Arsenic trioxide and mannitol for the treatment of acute promyelocytic leukemia relapse in central nervous system

Hong Wang¹, Fenglin Cao¹,², Jinmei Li¹, Limin Li¹, Yong Li¹,², Ce shi¹, Wenjia Lan¹, Dandan Li¹, Hui Zhao¹, Ying Zhang¹, Zhuo Zhang¹, Xiuhua Liu¹, Ran Meng¹, Baofeng Yang¹, Jin Zhou*,¹,²

¹Department of Hematology, First Affiliated Hospital, Harbin Medical University, Harbin, China and ²Heilongjiang Institute for Hematology and Oncology Researches, Harbin, China and ³Department of Hematology, Radiology Branch, First Affiliated Hospital, Harbin Medical University, Harbin, China

* Corresponding author: Jin Zhou, Department of Hematology, First Affiliated Hospital, Harbin Medical University, Harbin, Heilongjiang, 150001, China; e-mail: zhoujin1111@126.com; Phone: 86-451-53641824; Fax: 86-451-53670428

Running head: Mannitol and ATO Therapy for CNS APL
Key points

- Mannitol increased ATO concentration in CSF.
- ATO and mannitol prompted favorable treatment outcome for CNS APL.

Abstract

Acute Promyelocytic Leukemia (APL) relapse in the central nervous system (CNS) can be isolated or associated with bone marrow relapse. Management of CNS APL remains a challenge. In this study, we identified an effective therapeutic regimen for CNS APL that consisted of single-reagent intravenous infusion with arsenic trioxide (ATO) preceded and accompanied by mannitol. Seventeen patients with isolated or combined CNS relapse were enrolled in this study and underwent a treatment plan of sequentially administered induction, consolidation, and maintenance therapies. Induction therapy consisted of daily intravenous ATO (7 mg/m²/day for adults, 0.16 mg/kg/day for children ≤ 15 years) and 20% mannitol administered until patient cerebrospinal fluid (CSF) was free of blasts/promyelocytes. Measurements of CSF arsenic during induction showed comparable level to those in blood (i.e. 99.7% of those in blood). Subsequently, routinely scheduled consolidation and maintenance treatments were administered. Sixteen patients (94.1%) achieved complete molecular remission, of which 9 patients (52.9%) remained relapse-free for a median of 92 months (range: 70 - 125 months) after the first induction. Fourteen patients (82.4%) reached a median overall survival of 87
months (range: 66 - 125 months). In conclusion, intravenous ATO plus mannitol may represent an effective therapeutic option for treating CNS APL.

This study was registered at www.isrctn.org (Identifier No. ISRCTN94954912).

**Key words**

Acute promyelocytic leukemia, Central nervous system relapse, Arsenic trioxide, Mannitol
Introduction

Approximately three to five percent of acute promyelocytic leukemia (APL) patients will have an extramedullary relapse in their lifetimes, most commonly in the central nervous system (CNS).\(^1\) CNS APL can be isolated or associated with a bone marrow (BM) relapse. Regardless of type, CNS APL patients often present with headache, limb paresthesia, meningeal stimulation, or other central nerve compression syndromes. Since findings from magnetic resonance imaging (MRI) are usually normal, the golden standard for diagnosis remains the cerebrospinal fluid (CSF) test. The CSF diagnostic characteristics include high pressure, red blood cells presence, abnormal blasts/promyelocytes, high protein levels, and transcript expression of the promyelocytes or APL blast cells and retinoic acid receptor (PML/RAR\(^\alpha\)) gene.

The most appropriate approach for clinical management of CNS relapse in APL patients remains controversial. Several case reports have suggested intrathecal chemotherapy with allogenic or autologous hematopoietic stem cell transplantation (HSCT) as a promising therapeutic strategy;\(^2\text{-}^5\) however, the existence of unfavorable outcomes has limited the applicability of this approach.

The major obstacle to all treatments for CNS APL is the need for the therapeutic drugs to penetrate the blood brain barrier (BBB). Although ATO and all-trans retinoic acid (ATRA) are among the frontline medications for APL intra-marrow treatment,\(^6\text{-}^{10}\) these water soluble medicines have limited ability
to cross the BBB and cannot reach therapeutically effective levels in CSF.\textsuperscript{11,12} When taking regular oral dosages, the ATO level in CSF has been reported to reach only 17.7\% of the corresponding levels in plasma.\textsuperscript{11} Previously, we had carried out investigations of the potential efficacy of combining a mannitol intravenous infusion with the ATO therapy using a rabbit model, and we showed that the approach caused a transient increase in the BBB permeability for ATO, thereby increasing the ATO concentration in CSF to therapeutic levels.\textsuperscript{13} Our \textit{in vitro} experiments using human cortical neurons revealed a differential tolerance of APL blasts and to different concentrations of ATO.\textsuperscript{14,15} In subsequent studies we also identified a safe range of ATO concentrations in human CNS.\textsuperscript{16-18} The results from these collective studies allowed for an ATO concentration to be achieved in CSF that was both safe and therapeutic.\textsuperscript{19} Here, we describe our efforts to extend the application of our method to additional patients and we discuss the efficacy of this treatment regimen and the favorable prognosis that was observed during long-term follow-up.

\textbf{Patients and methods}

The study protocol was reviewed and approved by the University Medical Ethics Committee, and signed informed consent was obtained from all patients or their legal guardians. The study was conducted in accordance with the Declaration of Helsinki. Clinical records from the Hematology Department of the First Affiliated Hospital to Harbin Medical University, between 2000 and
2010, were reviewed for this study. In total, 17 APL patients with CNS relapse were included in this study, and were represented by 10 males and 7 females who were between 6 and 50 years old (median age: 41 years old). All patients had been diagnosed with CNS relapse based on clinical symptoms and confirmed by morphological and cytogenetic/molecular findings. Expression of the \textit{PML/RAR\alpha} gene (or \textit{t}(15;17)(q22;q21) transcripts) were detected in all patients CSF by reverse transcription-polymerase chain reaction (RT-PCR) assay. Clinical data of the patients are summarized in Table 1.

**Remission induction therapy**

For all patients, the induction treatment was started immediately upon diagnosis of the CNS relapse. The daily protocol was as follows: a bolus infusion of 125 ml 20\% mannitol mixed in 100 ml normal saline (NS) (for children \( \leq 15 \) years: 50 ml mannitol and 50 ml NS) administered intravenously via the antecubital vein at a flow rate of 12 \~ to 20 ml/min (about 8-11 minutes total); a slow intravenous infusion of 125 ml 20\% mannitol plus 7.0 mg/m\(^2\)/day ATO (for children \( \leq 15 \) years: 50 ml mannitol and 0.16 mg/kg/day ATO) in 500 ml NS at a flow rate of 1.0 ml/min (about 9-10.5 hours total). Patients were instructed to rest in bed during the entire infusion procedure. Urine flow was measured to ensure maintenance of a rate of at least 30-50 ml/hour. Daily infusions were continued until the patient’s CSF was found to be free of APL blasts/promyelocytes.
In addition to routine lab tests, the level of element arsenic metabolites was measured every other day in each patient’s CSF and blood samples which had been taken immediately after each day’s infusion. Inductively coupled plasma mass spectroscopy (ICP-MS; Agilent Technologies, Santa Clara, CA, USA) and high performance liquid chromatography (HPLC; AMTK, Tianjin, China) were used for the measurement of arsenic levels.

**Consolidation and maintenance therapy**

Consolidation therapy started two weeks after the induction therapy and was repeated at two-week intervals. A total of three cycles of consolidation therapy was given to all the patients who achieved normal CSF morphology with induction treatment. For each cycle of consolidation, daily ATO and mannitol infusion (administered as described previously for the induction treatment) continued for 14 consecutive days. At the end of consolidation treatment, promyelocytic leukemia–*PML/RARα* fusion transcripts in CSF and BM were tested.

Absence of *PML/RARα* transcripts in CSF and BM (defined as complete molecular remission (CMR)) was achieved prior to commencement of lifetime maintenance therapy (Figure 1). The first year after CMR, a 14-day cycle administration of ATO and mannitol was repeated at one-month intervals. In the second year, a protocol identical to that of year one was instituted, but using a three-month interval regimen. From the third year on, the protocol was administered at six-month intervals and maintained for life. *PML/RARα* levels
were monitored at six-month intervals. If a relapse was identified, another cycle of remission induction was started. Clinical monitoring and supportive treatment followed our departmental guidelines.⁶

Arsenic concentrations in urine, as well as functional markers of the cardiac system and gastrointestinal system were evaluated before and after each cycle of treatment. Arsenic levels were tested by hydride generation atomic fluorescence spectrometry (Haiguang Equipment Company, Guangzhou, China).

**Statistical analysis**

Patient characteristics were evaluated by descriptive statistics using the SPSS statistical software package, version 17.0 (Chicago, IL, USA). The two related samples nonparametric test was used to determine differences in outcome variables (within groups for different concentrations of element arsenic). Bivariate correlation analysis was used to analyze the correlation between variable groups and level of element arsenic in the blood and CSF. Overall survival (OS) was calculated as the time from the diagnosis of CNS relapse (on an intention-to-treat basis) until the last follow-up or death. Relapse free survival (RFS) was calculated as time of CMR until the last follow-up, relapse, death from any cause, or occurrence of severe side effects. OS and RFS were estimated by the Kaplan-Meier method. All tests were adapted to the reduced sample size Pearson’s test. P values < 0.05 were considered to be statistically significant.
Results

Patient response to induction treatment

In 16 of the 17 patients examined, abnormal blasts/promyelocytes from CSF were eliminated in 18 to 32 days (median 24 days) after start of induction treatment. Only one patient (Table 1, patient no. 3) was non-responsive to induction treatment after 49 days and later received ATRA and ATO alternative therapy.

All the patients tolerated the induction treatment well. There were no complaints of side effects (e.g. headache, blurred vision, pulmonary congestion, et cetera) associated with the use of mannitol. There were no documented cases of acute arsenic poisoning, which is indicated by the following symptoms: headache, nausea, vomiting, diarrhea, abdominal pain, hypotension, fever, hemolysis, seizures, and mental status changes. No patients discontinued use of ATO during the induction, and leukocytosis was rarely seen (white blood cell (WBC) count ranged from $0.7 \times 10^9$/L to $10.5 \times 10^9$/L for all patients). There were some cases of mild liver enzyme changes and mild non-hematologic toxicity associated with ATO, but in all instances these abnormalities resolved with the use of hydroxyurea and administration of dexamethasone for 3-5 days.

Arsenic metabolite levels in the blood and CSF during induction

There were no significant differences in the level of arsenic metabolites between children and adults (data not shown). The dynamic changes of functional ATO metabolites in paired blood and CSF samples are shown in
Figure 2. The correlation between each parallel blood and CSF arsenic levels was significant ($r=0.998$). Over the course of the entire induction treatment process, the concentrations of arsenic in the blood and CSF were fairly stable in each patient. For each individual, the arsenic level in CSF was approximately 99.7% of those in the paired blood samples. However, arsenic levels in different individuals were highly variable, with a range from 291.61 nmol/L to 609.53 nmol/L in blood and 287.28 nmol/L to 607.71 nmol/L in CSF.

Clinical outcome and chronic toxicity

Of the 16 patients who responded to induction therapy, all (94.1%) achieved CMR after the first consolidation cycle. Nine of these patients retained their CMR status during the follow-up period (median of 92 months, range of 70 to 125 months, so that the RFS rate after first CMR was 52.9% (Figure 3A). Among the other seven patients, there were one to three relapses in BM or in CNS after their first CMR. All seven of these patients responded well to ATO and mannitol during re-induction: five of them achieved CMR again and stayed free of relapse; two died after withdrawing treatment 3-5 months after their second or third remission. The only patient that did not respond to the treatment was a 6 year old female who died 15 months into the therapy despite vigorous treatment. Eventually, 14 of 17 patients (82.4%) reached a median OS of 87 months (66 to 125 months) (Figure 3B).

After careful evaluation of potential chronic toxicity induced by multiple exposures to ATO, there were no concerns. At the time of the last follow-up
appointment, all patients remained in generally good health without signs of chronic arsenic intoxication (including normal CNS, gastrointestinal tract and cardiac functions) or second malignancy. During the first two years of maintenance treatment, the concentration of arsenic in urine was higher than normal levels before each treatment cycle (P < 0.05). In spite of this, evaluations from the third year of maintenance and onward showed that the arsenic levels prior to each therapeutic cycle were decreased below the safety limit of 200 μg/L, as recommended by the U.S. Agency for Toxic Substances and Disease Registry.20

Discussion
At present, the most widely used method to treat APL CNS relapse is intrathecal combination chemotherapy of methotrexate (MTX), cytarabine (Arac), and hydrocortisone for induction therapy, with consolidation therapy using intrathecal chemotherapy plus systemic chemotherapy and followed by a mandatory HSCT.21,22 Intrathecal therapy requires a lumbar puncture, which is an invasive, time-consuming and painful maneuver that may induce trauma or drug misdistribution throughout the neuro-axis.23 Systemic chemotherapy could be restricted when severe adverse effects develop, such as cardiotoxicity or neutropenia. HSCT is indicated for maintenance therapy of CNS APL,24 but the morbidity and mortality associated with HSCT continue to limit its widespread application.
Another therapeutic option for CNS relapse is the use of the potent reagent ATO, which is also the first choice for treating a BM relapse. Experience from ours and other clinics have demonstrated that regular ATO intravenous infusion plus oral ATRA could induce complete remission in newly diagnosed APL and BM recurrence. However, combination ATRA and ATO therapy should be used cautiously because of the risk of severe side effects, including differentiation syndrome and cardiotoxicity. Therefore, in this study, we chose ATO only plus mannitol for treating extrathecal relapse. Conventional administration of ATO does not increase arsenic levels in CSF to a similar therapeutic level as found in blood, with CSF levels only reaching 17.7% of the corresponding plasma level. This is because ATO is a water soluble medicine and not capable of crossing the BBB and entering the CSF. This barrier, however, could be overcome (in a reversible manner) by intravenously administering the hyperosmotic agent mannitol. Combining mannitol with the ATO solution significantly increased arsenic migration into CSF. It has been shown that after antecubital venous injection of a 20% mannitol bolus, the BBB permeability to ATO was temporarily increased for at least 90 minutes. In the present study, immediately after the bolus of mannitol, ATO was infused at a relatively slow speed followed by another simultaneous dose of 20% mannitol. We believe this slow speed infusion strategy not only helped to maintain the BBB permeability to ATO at a consistently high level but also decreased ATO’s acute toxicity. Furthermore, the elemental arsenic levels in CSF were
approximately 99.7% of their parallel blood levels (Figure 2). Although the level of arsenic varied across different individuals in this study, it stabilized after the fourth infusion in all patients during the entire induction treatment. Because the therapeutic levels of ATO were stable and evenly distributed, ATO was able to efficiently eliminate leukemic blasts/promyelocytes from the patients’ blood and CSF. Sixteen of the 17 patients showed normal CSF morphology with only a median of 24 consecutive days (range: 18-32 days) of induction.

Leukocytosis is a side effect that frequently occurs during newly diagnosed APL induction treatment, but it was not seen in the CNS relapse cases of the current study. Although the ATO dosages were the same (7 mg/m²/day for adults, 0.16 mg/kg/day for children ≤ 15 years), the peripheral WBC count only remained low (ranging from 0.7 x 10⁹/L to 10.5 x 10⁹/L), and there were no reports of discontinuation or reduction of ATO due to this parameter. Differentiation syndrome-like respiratory distress did not develop in any patient. Other reported adverse effects, including asymptomatic QT prolongation, skin rash, facial edema, peripheral neuropathy, musculoskeletal pain, and dryness of mouth, were not reported as experienced by the patients in this study. Regarding mannitol, the dispensed dosage was 20-50 g/day dissolved in NS, and the urine output was greater than 30-50 ml/hour. Therefore, possible adverse effects of mannitol were efficiently prevented.

Another important feature of ATO therapy in this study was the practice of a life-long post-remission therapy. Unlike some European groups who used
2-year post-remission treatment and American groups who used 1-year postremission treatment, we found that maintenance therapy for the remainder of life benefited the CNS APL patients by decreasing relapse rates over the long-term. In a previous study from our group, the relapse rate was found to be highly correlated with post-remission therapy. In the current study, seven patients (41.1%) relapsed when they stopped treatment, and some relapsed after finishing a 3-year course of the maintenance treatment. With the intensive life-long therapy, however, nine patients (52.9%) remained RFS for a median of 92 months (70-125 months) after the first induction, and 14 patients (82.4%) reached a median of 87 months (66-125 months) OS due to their repetitive positive responses to ATO plus mannitol.

Certainly, any therapeutic benefit from extending the duration of post-remission therapy exists at the expense of increasing the potential risk of cumulative arsenic toxicities. Chronic arsenic retention carries a risk of developing skin lesions (pigmentation and keratosis), hypertension, cardiovascular diseases, diabetes mellitus, neurologic effects, and cancer of the skin, lung, and urinary bladder. Nevertheless, we found that periodic ATO therapy continued for more than three years was not associated with any severe side effects nor was any case of second malignancy encountered during the follow-up period which lasted up to at least 10 years after the diagnosis. Analysis of arsenic levels in urine samples revealed no significant accumulation of ATO in patients who started the third year of maintenance
therapy. The key advantages of this non-invasive method were that it seldom caused drug resistance and that the cost and toxicity of ATO was much lower than chemotherapy and myeloablative or nonmyeloablative HSCT.

In conclusion, the present study provided a novel protocol for the use of single-agent ATO preceded and accompanied by mannitol for APL relapse in CNS patients. Our results demonstrated that its therapeutic efficacy was comparable with that of newly diagnosed APL treated with ATO and that this cost-effective strategy seldom caused drug resistance. Furthermore, this approach was non-invasive, with minimal toxicity, and without significant risk for the development of second malignancy. Taken together, this regimen should be considered as a new therapeutic option for CNS APL.
Acknowledgement

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Authorship and Disclosure

Contribution: H. Wang and J. Zhou designed the study and wrote the manuscript; F. Cao, J. Li, L. Li, Y. Li, C. Shi, W. Lan, D. Li, Y. Zhang, Z. Zhang, X. Liu, R. Meng, and B. Yang performed the research; H. Zhao and B. Yang read and analyzed the data.

Conflict of interest statement

The authors declare no actual or potential conflict of interest including any financial, personal, or other relationships with other people or organizations within that could inappropriately influence (bias) their work.
References


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<th>Patient number</th>
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<th>Sanz score at 1st diagnosis</th>
<th>Duration of 1st remission in months</th>
<th>Treatment before CNS relapse</th>
<th>Status at CNS relapse</th>
<th>BM copies % at relapse</th>
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<th>Status at CNS relapse follow-up after treatment, months of follow-up</th>
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**Note:** Sanz score: low risk of relapse, white blood cell (WBC) < 10 x 10⁹/L, platelet (plt) ≥ 40 x 10⁹/L; intermediate risk of relapse, WBC < 10 x 10⁹/L, plt < 40 x 10⁹/L; high risk of relapse, WBC ≥ 10 x 10⁹/L; Ara-C: cytarabine; ATO: arsenic trioxide; ATRA: all-trans retinoic acid; BM: bone marrow; CNS: central nervous system; CR: complete remission; CSF: cerebrospinal fluid; RF: relapse-free.
Figure legends

Figure 1. Treatment protocol for CNS APL used in this study.

Figure 2. Element arsenic levels in patient-paired blood and CSF samples measured during induction treatment.

Figure 3. (A) Relapse-free survival and cumulative incidence of relapse for the 17 APL patients who experienced CNS relapse. (B) Overall survival for the 17 APL patients who experienced CNS relapse.
**Figure 1** Treatment protocol for CNS APL used in this study.

<table>
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<th>Induction Therapy</th>
<th>Intravenous 7mg/m²/day (0.16 mg/kg/day for ≤ 15 years) ATO + mannitol. Until free of blast/promyelocyte in CSF.</th>
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<td>Consolidation Therapy</td>
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| Maintenance Therapy | First year: intravenous 7 mg/m²/day ATO (0.16 mg/kg/day for ≤ 15 years) + mannitol for 14 days, repeated at 1 month intervals.  
Second year: intravenous 7 mg/m²/day ATO (0.16 mg/kg/day for ≤ 15 years) + mannitol for 14 days, repeated at 3 month intervals.  
Third year and after: intravenous 7 mg/m²/day ATO (0.16 mg/kg/day for ≤ 15 years) + mannitol for 14 days, repeated at 6 month intervals. |
Figure 2  Element arsenic levels in patient-paired blood and CSF samples measured during induction treatment.
Figure 3  (A) Relapse-free survival and cumulative incidence of relapse for the 17 APL patients who experienced CNS relapse. (B) Overall survival for the 17 APL patients who experienced CNS relapse.
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