Determinants of cerebrospinal fluid arsenic concentration in patients with acute promyelocytic leukemia on oral arsenic trioxide therapy

Wing-Yan Au,1 Sidney Tam,2 Bonnie M. Fong,2 and Yok-Lam Kwong1

Departments of 1Medicine and 2Clinical Biochemistry, Queen Mary Hospital, Hong Kong

The extent of and factors controlling arsenic penetration into the central nervous system (CNS) remain unclear. Elemental arsenic levels in 67 paired cerebrospinal fluid (CSF) and plasma samples from 9 patients with acute promyelocytic leukemia (APL) on oral arsenic trioxide (As2O3), obtained during intrathecal chemotherapy (treatment of CNS APL, n = 6; prophylaxis, n = 3) were measured. Median arsenic levels of CSF and plasma were 95.8 nmol/L (range, 3.5-318.9 nmol/L) and 498.9 nmol/L (range, 36.3-1892.8 nmol/L). As a group, CSF and plasma arsenic was linearly correlated (P < .001), with CSF at 17.7% the plasma level. The CSF/plasma arsenic ratio, which reflected the arsenic penetration efficiency, varied significantly in individual patients (P < .001). Repeated intrathecal chemotherapy and presence of blasts in CSF did not affect the CSF/plasma arsenic ratio. Plasma arsenic was the only significant determinant of CSF arsenic levels. CSF arsenic was present at therapeutically meaningful levels, implying that As2O3 therapy might be beneficial in CNS APL. (Blood. 2008;112:3587-3590)

Introduction

Central nervous system (CNS) relapse of acute promyelocytic leukemia (APL) occurs in 1% to 5% of patients.1,2 The most important risk for CNS relapse is a high leukocyte count (> 10 × 109/L) at diagnosis.2 CNS APL fares poorly despite intrathecal/systemic chemotherapy and hematopoietic stem cell transplantation.2 The effective treatment/prevention of CNS APL remains unclear.

Arsenic trioxide (As2O3) is a standard treatment for relapsed APL.1 We first showed in an APL patient with CNS relapse that arsenic entered the cerebrospinal fluid (CSF) during oral As2O3 treatment,4 a finding later confirmed independently in another patient receiving intravenous As2O3.5 However, the factors controlling arsenic penetration into CSF are undefined.

We studied a series of APL patients receiving intrathecal chemotherapy while on oral As2O3, which gave us the unique opportunity of documenting arsenic penetration into CSF, its extent, and the factors controlling it.

Methods

Patients

Fifty consecutive APL patients with marrow relapse were referred. Initial diagnosis was made morphologically and cytogenetically and/or molecularly, and reaffirmed at relapse.

Treatment of relapse

Oral As2O3 (10 mg/day)6 and idarubicin (6 mg/m2 per day × 3) were administered until complete remission (CR), followed by idarubicin consolidation (6 mg/m2 per day × 4)7 and maintenance (all-trans retinoic acid, 45 mg/m2 per day; oral As2O3, 5-10 mg/day; 2 weeks every 2 months for 2 years). As2O3 treatment was approved by the institutional review board at Queen Mary Hospital and performed in accordance with the Declaration of Helsinki.

Post-As2O3 relapses

Twenty patients developed post-As2O3 relapses, 5 of whom (cases 1, 2, 6-8; Table 1) had isolated CNS relapse. Case 7 had been reported previously.4

Treatment of CNS relapse

Intrathecal chemotherapy comprising methotrexate (12 mg) and cytarabine (50 mg; 2 times/week) and oral As2O3 (5-10 mg/day) were administered until CSF was negative morphologically and molecularly for APL cells. Cranial irradiation was subsequently given in 2 patients (cases 6, 7).

Intrathecal prophylaxis

Because of increased risks of CNS relapse in patients in complete remission (CR3) and beyond, 3 patients (cases 3, 4, and 9) consented to CNS prophylaxis. One complete remission (CR2) patient (case 5) with a high leukocyte count (32 × 109/L) at relapse also consented to prophylaxis. Treatment comprised methotrexate (12 mg) weekly for 3 doses.

Elemental arsenic measurement

Elemental arsenic in paired CSF and plasma (obtained immediately after lumbar puncture) was measured by inductively coupled plasma mass spectroscopy.4,8 Because most patients took the oral As2O3 at home, the CSF and plasma sampling could not be timed with oral As2O3 administration.

Statistical analyses

Statistical tests used were described with individual experiments. All analyses were performed with SPSS version 14 software (SPSS, Chicago, IL).
Intrathecal chemotherapy

Case sample of all patients were grouped, which provided the baseline increased arsenic penetration, the CSF/arsenic ratios of the first CSF arsenic CSF penetration. Repeated intrathecal chemotherapy did not affect efficiency of arsenic penetration into CSF. Individual patients showed significant individual variability existed in arsenic penetration into CSF and CSF arsenic (Figure 1A, B, C, and Figure S1, available on the Blood website; see the Supplemental Materials link at the top of the online article).

Results and discussion

Patients

At a median follow-up of 14 months (range, 12-28 months), 3 of 5 patients with CNS relapse were in remission (Table 1). Three of 4 patients receiving intrathecal prophylaxis were in remission, after a median follow-up of 3 months (range, 2-14 months). None of the surviving patients had CNS sequelae from the leukemia or its treatment/prophylaxis.

CSF and plasma arsenic levels

Arsenic levels were determined in 67 paired CSF and plasma samples (median per patient, 6; range, 2-19). CSF arsenic ranged from 3.5 to 318.9 nmol/L (median, 95.8 nmol/L) and plasma arsenic from 36.3 to 1892.8 nmol/L (median, 498.9 nmol/L). Previous pharmacokinetic studies showed that, after 10 mg of oral As$_2$O$_3$, the peak plasma arsenic varied from 200 to 600 nmol/L. The plasma arsenic levels observed herein were within the expected range, with the high plasma levels reflecting peak, and low plasma levels reflecting trough, levels after oral As$_2$O$_3$ administration.

CSF arsenic was positively correlated with plasma arsenic

As a group, there was a strong linear correlation between plasma and CSF arsenic (Figure 1A, $P < .001$), with CSF at 17.7% the plasma level (slope of the regression line, Figure 1A). Analyses of sequential samples of individual patients showed similar correlations (Figure 1B,C, and Figure S1, available on the Blood website; see the Supplemental Materials link at the top of the online article).

Significant individual variability existed in arsenic penetration into CSF

The CSF/plasma arsenic ratio was used as a measurement of the efficiency of arsenic penetration into CSF. Individual patients showed significant variations in their mean CSF/plasma ratios (Figure 1D).

Repeated intrathecal chemotherapy did not affect arsenic CSF penetration

To test whether chemotherapy damaged the meninges and increased arsenic penetration, the CSF/arsenic ratios of the first CSF sample of all patients were grouped, which provided the baseline efficiency of arsenic CSF penetration before chemotherapy. The CSF/plasma arsenic ratios of the second and subsequent CSF samples were similarly grouped. A comparison of the mean CSF/plasma ratios of sequential CSF samples showed no significant changes, implying that repeated intrathecal chemotherapy did not affect arsenic CSF penetration (Figure 1E).

Arsenic CSF penetration was unaffected by CNS leukemia

To investigate whether meningeal leukemia might increase arsenic CSF penetration, the CSF/plasma ratios of CSF showing leukemic cells ($n=38$) were compared with those without leukemic cells ($n=29$). The results showed that meningeal leukemia did not affect CSF/plasma arsenic ratios (Figure 1F).

Arsenic gradient in the CNS

We documented that arsenic penetrated the CSF over a broad range of plasma arsenic levels. Previous studies showed that arsenic levels in peritoneal dialysates were identical to plasma, indicating that the peritoneum did not possess an arsenic barrier. On the contrary, the difference between plasma and CSF arsenic implied that the blood-brain barrier maintained an arsenic gradient. Expectedly, individual patients varied in the efficiency of arsenic CSF penetration. Regression analysis of the group showed that CSF arsenic was 17.7% of plasma. This fraction was not significantly altered with repeated intrathecal chemotherapy, an important reassurance that CNS arsenic toxicity would not be increased with concomitant intrathecal chemotherapy.

Therapeutic significance of arsenic CSF penetration

The median CSF arsenic was approximately 100 nmol/L, highest being more than 300 nmol/L. In primary APL cells, significant cytotoxicity starts with arsenic at 100 to 400 nmol/L, with approximately 50% cell death at 500 nmol/L. Because of variable CSF sampling time after oral As$_2$O$_3$, some patients had low plasma and hence CSF arsenic, reflecting sampling at trough levels. However, in at least half of the CSF samples in this study, arsenic was still present at therapeutically meaningful concentrations. Given that the peak plasma arsenic after intravenous As$_2$O$_3$ may be several-fold that of oral As$_2$O$_3$, even higher CSF arsenic levels may be reached with better therapeutic efficacy after intravenous As$_2$O$_3$, although this needs to be

Table 1. Features and treatment outcome of 9 patients with acute promyelocytic leukemia receiving intrathecal chemotherapy for treatment or prophylaxis of central nervous system leukemia

<table>
<thead>
<tr>
<th>Case*</th>
<th>Sex/age, y</th>
<th>Status at treatment</th>
<th>Intrathecal chemotherapy</th>
<th>Additional treatment</th>
<th>Systemic relapse (time)†</th>
<th>Outcome (follow-up)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F/67</td>
<td>Relapse‡</td>
<td>Treatment MTX + Ara-C (6)</td>
<td>None</td>
<td>Yes (12 mo)</td>
<td>CR4, refused AHSCT, (14+ mo)</td>
</tr>
<tr>
<td>2</td>
<td>M/38</td>
<td>Relapse‡</td>
<td>Treatment MTX + Ara-C (6)</td>
<td>None</td>
<td>Yes (13 mo)</td>
<td>CR5 after AHSCT (14+ mo)</td>
</tr>
<tr>
<td>3</td>
<td>M/65</td>
<td>Normal</td>
<td>Prophylaxis MTX (3)</td>
<td>None</td>
<td>Yes (10 mo)</td>
<td>Refused AHSCT, died of relapse (14 mo)</td>
</tr>
<tr>
<td>4</td>
<td>M/85</td>
<td>Normal</td>
<td>Prophylaxis MTX (3)</td>
<td>None</td>
<td>No</td>
<td>CR3 (3+ mo)</td>
</tr>
<tr>
<td>5</td>
<td>M/29</td>
<td>CR2</td>
<td>Prophylaxis MTX (3)</td>
<td>None</td>
<td>No</td>
<td>CR2 (2+ mo), on As$_2$O$_3$</td>
</tr>
<tr>
<td>6</td>
<td>M/44</td>
<td>Relapse‡</td>
<td>Treatment MTX + Ara-C (19)</td>
<td>Cranial irradiation</td>
<td>No</td>
<td>CR2 (24+ mo)</td>
</tr>
<tr>
<td>7</td>
<td>M/69</td>
<td>Relapse‡</td>
<td>Treatment MTX + Ara-C (9)</td>
<td>Cranial irradiation</td>
<td>Yes (28 mo)</td>
<td>Died of relapse (28 mo)</td>
</tr>
<tr>
<td>8</td>
<td>M/46</td>
<td>Relapse‡</td>
<td>Treatment MTX + Ara-C (17)</td>
<td>None</td>
<td>Yes (7 mo)</td>
<td>Died of relapse (12 mo)</td>
</tr>
<tr>
<td>9</td>
<td>M/47</td>
<td>Normal</td>
<td>Prophylaxis MTX (3)</td>
<td>None</td>
<td>No</td>
<td>CR3 (3+ mo)</td>
</tr>
</tbody>
</table>

CNS indicates central nervous system; MTX, methotrexate (12 mg); Ara-C, cytosine arabinoside (50 mg); CR, complete remission; and AHSCT, autologous hematopoietic stem cell transplantation.

*Cases were arranged according to the alphabetical order of their names, not the order of presentation.
†Time from first dose of intrathecal chemotherapy.
‡Relapse was meningeal without demonstrable leukemic mass lesions in the CNS.
§Two courses of intrathecal chemotherapy, 12 doses for first course, 7 doses for second course.
∥Two courses of intrathecal chemotherapy, 12 doses for first course, 5 doses for second course.
validated. However, the relative cardiac safety of oral As$_2$O$_3$ remains an important factor in considering the administration route. Because CNS APL is unlikely to be treated with As$_2$O$_3$ solely without intrathecal chemotherapy, the issue of whether systemic As$_2$O$_3$ alone would be adequate for CNS disease will not be resolved.

Implications in APL treatment

None of the drugs at the dosages used in APL enters the CSF at significant levels, explaining why the CNS may be a leukemia sanctuary site. Patients at high risk for CNS relapse may therefore need intrathecal prophylaxis. Findings here suggest that prophylactic As$_2$O$_3$ may be another option. Our routine maintenance during CR comprised oral As$_2$O$_3$ (5-10 mg/day) 2 weeks every 2 months for 2 years, which was well tolerated without untoward toxicities. Whether a more intensive arsenic maintenance might be beneficial for patients at high risk for CNS relapse will need to be validated.

Clinical aspects of arsenic CSF penetration

Our results showing arsenic penetration into the CSF are of obvious significance in toxicology studies of environmental/accidental arsenic poisoning. Finally, we and others have shown that aquaglyceroporin 9 is involved in transmembrane trafficking of arsenic. Its role in controlling arsenic CSF penetration awaits to be evaluated.

Acknowledgments

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Authorship

Contribution: W.-Y.A. conceived the study, treated the patients, obtained the specimens, and wrote and approved the manuscript; S.T. and B.M.F. performed the arsenic analysis and approved the manuscript; and Y.-L.K. conceived the study, treated the patients, and wrote and approved the manuscript.

Conflict-of-interest disclosure: The University of Hong Kong holds a provisional patent on the use of oral arsenic trioxide in the treatment of leukemia. W.-Y.A., S.T., and Y.-L.K. are associated with or employed by the University of Hong Kong. B.M.F. declares no competing financial interests.

Correspondence: Yok-Lam Kwong, Department of Medicine, Professorial Block, Queen Mary Hospital, Pokfulam Road, Hong Kong; e-mail: ylkwong@hkuc.hku.hk.
References


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