Oral Tetra-Arsenic Tetra-Sulfide Formula Versus Intravenous Arsenic Trioxide As First-Line Treatment of Acute Promyelocytic Leukemia: A Multicenter Randomized Controlled Trial

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ABSTRACT

Purpose
This randomized, multicenter, phase III noninferiority trial was designed to test the efficacy and safety of an oral tetra-arsenic tetra-sulfide (As$_4$S$_4$)−containing formula named the Realgar-Indigo naturalis formula (RIF) compared with intravenous arsenic trioxide (ATO) as both induction and maintenance therapies for newly diagnosed acute promyelocytic leukemia (APL).

Patients and Methods
In all, 242 patients with APL were randomly assigned (1:1) to oral RIF (60 mg/kg) or ATO (0.16 mg/kg) combined with all-trans retinoic acid (ATRA; 25 mg/m$^2$) during induction therapy. After achieving complete remission (CR), all patients received three courses of consolidation chemotherapy and maintenance treatment with sequential ATRA followed by either RIF or ATO for 2 years. The primary end point was the rate of disease-free survival (DFS) at 2 years, which was assessed for noninferiority with a 10% noninferiority margin.

Results
The median follow-up time was 39 months. DFS at 2 years was 98.1% (106 of 108) in the RIF group and 95.5% (107 of 112) in the ATO group. The DFS difference was 2.6% (95% CI, −3.0% to 8.0%). The lower limit of the 95% CI of DFS difference was greater than the −10% noninferiority margin, confirming noninferiority (P < .001). No significant differences were noted between the RIF and ATO groups with regard to the CR rate (99.1% v 97.2%; P = .62) or the overall survival at 3 years (99.1% v 96.6%; P = .18). The rates of adverse events were similar in the two groups.

Conclusion
Oral RIF plus ATRA is not inferior to intravenous ATO plus ATRA as first-line treatment of APL and may be considered as a routine treatment option for appropriate patients.

INTRODUCTION

Acute promyelocytic leukemia (APL) has changed from a highly fatal disease to a highly curable disease. The chromosomal aberration t(15;17) plays a central role in the development of APL and results in the formation of the promyelocytic leukemia/retinoic acid receptor alpha (PML/RAR$\alpha$) fusion protein.1 Arsenic trioxide (ATO) and all-trans retinoic acid (ATRA) target the PML and RAR$\alpha$ proteins, respectively,2,3 and both drugs represent successful molecular target–based induction that targets differentiation and apoptosis, respectively. Previous studies from our group and others have demonstrated that high complete remission (CR) and 5-year disease-free survival (DFS) rates above 90% can be achieved by a combination of ATRA and ATO during induction followed by their sequential application during maintenance therapy.4-7

Although this treatment leads to improved outcomes, ATO must be intravenously administered in a hospital setting. Therefore, the development of an orally active arsenic-containing formulation with comparable efficacy and adverse effects is highly desirable. In a pilot trial in patients with APL, we demonstrated that an oral tetra-arsenic tetra-sulfide (As$_4$S$_4$) treatment alone can serve as a highly effective and safe remission induction and maintenance therapy, which was prepared in our hospital.8 We also demonstrated that another oral As$_4$S$_4$−containing formula named the Realgar-Indigo naturalis formula (RIF), which contains realgar (As$_4$S$_4$), Indigo naturalis, Radix salviae miltiorrhizae, and Radix pseudostellariae, exhibited anti-APL activity
in an in vivo murine APL model and an APL cell line in vitro. The components Indigo naturalis and Radix salviae miltiorrhizae, which promote transporting arsenics into intracellular and triggered by higher aquaglyceroporin 9 (AQP9) expression, had clear synergistic effects with As$_4$S$_3$ on the differentiation and apoptosis of APL cells. The efficacy and safety of this formula has been confirmed by a multicenter phase II clinical trial in China that observed a CR rate of 96.7% and a reasonable safety profile; RIF has been commercialized and is commonly available in China.

To determine whether oral RIF was noninferior to intravenous ATO as first-line treatment of APL, the Chinese APL Cooperative Group conducted a randomized controlled phase III study (APLO7) comparing oral RIF and ATO as both induction and maintenance therapies.

### Patients and Methods

#### Eligibility

This study enrolled 242 patients with APL in seven centers from November 2007 through September 2011. Eligibility criteria included age 15 to 60 years, a diagnosis of de novo APL with t(15;17) or PML/RAR rearrangement, a WBC less than 50 × 10$^9$/L, adequate hepatic and renal reserve (defined as total bilirubin, ALT, AST, and creatinine ≤ 2.0 × the institutional upper limit of normal), and a WHO performance status score of 2 or lower. All participants signed informed consent in accordance with the Declaration of Helsinki. This study was approved by the Ethical Committee of Peking University People’s Hospital in Peking, China. This study was registered with the Chinese Clinical Trial Registry (ChiCTR; ChiCTR-TRC-12002151).

#### Study Design

This study was designed by the Chinese APL Cooperative Group (Fig 1) as a randomized controlled trial. Patients with APL were randomly assigned by using a computer-generated random allocation schedule to receive the following induction therapies: oral RIF (60 mg/kg; n = 121) or ATO (0.16 mg/kg; n = 121). The dose of RIF was determined according to the previous results of phase I and II clinical trials. All patients, regardless of their induction group assignment, also received ATRA (25 mg/m$^2$). ATO (10 mg per vial) was provided by Harbin Yida Pharmaceutical Company (Jianyang, Harbin, Heilongjiang, China), and RIF (270 mg per pill) was provided by the Anhui Tianxang Group Pharmaceutical Resin Company, Tianchang, Anhui, China. RIF contained Realgar (30 mg per pill), Indigo naturalis (125 mg per pill), Radix salviae miltiorrhizae (50 mg per pill), Radix pseudostellatae (45 mg per pill), and Garrett film (20 mg per pill). Mitoxantrone was added at a dose of 1.4 mg/m$^2$ per day for 5 days on the fourth day of the treatment or on the first day in patients with a WBC count above 10 × 10$^9$/L. The treatment of differentiation syndrome included dexamethasone (10 mg per day) and temporary stopping of ATRA.

All the participants who achieved CR received three sequential courses of the following consolidation chemotherapy: homoharringtonine 2 mg/m$^2$ for 7 days, cytarabine 100 mg/m$^2$ for 5 days; daunorubicin 40 mg/m$^2$ for 3 days, cytarabine 100 mg/m$^2$ for 5 days; and mitoxantrone 6 mg/m$^2$ for 3 days, cytarabine 100 mg/m$^2$ for 5 days.

The maintenance treatment included eight cycles that consisted of the sequential use of ATRA (25 mg/m$^2$ for 15 days for the first month) with oral RIF (60 mg/kg for 15 days for the second and third months for those who received oral RIF during induction) or ATO (0.16 mg/kg for 15 days for the second and third months for those who received ATO during induction) without cessation for 2 years. CNS leukemia prophylaxis was performed in all the patients, and it included seven intrathecal injections of cytarabine (50 mg) and methotrexate (10 mg) plus dexamethasone (5 mg).

The follow-up time points and bone marrow samples collection points included pretreatment, CR, the end of consolidation chemotherapy, every 3 months during maintenance therapy, and then every 6 to 12 months afterward for 2 years. Quantitative reverse transcriptase polymerase chain reaction was used as in a previous study.

### End Points and Response Criteria

The primary end point was the rate of DFS at 2 years. Secondary end points were CR rate, overall survival (OS), and safety. DFS was defined as the time from random assignment to the date of relapse or death as a result of any cause. OS was defined as the time from random assignment to the date of death as a result of any cause. CR was defined as less than 5% bone marrow blasts, the absence of blasts with Auer rods, the absence of extramedullary disease, an absolute neutrophil count of more than 1.0 × 10$^9$/L, and a platelet count of more than 100 × 10$^9$/L with no red-cell transfusions. Relapse was defined as the recurrence of ≥ 5% bone marrow blasts and the reappearance of blasts in the blood or the development of extramedullary disease infiltrates at any site. Early death was defined as any death during induction therapy. Toxic effects were graded according to the National Cancer Institute’s Common Toxicity Criteria.

### Detection of Arsenic Concentration and AQP9

The arsenic concentration in plasma, urine, and hair, and nail samples was determined by hydride generation atomic fluorescence spectrometry. Plasma specimens were collected at pretreatment, during the arsenic treatment (the eighth day), and at 1, 6, and 12 months after cessation of arsenic treatment. Urine, hair, and nail specimens were collected during the arsenic treatment (12 months) and at 6 and 12 months after cessation of arsenic treatment. Bone marrow was collected for the detection of intracellular arsenic content and AQP9 messenger RNA expression after 14 days of induction therapy. Plasma and urine specimens were stored at 4°C and analyzed within 2 weeks. Other specimens were collected in polypropylene tubes. For each assay, 2 mL of plasma, 5 mL of urine, or 1 g of nails or hair was used. Arsenic fluorescence intensity data were assayed with an AFS-9800 double-channel atom fluorophotometer (Jiangmen Pengjiang Haiguang Drinking Water Equipment Company, Pengjiang, Jiangmen City, Guangdong Province, China), and a standard curve was generated with a linear range of 0 to 30 ng/mL and a detection limit of 0.01 μg/L.

### Statistical Analysis

The primary objective was to demonstrate the noninferiority of oral RIF to intravenous ATO in the rate of DFS at 2 years. DFS was analyzed as binomial outcomes rather than as time-to-event outcomes. Assuming a 95% rate of DFS in the control (ATO) group, and conservatively assuming a 94% rate of DFS in the RIF group (because the data on DFS for the RIF group were rare), a noninferiority margin of −10%, follow-up of 2 years, 5% type I error (one-sided), 90% power, and sample size calculation by using PASS software (NCSS, Kaysville, UT), 110 evaluable patients per group were required to draw a noninferiority conclusion. When considering a withdrawal rate of 10%, 121 patients per group were required. Therefore, we actually enrolled and randomly assigned 242 patients into two groups (1:1). We did not plan an interim analysis but we did plan a final analysis when all of the 220 required patients completed 2 years of follow-up. Noninferiority was to be concluded if the lower limit of the 95% CI for the rate difference of DFS was greater than −10% noninferiority margin. Analysis was per protocol.

The survival functions were estimated by using the Kaplan-Meier method and were compared by using the log-rank test. Dichotomous variables were compared with Fisher’s exact test or χ$^2$ test, and continuous variables were compared with the Wilcoxon rank sum test. All statistical tests were two-tailed with a significant level of 0.05 except for the noninferiority hypothesis.

### Results

This study enrolled 242 patients at seven centers in China between November 2007 and July 2011. Of the 242 patients, 11 were excluded from the final analysis for the following reasons: lack of genetic confirmation of APL (n = 4), failure to meet the entry criteria for low performance status (n = 3), and patient refusal to continue induction treatment in the trial (n = 4). Finally, a total of 231 patients with APL received allocated treatment, among whom 220 patients whose follow-up time was more than 2 years were analyzed for the primary end point. The median age of the 231 patients was 36 years (range, 15 to 60 years). Patient characteristics are...
provided in Table 1. Patients in the ATO group and the RIF group did not differ significantly in any demographic feature or disease characteristic. The median follow-up time was 39 months (range, 21 to 64 months).

Primary End Point

For 220 patients whose follow-up time was more than 2 years, DFS at 2 years was 98.1% (106 of 108) in the RIF group and 95.5% (107 of 112) in the ATO group. DFS difference was 2.6% (95% CI, -3.0% to 8.0%). The lower limit of the 95% CI for DFS difference was greater than -10% noninferiority margin, confirming noninferiority (noninferiority P < .001).

Secondary End Points

Altogether, 227 (98.3%) of the 231 patients achieved CR. The CR rate did not differ between the RIF group (113 [99.1%] of 114 patients) and the ATO group (114 [97.4%] of 117 patients; P = .62; Appendix Table A1, online only). The median time to CR was 29 days (range, 14 to 45 days) in the overall analysis and was not significantly different between the RIF group (29 days; range, 14 to 45 days) and the ATO group (29 days; range, 16 to 45 days).

The early death rate (death during induction therapy) did not differ significantly between the RIF and ATO groups (0.9% v 2.6%; P = .60). The causes of death in these patients included pulmonary
hemorrhage in the RIF group (n = 1) and disseminated intravascular coagulation (n = 1) and renal failure (n = 2) in the ATO group.

Of the 227 patients receiving consolidation chemotherapy and maintenance treatment, one patient in the ATO group died of intracranial hemorrhage after the second cycle of consolidation chemotherapy. Relapse occurred in two patients (one patient in the ATO group relapsed at 17 months and one patient in the RIF group relapsed at 16 months) as of the last follow-up on April 19, 2013; the remaining 224 patients were alive after first consolidation, 83 after second consolidation, and 91 after third consolidation. PML-RARα transcript levels were 93 at pretreatment, 32 at 14 days of induction, 90 at CR, 85 after remission induction, and 91 after each cycle of consolidation therapy (Fig 3). At the end of consolidation therapy, the PML-RARα transcript was undetectable in any patient in both the RIF group and ATO group. The two relapsed patients had detectable PML-RARα transcript levels before hematologic relapse.

**Adverse Events**

The rate of grade 3 to 4 nonhematologic adverse events did not differ between the two study groups during induction therapy (Table 2). The rate of treatment-related grade 3 to 4 liver adverse events was 10.8% (9.6% vs 12.0% in the RIF and ATO groups, respectively; P = .67). The rate of grade 1 to 2 liver adverse events was also similar between the RIF and ATO groups (62.5% vs 55.3%; P = .32). These conditions were treated primarily with a temporary (< 2-week duration) dose reduction or discontinuation. The symptoms/signs dissipated, and all patients were able to resume their treatment regimen.

**Molecular Kinetics**

To closely observe the molecular kinetics, serial bone marrow samples from 93 patients in Peking University People’s Hospital were analyzed. The numbers of samples at different time points were 93 at pretreatment, 32 at 14 days of induction, 90 at CR, 85 after first consolidation, 83 after second consolidation, and 91 after third consolidation. PML-RARα expression in the RIF group and ATO group was similar at diagnosis (median, 43.9% [range, 11.3% to 141.7%] vs 43.6% [range, 9.4% to 117.9%]) and then increased significantly 14 days after induction (median, 76.5% [range, 18.4% to 136.0%] vs 52.6% [range, 19.9% to 146.6%]) and slightly decreased after induction therapy (median, 15.0% [range, 0% to 77.4%] vs 2.3% [range, 0% to 243.1%]), and then further reduced after each cycle of consolidation therapy (Fig 3). The end of consolidation therapy, the PML-RARα transcript was undetectable in any patient in both the RIF group and ATO group. The two relapsed patients had detectable PML-RARα transcript levels before hematologic relapse.
Oral Arsenic Versus Intravenous Arsenic in Treating APL

Table 2. Toxicity Profile

<table>
<thead>
<tr>
<th>Toxicity Site</th>
<th>RIF Group</th>
<th></th>
<th></th>
<th>ATO Group</th>
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<th></th>
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<tr>
<td></td>
<td>Grade</td>
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<td>3 to 4</td>
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<td>1 to 2</td>
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<tr>
<td></td>
<td>No. %</td>
<td>No. %</td>
<td>No. %</td>
<td>No. %</td>
<td>No. %</td>
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<tr>
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<td>0.05</td>
<td>0.00</td>
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<tr>
<td>During maintenance</td>
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<tr>
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<tr>
<td>Renal</td>
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<td></td>
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<tr>
<td>Cardiac</td>
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<tr>
<td>Fever</td>
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</tr>
<tr>
<td>Differentiation syndrome</td>
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<td></td>
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</table>

NOTE. No difference was found between the Realgar-Indigo naturalis formula (RIF) group and the arsenic trioxide (ATO) group according to toxicity and differentiation syndrome.

During maintenance therapy, no patient experienced grade 3 to 4 hematologic or nonhematologic toxicity. No patients developed secondary neoplasms until the last follow-up.

Arsenic Retention on Follow-Up

Arsenic concentration was assayed in plasma and urine samples during and after the cessation of arsenic treatment for 26 patients (n = 13 for each group). Twenty-nine healthy donors were used as the control group. While receiving the arsenic-containing treatment, the ATO group had higher plasma arsenic concentration (median, 56.3 μg/L; range, 21.7 to 89.5 μg/L) vs. 24.4 μg/L (range, 11.5 to 64.0 μg/L; P = .0048; Figure 4A), intracellular arsenic content (median, 1.0 ng/10⁶ cells [range, 0.2 to 4.3 ng/10⁶ cells] vs. 0.2 ng/10⁶ cells [range, 0.09 to 0.8 ng/10⁶ cells]; P = .002; Appendix Fig A1A, online only), and AQP9 expression (AQP9/ABL; median, 205.7% [range, 33.8% to 1,118%] vs. 50.4% [range, 15.6% to 472.4%]; P = .02; Appendix Fig A1B) when compared with the RIF group. One month after the trial was terminated, the median plasma arsenic concentration decreased to 1.87 μg/L which was still statistically higher than that in the healthy controls (median, 0.82 μg/L; P = .003; Fig 4A). A similar pattern of urine arsenic concentration is shown in Figure 3B. Figures 3C and 3D show the kinetics of arsenic concentration in hair and nail samples from seven patients at three time points (during the treatment at 12 months and at 6 and 12 months after cessation of arsenic treatment). The median arsenic concentrations in the plasma, urine, hair, and nail samples after completing 12 months of therapy were all below the lower limit of the normal range described for normal controls.

Obtaining a high CR rate is important for achieving long-term survival in patients with APL. The rates of CR in this study were comparable or slightly higher than those in previous reports that used ATRA and chemotherapy or an arsenic-based first-line treatment (86% to 95%). These high CR rates could reflect a previously reported synergy between ATRA and arsenic. In addition, the enhanced arsenic uptake by leukemic cells due to the upregulation of the ATRA-triggered transmembrane protein AQP9 as well as the lack of cross-resistance between ATRA and arsenic could have contributed to the high efficacy and low toxicity profile in this study.

The low early death rate (0.9% in the RIF group and 2.6% in the ATO group) in this study also provided more patients with an opportunity to achieve CR. Other contributing factors were sufficient support therapy, enrolling only patients with a WBC less than 50 × 10⁹/L, favorable characteristics of the enrolled patients (good performance status and exclusion of patients older than age 60 years), and experience in treating APL; the latter is recognized as a potentially important factor in the outcome.

Survival should be the primary end point for assessing the efficacy of a new treatment protocol in APL. Our results showed that DFS at 2 years was 98.1% in the RIF group and 95.5% in the ATO group. Most importantly, we demonstrated the noninferiority of oral RIF versus intravenous ATO as first-line treatment of APL. Therefore, RIF may be a promising alternative to ATO in the future. Patient survival in this study (3-year OS of 99.1% in the RIF group and 96.6% in the ATO group) was higher than that observed in previous reports (64% to 92%). Several factors may contribute to this result. First, first-line induction and sufficient maintenance treatment with arsenic for 2 years were likely key factors. ATO, but not ATRA, has been demonstrated to be able to eliminate leukemic stem cells in APL, and prolonging the duration of postremission therapy with ATO could remarkably decrease the relapse rate. Second, this study excluded patients with a high risk of relapse (WBC > 50 × 10⁹/L). Finally, the routine intrathecal injections performed in this study may have prevented CNS relapse.

Our study demonstrated for the first time (to our knowledge) that oral RIF plus ATRA is not inferior to intravenous ATO plus ATRA in the rate of DFS at 2 years as first-line treatment of APL, and the rates of adverse events were similar in the two groups. The results may indicate that oral RIF may be used in place of ATO as a first-line treatment in newly diagnosed APL.

DISCUSSION

Our study demonstrated for the first time (to our knowledge) that oral RIF plus ATRA is not inferior to intravenous ATO plus ATRA in the rate of DFS at 2 years as first-line treatment of APL, and the rates of adverse events were similar in the two groups. The results may indicate that oral RIF may be used in place of ATO as a first-line treatment in newly diagnosed APL.
Arsenic concentration is associated with its anti-APL effects. Our previous study showed that apoptosis of APL cells could be induced over a wide range of arsenic concentrations (0.1 to 2.0 µmol/L). In this study, we found that both RIF and ATO could achieve arsenic concentrations within this effective range, which may explain why both drugs had comparable efficacies. Moreover, the ATO group had higher plasma and intracellular arsenic content than the RIF group, which may be triggered by higher levels of AQP9 expression in APL cells. Our study indicated that the commonly used dose of ATO (0.16 mg/kg) could be further decreased. One previous observation, that a reduction in ATO dose from 0.16 mg/kg per day to 0.08 mg/kg per day did not affect the efficacy and toxicity profiles, is in agreement with our opinion.

The toxicity of arsenic-containing agents is a major concern. This study showed no severe adverse effects despite the 2-year continuation period, with a cumulative dose of approximately 2,500 mg. The analysis of arsenic levels in the plasma, urine, nails, and hair of patients indicated that there was no significant accumulation. Previous studies showed that the frequency and extent of arsenic toxicity are much milder during maintenance therapy than during induction therapy. Secondary malignancies associated with arsenic were reported in only one study. This study also failed to identify any secondary malignancies associated with arsenic. However, our results on the long-term toxicity of arsenic must be interpreted cautiously because of the limited follow-up time; studies with longer-term follow-up are needed.

In conclusion, oral RIF plus ATRA is not inferior to intravenous ATO plus ATRA as first-line treatment of APL and may be considered as a routine treatment option for appropriate patients.

**Authors’ Disclosures of Potential Conflicts of Interest**

Although all authors completed the disclosure declaration, the following author(s) and/or an author’s immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a “U” are those for which no compensation was received; those relationships marked with a “C” were compensated. For a detailed description of the disclosure categories, or for more information about ASCO’s conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

**Employment or Leadership Position:** None

**Consultant or Advisory Role:** Jian-Xiang Wang, Novartis (C), Bristol-Myers Squibb (C)

**Stock Ownership:** None

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**Expert Testimony:** None

**Patents:** None

**Other Remuneration:** None

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![Fig 4. Arsenic retention in follow-up patients. The kinetics of arsenic concentration in (A) plasma during induction, (B) urine concentration, (C) hair arsenic content, and (D) nail arsenic content. ATO, arsenic trioxide; RIF, Realgar-Indigo naturalis formula.](image-url)
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REFERENCES

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Appendix

Table A1. Outcomes of Patients With APL in the RIF and ATO Groups

<table>
<thead>
<tr>
<th>Outcome</th>
<th>RIF Group (n = 114)</th>
<th>ATO Group (n = 117)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>113/114</td>
<td>114/117</td>
<td>.62</td>
</tr>
<tr>
<td>Induction failure</td>
<td>1/114</td>
<td>3/117</td>
<td>.62</td>
</tr>
<tr>
<td>Dead</td>
<td>1/114</td>
<td>3/117</td>
<td></td>
</tr>
<tr>
<td>No CR</td>
<td>10/114</td>
<td>0/117</td>
<td></td>
</tr>
<tr>
<td>DFS (2 years)</td>
<td>98.1/112</td>
<td>95.5/112</td>
<td>.45</td>
</tr>
<tr>
<td>Living in CR</td>
<td>98.1/112</td>
<td>95.5/112</td>
<td></td>
</tr>
<tr>
<td>Death during CR</td>
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</tr>
<tr>
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<td>1/112</td>
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<td></td>
</tr>
<tr>
<td>OS</td>
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<td>96.6/113</td>
<td>.18</td>
</tr>
<tr>
<td>Living</td>
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<td></td>
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<tr>
<td>Dead</td>
<td>1/113</td>
<td>4/113</td>
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</table>

Abbreviations: APL, acute promyelocytic leukemia; ATO, arsenic trioxide; CR, complete remission; DFS, disease-free survival; OS, overall survival; RIF, Realgar-Indigo naturalis formula.

Fig A1. (A) The intracellular arsenic content and (B) aquaglyceroporin 9 (AQP9) expression of leukemic cells in Realgar-Indigo naturalis formula (RIF) and arsenic trioxide (ATO) groups during induction treatment. mRNA, messenger RNA.