Arsenic Trioxide in the Treatment of Newly Diagnosed Acute Promyelocytic Leukemia: A Single Center Experience

Vikram Mathews,* Poonkuzhali Balasubramanian, Ramachandran Velayudhan Shaji, Biju George, Mammen Chandy, and Alok Srivastava

Department of Haematology, Christian Medical College and Hospital, Vellore, India

Arsenic trioxide (As₂O₃) has been found effective in the treatment of acute promyelocytic leukemia (APML). Most studies with As₂O₃ involve patients with APML who have relapsed following standard therapy. Between January 1998 and July 2000, 14 patients were recruited for an ongoing trial of As₂O₃ in the treatment of newly diagnosed APML. Arsenic trioxide was administered at a dose of 10 mg/day until complete remission (CR) was achieved. Afterward, a consolidation course and a maintenance schedule consisting of As₂O₃ as a single agent were administered over 6 months. There were 3 early deaths related to intra-cerebral hemorrhage: two on day 3 and one on day 4. Of the 11 evaluable patients, one died on day 21 secondary to uncontrolled sepsis, while the remaining 10 (91%) have attained CR. The average time to CR was 52.3 days (range: 34–70 days). One patient developed an isolated central nervous system (CNS) relapse and subsequently went into a second CR following therapy with triple intrathecal chemotherapy, cranial irradiation, and an additional 4-week course of systemic As₂O₃. This patient, as well as the remaining nine, has continued to remain in CR at a median follow up of 15 months (range: 2–33 months). Eight out of 10 patients achieved molecular remission at variable periods during their consolidation and maintenance schedules. One patient developed an ATRA syndrome and was administered daunorubicin (40 mg/day) for 2 days. The side effects with this therapy were minimal and did not require cessation of therapy in any patient. There was no significant hepatic toxicity. In our experience, arsenic trioxide is effective in inducing and maintaining remission in patients with APML with minimal side effects. The optimal regimen and total dose required need to be defined. Am. J. Hematol. 70:292–299, 2002. © 2002 Wiley-Liss, Inc.

Key words: acute promyelocytic leukemia; arsenic trioxide

INTRODUCTION

Arsenical compounds were used as early as 2000 B.C., both as a medicine and as a poison [1]. In 1931, Forkner and Scott used Fowler’s solution in the treatment of chronic myeloid leukemia [2]. This was continued until the introduction of busulphan in 1953. Until recently the use of arsenical compounds was limited to the use of organic arsenical, “melarsoprol,” in the treatment of trypanosomiasis. In the 1970s, As₂O₃ was introduced into the treatment of acute promyelocytic leukemia (APML) in China and was found to be extremely effective in treating this condition [3]. Two patients, the first in 1989, with APML who had relapsed following standard chemotherapy at our institution have been treated with an Ayurvedic preparation containing arsenic. These patients had shown a good response to the therapy they received. One of these patients continues to remain in complete remission (CR), five years after stopping his therapy, though he has severe arsenic keratosis and has recently developed cutaneous squamous cell carcinoma. Subsequently there have been numerous other reports, both in vitro and in vivo, which have established the

*Correspondence to: Vikram Mathews, Department of Haematology, Christian Medical College and Hospital, Vellore 632004, India. E-mail: vikrammathews@hotmail.com

Received for publication 2 February 2002; Accepted 15 March 2002

Published online in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/ajh.10138

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effectiveness of As$_2$O$_3$ in the treatment of APML [3–12]. The majority of the available data refers to patients with relapsed APML treated with arsenic trioxide [7, 9–17]. Few studies have addressed the role of arsenic trioxide in the treatment of newly diagnosed cases [12], there is limited follow-up data in these series, and therapy following achievement of CR is varied. The clinical experience with this drug, potential adverse effects, and its position in the algorithm in the therapy of acute promyelocytic leukemia is still being defined. The optimum cumulative dose that will maximize the beneficial effect with respect to disease-free survival and minimize long-term side effects remains to be determined.

In this article, we present our clinical experience and outcome in the treatment of newly diagnosed cases of APML with arsenic trioxide as a single agent for both induction and consolidation.

**PATIENTS AND METHODS**

A trial using arsenic trioxide as a single agent in newly diagnosed cases of APML, both in induction and consolidation, was initiated in January 1998 at our institution. This was an open, non-randomized single-center study. The study was reviewed and approved by the institution’s research and ethics committee. Fourteen patients were recruited by July 2000, and they are analyzed in this article. Patients were included in this trial if they were diagnosed to have APML, morphologically on FAB criteria. This was sufficient to initiate therapy with arsenic trioxide, but the diagnosis had to be subsequently confirmed by karyotyping or by reverse transcriptase polymerase chain reaction assay (RT-PCR) for promyelocytic leukemia and retinoic acid (RA) receptor α fusion (PML-RARα) transcripts in order to be included in the analysis.

The other inclusion criteria were that all these patients would have in the absence of this study received palliative therapy, due to the lack of resources to support standard chemotherapy. Exclusion criteria included (1) women who were pregnant; (2) patients who are <10 years of age; and (3) patients who were >55 years of age.

Patients who fit the above criteria were admitted by one of the clinical investigators after the details of this trial were explained and written informed consent had been obtained.

One exception to the above criteria was made when a 7-year old child was included into this trial on a compassionate basis.

**Intravenous Arsenic Trioxide**

This was prepared by dissolving specified quantities of arsenic trioxide (As$_2$O$_3$ AR grade [99.8% purity] from SD Fine Chemicals Ltd, Boisar, India) in sterile pyrogen-free distilled water at 60°C for 20 min. No other additives were used in its preparation. The final product had a concentration of 1 mg/mL and was supplied as 10-mL vials.

**Treatment With Arsenic Trioxide**

Arsenic trioxide (10 mg/10 mL) was diluted in 500 mL of dextrose saline and infused intravenously over 3 hr once a day. The protocol used for induction and subsequent consolidation is summarized on Table II.

Because one of our patients was a 7-year old child, a dose modification of 5 mg/day was made in this case for the entire protocol.

The initial induction course was continued till the patient had an ANC > 1.5 × 10$^9$/mm$^3$ and platelet count >100,000/mm$^3$. Once this was achieved, the bone marrow was observed; if it was in CR (blasts + promyelocytes <5% in normocellular to mildly hypoplastic marrow), then arsenic trioxide was discontinued; if not in CR, it was continued for an additional week and the bone marrow was observed again at the end of the week. The time taken to reach the above parameters was taken as the time to achieve CR. This would be continued for a maximum period of 75 days, following which the patient would be considered a non-responder/partial responder and excluded from the trial.

**Supportive Care**

During induction, complete blood counts were done on alternate days. Coagulation parameters were also measured on alternate days initially; this included a prothrombin time (PT), activated partial thromboplastin time (aPTT), and thrombin time (TT). Once the patient was clinically stable, platelet count was >50,000/mm$^3$, and more than three serial readings of his coagulation parameters were normal, then the frequency of testing was reduced to once a week.

Platelet concentrates were transfused to maintain a platelet count >20,000/mm$^3$ and fresh frozen plasma (15 mL/kg) was infused if the PT or aPTT were deranged. Cryoprecipitate was infused if the TT was prolonged as well. Packed red cell transfusions were infused to maintain a hemoglobin level above 8 g%. Antibiotics were administered for fever as required.

Liver function tests were done prior to initiating therapy, followed by biweekly and subsequently monthly until completion of therapy.

Hydroxyurea was administered to control leucocytosis if required as per the guidelines laid out in the protocol on Table II. One patient was administered daunorubicin when she developed a rapid rise in leucocytes associated with features of an ATRA syndrome.

**RT-PCR**

RT-PCR analysis for PML-RARα fusion transcripts was done according to established protocols [18]. RT-PCR analysis was to be done at diagnosis, at first CR, at
the start of consolidation and at the start of the 2nd, 4th, and 6th maintenance courses. Following this, analysis was to be done at intervals of 3 months for the first year after completion of therapy. The RT-PCR used had a sensitivity of 1 in 10^5.

RESULTS

Seventeen patients during this period were eligible to participate in the trial. Two were excluded at the onset: one patient was terminally ill and was excluded by the investigators, and another refused to give consent and opted for palliation. The remaining 15 patients were initially included on the basis of FAB criteria, but one patient was then excluded because neither the karyotype nor the RT-PCR was consistent with a diagnosis of APML. Fourteen patients were finally enrolled in this study.

The clinical details, blood counts, lactic dehydrogenase (LDH) level, coagulation parameters, and bone marrow findings at diagnosis of patients enrolled in this study are summarized on Table I. The details of the time taken to achieve CR, additional hydroxyurea used, cumulative doses of arsenic trioxide, and status at last follow up are summarized on Table III.

Three patients died of intra-cerebral hemorrhage: two on day 3 and one on day 4. Ten out of 11 patients evaluable for response achieved CR (91%), but one patient had uncontrolled sepsis and died on day 21 of an intra-cerebral bleed. The overall CR rate was 11/14 (71.4%).

Among the 10 patients who achieved CR, the average time to CR was 52.3 days (range: 34–70 days) and the median cumulative dose during the initial induction therapy was 493 mg (215–700 mg). Five of these patients have completed the scheduled course of therapy as given on Table II. Among the remaining 5 patients, 3 are on their maintenance schedule (one each having completed 4, 3, and 1 course of maintenance therapy), one patient has completed the consolidation course, and one patient has just completed the induction course.

One patient, a 19-year-old male, achieved CR with the initial induction course of arsenic trioxide; he subsequently received his consolidation therapy uneventfully as per the protocol and was then started on his maintenance therapy. Prior to the initiation of the second of his monthly maintenance schedules, he complained of a mild nonspecific headache. Peripheral blood counts and bone marrow were normal. Cerebrospinal fluid analysis revealed a leucocyte count of 200/mm^3 with 98% abnormal promyelocytes. The presence of the bcr-1 transcript of the PML-RARα fusion gene was confirmed in these cells by RT-PCR. He was treated with triple intrathecal chemotherapy consisting of methotrexate 12.5 mg, cytosine 40 mg, and hydrocortisone 50 mg (administered twice a week for 6 weeks), cranial irradiation (24 Grays in 12 fractions), and an additional 4-week course of intravenous As2O3, administered simultaneously. At the end of this period, his CSF analysis was normal. Blood and bone marrow evaluation repeated at the end of this course continued to be in remission. He subsequently received

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**TABLE I. Baseline Characteristics**

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age/sex</th>
<th>Hb (g %)</th>
<th>TC (×10^9/L)</th>
<th>Plat (×10^9/L)</th>
<th>LDH (U/L)</th>
<th>PTa</th>
<th>aPTTb</th>
<th>Bone marrow (B+PM)c</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>19/M</td>
<td>5.3</td>
<td>2.8</td>
<td>15</td>
<td>383</td>
<td>16.5/15</td>
<td>26.4/27</td>
<td>Imprints replaced by B+PM</td>
</tr>
<tr>
<td>2</td>
<td>27/M</td>
<td>10</td>
<td>3.7</td>
<td>8</td>
<td>1,219</td>
<td>17/14</td>
<td>25/30</td>
<td>95% B+PM</td>
</tr>
<tr>
<td>3</td>
<td>16/M</td>
<td>4.5</td>
<td>6.7</td>
<td>2</td>
<td>892</td>
<td>18/15</td>
<td>43/29</td>
<td>59% B+PM</td>
</tr>
<tr>
<td>4</td>
<td>28/F</td>
<td>9.4</td>
<td>1.4</td>
<td>47</td>
<td>378</td>
<td>14.6/14</td>
<td>23.9/28</td>
<td>66% B+PM</td>
</tr>
<tr>
<td>5</td>
<td>14/F</td>
<td>3.7</td>
<td>1.6</td>
<td>16</td>
<td>481</td>
<td>10.1/10</td>
<td>31/28</td>
<td>79% B+PM</td>
</tr>
<tr>
<td>6</td>
<td>21/F</td>
<td>11</td>
<td>1.2</td>
<td>12</td>
<td>403</td>
<td>10.2/11</td>
<td>18.9/30</td>
<td>37% B+PM</td>
</tr>
<tr>
<td>7</td>
<td>46/F</td>
<td>5.7</td>
<td>0.5</td>
<td>30</td>
<td>640</td>
<td>12.5/11</td>
<td>30.6/30</td>
<td>Imprints with 65% B+PM</td>
</tr>
<tr>
<td>8</td>
<td>28/M</td>
<td>7.1</td>
<td>1.9</td>
<td>20</td>
<td>708</td>
<td>12.3/11.4</td>
<td>33/29</td>
<td>53% B+PM</td>
</tr>
<tr>
<td>9</td>
<td>14/F</td>
<td>6.1</td>
<td>1.9</td>
<td>89</td>
<td>561</td>
<td>12/11.5</td>
<td>28/29.6</td>
<td>Imprints replaced by B+PM</td>
</tr>
<tr>
<td>10</td>
<td>17/F</td>
<td>14</td>
<td>6.7</td>
<td>20</td>
<td>1,520</td>
<td>17.6/11.2</td>
<td>33/30</td>
<td>Imprints with 55% B+PM</td>
</tr>
<tr>
<td>11</td>
<td>33/F</td>
<td>10</td>
<td>20.2</td>
<td>11</td>
<td>760</td>
<td>18.5/11.6</td>
<td>42/30</td>
<td>64% B+PM</td>
</tr>
<tr>
<td>12</td>
<td>30/M</td>
<td>9.7</td>
<td>21</td>
<td>17</td>
<td>2,000</td>
<td>17/10</td>
<td>59/30</td>
<td>Implants with 85% B+PM</td>
</tr>
<tr>
<td>13</td>
<td>7/F</td>
<td>9.5</td>
<td>9.8</td>
<td>2</td>
<td>493</td>
<td>12.6/11.7</td>
<td>23.8/28</td>
<td>90% B+PM</td>
</tr>
<tr>
<td>14</td>
<td>15/F</td>
<td>6</td>
<td>5.8</td>
<td>14</td>
<td>668</td>
<td>11/10</td>
<td>33/31</td>
<td>80% B+PM</td>
</tr>
</tbody>
</table>

^aPT, prothrombin time.  
^bPTT, activated partial thromboplastin time.  
^cB+PM, blasts + promyelocytes.

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**TABLE II. Arsenic Trioxide Study Protocol**

<table>
<thead>
<tr>
<th>Induction: As2O3 10 mg/day till CR (max 75 days)</th>
<th>4 weeks rest</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consolidation: As2O3 10 mg/day × 4 weeks</td>
<td>4 weeks rest</td>
</tr>
<tr>
<td>Maintenance: As2O3 10 mg/day × 10 days, once a month × 6 months</td>
<td></td>
</tr>
</tbody>
</table>

Guidelines for administration of hydroxyurea during induction

| WBC <5000/mm^3 | No hydroxyurea |
| WBC >5000–10,000/mm^3 | 500 mg od |
| WBC >10,000–15,000/mm^3 | 500 mg bd |
| WBC >15,000–20,000/mm^3 | 500 mg tid |
| WBC >20,000–50,000/mm^3 | 500 mg qid |
| WBC >50,000/mm^3 | 1.0 g qid |

^aAdministered if in CR.

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the next 4 monthly cycles of As$_2$O$_3$ as per the initial protocol. Seventeen months have elapsed since his last course of As$_2$O$_3$, and he continues to remain in complete molecular remission.

The remaining patients have all been in continuous CR.

Hyperleukocytosis and ATRA-like Syndrome

Seven of these 10 (70%) patients had a hyperleukocytosis response as defined by a count $>10 \times 10^9$/mm$^3$ following initiation of therapy with arsenic trioxide. Figure 1a,b illustrates the white cell count seen among patients with and without a leukocytic response to arsenic trioxide, while Fig. 2 illustrates the average white cell response among these patients. One patient who received daunorubicin during induction and had a leukocytic response is not included in the above figures. All patients who developed leucocytosis received additional hydroxyurea as per the protocol. Hydroxyurea was administered for an average of 10.5 days (range: 2–21 days) and a median cumulative dose of 13.5 g (range: 3.5–40.5 g). One patient developed significant leucocytosis (maximum $61 \times 10^9$/mm$^3$) associated with features similar to a retinoic acid syndrome [19] with pulmonary interstitial infiltrates, tachypnea, pleural effusion, pedal edema, and fever. This patient was administered daunorubicin 40 mg/day on day 6 and day 7 of her induction therapy, and arsenic trioxide was temporarily stopped for 4 days as well. Arsenic trioxide was restarted after 4 days, and the rest of her therapy was uneventful. No other anti-mitotic agents were used in any of these patients.

Other Adverse Effects of Arsenic Trioxide

Adverse effects were minimal and warranted temporary discontinuation in only one patient who developed features suggestive of a retinoic acid syndrome. Most side effects documented were transient and did not require any intervention (Table IV). At the end of their therapy, all five patients who completed their course of arsenic trioxide had normal electrocardiogram, echocardiogram, and nerve conduction studies. This included one patient who had severe paresthesias, which warranted therapy with amitriptyline, and had evidence of conduction defects in an earlier nerve conduction study.

All 10 patients who achieved hematological CR with arsenic trioxide including the patient who had an isolated CNS relapse and went into a second remission have remained in continuous CR, at a median follow up of 15 months (range: 2–33 months). Although it was initially intended that RT-PCR samples be taken at regular intervals, this was not possible due to intermittent availability of this facility in the early phase of the trial. Hence it is not possible to determine the time frame in which molecular remission is achieved. The results of all the RT-PCR samples that were taken from these patients are illustrated in Fig. 3. All patients who completed therapy are in molecular remission. Among the patients still receiving their scheduled course of arsenic trioxide, 3/5 are in molecular remission, while 2/5 are still positive for the PML-RAR$\alpha$/H9251 fusion product (Fig. 3). Of the two who are positive, one patient has just completed induction and the second has completed induction and consolidation.

DISCUSSION

In this series of patients we have established the efficacy of arsenic trioxide as a single agent both in induction and consolidation for the management of newly diagnosed cases of APML. From a MEDLINE search, four

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**Table III. Summary of Response to As$_2$O$_3$, Time to CR, Status at Last Follow Up, and Cumulative Doses of As$_2$O$_3$ and Hydroxyurea Used**

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Response to As$_2$O$_3$</th>
<th>Days to CR</th>
<th>Completed therapy</th>
<th>Status at last follow up</th>
<th>Cumulative dose of As$_2$O$_3$ (mg)</th>
<th>Hydroxyurea used in induction</th>
<th>Hydroxyurea days [cumulative dose]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CR</td>
<td>70</td>
<td>Yes</td>
<td>CR</td>
<td>1,760$^a$</td>
<td>Yes</td>
<td>21 days [40.5 g]</td>
</tr>
<tr>
<td>2</td>
<td>Early death</td>
<td>NA</td>
<td>NA</td>
<td>Died</td>
<td>30</td>
<td>No</td>
<td>NA</td>
</tr>
<tr>
<td>3</td>
<td>Early death</td>
<td>NA</td>
<td>NA</td>
<td>Died</td>
<td>200</td>
<td>No</td>
<td>NA</td>
</tr>
<tr>
<td>4</td>
<td>CR</td>
<td>50</td>
<td>Yes</td>
<td>CR</td>
<td>1,380$^a$</td>
<td>No</td>
<td>NA</td>
</tr>
<tr>
<td>5</td>
<td>CR</td>
<td>60</td>
<td>Yes</td>
<td>CR</td>
<td>1,480$^a$</td>
<td>Yes</td>
<td>4 days [2.5 g]</td>
</tr>
<tr>
<td>6</td>
<td>CR</td>
<td>52</td>
<td>Yes</td>
<td>CR</td>
<td>1,400$^a$</td>
<td>Yes</td>
<td>11 days [14 g]</td>
</tr>
<tr>
<td>7</td>
<td>CR</td>
<td>34</td>
<td>Yes</td>
<td>CR</td>
<td>1,220$^a$</td>
<td>No</td>
<td>NA</td>
</tr>
<tr>
<td>8</td>
<td>CR</td>
<td>55</td>
<td>No</td>
<td>CR on Rx</td>
<td>1,230</td>
<td>Yes</td>
<td>11 days [11.5 g]</td>
</tr>
<tr>
<td>9</td>
<td>CR</td>
<td>47</td>
<td>No</td>
<td>CR on Rx</td>
<td>950</td>
<td>No</td>
<td>NA</td>
</tr>
<tr>
<td>10</td>
<td>Early death</td>
<td>NA</td>
<td>NA</td>
<td>Died</td>
<td>60</td>
<td>No</td>
<td>NA</td>
</tr>
<tr>
<td>11</td>
<td>CR</td>
<td>58</td>
<td>No</td>
<td>CR on Rx</td>
<td>880</td>
<td>Yes</td>
<td>2 days [3 g]$^b$</td>
</tr>
<tr>
<td>12</td>
<td>Early death</td>
<td>NA</td>
<td>NA</td>
<td>Died</td>
<td>40</td>
<td>No</td>
<td>NA</td>
</tr>
<tr>
<td>13</td>
<td>CR</td>
<td>43</td>
<td>No</td>
<td>CR on Rx</td>
<td>355</td>
<td>Yes</td>
<td>15 days [15.5 g]</td>
</tr>
<tr>
<td>14</td>
<td>CR</td>
<td>54</td>
<td>No</td>
<td>CR on Rx</td>
<td>540</td>
<td>Yes</td>
<td>10 days [8 g]</td>
</tr>
</tbody>
</table>

$^a$NA, not applicable; CR, complete remission.

$^b$CR on Rx, complete remission on treatment.

$^a$Completed therapy.

$^b$Received daunorubicin.
other major trials [7,10–12] and a few case reports [14–17] in which arsenic trioxide was used in the treatment of APML were found. These trials and case reports predominantly involved patients with relapsed APML. The earliest clinical data available on the use of arsenic trioxide in the treatment of acute promyelocytic leukemia are from Zhang et al. [9] and Sun et al. [13]. In these studies, the CR rate achieved varied from 65.6% to 84%, and long-term survival (>10 years) was seen in 9/32 patients in another study [10].

Consolidation therapy following achievement of CR has not been addressed in most of these studies. The study by Niu et al. [12] has addressed this issue, with respect to the currently used schedules, and they have clearly demonstrated that chemotherapy following remission induction is significantly superior to consolidation with arsenic trioxide as a single agent [12]; however, the optimal cumulative dose, if it exists, is yet to be defined.

In the present series we have used arsenic trioxide as a single agent both for induction and consolidation. Hydroxyurea was also used during induction alone to control the leukocytosis seen in a proportion of patients. In only one patient was additional daunorubicin used in induction due to the development of a retinoic acid-like syndrome.

Of the 11 patients evaluable for response to therapy, 10 achieved CR (91%) while one patient died on day 21 secondary to uncontrolled sepsis.

It is of interest to note that all patients in this study who completed their scheduled course of arsenic trioxide have also achieved molecular remission. Among the patients still on treatment, three at 5, 7, and 10 months since diagnosis are in molecular remission while two are still positive for the PML-RARα transcript at 2 and 3 months since diagnosis. Although we had initially planned to do RT-PCR on a regular basis, this was not possible due to the intermittent availability of this test in the early phase of this trial. Hence, though we know that almost all patients who achieve CR will eventually achieve molecular remission with this therapy, the exact time frame in which this happens is not known. We are evaluating this issue in this ongoing trial.

Another interesting aspect of therapy with As$_2$O$_3$ is the variable leukocytic response in patients treated with this...
drug: approximately 30%–50% have leukocytosis following the initiation of therapy, while in the remainder this effect is not seen. The significance of this differential response is not clear. An “ATRA-like syndrome” [19] has been reported in 8 patients (31%), in the study by Chamacho et al. [20]. Most other series have not reported an ATRA-like syndrome with arsenic, and in the present series it was seen in only one patient in spite of 70% of our patients having a leukocytic response to arsenic trioxide.

Our observation in patients with the hypergranular variant of APML who have a leukocytosis following initiation of therapy is that they have a triphasic response: initial leucopenia at diagnosis followed by leucocytosis and, prior to achieving CR, a second phase of leucopenia (Figs. 1a and 2). The patients who do not have a leukocytic response have a prolonged leucopenia, although the proportion of neutrophils steadily improves and the leucopenia corrects in 30–50 days (Fig. 1b).

One patient developed an isolated CNS relapse during the course of maintenance therapy [21]. It has been observed that CNS relapse with APML is extremely rare, especially in the pre-ATRA era [22–25]. Following the use of ATRA, there has been some concern about the increase in incidence of extramedullary and CNS relapses. The increase in extramedullary relapses following the use of ATRA is believed to be due to the up regulation of cellular and endothelial adhesion molecules [23,26]. More recently it has been demonstrated that the differentiation induced by ATRA promoted the acquisition of β3-integrin-dependent firm adherence and transmigration of the promyelocytes through the endothelium [27]. It was thus hypothesized that ATRA-mediated differentiation could favor migration of differentiating blasts into skin, CNS, and other tissues, resulting in a reservoir of viable blasts. These could proliferate at a latter date. While the exact mechanism by which As₂O₃ induces remission is uncertain, it appears that a similar differentiation effect as that seen with ATRA occurs with As₂O₃. It is possible that a similar up-regulation of adhesion molecules, as seen with ATRA therapy, occurs with the use of As₂O₃. It has also been demonstrated in animal experiments that the choroid plexus protects the brain against toxic metals, such as arsenic, by concentrating the metal up to 40 times higher within the choroid plexus, thereby reducing the levels in the brain and cerebrospinal fluid [28]. These two mechanisms could theoretically contribute to an increased incidence of CNS relapses in patients treated with arsenic trioxide. This could be of some concern in future protocols that would utilize arsenic trioxide in the treatment of APML.

The usual toxicity seen with standard chemotherapy, such as myelosuppression, hair loss, severe vomiting, and exacerbation of the underlying coagulopathy, were not seen with this therapy. Of concern was the recent publication by Niu et al. [12], in which 58 patients with
APML, 11 newly diagnosed and 47 relapsed cases, were treated with \( \text{As}_2\text{O}_3 \). In these two groups, CR was achieved in 72.7% and 85.1% of cases, respectively. However, in 7/11 (63.6%) of the newly diagnosed patients with APML there was evidence of hepatic toxicity, which included two deaths. In the group of relapsed patients, one-third of the cases had evidence of hepatic toxicity. On the basis of this data, the authors had recommended that this drug should not be used in initial therapy and should be reserved only for patients who relapsed following standard chemotherapy. This data is in contrast to our own experience with this drug and other published data [7,10,11,15], where a similar hepatic toxicity profile was not seen.

The lethal dose recorded in the literature is a single dose of more than 100 mg [10]. At the relatively small doses used in the treatment of APML, the toxicity profile has been favorable with acceptable acute complications; however, chronic complications at these doses are yet to be defined. An issue of some concern is the possibility of late secondary malignancies as a result of chronic exposure to arsenic, as seen in one of our earlier patients treated with a prolonged course of arsenic-based Ayurvedic medications.

In vitro data suggest that there could be permanent defects related to inhibition of methylation of DNA [29] and large deletional mutations related to the generation of reactive oxygen species [30].

The mechanism by which arsenic trioxide induces remission in APML is still under evaluation. Some of the hypothesized mechanisms include induction of apoptosis in APL (NB4) cell lines by down-regulation of Bcl-2 [3], increased expression of cysteine proteases [7], reorganizing a nuclear organelle known as the PML oncopgenic domain (POD), which is disrupted following the PML-RAR\(\alpha\) fusion or through activation of the Jun kinases in a p53-independent pathway [31]. Arsenic compounds also bind to sulphydryl-rich proteins/enzymes and affect their function. Important in this group is glutathione; reduction in its level could lead to increased oxidative stress, DNA damage, and result in apoptosis [32,33]. Differentiation similar to that seen with ATRA, especially at low doses probably by degradation of the PML-RAR\(\alpha\) fusion product [4], has also been reported. No single mechanism can explain all the effects seen with arsenic trioxide; it probably acts at multiple levels, and this effect can vary with the concentration of the drug. Additional factors are still being defined, and understanding these could be crucial in maximizing efficacy while reducing toxicity.

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Fig. 3. Each line adjacent to the serial number on the y axis illustrates the duration of follow up of each of these patients. Symbols on these lines indicate times at which samples for RT-PCR were taken. Solid arrows indicate RT-PCR positive. At diagnosis RT-PCR was positive in 13 patients, while in one patient a sample was not available (this patient’s karyotype was positive for t(15;17)). Open arrows indicate RT-PCR negative. Eight out of the 10 patients who are alive are in molecular remission. Solid ovals indicate deaths: 4 patients died, and all were early deaths.
While there is no doubt as to the efficacy of As$_2$O$_3$ in the management of APML, its position in the algorithm of treatment for APML is yet to be defined. For patients who cannot afford standard chemotherapy as in the present series, the role of As$_2$O$_3$ as a single agent for induction remission and consolidation has been addressed and has been found to be very effective when used in the present schedule.

REFERENCES