ORIGINAL RESEARCH

Population Pharmacokinetics and Safety of Oral Tetra-Arsenic Tetra-Sulfide Formula in Pediatric Acute Promyelocytic Leukemia

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Background: An oral tetra-arsenic tetra-sulfide (AS_4S_4) formula has been recommended as an outpatient post-remission treatment for Chinese adults with acute promyelocytic leukemia (APL) but limited data are available for children. In this exploratory study, we aimed to evaluate the pharmacokinetics and safety of the AS_4S_4 formula in children.

Methods: Eleven newly diagnosed and one relapsed pediatric patient (4–14 years of age) treated with the AS_4S_4 formula were included. Blood samples were collected from 12 children, and drug concentrations were quantified by ICP-MS. Population pharmacokinetic analysis and Monte-Carlo simulation were performed using NONMEM software. Toxic effects were graded according to the NCI-CTCAE, Version 3.

Results: A total of 107 arsenic concentrations (0.1–75.0 μg L^{-1}) were used for population pharmacokinetic analysis. The median (range) of estimated weight-normalized CL and volume distribution at steady-state were 45.26 (35.63–82.18) L h^{-1} kg^{-1} and 230.37 (85.96–495.68) L kg^{-1}, respectively. No patients discontinued AS_4S_4 treatment owing to adverse events, and there were no drug-related adverse events over grades 3–4. All newly diagnosed APL patients were in MCR with a median follow-up of 28 months (range, 23 to 37 months). Both the estimated 3-year EFS and OS rates were 100%.

Conclusion: The pharmacokinetics and safety oral AS_4S_4 formula was evaluated for the first time in pediatric APL. The pharmacokinetic assessment demonstrated that the dosing regimen of 60 mg/kg/d TID resulted in a higher steady-state through concentration in children than that which was achieved in adults. The results of this study indicate that the AS_4S_4 formula is safe in newly diagnosed pediatric APL patients.

Keywords: acute promyelocytic leukemia, Realgar-Indigo Naturalis Formula, pediatric, safety, population pharmacokinetics

Introduction

The combination of all-trans-retinoic acid (ATRA) and arsenic trioxide (ATO) has become the first-line treatment for patients with acute promyelocytic leukemia (APL). Several large multicenter trials have resulted in complete response in 94–100% of patients and long-term survival in more than 95% of patients.[1–7] However, ATO is administered intravenously and patients must stay in the hospital. In pursuit of high cost-effectiveness and convenience, home-based therapy with oral arsenic could increase compliance with therapy and should be highly recommended in children to improve the long-term efficacy and safety of the treatment.

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Tetra-arsenic tetra-sulfide (AS_4S_4) as the only commercially oral arsenic agent was launched in China in 2009. Several clinical trials have shown that the efficacy and safety of oral arsenic AS_4S_4 are similar to ATO in adults and improve the quality of life.[8–13] Oral AS_4S_4 formula has been recommended as substitute therapy in adults with acute promyelocytic leukemia (APL).[8–13] Furthermore, an outpatient post-remission therapy model had been developed in adults.[11,14] However, limited information is available for children with APL.[15] This study aimed to evaluate the pharmacokinetics and safety of AS_4S_4 as consolidation and/or maintenance therapy for children with APL after induction therapy with ATRA and ATO.

Patients and Methods
Study Design
A prospective, open-label study of oral AS_4S_4 formula Realgar-Indigo Naturalis Formula (RIF, Yifan Pharmaceutical Co., Tianchang, China), from July 2016 to July 2019, was conducted at the State Key Laboratory of Experimental Hematology, Institute of Hematology & Blood Diseases Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Tianjin, China. Both non-high-risk and high-risk diagnosed APL children receiving RIF as part of their treatment were enrolled in the study. A genetic diagnosis was established by detecting the PML/RARa fusion gene using polymerase-chain-reaction (PCR) assays. Children age 2 to 18 years with APL in complete remission were eligible for the study. Patients with organ dysfunction (abnormal renal and liver function) were excluded. The enrolled children were required an Eastern Cooperative Oncology Group (ECOG) score of 0. This study was approved by the Ethics Committee of the Institute of Hematology & Blood Diseases Hospital. Signed informed consent was obtained from the patients' parents or guardians. This trial was conducted in accordance with the Declaration of Helsinki and registered in the Chinese Clinical Trial Registry (ChiCTR-OIC-16010014).

Treatment Protocol and Pharmacokinetic Sampling
All patients received ATRA (25 mg/m²/d, days 1–42) and ATO (0.15 mg/kg/d, days 1–28) for induction therapy and achieved complete remission. For patients in maintenance therapy, which was designated as regimen A, they received maintenance therapy with RIF (60 mg/kg/d, three times daily,

TID) and ATRA after receiving four sequential courses of the following consolidation chemotherapy: idarubicin (IDA) 10 mg/m²/d for days 1–3; ATO 0.15 mg/kg/d for days 1–28; and two cycles of daunorubicin (DNR) 45 mg/m²/d for days 1–3. For newly diagnosed APL patients in consolidation therapy, which was designated as regimen B, they received also ATRA (25 mg/m²/d, days 1–42) and ATO (0.15 mg/kg/d, days 1–28) as remission induction therapy. After achieving hematologic remission, patients with an initial WBC count less than 10×10^9 L-1 were treated with consolidation therapy as follows: ATRA (25 mg/m²/d, days 1–28) and RIF (60 mg/kg/d, days 1–28) for two cycles, then ATRA (25 mg/m²/d, days 1–21) and RIF (60 mg/kg/d, days 1–21) for another two cycles. For low-risk patients, RIF and ATRA were sequentially used as a maintenance treatment. The patients with an initial WBC count above 10×10^9 L^{-1} were treated with two courses of IDA (8 mg/m²/d, days 1–3), ATRA (25 mg/m²/d, days 1–28), and RIF (60 mg/kg/d, days 1–28). Maintenance therapy for the high-risk patients consisted of five similar cycles. Each cycle for the high-risk patients included ATRA (25 mg/m²/d, days 1–21, 43–63), RIF (60 mg/kg/d, days 1–21), mercaptopurine (6-MP, 50 mg/m²/d, day 29–84) and methotrexate (MTX, 25 mg/m²/w, days 29–84). The regimen A and B group information is shown in Supplementary Figure.

Blood samples for measuring arsenic concentrations were collected before administration and at 1, 2, 4, 6, 7, 8, 9, 10, 16, 20, 24 and 28 hours post-administration on day 1. From days 8 to 28, blood samples were collected once a week before medication. Four blood samples were collected during a 2-week period after cessation of arsenic treatment. Only the samples with validated sampling information were included. Plasma specimens were stored at 4°C and analyzed within 2 weeks. The arsenic concentration was analyzed with Agilent 7700xICP-MS (Agilent Technologies, USA) equipped with a pure He octopole reaction system (ORS) was used for total arsenic analysis as reported previously.[7] The calibration curve ranged from 0.015 to 50 μg L^{-1}. The inter- and intra-day coefficients of variation (CVs) of controls were 3.71% and 4.42%, respectively. The lower limit of detection was 0.015 μg L^{-1}.

Population Pharmacokinetic Modeling of Oral AS_4S_4 Formula
Pharmacokinetic analysis was performed using the nonlinear mixed-effects modeling software NONMEM V 7.2 (Icon Development Solutions, USA). Pharmacokinetic

parameter estimates were obtained using the first-order conditional estimation (FOCE) method with interaction. Inter-individual variability of the pharmacokinetic parameters was estimated using an exponential model as previously described.[16]

Covariates of body weight, age, serum creatinine concentration, albumin concentration (ALB), aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were investigated to determine the covariate-parameter relationships using the likelihood ratio test. During the forward selection process of covariate model development, a covariate was included if a statistically significant drop in the objective function value (OFV) (reduction >3.84, $p < 0.05$, χ^2 distribution with one degree of freedom) was observed together with a reduction in the variability of the pharmacokinetic parameter. All selected significant covariates were then incorporated simultaneously into a "full" model. Subsequently, the final model was declared after backward elimination of each covariate when the covariate remained statistically significant effect to the pharmacokinetic parameter in the final model ($\Delta OF > 6.635$, $P<0.01$, χ^2 distribution).[16] Goodness-of-fit plots included plots of observed (DV) versus either the population prediction (PRED) or the individual prediction (IPRED); conditional weighted residuals (CWRES) over either range in time or PRED were initially used for graphical diagnostic purposes.[17] The performance and stability of the final model were validated based on graphical and statistical analyses obtained from nonparametric bootstraps (n=1000) and prediction distribution errors (NPDE).[17–20] One thousand datasets were simulated using the final population model parameters. A QQ-plot and histogram of the NPDE were provided graphically by the NPDE R package (v1.2).[21] The NPDE was expected to follow the N (0, 1) distribution.

Safety

Toxic effects were graded according to the NCI Common Terminology Criteria for Adverse Events, Version 3. Patients underwent a blood routine and electrocardiogram once a week, liver and kidney function were monitored twice per month.

Statistical Analysis

EFS and OS were estimated using the Kaplan–Meier method, and Log rank tests were used for comparisons. All statistical analyses were performed using SPSS 16.0 software (SPSS, Chicago, IL, USA).

Results
Study Population

Eleven newly diagnosed APL patients and one relapsed patient with a median age of 8 (range 4–14) years were included in the present study. The main clinical and biological characteristics of these 12 patients are shown in Table 1. Seven patients were enrolled and treated with oral AS_4S_4 formula RIF in maintenance therapy (regimen A), and five patients were enrolled and administered consolidation therapy that included RIF on a schedule of 3 to 4 weeks for 8 months (regimen B). Two (18.2%) of the 11 newly diagnosed patients who were tested after induction were negative for PML/RARa fusion transcripts. After the first consolidation cycle, 11 (100%) of the patients were negative (Supplementary Figure). All newly diagnosed APL patients were in MCR with a median follow-up of 28 months (range, 23 to 37 months). Both the estimated 3-year EFS and OS rates were 100%. However, the relapsed patient who began the study relapsed again and gave up further treatment.

Table 1 Baseline Characteristics in 12 Patients

	Number	Mean (SD)	Median (Range)
Patients	12		
Race	12 Chinese		
AGE (years)		7.73 (3.169)	8.0 (4.0–14.0)
CW (kg)		30.03 (14.06)	27 (16.0–63.0)
CREA (μmol L^{-1})		32.59 (9.56)	32.6 (18.4–58.4)
ALT (U L^{-1})		20.68 (11.82)	15.2 (9.0–4.4)
AST (U L^{-1})		27.37 (6.72)	26.2 (17.7–38.0)
ALB (g L^{-1})		44.13 (2.59)	43.8 (40.4–49.6)
TP (g L^{-1})		69.52 (4.69)	69.9 (62.9–77.0)
TBIL (μmol L^{-1})		9.68 (3.83)	9.2 (5.5–19.9)
ALP (U L^{-1})		274.21 (85.34)	234.75 (182.0–410.0)
RIF treatment			
Dose (mg dose^{-1})		588.79 (285.13)	540 (320–1350)

Abbreviations: CW, current weight; CREA, serum creatinine concentration; ALT, alanine transaminase concentration; AST, aspartate transaminase concentration; ALB, albumin concentration; TP, total protein; TBIL, total bilirubin; ALP, alkaline phosphatas.

Population Pharmacokinetic Analysis

A total of 107 arsenic concentrations were used for PopPK analysis. The arsenic concentrations of the blood samples ranged from 0.1 to 75.0 μg L^{-1}. A one-compartment model with first-order elimination fitted the data. The model was parameterized in terms of volume of distribution (V) and clearance (CL) of AS$_4$S$_4$. Inter-individual variability was best described by an additive model and was then estimated for V and CL. A proportional model best described residual variability.

Body weight, age, serum creatinine concentration, ALB, AST and ALT were evaluated as clinically relevant and physiologically plausible covariates. All covariates were screened, selected, then introduced separately into the structural model to identify a set of significant covariates. Body weight brought a significant impact on pharmacokinetic parameters with a decrease in OFV by 13.141 points on CL. No other tested covariate caused further significant improvement of the model. Acceptable goodness-of-fit plots for the developmental PopPK model of the oral AS$_4$S$_4$ formula is presented in Figure 1. The predictive values shown in Figure 1A and B demonstrate that this model has no significant bias. No trend in the plots of CWRES versus time or PRED was observed (Figure 1C and D). Besides, the results of bootstrap analysis on the final model revealed that the median parameter estimates were within the 95% confidence interval, thus indicating that the final model has a good predictive performance and could re-determine the estimates of PopPK parameters (Table 2). The NPDEs are presented in Figure 1E and F. NPDE distribution and histograms closely resembled the theoretical N (0, 1) distribution and density, indicating a good fit of the model to the individual data. The mean and variance of NPDE were –0.118 and 0.93, respectively.

Table 2 summarizes the parameter estimates of the final pharmacokinetic model. The median (range) of the estimated weight-normalized CL and volume distribution at steady-state were 45.26 (35.63–82.18) L h^{-1} kg^{-1} and 230.37 (85.96–495.68) L kg^{-1}, respectively. The AUC$_{0-24}$ at steady-state for the evaluated dose regimen ranged from 0.24 to 0.56 mg•h L^{-1}. When administered orally at 60 mg/kg/d TID of RIF, the plasma arsenic concentration was from 0.17 μg L^{-1} to 5.6 μg L^{-1} after 24 hours. The steady-state trough plasma arsenic concentration during the AS$_4$S$_4$ formula treatment was 47.43 (range, 25.74–62.97) μg L^{-1}. Monte Carlo simulation showed that the median steady-state Cmin (Css min) were 25.38, 38.17, and 50.66 μg L^{-1} when patients receive RIF with dosing regimens of 30, 45, and 60 mg/kg/d TID, respectively.

Safety

RIF-related adverse effects are listed in Table 3. During the RIF treatment, no grade 3–4 liver and kidney adverse events occurred in any of the patients. Two (16.7%) patients had moderate hepatic toxic effects (increased liver ALT and AST). Three (25.0%) patients had a transience asymptomatic QTc prolongation on electrocardiography (QTc interval range, 451–458 ms). Other RIF related adverse reactions included anemia (16.7%) and nausea (8.3%). All RIF-related side-effects were moderate and reversible after appropriate management was provided.

Discussion

The PopPK and safety of oral AS$_4$S$_4$ formula were evaluated for the first time in Chinese pediatric APL patients. ATRA-ATO was recently shown to have an advantage over ATRA-chemotherapy on APL treatment.[1–3] The pharmacokinetic assessment demonstrated that the current dosing regimen of 60 mg/kg/d TID resulted in a higher steady-state through concentration in children than that which was achieved in adults (24.4 μg L^{-1}, range: 11.5–64 μg L^{-1}).[9] It is also noteworthy that Monte Carlo simulation based on developmental PopPK modeling showed that a median steady-state Cmin (Css min) was 25.38μg L^{-1} if pediatric patients received RIF 30 mg/kg/d TID, which was generally comparable to that on adults receiving RIF at 60 mg/kg/d TID. Along with the effectiveness and safety results, the proposed dose could be further used in the following studies in a future study. A dose reduction might be considered appropriate in patients who experience concentration-related adverse reactions. Yang et al[15] is ongoingly evaluated a much higher dose of 135 mg/kg/d in pediatric APL patients. Obviously, the higher dosage of AS$_4$S$_4$ formula is likely unnecessary, as it may not further improve the outcome and a higher cumulative dose may lead to more long-term side-effects, especially in children.

Regarding the safety evaluation, AS$_4$S$_4$ formula-related adverse reactions included hepatotoxicity (especially in
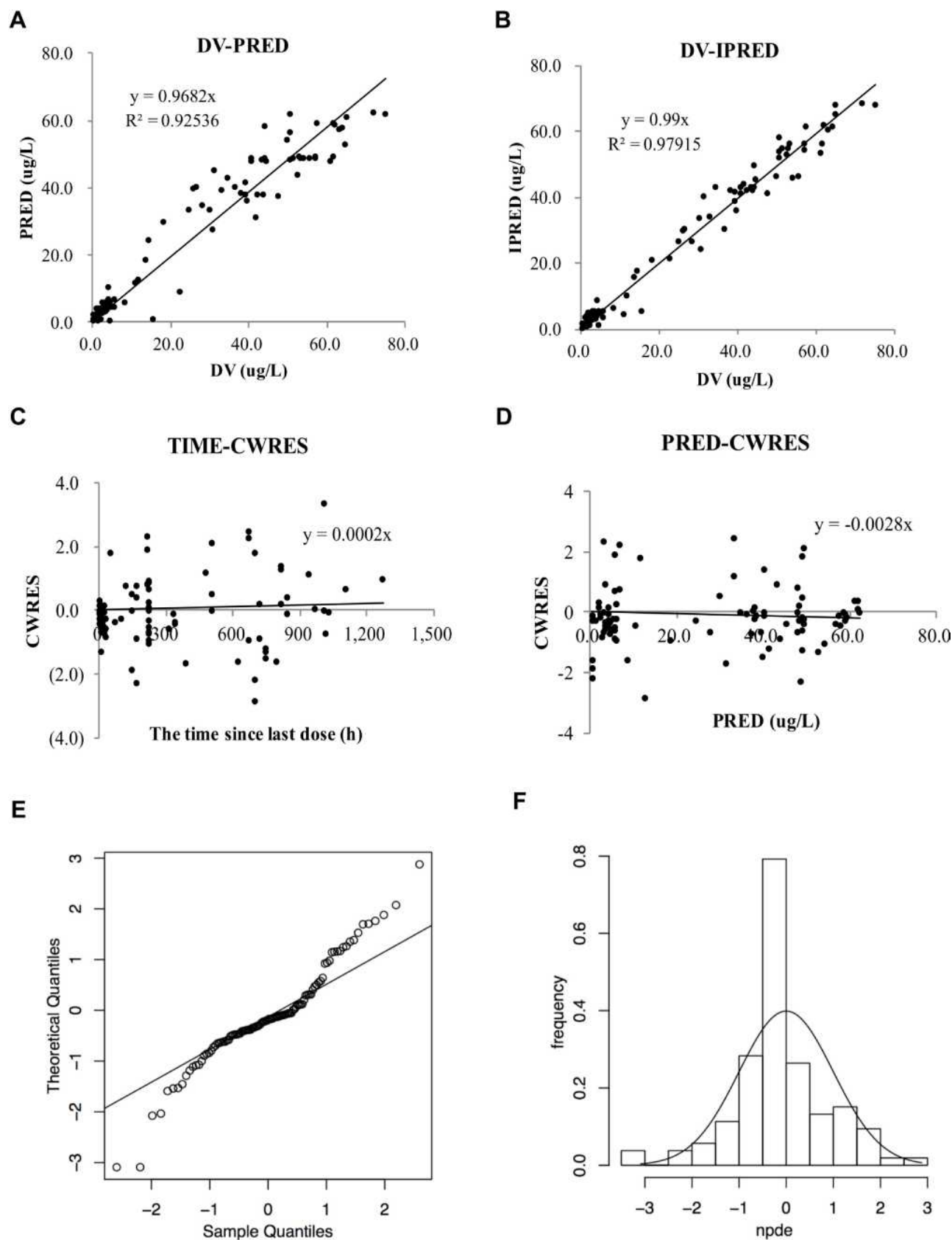
A

DV-PRED

$y = 0.9682x$
$R^2 = 0.92536$

PRED (ug/L)

DV (ug/L)

B

DV-IPRED

$y = 0.99x$
$R^2 = 0.97915$

IPRED (ug/L)

DV (ug/L)

C

TIME-CWRES

$y = 0.0002x$

CWRES

The time since last dose (h)

D

PRED-CWRES

$y = -0.0028x$

CWRES

PRED (ug/L)

E

Theoretical Quantiles

Sample Quantiles

F

frequency

npde

Figure 1 Diagnostic goodness-of-fit plots for the final population pharmacokinetic model of AS_4S_4 formula. (**A**) Observed (DV) versus population predicted (PRED) concentrations; (**B**) DV versus individual predicted (IPRED) concentrations; (**C**) time versus conditional weighted residuals (CWRES); (**D**) PRED versus CWRES; and (**E**) QQ plot of the distribution of the normalized prediction distribution errors (NPDE) versus theoretical N (0, 1) distribution; (**F**) histogram of the distribution of the NPDE, overlaid with the density of the standard Gaussian distribution.

Table 2 Population Pharmacokinetic Parameters of AS_4S_4 Formula and Bootstrap Results

Parameters	Full Dataset		Bootstrap	
	Final Estimate	RSE (%)	Median	5th–95th
Absorption rate constant (h^{-1}) Ka				
Ka $=\theta_1 \times EXP(\eta_1)$				
θ_1	0.013	17.3	0.013	0.0098–0.0180
Oral clearance (L h^{-1}) CL/F				
CL/F $=\theta_2 \times F_{WT\text{-}CL} \times EXP(\eta_2)$				
θ_2	1380	7.0	1350	1220–1530
Volume of distribution (L) V/F				
V/F $=\theta_3 \times EXP(\eta_3)$	7080	44.6	6450	3370–13600
θ_3				
$F_{WT\text{-}CL}= (CW/27)^{\theta 4}$				
θ_4	0.629	23.2	0.622	0.361–0.887
Inter-individual variability (%)				
Ka	0.353	48.2	0.339	0.075–0.445
CL	0.167	39.3	0.139	0.078–0.196
V	0.787	52.6	0.781	0.023–1.148
Residual variability (%)	3.619	31.9	3.688	2.747–4.609

Notes: θ_1, typical value of Ka; θ_2, typical value of oral clearance; θ_3, typical value of volume of distribution; θ_4, typical value of exponent for body weight effect on CL; $F_{WT\text{-}CL}$, effect of body weight on CL.

terms of an increase in liver enzymes), diarrhea and prolongation of the QTc interval. When AS_4S_4 formula was used as a monotherapy, the rate of hepatotoxicity occurred in 7.8–10% in adults.[22,23] After combining AS_4S_4 formula with ATRA, the rate of hepatotoxicity increased to about 60%.[9,11] All incidences of hepatotoxicity were resolved with a decrease or temporary discontinuation of arsenic and-/or ATRA. When AS_4S_4 formula was used, diarrhea occurred in 7.7–15% in adults.[11,22,23]. A prolonged QTc interval was not a common side effect of AS_4S_4 formula at the dose of 60 mg/kg/d in adults.[8] Although mild QTc prolongation was found in three patients without any symptoms of arrhythmia, QTc prolongation did not occur afterward during the continued AS_4S_4 formula-therapy; therefore, QTc prolongation was not related to AS_4S_4 formula-therapy. Diarrhea and hepatotoxicity were less common in children than in adults.

The oral AS_4S_4 formula had been proved highly effective in the treatment of adult APL.[8–12] Zhu et al demonstrated that in adult APL patients, a first-line therapy that included both ATRA and AS_4S_4 formula was safe and effective.[8–12] The APL07 trial showed that the estimated 7-year cumulative incidences of relapse (CIRs) and event-free survival (EFS) and OS rates were similar between the AS_4S_4 formula and ATO groups in both low- and high-risk APL patients. In our present study, the efficacy results supported the findings in adults. No newly diagnosed patients relapsed. The EFS and OS at 3 years were 100% with a median follow-up of 28 months. Of note, the patient who had relapsed prior to this study relapsed again during the AS_4S_4 formula and ATRA treatment.

A limitation of this study was the small number of patients and the short length of the follow-up period.

Table 3 Incidence of All Non-Haematological and Haematological Toxic Effects During AS_4S_4 Formula Treatment in 12 Patients

Toxicity Sites	Grade 1	Grade 2	Grade 3	Grade 4	Total
Nausea	1	0	0	0	1 (8.3%)
Vomiting	0	0	0	0	0
Neutropenia with fever	0	0	0	0	0
Anaemia	1	1	0	0	2 (16.7%)
Thrombocytopenia	0	0	0	0	0
Prolonged QTc interval	3	0	0	0	3 (25.0%)
Infection	0	0	0	0	0
Increased liver ALT or AST concentrations	0	2	0	0	2 (16.7%)
Hyperbilirubinemia	2	0	0	0	2 (16.7%)
Raised creatinine	0	0	0	0	0

However, this study provided preliminary PK and safety data in children. Thus, a Phase 2/3 trial with a long term follow-up period has been initiated in China, and patient recruitment has begun.

Conclusion

The pharmacokinetics of AS_4S_4 formula (60 mg/kg/d TID) used for children was evaluated in this exploratory study. The PopPK analysis revealed that body weight had a significant impact on oral AS_4S_4 formula pharmacokinetics. The results of this study supported the rational use of AS_4S_4 formula in newly diagnosed pediatric APL patients.

Data Sharing Statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation, to any qualified researcher. The data can be shared by emailing requests to the corresponding author Prof.Dr. Wei Zhao or Prof.Dr. Xiao-Fan Zhu.

Ethics Approval

All procedures performed in studies involving human participants were approved by the Ethics Committee of the Institute of Hematology & Blood Diseases Hospital and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Consent to Participate

Signed informed consent was obtained from the patients' parents or guardians.

Clinical Trial Registry

This trial was registered in the Chinese Clinical Trial Registry (ChiCTR-OIC-16010014).

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

Li Zhang, Xin-Mei Yang, Jing Chen, Lei Hu, Fan Yang, Yue Zhou, Bei-Bei Zhao, Wei Zhao and Xiao-Fan Zhu declare that they have no conflicts of interest relevant to this article to disclose.

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