Arsenic trioxide *versus* Realgar-Indigo naturalis formula in non-high-risk acute promyelocytic leukemia: a multicenter, randomized trial

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Abstract

Realgar-*Indigo naturalis* formula (RIF) is an oral form of arsenic that is effective against acute promyelocytic leukemia (APL). This multicenter, randomized, controlled trial compared the efficacy of all-*trans* retinoic acid (ATRA) plus RIF with ATRA plus arsenic trioxide (ATO) in a simplified regimen for non-high-risk APL. Following induction therapy with ATRA and ATO, participants were randomly assigned to receive either ATRA plus ATO or ATRA plus RIF both in a 2-week on 2-week off schedule for consolidation therapy. Once achieving molecular complete remission, the regimen was administered for a total of six cycles. All of 108 eligible patients achieved hematological complete remission after induction therapy. The median follow-up time was 29 months. The primary endpoint of 2-year disease-free survival was 97% in the ATRA-RIF arm and 98% in the ATRA-ATO arm, respectively (the ATRA-RIF arm was found to be non-inferior to the ATRA-ATO arm, [P<0.01], with a percentage difference of -1% [95% confidence interval: -4.8 to 6.9]). No deaths have been observed. Most adverse events were moderate. This study confirms the non-inferiority of RIF to ATO for non-high-risk APL, while also offering a more favorable regimen schedule for post-remission therapy (*clinicaltrials gov. identifier: NCT02899169*).

Introduction

The pivotal study of acute promyelocytic leukemia 0406 (APL0406) demonstrated that the combination of all-*trans* retinoic acid (ATRA) and arsenic trioxide (ATO) resulted in improved survival and quality of life compared to using ATRA plus chemotherapy in non-high-risk APL.[1,2] In the era of arsenic-based therapy, oral arsenic offers the advantage of reduced medical costs and a shorter hospital stay.[3] Realgar-*Indigo naturalis* formula (RIF), a traditional Chinese medicine, has been shown to be effective against APL and is available in China.[4-7] RIF is an oral arsenic compound consisting of realgar (contains approximately 90% As_4S_4), *indigo naturalis, salvia miltiorrhiza,* and *radix pseudostellariae* (adjuvant components to assist the effects of realgar).[6,8] Furthermore, a recent long-term clinical trial has confirmed the efficacy of RIF in a chemotherapy-containing regimen for pediatric patients.[9]

APL patients require prolonged hospital stays for intravenous ATO treatment. A completely oral combination of ATRA and RIF presents a prominent advantage in China, where there is a large population and limited medical resources. Although oral ATO was available in Hong Kong, the 3-year event-free survival rate was only 83.7% in an oral ATO containing maintenance therapy.[10] RIF remained the most prevalent oral arsenic agent in China.[11]

Previous studies of APL used an alternating administration of ATO for 4 weeks on and 4 weeks off, and ATRA for 2 weeks on and 2 weeks off as the post-remission regimen.[1,12] However, this approach may be inconvenient for clinical management and confusing for patients due to the different intervals of the two drugs. In a prior study,

we applied a simplified regimen in which both drugs were administered on the same schedule of 2 weeks on and 2 weeks off. The safety and efficacy of the aforementioned regimen were found to be comparable to those of the previous regimen schedule, although further validation was deemed necessary.[13]

Relapse remains a challenge to achieving favorable long-term outcomes. In a study conducted by the Chinese APL Cooperative Group, the 2-year cumulative incidence of relapse (CIR) was 2.9% (2/69) in the ATRA-RIF group.[12] Given the evidence that the combination of ATRA and arsenic shows synergy in eradicating leukemia cells *in vitro* and *in vivo*,[14,15] we propose that a schedule of simultaneous administration of ATRA and arsenic may improve efficacy. Consequently, we initiated a multicenter randomized trial APL16 to compare the efficacy and safety of RIF *versus* ATO during the consolidation phase in the simplified regimen. Here, we reported the results of the APL16 study to determine whether RIF is inferior to ATO in post-remission therapy.

Methods

Participants and eligibility

We recruited patients aged 14 to 75 years with newly diagnosed APL, classified as low to intermediate risk, from four independent medical centers in China. All participants provided written informed consent. This open-label study was approved by the Ethical Committee of the First Affiliated Hospital of Xi'an Jiaotong University in Xi'an, China (approval no. XJTU1AF2016LSL-017).

Study design and regimen

Participants were randomly assigned (1:1) to two arms by using a computer-generated random sequence, stratified by age group and treatment institution. Per procedures in this research was in accordance with the Declaration of Helsinki.

Patients initially received ATRA when suspected of having APL, and ATO was administered after genetic confirmation. During the induction therapy, patients were admitted to hospital to receive ATRA at a dose of 60 mg/day (d) (20-45 mg/m^2/d) plus ATO at 0.15 mg/kg/d until hematological complete remission (HCR). They were then randomized to receive either ATRA plus ATO or ATRA plus RIF (60 mg/kg/d of the compound) as consolidation therapy. ATRA in combination with ATO/RIF was administered in cycles of 2 weeks on and 2 weeks off, with a total of six cycles after achieving molecular complete remission (MCR) (Figure 1). ATRA and RIF were administered orally in three divided doses per day. Patients in the ATRA-RIF group took oral medication at home and were followed-up in an outpatient model during consolidation therapy. ATRA was administered at 20-45 mg/m^2 because previous studies[16-18] have demonstrated that a lower dose of ATRA can achieve the same efficacy as the dose of 45 mg/m^2. A dosage of 60 mg/d of ATRA (equivalent to 3 pills per day) is a convenient option for patients.

All patients received standard supportive care, including

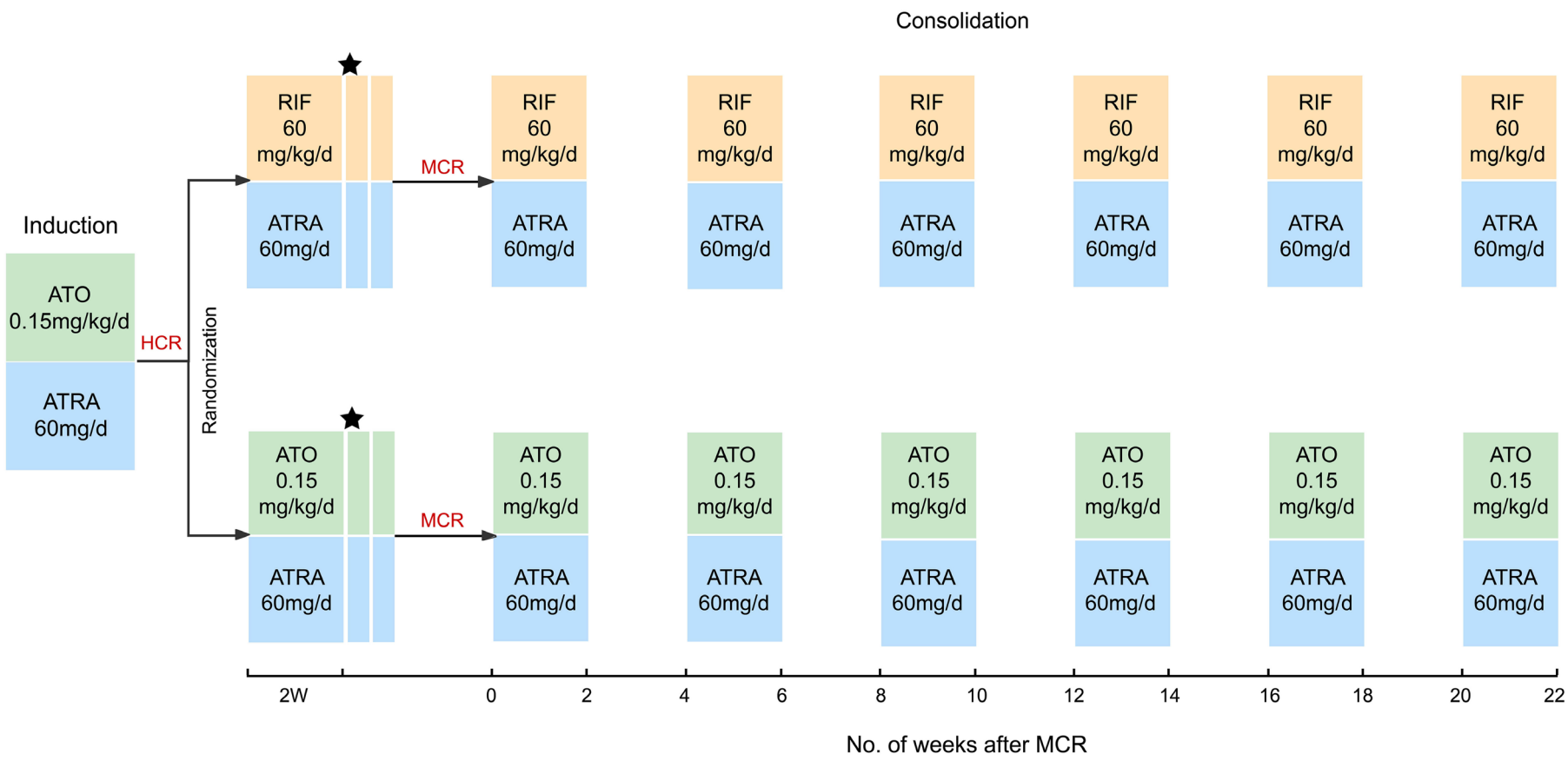

Figure 1. Treatment regimen. *Indicates 1 or several repeated cycles of treatment until achieving molecular complete remission (MCR) (1-3 cycles in this trial). ATO: arsenic trioxide; ATRA: all-*trans* retinoic acid; RIF: Realgar-*Indigo naturalis* formula; HCR: hematological complete remission; MCR: molecular complete response.

prophylactic and therapeutic antibiotics and blood product transfusions. The treatment protocol details were previously published[19] and also presented in the *Online Supplementary Appendix*.

Outcomes

The primary endpoint of this study was 2-year disease-free survival (DFS). Secondary endpoints included the incidence of adverse events and quality of life. Quality of life was assessed using the European Organization for Research and Treatment of Cancer QLQ-C30 questionnaire.[20]

Statistics

This multicenter randomized trial was designed with a non-inferiority margin of -5%, a type I error of 5% (two-sided), and a power of 90%. Assuming 97% DFS in the ATRA-ATO group and 99% DFS in the ATRA-RIF group, we used PASS (version 11) to calculate a required sample size of 53 evaluable patients per group to draw a conclusion of non-inferiority.

The primary analyses were based on an intention-to-treat (ITT) population, which included patients who received at least one dose of the assigned treatment after random-

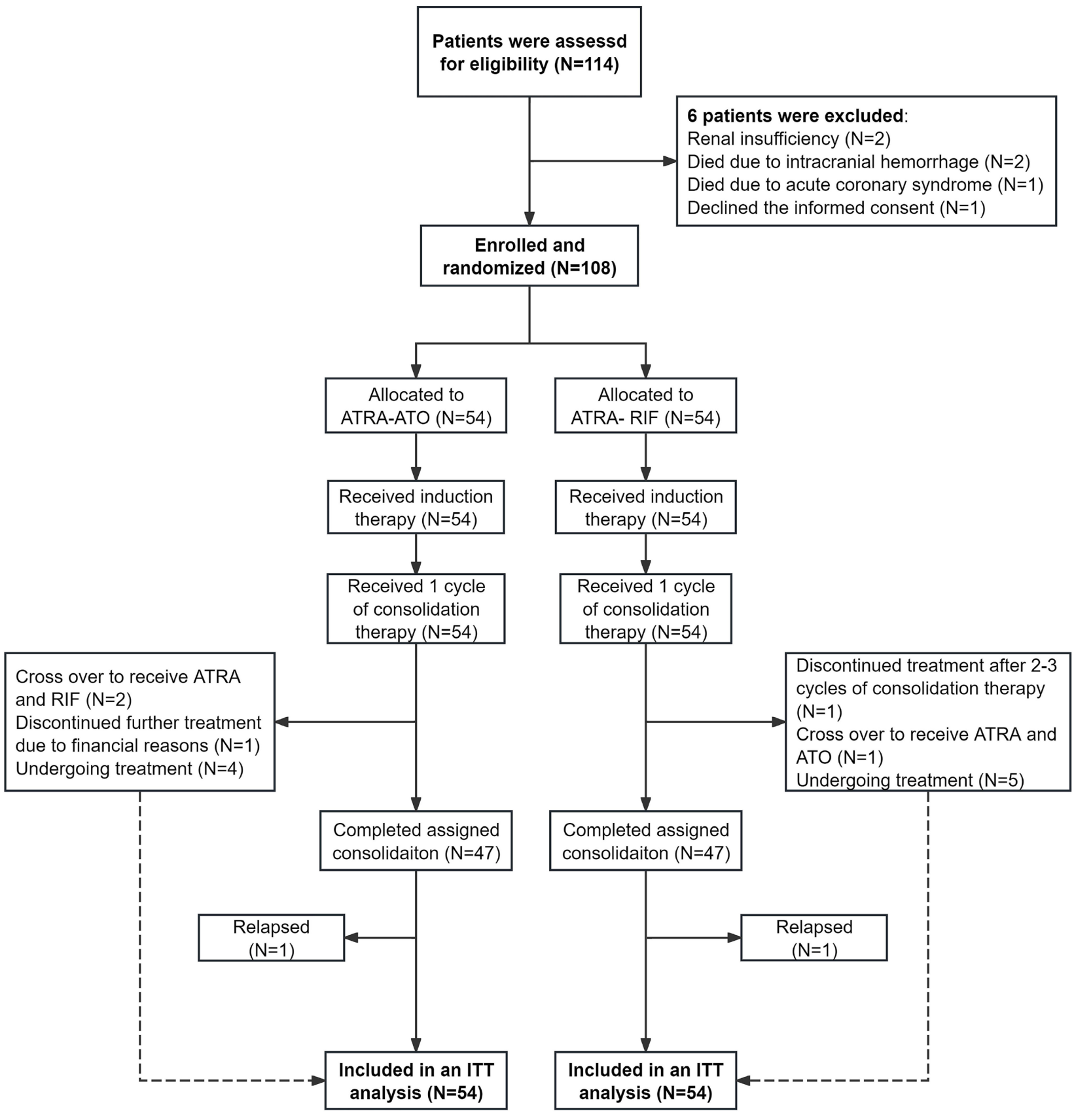

Figure 2. CONSORT diagram. ATO: arsenic trioxide; ATRA: all-*trans* retinoic acid; RIF: Realgar-*Indigo naturalis* formula; ITT: intention-to-treat.

ization. Non-inferiority was evaluated by the difference in the 95% confidence interval between the two groups in 2-year DFS. We also performed per-protocol analysis for non-inferiority, which included patients who completed all treatments as planned. Baseline characteristics were summarized descriptively. The χ^2 test was used to compare the category variables. Survival distributions were estimated using the Kaplan-Meier method and were compared using the log-rank test (two-sided α= 5%). The significance level for all statistical tests was 0.05. Data were analyzed using SPSS Statistics, version 26.0, and Medcalc software, version 15.0.

Results

Patient characteristics

The enrollment of 114 patients started from September 19, 2016, to November 20, 2023. The analysis was completed in February 2024. Three patients who died within 72 hours were excluded: two due to intracranial hemorrhage and one due to acute myocardial infarction. Three of 111 patients were not evaluated for the following reasons: severe renal dysfunction in two patients and failure to provide informed consent in one patient. The ITT analysis included 108 patients who received at least one cycle of consolidation therapy. These patients were randomly assigned (1:1) to receive ATRA plus ATO or ATRA plus RIF. Two patients (5%) discontinued treatment in the consolidation phase due to poor compliance. Three patients did not receive assigned treatment and crossed over to another group (Figure 2). The median follow-up time was 29 months (range, 2 to 88) and 62% (67/108) of patients were followed-up for more than 2 years.

The final analyses included 56 males and 52 females with a median age of 40 years. The demographic and clinical characteristics of the two groups were not significantly different. Detailed information is illustrated in Table 1.

Response data

All 108 patients achieved HCR with a median time of 32 days and followed the consolidation therapy. The MCR rate reached 70% (76/108) after one cycle of consolidation. The MCR rate achieved 100% after four cycles of consolidation therapy. The median time to MCR was 2 months and 1.8 months in the ATRA-RIF and ATRA-ATO arms, respectively (*P*=0.41) (*Online Supplementary Figure S1*). The median number of cycles in the consolidation phase was 6.6 (range, 6-10), excluding patients with protocol violations.

The primary endpoint of the 2-year DFS was 97% in the ATRA-RIF group and 98% in the ATRA-ATO group in the ITT analysis (*P*=0.98). The percentage difference in DFS was -1% (95% confidenec interval [CI]: -4.8 to 6.9), confirming the non-inferiority of the ATRA-RIF group based on a non-inferiority margin of -10% (Figure 3).

The per-protocol analysis included 47 patients in the AT-

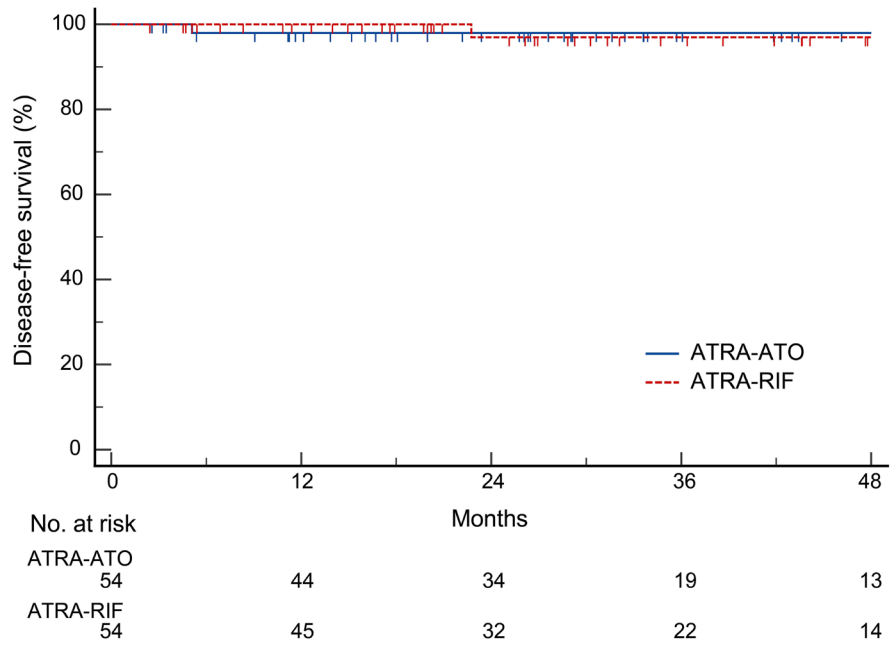

Figure 3. Disease-free survival in intention-to-treat analysis. Disease-free survival curves in the per-protocol (PP) analysis are not shown because the cases censored in the PP and intention-to-treat (ITT) analyses were consistent. ATO: arsenic trioxide; ATRA: all-*trans* retinoic acid; RIF: Realgar-*Indigo naturalis* formula.

Table 1. Baseline characteristics.

Characteristics N=108	ATRA-RIF N=54	ATRA-ATO N=54
Age in years median (range)	38 (16-73)	41 (14-74)
Sex, N (%) female male	29 (53.7) 25 (46.3)	23 (42.6) 31 (57.4)
Sanz risk, N (%) intermediate-risk low-risk	34 (63.0) 20 (37.0)	37 (68.5) 17 (31.5)
WBC count $\times 10^9$/L median (range)	1.4 (0.4-9.5)	1.7 (0.3-8.6)
Platelet count $\times 10^9$/L median (range)	33 (2-165)	21 (2-143)
FLT3-ITD mutation, N (%) *FLT3*-ITD positive *FLT3*-ITD negative Unknown*	8 (14.8) 36 (66.7) 10 (18.5)	9 (16.7) 39 (72.2) 6 (11.1)
PML-RARα breakpoint,† N (%) L S V Unknown*	29 (53.7) 17 (31.5) 6 (11.1) 2 (3.7)	31 (57.4) 18 (33.3) 3 (4.5) 2 (2.0)

*In 16 patients the *FLT3*-ITD mutation was not detected and in 4 patients the type of PML-RARA breakpoint of the bone marrow was not detected for financial reasons. †The PML-RARα breakpoint includes the long (L), variant (V), and short (S) isoforms. ATO: arsenic trioxide; ATRA: all-*trans* retinoic acid; RIF: Realgar-*Indigo naturalis* formula; WBC: white blood cell; ITD: internal tandem duplication.

RA-RIF group and 47 patients in the ATRA-ATO group who completed treatment as planned. The 2-year DFS was also 97% *versus* 98% in the ATRA-RIF group and ATRA-ATO group in the per-protocol analysis (*P*=00.99). The percentage difference between the two groups was -1% (95% CI: -4.9 to 7.0), confirming non-inferiority.

Two patients experienced APL relapses, giving a cumulative relapse incidence of 2%. One patient in the ATRA-RIF group experienced a molecular relapse at 21 months after MCR, and then 71% of blasts were observed in his bone marrow aspirate 10 days later. He received salvage therapy of ATRA with ATO plus venetoclax and achieved another MCR. However, he experienced a molecular relapse 4 months after the second MCR and prepared for an allogeneic bone marrow transplant. One patient in the ATRA-ATO group had central nervous system (CNS) relapse 1 month after achieving MCR. Promyelocytic blasts were detected in the cerebrospinal fluid aspirate, but no promyeloblasts were found in the bone marrow. He received chemotherapy with four sequential intrathecal injections. He experienced MCR after 3 months of salvage therapy and remained in complete remission until the last follow-up in January 2024.

As of the end of the follow-up period, there have been no deaths or occurrences of secondary malignancies. The 2-year overall survival rate was 100% in both groups. The median hospitalization days of patients in the ATRA-ATO group were 69 days. In contrast, patients in the ATRA-RIF group received consolidation therapy at home and completed disease monitoring under an outpatient model. They were able to continue working and maintain their functional and social well-being.

Adverse events and supportive care

In the induction phase, leukocytosis was developed in 61% (66/108) of patients with a median white blood cell (WBC) count peak of 16.9×10^9/L (range, 11.8-71.0), and the median time to peak was 6 (range, 3-17) days. A median total dosage of 24 g of hydroxyurea was given to manage. As a consequence, 71% of patients who were given hydroxyurea experienced a transient elevation of blood uric acid level. Renal insufficiency was rare (5% assessed by blood creatinine level) through active supportive care. Differentiation syndrome occurred in 17 (16%) patients, which was all mild and successfully managed by dexamethasone and drug dose reduction. Grade 3 to 4 disseminated intravascular coagulation was reported in 14 (14%) patients. Grade 3-4 neutropenia and thrombocytopenia that lasted for more than 14 days occurred in 12% (13/108) and 17% (18/108) patients, respectively.

Grade 3 to 4 non-hematological toxicity occurred relatively rarely except for infection. Grade 3-4 infection was reported in 19% (21/108) of patients. We gave intravenous antibiotics to 83% (90/105) of patients for preventive and curative aims with a median duration of 13 days. Major treatment-related adverse events during induction therapy are listed in *Online Supplementary Table S1*.

The adverse event surveys during the consolidation therapy were available for 99 patients (Table 2). Most adverse events were grade 1 to 2. The most frequently reported

Table 2. Incidence of main adverse events during consolidation therapy.

Adverse events	ATRA-RIF N=49		ATRA-ATO N=49		*P*
	Grade 1-2	Grade 3-4	Grade 1-2	Grade 3-4	Grade 3-4
Anemia	10 (20.4)	0	15 (30.6)	1 (2.0)	-
Hemorrhage/ thrombosis	3 (6.1)	0	4 (8.1)	0	-
Increased AST or ALT	7 (14.3)	0	9 (18.4)	0	-
Hypertriglyceridemia	25 (51.0)	5 (10.2)	28 (57.1)	2 (4.1)	0.44
Nausea	16 (32.7)	1 (2.0)	18 (36.7)	0	-
Vomit	10 (20.4)	0	8 (16.3)	0	-
Diarrhea	9 (18.4)	0	3 (6.1)	0	-
Rash	8 (16.3)	0	7 (14.3)	0	-
Headache	14 (28.6)	1 (2.0)	11 (22.4)	0	-
Dry skin or mouth	7 (14.3)	0	9 (18.4)	0	-
Tinnitus	3 (6.1)	0	3 (6.1)	0	-
Prolonged QTc	2 (4.1)	0	4 (8.2)	0	-
Heart failure	3 (6.1)	0	4 (8.2)	0	-
Insomnia	6 (12.2)	0	8 (16.3)	0	-

Data are expressed as N (%). ATO: arsenic trioxide; ATRA: all-*trans* retinoic acid; RIF: Realgar-*Indigo naturalis* formula; AST: aspartate aminotransferase; ALT: alanine aminotransferase; QTc: the corrected QT interval.

adverse effect was hypertriglyceridemia (67% *vs*. 56%, respectively; *P*= 0.25). The incidence of main adverse effects in the two groups did not differ. Diarrhea occurred in 18% of the ATRA-RIF group, which appeared to be more than the ATRA-ATO group, but the difference was not statistically significant (18% *vs*. 6%; *P*=0.06).

Discussion

We have verified that RIF is not inferior to ATO for post-remission therapy, even when using a simplified regimen with ATRA and arsenic given simultaneously. In our prior study APL15 and this study, we administered ATRA and arsenic agents on a 2-week on and 2-week off schedule to a total of 236 patients.[13] The simple regimen protocol yielded a CIR of 2.1% (5/236), which was comparable to previous studies[12,21,22]

ATRA and ATO target the RARA and PML moieties, respectively, to degrade the PML-RARA oncoprotein.[14,23] In addition, ATRA and ATO have synergistic anti-leukemia effects through different pathways.[24,25] This may be essential in eradicating PML-RARA-positive leukemic stem cells to make APL curable. Therefore, we administered ATRA and arsenic simultaneously instead of in separate cycles to maintain a constant plasma concentration during consolidation therapy. The co-administration of ATRA and ATO/RIF in a concurrent dosing regimen appears to be safe and may improve patient compliance, which is critical for home-based therapy. The results of our trial indicated that the median time to MCR was 2 and 1.8 months in the respective groups. This is shorter than the duration reported in previous studies, which may be attributed to the concurrent administration of the treatment.[7,12]

Despite the high cure rate, a minority of APL patients will relapse and the risk factor is still unclear. The CIR in this study was 2%. It is noteworthy that one patient who relapsed in the ATRA-RIF group experienced recurrent diarrhea during RIF treatment. Although diarrhea was readily managed, it could potentially affect the absorption of arsenic, leading to a reduction in plasma arsenic concentration.[26] Inadequate plasma arsenic concentration has been suggested to be associated with relapse.[9] It is postulated that the plasma arsenic concentration may decrease due to diarrhea, although this was not directly tested. Another patient who relapsed experienced headache during induction therapy and received a prophylactic intrathecal injection before achieving HCR. One month after HCR, APL blasts were later detected in the cerebrospinal fluid but not in the bone marrow. He achieved remission once more with intrathecal injections and ATRA plus ATO treatment. The safety and benefit of early prophylactic intrathecal injection before HCR remains uncertain.

Achieving minimal residual disease negativity is critical to avoid relapse.[27,28] A large cohort study has demonstrated that PML-RARA transcript levels at the end of induction therapy are associated with prognosis in non-high-risk APL. However, one study found that only 10% of patients achieved MCR after induction therapy.[29] In previous studies,[1,12] patients received a fixed number of cycles of consolidation therapy following induction therapy. This suggests that some patients may experience a shorter course of treatment following MCR. However, for those who achieve MCR later, a longer treatment may be necessary. All patients in the study received six cycles of post-remission therapy after MCR in order to achieve the best possible outcome. The toxicity of RIF is a major concern. The results of our study indicate that RIF does not exhibit a significant increase in toxicity compared to ATO during consolidation therapy. Based on a chemotherapy-free consolidation therapy, the incidence of cardiotoxicity and hepatotoxicity was relatively lower than that reported in previous studies.[5,22,30] No cases of grade 3-4 cardiotoxicity or hepatotoxicity were observed in this study. The frequency of QTc prolongation was less in the ATRA-RIF group than in the ATRA-ATO group, which may indicate a potential advantage of RIF. However, the difference was not statistically significant, and a larger sample size is still required to confirm this result. The incidence of diarrhea was 18% in the ATRA-RIF group, which is slightly higher than that reported in previous studies.[12,31] Further investigation is warranted to assess the impact of diarrhea on the absorption and efficacy of RIF.

Although a convenient oral regimen was employed for consolidation, it was not extended to induction therapy due to the higher WBC count peak observed in the RIF group in previous studies.[32] A limitation of this study is the absence of a direct comparison between the 2-week on and 2-week off regimen and a conventional regimen. However, the relapse rate in both groups was comparable to that observed in previous studies. A historical cohort comparison will be performed later to provide further validation. The secondary endpoint of the study was the quality of life. To our knowledge, no prospective study has reported differences in patient quality of life between RIF and ATO. We will report quality-of-life outcomes and the long-term prognosis of the APL16 trial later. In conclusion, the results of this multicenter randomized trial APL16 confirmed that oral RIF is not inferior to intravenous ATO for APL in a simplified protocol. This study proposes the simplest home-based treatment manner with RIF. Our study will inspire subsequent studies to simplify treatment and improve the treatment experience for APL patients.

Disclosures

No conflicts of interest to disclose.

Contributions

H-YW designed the study. SC analyzed the data. LL, Xiaohong Lu and W-WQ wrote the manuscript. Y-SZ, P-CH, S-HW, RZ, X-HW, H-YZ, GS, H-RD and Xin-Hua Lu contributed to data

collection. D. Wu, JL, H-TZ and X-JZ performed the cytogenetic analysis. OA, RS, and D. Wald reviewed the manuscript and modified the content. All authors contributed to the final draft.

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Data-sharing statement
The data that support the findings of this study are available on request from the corresponding author upon reasonable request.

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