Single-agent arsenic trioxide in the treatment of children with newly diagnosed acute promyelocytic leukemia

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Keywords
childhood acute promyelocytic leukemia, arsenic trioxide, differentiation therapy

Short title for running head: ATO therapy for children with de novo APL

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Abstract

The aim of this study was to determine the efficacy and safety of treatment of pediatric acute promyelocytic leukemia (APL) with single-agent arsenic trioxide (ATO). A total of 19 children (≤ 15 years old) with newly diagnosed APL were treated with single-agent ATO for remission induction and postremission therapy. Seventeen of the children (89.5%) achieved complete hematologic remission (CR), and two early deaths occurred from intracranial hemorrhage. ATO-induced leukocytosis was observed in 13 (68.4%) patients. Other ATO-related toxicities were minimal and transient. Postremission ATO therapy continued for three years; the most common side effect was ATO-induced neutropenia. With a median follow-up of 53 months (range: 23-76 months), the calculated five-year overall survival (OS) and event-free survival (EFS) were 83.9% and 72.7%, respectively, which are comparable with results achieved using ATRA plus chemotherapy, which is the standard therapy for APL. No chronic arsenic toxicity or second malignancies were found during the follow-up period, and arsenic retention was not significant in patients off treatment more than 24 months. ATO resistance was observed in only one patient with a complex karyotype. The results indicate the high efficacy and safety of single-agent ATO regimens in the treatment of children with de novo APL.
Introduction

Acute promyelocytic leukemia (APL) accounts for approximately 10% of childhood acute myeloid leukemia. APL is characterized by the FAB M3 subtype morphology, distinctive immunophenotype and, in the majority of cases, there is a t(15;17) chromosomal translocation that generates the promyelocytic leukemia-retinoic acid receptor-alpha (PML-RARa) fusion gene. This specific genetic lesion determines the unique response to treatment with all-trans retinoic acid (ATRA) or arsenic trioxide (ATO).

Since the introduction of ATRA in the 1980s and ATO in the 1990s, the strategy for treating APL has shifted from conventional chemotherapy to cancer cell differentiation and cancer targeted therapy. The combination of ATRA and anthracycline-based chemotherapy is currently the standard approach to treat newly diagnosed APL. With this regimen, the hematologic complete remission (HCR) rate has improved significantly, to over 90%; five-year disease free survival is over 70%. However, some problems still remain; notably, ATRA-related side effects appear to be more pronounced in children than in adult patients, the optimal postremission therapy still remains to be defined, and approximately 20%-30% of patients eventually relapse and develop drug resistance.

ATO has proven to be another highly effective agent in APL therapy. ATO differs from ATRA due to its dual effects of inducing partial differentiation and apoptosis of
APL cells. Although highly efficacious, ATO is most commonly used in refractory or relapsed APL for inducing remission. It has previously been shown that single-agent ATO is equally effective in inducing remission in newly diagnosed cases of adult APL. However, little is known about the use of single-agent ATO in the treatment of children with APL. The optimal dosage and route of administration during remission induction and postremission therapy, the HCR rate and long-term efficacy and, most importantly, ATO-induced toxicity and long-term safety have yet to be determined.

It was in our hospital that ATO was initially used with success in treating adult APL.\(^{14}\) We have since modified the ATO protocol for childhood APL. Here, we report our experience with ATO as a single agent for remission induction and postremission therapy for children with newly diagnosed APL.

**Patients and methods**

**Patients**

The study was open to children with newly diagnosed APL being treated in the First Affiliated Hospital of Harbin Medical University from August 2002 to January 2007. The study protocol was reviewed and approved by the Heilongjiang Provincial Medical Ethics Committee. During this period, a total of 28 children aged less than 16 years were diagnosed with APL. Of these patients, 9 (6 females, 3 males) did not receive any treatment after diagnosis for personal economic reasons. Informed consent was
obtained from 19 patients and they were treated with the ATO protocol. All patients were diagnosed with APL based on the characteristic FAB M3 bone marrow morphology and peripheral blood leukemia cells. Confirmation was obtained with bone marrow mononuclear cells using conventional cytogenetics, showing t(15;17) and/or by positive reverse transcription polymerase chain reaction (RT-PCR) assay or fluorescence in situ hybridization (FISH) tests for PML/RARa fusion.

**Induction therapy protocol**

ATO solution (10 mg/10mL) was supplied by the Harbin Yida Pharmaceutical Company, China. Intravenous ATO infusion, prepared in 5% dextrose, was administered daily at the dose of 0.20 mg/kg for children 4-6 years old and 0.16 mg/kg for those above 6 years old, with a maximum daily dose of 10 mg. The total daily dose was infused intravenously over two to four hours. ATO infusion was given daily until achievement of HCR or to a maximum of 60 doses.

**Postremission therapy**

Postremission therapy continued for three years. Usually, ATO was administered daily for a total of 14 doses per course, and daily dose was modulated according to age and body weight. A 14-day course was repeated with four-week intervals during the first year following HCR. The interval between courses was increased to two months during the second year and three months during the third year. But the therapeutic regimen would be adjusted based on specific conditions. If one of the
following events occurred, i.e., the PML/RARA fusion gene reappeared, the blasts plus promyelocytes in bone marrow increased to 3.5-5%, or the white blood cell (WBC) count did not decrease markedly after 14 days of ATO administration compared to that before the ATO administration, the duration of one cycle would be extended to 21-28 days and the interval would be suitably shortened. From our experience, patients under the above-mentioned conditions were at risk of relapse.

Patients received postremission therapy as outpatients. Prophylactic intrathecal injection of methotrexate 4-5 mg, Ara-C 10-15 mg and dexamethasone 2-3 mg was given once or twice a week up to six times after remission. Commonly when the first cycle of postremission therapy was initiated, prophylactic intrathecal injections were begun at the same time. Cerebrospinal fluid was simultaneously obtained and examined in hematology and chemistry.

**Monitoring**

During induction therapy, complete blood count (CBC) results were observed every other day. Coagulation parameters, including prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen and D-dimer were observed every other day during coagulopathy. Liver functions, renal functions and electrolytes were tested twice weekly. Electrocardiograms (ECGs) were required weekly. Bone marrow examination was performed two to three weeks after therapy started, and was repeated weekly until HCR was confirmed.
In patients who did not achieve molecular complete remission (MCR) immediately after HCR, RT-PCR assays for the PML/RARa fusion transcript using bone marrow specimens were done every three months, before or after a certain course of postremission therapy (not after each course of therapy), until MCR was achieved. For patients who achieved MCR, molecular monitoring was done every three to six months for five years after HCR, afterwards, once a year for three years.

For every ATO course during postremission therapy, CBCs were done before the administration of ATO and were repeated once a week thereafter.

Throughout postremission therapy and for at least three years after completion of all therapy, complete physical examinations and the following tests were performed every three to six months: liver function, renal function, electrolytes, ECGs, dermatologic consultations, and detailed neurologic examinations.

The arsenic concentrations in urine samples and the arsenic content in nails and scalp hair were measured in nine patients 10-38 months after treatment ended. Arsenic concentrations were determined by hydride generation atomic fluorescence spectrometry. The collected specimens were placed into polypropylene tubes. Urine specimens were stored at 4°C and were analyzed in two weeks. For each assay, 5.0 mL of urine, or 1 g of nails or hair was needed. For wet digestion, samples were digested with repeated additions of nitric acid, sulfuric acid, and perchloric acid, and
heated on an electric hot plate. Mixtures were then treated with thiocarbamate to ensure quinquevalent arsenic was reduced to trivalent arsenic. Arsenic fluorescent intensity data was assayed by AFS-9800 double-channel atom fluorophotometer (Haiguang Equipment Company, Beijing). Arsenic concentrations were obtained with the standard-curve method (linear range, 0-200 ng/mL). The detection limit of the method was 0.01 ug/L.

**Supportive therapy**

Platelet transfusions were given to maintain platelet counts above 20×10⁹/L. Fresh frozen plasma (FFP; 15 mL/kg per day) was infused repeatedly when there were indications of coagulopathy or clinical indications of active bleeding. If fibrinogen remained < 0.8-1 g/L after multiple infusions of FFP, then cryoprecipitate was administered to raise fibrinogen level. Intravenous fluids and supplemental electrolytes were administered to maintain levels within the normal range; in particular, the potassium level was kept above 4 mEq/dL, magnesium was kept above 1.8 mg/dL and the serum calcium level was kept within the normal range (2.25-2.74 mmol/L). Antibiotics were administered as required for controlling infections and fevers. When total WBC count was ≥20×10⁹/L, hydroxyurea (HU; 1.0-2.0 g) was taken orally each day, in two or three divided doses. During the period of HU use, the CBC was closely monitored (tested once a day), and as soon as the WBC count dropped to 20×10⁹/L or below, HU was discontinued. When WBC count was > 20×10⁹/L, NaHCO₃ and allopurinol were commonly used orally, and no extra hydration was needed. If patients
developed APL differentiation-like syndrome, dexamethasone (5 mg twice daily) was used for at least three days and, if necessary, ATO was discontinued temporarily.

Outcome definitions

HCR was defined as the presence of all of the following: no clinical evidence of APL, peripheral-blood neutrophil count $\geq 1.5 \times 10^9$/L, platelet count $\geq 100 \times 10^9$/L, no blasts or promyelocytes in blood and $< 5\%$ blasts plus promyelocytes in the bone marrow. Hematologic relapse was defined as the recurrence of leukemic blasts in blood or as the recurrence $> 5\%$ blasts plus promyelocytes in the bone marrow after a HCR was achieved. MCR was defined as negative RT-PCR test results obtained after HCR in patients with a positive RT-PCR test at diagnosis.

Early death (ED) was defined as death within the first two weeks of induction treatment. Overall survival (OS) was calculated as the time from the initiation of ATO treatment to death, and patients still alive were censored at the time of last contact; event-free survival (EFS) was calculated as the time from the first day of therapy to death or relapse; in the absence of these events, patients were censored at the last visit.

Statistical methods

Patient characteristics were evaluated by descriptive statistics. OS and EFS were derived using the Kaplan-Meier method. A one-way analysis of variance (ANOVA),
followed by a Dunnett's test, were used to compare arsenic levels in treated groups with those in the healthy control group.

**Results**

**Remission induction**

A total of 19 patients, 4-15 years of age, were treated with ATO and included in this study. The clinical and hematological features at diagnosis are summarized in Table 1. Karyotyping was performed in 11 cases at diagnosis. Ten of them had t(15;17) and one did not. In addition, a complex karyotype, 46,XY,t(15;17)[3]/46,XY,t(15;17),+8,-19[1]/47,XY,t(15;17),+8[17], was observed in case 19.

Of the 19 patients, 17 (89.5%) achieved HCR with the single-agent ATO regimen. The median duration required to achieve HCR was 38 days (range: 26-55 days). The median cumulative dose of ATO for HCR was 6.1 mg/kg (range: 3.68-10.8 mg/kg).

The failure to achieve HCR in two patients was attributed to early death. They both have the M3a of APL and died on day 6 of the ATO therapy (Table 1). It is worth noting that these two patients presented with the two highest leukocyte counts at diagnosis (patients 4 and 9, Table 1) and both had severe leukocytosis. Their WBC counts rose dramatically in response to ATO treatment, from $38.6 \times 10^9/L$ and $89.6 \times 10^9/L$ to $177.7 \times 10^9/L$ and $251.7 \times 10^9/L$ in four to six days, respectively. The
deaths in them were presumably from intracranial hemorrhage. CT or MRI scans on them were not obtained because in both of them the symptoms of raised intracranial pressure appeared suddenly and the disease progression was so rapid that they shortly become unconscious. Considering that patients with intracranial hemorrhage were not suitable to be moved, we had planed to perform MRI scans on them as soon as their conditions became stable. But they died 2.5 hours and 7 hours later, respectively, from the appearance of symptoms of intracranial hyperpressure.

According to RT-PCR measurements, with a sensitivity of $1 \times 10^{-4}$, 9 of the 17 patients achieved HCR and had molecular monitoring of PML/RARA fusion. One patient achieved MCR immediately after HCR, and eight others did so within three to nine months after HCR (median: three months). No isolated molecular relapse (not leading to hematological relapses) occurred during follow-up period.

**ATO-induced leukocytosis and toxicity during induction**

An increase in leukocyte counts occurred in all 19 patients during ATO induction. Thirteen patients (68.4%) developed marked leukocytosis with a total WBC count ranging from $21.9 \times 10^9/L$ to $251.71 \times 10^9/L$ (median: $34.7 \times 10^9/L$). The median duration of leukocytosis was 16 days (range: 8-25 days). In three patients, the ATO dose was reduced due to significant leukocytosis. Two patients developed differentiation syndrome-like respiratory distress. They were treated successfully by controlling progressive leukocytosis using hydroxyurea, temporary discontinuation of ATO and
administration of dexamethasone for three to five days.

Other side effects of ATO included asymptomatic QTc prolongation (1/19), headache (3/19), skin rash (2/19), facial edema (1/19), peripheral neuropathy (1/19), musculoskeletal pain (3/19), hepatic toxicity (3/19) and dryness of the mouth (2/19). The headache and hepatic toxicity were grade I or II, according to the National Cancer Institute’s common toxicity criteria. All the non-hematologic toxicities were mild and resolved quickly on discontinuation of ATO.

**Postremission therapy and tolerance**

Sixteen patients who achieved HCR proceeded with postremission therapy except one patient was lost to follow-up (case 10). Postremission therapy continued for three years in this study. The periodic ATO infusion regimen was well-tolerated. The most common side effect was ATO-induced neutropenia. All 16 patients developed grade I neutropenia, but no febrile neutropenia occurred. Other side effects included grade I headache (4 patients), skin rash (3 patients) and peripheral neuropathy (2 patients). All the toxicity was reversible and needed no management.

**Outcomes and long-term toxicity**

The study included follow-up data until December 2008. Of the 16 patients who achieved HCR and received postremission therapy, 13 remained in first HCR for a period of 21 to 75 months (Table 1). Three patients had hematological relapse. Two of
the relapses occurred 14 and 56 months after HCR, respectively. A second HCR was achieved in both, following repeated ATO induction therapy. These two patients have remained in second HCR for 53 and 14 months, respectively. The third relapse (case 19) occurred 17 months after HCR, and failed to respond to repeated ATO induction. Subsequently, the patient was administered ATRA in combination with chemotherapy and achieved a second HCR. However, the patient died in a second relapse that occurred seven months later. It is worth noting that this patient was the case with a complex karyotype. Overall, with a median follow-up duration of 53 months (range: 23-76 months), the Kaplan-Meier estimate of five-year OS and EFS were 83.9% (95% C.I.: 67.2%-100%) and 72.7% (95% C.I.: 52.3%-93.2%), respectively (Fig 1).

One issue of concern was the long-term toxicity induced by exposure to multiple cycles of ATO. Careful evaluation showed that until the final follow-up, all of the 15 patients remaining in HCR were in generally good health, and that neither chronic arsenic intoxication (including neurologic toxicity) nor second malignancy have been observed.

The other major concern about the use of ATO was arsenic retention. Urine arsenic concentrations and arsenic contents in nails and hair, which are good indicators of long-term exposure and in vivo accumulation of arsenic, were analyzed in nine patients at the last follow-up visit, when all therapy had been completed 10-38 months before. Although the arsenic levels in urine, hair and nails from patients who had
ceased treatment for less than 24 months were significantly higher than those in healthy controls (patients' parents) ($P_{\text{urine}} = 0.000$, $P_{\text{hair}} = 0.003$, $P_{\text{nails}} = 0.000$), no significant difference was found between patients who had ceased treatment for more than 24 months and healthy controls ($P_{\text{urine}} = 0.556$, $P_{\text{hair}} = 0.542$, $P_{\text{nails}} = 0.436$; Fig 2). The urine arsenic concentrations in patients who had ceased treatment for more than 24 months were all below the safe limit of 200 µg/L set by the U.S. Agency for Toxic Substances and Disease Registry (ARTSDR).

**Discussion**

This study presents a small but significant series using a single-agent ATO regimen for both remission induction and postremission therapy of children with newly diagnosed APL. Similar studies have been carried out in small series of patients, and we summarize the main results from a study by George et al. in comparison with ours in Table 2. In both studies, with a similar HCR rate of about 90%, no patient failed to respond to ATO induction. The only reason for failure to achieve HCR was early death, with two early deaths among 19 patients in our study and one early death among 11 in George et al. Considering the abrupt onset and rapidly deterioration of the two catastrophic events, we speculate that the two sudden deaths in our study were most likely secondary to uncontrollable intracranial hemorrhage though the possibility of fatal hemorrhagic infarction of the brain induced by severe leucocytosis and hyperviscosity cannot be excluded in the absence of imaging studies. In the study
by George et al, single-agent ATO was also used for postremission therapy. Although the postremission therapy was less intensive than ours, and the estimated five-year OS and EFS were higher than ours, this can be attributed to the small sample sizes in both studies and another speculative factor, the different ethnicities of the study participants who had various genetic backgrounds and distinct reactivities to ATO.

Similar to the results in adult patients, the combination of ATRA and intensive chemotherapy has been proven effective in children with APL.\textsuperscript{2, 3, 4} When single-agent ATO is used for remission induction and postremission therapy in children with newly diagnosed APL, it appears to achieve an HCR rate and durable remission comparable with those obtained using the combination of ATRA and chemotherapy (Table 2).

Regardless of the presenting leukocyte counts, leukocytosis occurred in response to ATO during remission induction. This is consistent with the ATO effect inducing APL differentiation. An increase in leukocyte count was observed in all patients in this study. Severe leukocytosis with a WBC count of over 100 × 10^9/L was observed in five of the 19 patients, including two early deaths and two other patients who developed differentiation-like syndrome. It is interesting to note that, in contrast to leukocytic response to ATO induction, postremission ATO therapy invariably induced neutropenia in patients in HCR. This likely reflects the differential effects of ATO on APL cells and maturing granulocytes. ATO apparently induces differentiation of APL cell by degrading the PML-RARa fusion transcript. In addition, it also activates the
apoptotic cascade. ATO-induced neutropenia in HCR patients was likely attributed to its apoptotic effect on maturing cells and possibly normal granulocytes.

Of the three relapsed patients, a second HCR was achieved in two following repeat ATO induction therapy and remained for 14 and 53 months, respectively. This suggests that the single-agent ATO regimen for APL may not increase ATO-resistance rates.

It is worth mentioning that a higher dose of ATO (0.20mg/kg) was used in younger patients (4-6 years of age) in this study. In 1970’s, when ATO was first used for clinical treatment of APL in our hospital, the dose for younger patients was not defined, and then no report could provide a reference. Considering that a faster metabolism in children probably promotes drug excretion, we tried to give them a little higher dose of ATO, just as the usage of some antibiotics. During treatment toxic response to ATO was observed carefully. Although higher dose of ATO was used as a single-agent for induction therapy, it caused only minimal toxicity except severe leukocytosis in our patients, as in adults. Pharmacokinetics study of ATO in children was requested urgently, but because of the need for multiple blood samples and bleeding diathesis in patients, it was always refused by children’s parents.

Another important feature of ATO therapy in this study is that the postremission therapy lasts for three years. The Europeans have been using two years, while the North Americans have been using only one year of "maintenance" therapy for APL in
children. According to our previous experience, HCR rate was mainly influenced by remission induction therapy while relapse rate was highly correlated with postremission therapy. By careful observation we have found that when the postremission therapy continued for no more than two years here, about half of the patients (including adult) eventually relapsed in 1-3 years after the treatment had ended. Prolonging the duration of postremission therapy to three years could remarkably decrease the relapse rate. Of course, extending the duration of postremission therapy to reduce potential relapse risk has to be at the expense of increasing the potential risk of cumulative toxicities.

So, a matter of great concern is whether long-term postremission therapy for children with ATO can result in chronic arsenic toxicity, such as skin lesions (pigmentation and keratosis), hypertension, cardiovascular diseases, diabetes mellitus, neurological effects, cancer of skin, lung and urinary bladder, etc.\(^{23}\) The present study shows that although periodic ATO therapy continued for more than three years, no severe side effects were documented, nor was a second malignancy encountered, with follow up to three or more years following completion of therapy. The analysis of arsenic levels in urine, nails and hair from patients indicated that no significant ATO accumulation was observed in patients who had been off ATO therapy for more than two years.

Decreased hospital time and decreased medical care expenses are the other benefits of our treatment approach. The absence of the toxicities of conventional
chemotherapy and of hospitalization during postremission therapy make the ATO treatment regimen less expensive and more acceptable than the ATRA plus chemotherapy regimen in our setting, especially for pediatric patients.

In conclusion, the present study provides additional information on the use of single-agent ATO for induction and postremission therapy in childhood APL. Our results showed that the therapeutic efficacy of the ATO treatment regimen is comparable with that of ATRA plus chemotherapy. Furthermore, this regimen is safe, with minimal toxicity and without significant risk for the development of chronic arsenic toxicity or second malignancy. The advantages of this regimen are that it can avoid the use of chemotherapy in children and that it seldom causes drug resistance; these properties make ATO a particularly attractive therapeutic regime. Further investigation with larger sample sizes and risk-adapted postremission therapy are needed.

Acknowledgements

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Table 1. Clinical characteristics of the patients and results of arsenic trioxide (ATO) therapy and follow-up

<table>
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<th>Patient no.</th>
<th>Sex/age (years)</th>
<th>WBC, ×10⁹/L</th>
<th>Platelets, ×10⁹/L</th>
<th>Blasts-promyelocytes in BM (%)</th>
<th>t(15;17)/PML/RARa</th>
<th>Days to achieve HCR</th>
<th>Treatment results</th>
<th>Follow up (months)</th>
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<td>69</td>
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• PML/RARa was detected by FISH.

M, male; F, female; WBC, white blood count; ND, not done; HCR, complete hematologic remission; ED, early death; NA, lost to follow-up; --, not applicable.
Table 2. Primary published clinical studies of childhood acute promyelocytic leukemia (APL) treated with arsenic trioxide (ATO) or all-trans retinoic acid (ATRA) plus chemotherapy

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<thead>
<tr>
<th>Study, year</th>
<th>No. of patients</th>
<th>Age (years)</th>
<th>Induction</th>
<th>HCR (%)</th>
<th>Postremission therapy</th>
<th>Duration of post remission therapy</th>
<th>Estimated 5-year OS (%)</th>
<th>Estimated 5-year EFS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>George et al,22 2004</td>
<td>11</td>
<td>≤15</td>
<td>ATO</td>
<td>91</td>
<td>ATO</td>
<td>8 months</td>
<td>91</td>
<td>81</td>
</tr>
<tr>
<td>Present study</td>
<td>19</td>
<td>≤15</td>
<td>ATO</td>
<td>89</td>
<td>ATO</td>
<td>3 years</td>
<td>84</td>
<td>73</td>
</tr>
<tr>
<td>De Botton et al,3 2004</td>
<td>31</td>
<td>≤18</td>
<td>ATRA + daunorubicin-cytarabine</td>
<td>97</td>
<td>CT and/or ATRA, BMT (n=2)</td>
<td>2 years and 2 months</td>
<td>90</td>
<td>71</td>
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<tr>
<td>Testi et al,4 2005</td>
<td>107</td>
<td>≤18</td>
<td>ATRA + idarubicin</td>
<td>96</td>
<td>CT and/or ATRA, BMT (n=3)</td>
<td>2 years and 3 months</td>
<td>89</td>
<td>81</td>
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<tr>
<td>Ortega et al,2 2005</td>
<td>66</td>
<td>≤18</td>
<td>ATRA + idarubicin</td>
<td>92</td>
<td>CT+ATRA</td>
<td>2 years and 3 months</td>
<td>87</td>
<td>77</td>
</tr>
</tbody>
</table>

*• denotes the number of patients who had a BMT in first remission.

CT, chemotherapy; BMT, bone marrow transplantation; OS, overall survival; EFS, event-free survival.
Fig 1. The Kaplan-Meier overall survival (OS) and event-free survival (EFS) curves for 19 children treated with arsenic trioxide (ATO).

+ denotes censoring time.

5-year OS 83.9% (C.I. 95%: 67.2-100)

5-year EFS 72.7% (C.I. 95%: 52.3-93.2)
Fig 2. The arsenic levels in hair, nails and urine samples from different groups.

ATO denotes arsenic trioxide.
Single-agent arsenic trioxide in the treatment of children with newly diagnosed acute promyelocytic leukemia

Jin Zhou, Yingmei Zhang, Jinmei Li, Xiaoxia Li, Jinxiao Hou, Yanqiu Zhao, Xihuai Liu, Xueying Han, Longhu Hu, Shuye Wang, Yanhong Zhao, Ying Zhang, Shengjin Fan, Chengfang Lv, Limin Li and Lingling Zhu