.335 μmol/L vs 0.75 μmol/L, $p = 0.048$). In addition, after 10 days of treatment, WBC was significantly higher in the RIF group compared to the ATO group (9.22×10^9/L vs 4.10×10^9/L, $p = 0.015$), suggesting RIF of 60 mg/kg/day might not be sufficiently effective.[31] In our study, we found that a 135 mg/kg/day dose of RIF was as effective and safe as a 0.16 mg/kg/day dose of ATO. We also confirmed that arsenic concentration reached a steady state by day 7, with the mean steady-state trough and peak concentrations being similar between the ATO and RIF groups, both ranging from 0.5 to 1 μmol/L.[32]

In adult APL, arsenic trough concentration has predictive value for treatment efficacy, necessitating arsenic concentration monitoring in APL patients undergoing ATO treatment.[33] Similarly, our study found that lower arsenic trough and peak concentrations on day 7 were associated with higher MRD levels. The negative correlation highlights the need for careful monitoring of arsenic levels during induction therapy. Arsenic trioxide's efficacy in APL is dose-dependent, and maintaining appropriate blood levels is essential for maximizing its therapeutic benefits. Variability in arsenic levels could be attributed to differences in absorption, metabolism, or patient compliance. This variability underscores the importance of therapeutic drug monitoring (TDM) for arsenic in pediatric APL to ensure adequate drug exposure and improve treatment efficacy. Further research is needed to establish specific arsenic concentration targets and develop standardized TDM protocols for arsenic in pediatric APL.

Clinical implications and future directions

The integration of MRD assessment and arsenic concentration monitoring into clinical practice has the potential to significantly improve outcomes in pediatric APL. MRD assessment can identify patients at higher risk of relapse, allowing for more tailored treatment strategies. Arsenic concentration monitoring can ensure adequate drug exposure, enhancing treatment efficacy and reducing the risk of relapse. These approaches align with the principles of personalized medicine, aiming to optimize treatment based on individual patient characteristics and responses.

Future studies should focus on validating our findings in larger, prospective cohorts and exploring the impact of TDM on long-term outcomes in pediatric APL. In addition, research should investigate the pharmacokinetics of arsenic in pediatric patients to identify factors influencing arsenic levels and optimize dosing regimens. Developing standardized protocols for MRD assessment and TDM will be crucial for integrating these approaches into routine clinical practice.

Limitations of the study

Given the retrospective nature of this study and the limited sample size for arsenic concentration monitoring, we acknowledge that our conclusions should be interpreted with caution. Retrospective analyses are inherently subject to selection bias and potential confounding factors, which may affect the generalizability of the findings. The small subset of patients monitored for arsenic concentrations limits the ability to draw definitive conclusions about the relationship between arsenic levels and MRD. Prospective studies with larger cohorts and more frequent arsenic level assessments are needed to confirm these findings and refine the optimal arsenic concentration targets. Furthermore, the study did not assess the potential impact of genetic factors on MRD and arsenic levels, which could provide additional insights into the mechanisms underlying treatment response and resistance. Future research should explore these factors to enhance our understanding of the biological determinants of MRD and arsenic pharmacokinetics in pediatric APL.

Conclusion

Our study suggests the prognostic significance of MRD assessment post-induction in pediatric APL and reveals a critical link between arsenic concentration levels during induction therapy and MRD status. These findings have important implications for optimizing treatment strategies in pediatric APL, emphasizing the need for regular MRD monitoring and potential TDM of arsenic to enhance treatment efficacy and reduce relapse rates. By integrating MRD assessment and arsenic concentration monitoring into standard clinical practice, we can move toward more personalized and effective treatment protocols for pediatric APL. This approach has the potential to improve long-term outcomes for pediatric patients, reducing the risk of relapse and enhancing OS. We recommend that future studies focus on validating these findings in larger cohorts and developing standardized protocols for MRD assessment and TDM to optimize treatment outcomes in pediatric APL.

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Committee of the First Affiliated Hospital of Sun Yat-Sen University. The patients and guardians have signed the informed consent form.

Consent for publication

This retrospective study involved the analysis of existing data and records.

Author contributions

Zhong Fan: Data curation; Formal analysis; Software; Visualization; Writing – original draft; Writing – review & editing.

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Competing interests

The authors declare that there is no conflict of interest.

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The datasets generated during the study are available from the corresponding author.

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