Arsenic Trioxide as Effective Therapy for Relapsed Acute Promyelocytic Leukemia

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Arsenic is a natural substance that has been used therapeutically for more than 2,400 years (Antman, 2001; Waxman & Anderson, 2001). Medicinal preparations containing arsenic derivatives were used widely to treat many ailments in the United States in the 1800s, and a potassium bicarbonate-based solution of arsenic trioxide (As$_3$O$_3$; ATO), known as Fowler’s solution, was used to treat a variety of illnesses until the beginning of the 20th century (Antman; Waxman & Anderson). This preparation was a key therapy for chronic myelogenous leukemia until it was replaced by radiation and cytotoxic chemotherapy (Waxman & Anderson). The therapeutic use of arsenic declined as a result of widespread negative perceptions of arsenic as a poison and carcinogen (Waxman & Anderson).

A resurgence of interest in arsenic therapy occurred in the 1970s when physicians in China specializing in the integration of traditional Chinese and Western medicine recognized that ATO was strikingly effective in the treatment of acute promyelocytic leukemia (APL) (Shen et al., 1997). In these initial studies, the oral administration of an impure preparation of ATO was associated with severe gastrointestinal and hepatic side effects, but researchers quickly determined that low doses of purified ATO (8–10 mg/day) administered via IV offered safe, effective treatment of patients with APL (Shen et al.; Sun, Ma, Hu, & Zhang, 1992; Zhang, Wang, & Hu, 1996). In fact, in one study, complete remission (CR) was seen in 9 (90%) of 10 patients with relapsed APL who were treated with ATO alone (Shen et al.). Additional studies found that CR was achieved in 78%–90% of previously untreated patients and in 64%–90% of relapsed patients; the one-year disease-free survival was estimated to be 64% (Niu et al., 1999; Shen et al.; Zhang et al., 1996). ATO had a favorable side effect profile and no cross-resistance with all-trans retinoic acid (ATRA) or other anticancer drugs (Shen et al.; Zhang et al., 1996).

Subsequently, ATO was formulated into an injectable solution, Trisenox® injection (Cell Therapeutics, Inc., Seattle, WA), and was studied in the United States. It first was evaluated in relapsed APL in a pilot study, followed by a multicenter clinical trial (Soignet et al., 1998, 2001). Similar to the results obtained in China, 87% of relapsed patients with APL treated with Trisenox achieved CR. Kaplan-Meier estimates of 18-month overall survival and relapse-free survival were 66% and 50%, respectively (Soignet et al., 2001). Trisenox gained U.S. Food and Drug Administration approval for marketing in September 2000 for the induction of remission and consolidation in patients with APL who are refractory to or have relapsed from retinoid and anthracycline chemotherapy (Cell Therapeutics, Inc., 2002). Figures 1 and 2 outline the appropriate dosage and administration of Trisenox and infusion considerations.

The standard of treatment for newly diagnosed patients with acute promyelocytic leukemia (APL) is all-trans retinoic acid (ATRA) plus anthracycline-based cytotoxic chemotherapy, a combination that is highly effective for remission induction. However, 20%–30% of patients relapse and require salvage therapy. Reports from China on the striking efficacy and safety of arsenic trioxide in patients with APL led to clinical trials in the United States, which culminated in U.S. Food and Drug Administration approval in September 2000. Trisenox® (Cell Therapeutics, Inc., Seattle, WA) is an injectable formulation of arsenic trioxide indicated in the treatment of refractory or relapsed APL. The common side effects of Trisenox therapy are mostly mild and self-limiting and do not require interruption of therapy. Serious adverse effects that can occur include hyperleukocytosis, electrocardiographic abnormalities, and APL differentiation syndrome. These effects can be prevented or managed successfully with careful patient monitoring during treatment. Trisenox has no known cross-resistance with ATRA or other anticancer agents. It does not cause hair loss and is not myelosuppressive in patients with APL. Oncology nurses can play a major role in educating patients about this new drug, explaining its clinical benefits and side effects and the precautions that are necessary for its use.
Induction phase of treatment
- Administer Trisenox® (Cell Therapeutics, Inc., Seattle, WA), 0.15 mg/kg IV, daily (including weekends), until bone-marrow aspirate shows morphologic remission and < 5% blasts.
- Perform bone-marrow assessment at 30 days; if patient is not in remission, continue induction therapy for up to 60 days.
- Do not exceed 60 doses.

Consolidation phase of treatment
- Administer Trisenox, 0.15 mg/kg per dose, for 25 doses, daily or five days per week for five weeks (three to six weeks after induction for patients in complete remission).
- Confirm remission with bone-marrow assessment no sooner than 30 days after initial remission.
- Confirm molecular remission with reverse transcriptase-polymerase chain reaction for the promyelocytic leukemia gene-retinoic acid receptor gene transcript.

FIGURE 1. DOSAGE AND ADMINISTRATION OF TRISENOX® FOR PATIENTS WITH RELAPSED ACUTE PROMYELOCYTIC LEUKEMIA
Note. Based on information from Cell Therapeutics, Inc., 2002.

Characteristics of Acute Promyelocytic Leukemia

APL, designated as M3 in the French-American-British classification of leukemias, represents 10%–15% of cases of acute myelogenous leukemia (AML) in adults (Stone & Mayer, 1990). Patients with the APL subtype of AML have a characteristic genetic translocation between chromosomes 15 and 17 (t(15;17) that is virtually diagnostic of the condition (Soignet, 2001). At the molecular level, this genetic abnormality involves disruption of the promyelocytic leukemia gene (PML) on chromosome 15 and of the retinoic acid receptor gene (RARα) on chromosome 17. The resulting fusion gene encodes the abnormal fusion protein PML-RARα, which is found in almost all patients with APL. This protein inhibits myeloid differentiation, causing an accumulation of leukemic cells at the promyelocytic stage of development (Soignet). ATRA is capable of inducing differentiation of APL promyelocytes in experimental studies. The incorporation of ATRA into modern chemotherapeutic regimens for APL has resulted in a high percentage of CR and reduced the risk of relapse to about 20% in patients who initially achieve remission (Soignet, Fleischauer, Polyak, Heller, & Warrell, 1997). In clinical studies of 40 patients with relapsed APL who achieved CR with Trisenox, 33 patients (83%) became negative for the PML-RARα transcript (i.e., achieved molecular remission) as measured by reverse transcriptase-polymerase chain reaction (RT-PCR) (Soignet et al., 1998, 2001). Patients who achieve molecular remission, an indication of the absence of minimal residual disease, have a better prognosis (lower risk of relapse) than patients who remain positive for the PML-RARα transcript after achieving hematologic CR (Gameiro et al., 2001).

Experimental studies have demonstrated several potential mechanisms of action of ATO that may contribute to the drug’s anticancer activity. These mechanisms include induction of apoptosis (i.e., programmed cell death), inhibition of cell proliferation, and inhibition of angiogenesis (Chen et al., 1997; Soignet et al., 1998; Waxman & Anderson, 2001; Zhang et al., 1996). The diverse mechanisms of action of ATO suggest that Trisenox may have potential efficacy in malignancies other than APL, such as myelodysplastic syndromes, multiple myeloma, and chronic myeloid leukemia, either alone or in combination with agents that enhance its activity (Bachleitner-Hofmann, Gisslinger, Grumbeck, & Gisslinger, 2001; Perkins, Kim, Fang, & Bhalla, 2000; Porosnicu et al., 2001; Zhang et al., 1998; Zhu et al., 1999).

Risk and Benefit Profile of Trisenox

Trisenox fulfills an unmet treatment need among patients with relapsed or refractory APL. Until the introduction of Trisenox, treatment options for these patients were limited, consisting primarily of ATRA plus cytotoxic chemotherapy and bone marrow transplantation (BMT) or peripheral blood stem cell transplantation (PBSC). ATRA as a single agent effectively induces high initial remission rates of approximately 85%, but long-term survival is short, with a median overall survival of less than 20 months (Cortes et al., 1994; Soignet et al., 1997; Warrell et al., 1994). Furthermore, once patients have relapsed from ATRA, maintenance therapy is not as effective as initial treatment (Warrell et al.). In contrast, Trisenox therapy yields high rates of CR (85%–92%) in patients with relapsed APL, inducing molecular remission in a large proportion of patients (83%) (Soignet et al., 1998, 2001). Trisenox has a favorable side effect profile compared with traditional chemotherapeutic agents (Soignet et al., 1998, 2001). Unlike most cytotoxic agents, Trisenox does not cause hair loss (Slack, Waxman, Tricot, Tallman, & Bloomfield, 2002). Autologous BMT or PBSC also may be useful in patients with APL. However, autologous and allogeneic transplantation usually are limited to patients younger than 60; allogeneic transplantation, in particular, is associated with considerable morbidity and mortality (Thomas et al., 2000).

Adverse events that commonly are associated with the use of Trisenox in patients with relapsed APL are relatively mild and generally do not require interruption of therapy. Common adverse events include leukocytosis, gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea, abdominal pain), fatigue, edema, hyperglycemia, dyspnea, cough, QT prolongation, rash or itching, headaches, and dizziness (Cell Therapeutics, 2002; Soignet et al., 1998). However, serious adverse events, such as hyperleukocytosis, electrocardiographic abnormalities, and APL differentiation syndrome (APLS), can occur and necessitate careful patient monitoring and management during treatment (Soignet, 2001; Soignet et al., 1998, 2001). In the Chinese studies, significant myelosuppression was not associated with ATO treatment (Shen et al., 1997). To date, Trisenox therapy has been

FIGURE 2. TRISENOX® INFUSION CONSIDERATIONS
Note. Based on information from Cell Therapeutics, Inc., 2002.

- Central line is not required but may be used if already in place.
- In-line filter is not required.
- Prophylactic antiemetics are not necessary.
- Infuse over one to two hours (extend up to four hours if acute vasomotor reactions occur).
- Monitor vital signs frequently.
- Interrupt infusion for severe tachycardia or hypotension.
- Resume infusion at decreased rate after resolution.
- Keep IV fluids on hand for treatment of hypotension.
- Vasomotor symptoms (flushing, tachycardia, dizziness, and light-headedness)
  - Decrease rate of infusion.
  - Hold infusion until resolution if symptoms are severe.
  - Then resume infusion at decreased rate.
  - Encourage adequate fluid intake.
- Headache
  - Can occur with infusions shorter than two hours
  - Treat with acetaminophen and consider premedicating for future doses.
- Treat nausea and vomiting as necessary per institutional guidelines.
- IV infiltration
  - Not an irritant or vesicant when diluted and administered as recommended
  - Follow institutional guidelines for IV infiltration.
- Pruritic macular rash
  - Interrupting Trisenox therapy is not necessary.
  - Treat with topical steroids.
associated with lower rates of myelo-suppression and APL-related conditions than those that usually occur after treatment with conventional chemotherapeutic agents (Soignet et al., 2001; Waxman & Anderson, 2001). Adverse events associated with Trisenox tend to occur less frequently when the drug is administered during the consolidation phase (Rust & Soignet, 2001). Proper monitoring of patients during Trisenox therapy allows appropriate management of serious adverse events if they occur. Monitoring considerations for patients on Trisenox are summarized in Figure 3 (Cell Therapeutics, 2002).

Hyperleukocytosis (≥ 10 x 10⁶ leukocytes/mL) occurs in approximately 50% of patients treated with Trisenox. Hyperleukocytosis is self-limiting in these patients, typically normalizing by the time of bone marrow remission, thus obviating the need for cytotoxic chemotherapy or leukapheresis (Cell Therapeutics, 2002; Soignet et al., 2001). Therefore, this problem is not a cause for interrupting Trisenox therapy.

APLS, which clinically is identical to the retinoic acid syndrome observed with ATRA administration, was seen in 25% of patients with APL (10 of 40) treated with Trisenox in a multicenter trial (Soignet et al., 2001). The syndrome consists of fever, weight gain, generalized edema, and pleural or pericardial effusions without evidence of infection that can lead to respiratory failure. Three of the patients in this trial were judged to have serious APLS, but all ultimately achieved CR. ATO therapy was interrupted for one to five days in eight patients. Symptoms of APLS may be subtle and easy to overlook (see Figure 3). Therefore, patients must be weighed daily and instructed to immediately report fever, sudden weight gain, fluid retention, or difficulty breathing. This syndrome is effectively treated when dexamethasone (10 mg twice daily for at least three days or until symptoms resolve) is given promptly.

QT prolongation should be anticipated during treatment of patients with APL with Trisenox. Both torsades de pointes and complete heart block have been reported (Cell Therapeutics, 2002). Vigilant cardiovascular monitoring of all patients therefore is warranted, particularly during the induction phase of treatment. Twelve-lead electrocardiography should be performed weekly during therapy and more frequently in patients who are at risk for cardiac events. Serum potassium levels should be maintained at greater than 4 mEq/L and serum magnesium levels should be maintained at greater than 1.8 mg/dL during treatment with Trisenox. Immediate intervention is required if the absolute QT interval exceeds 500 msec, including reconsideration of the risks and benefits of continued therapy and discontinuation of other therapeutic agents known to prolong the QT interval (Soignet, 2001; Soignet et al., 2001). If syncope or rapid or irregular heartbeat occurs, Trisenox should be discontinued temporarily. Patients may need to be hospitalized for telemetry monitoring, and all pertinent risk factors, including serum electrolyte levels, need to be addressed. Trisenox administration may be resumed when the QTc interval falls below 460 msec and all cardiac symptoms resolve. A reference list of drugs currently known to prolong the QT interval can be obtained online at www.torsades.org.

Impact of Arsenic Trioxide Treatment: A Case Study

Mr. A, a 43-year-old man, was diagnosed with APL in 1994 and treated with conventional therapy through his third remission (see Table 1). Treatment included anthracyclines, cytarabine, ATRA, fludarabine, anti-CD33, vinorelbine, and trimetrexate. At the time of his third relapse, he underwent myeloablation with melphalan and VP-16 (etoposide), followed by autologous BMT. He achieved a fourth remission, which was maintained with IV ATRA and lasted 14 months.

Mr. A was a resourceful patient, and he began investigating alternative treatment options after his fourth relapse when he was told his prognosis was poor. He actively planned and anticipated his next treatment options, researching the literature on ATO and eventually traveling to China to obtain the drug. He underwent treatment at the Arlington Cancer Center in Texas. His first treatment cycle consisted of ATO 10 mg IV infused over two to three hours once daily for 28 days. This was followed by one month of rest. After each succeeding treatment cycle, the rest interval was increased by an additional month.

With this treatment using single-agent ATO, Mr. A achieved a complete hematologic, cytologic, and molecular remission that lasted 17 months, significantly longer...
than any remission he had achieved with ATRA, combination chemotherapy, or autologous BMT. He subsequently relapsed, however, and was retreated with ATO-based therapy for his fifth, sixth, and seventh relapses. The protocols for Mr. A’s initial and three subsequent postrelapse treatments are detailed in Table 2. Overall, Mr. A survived for six years following his first relapse and four years after his first ATO treatment. Until he died two months after the last cycle of ATO, his course was one of significant response to ATO.

**Case Discussion**

The efficacy of ATO as an induction or consolidation therapy for patients with relapsed APL is well established (Soignet et al., 1998, 2001). Mr. A’s experiences illustrate the potential clinical utility and feasibility of repeated courses of ATO for patients with relapsed disease. Despite four prior treatment courses that included chemotherapy with anthracyclines and cytarabine, differentiation therapy with ATRA, anti-CD33 antibodies, and BMT, Mr. A’s APL continued to relapse. ATO, however, appeared to exert an effect that overcame the resistance seen with the other agents and may have prolonged Mr. A’s survival significantly (Soignet et al., 1998). The remission achieved with the first course of ATO was longer than that produced by autologous BMT. This effect of ATO may be attributed to its multiple proposed mechanisms of action, which include promotion of apoptosis, induction of cellular differentiation, antiproliferative activity, and inhibition of angiogenesis (Chen, Chen, Shen, Chen, & Wang, 2001; Park et al., 2000; Roboz et al., 2000).

At the time of Mr. A’s fifth relapse, the course of his disease was complicated by clonal evolution involving the appearance of trisomy 8; at his seventh relapse, trisomy 6 appeared (see Table 3). Accumulation of cytogenetic abnormalities is a common feature of tumorigenesis and is not uncommon in various acute leukemias, including APL (Mrozek, Heinonen, & Bloomfield, 2000; Wetzler, 2000). Trisomy 8 is the most frequent additional chromosome abnormality and has been reported in 46% of cases of APL (De Botton et al., 2000). Trisomy 6 is less common. Secondary cytogenetic abnormalities may limit the response to both ATO and conventional chemotherapy. Such cytogenetic abnormalities as occurred in Mr. A may have contributed to his ultimate treatment refractoriness.

**Conclusion**

Trisenox is a well-tolerated, effective treatment for patients with relapsed APL. It has a favorable side-effect profile, requiring minimal supportive care, and it usually can be administered in an outpatient setting. Lack of bone marrow suppression and hair loss with Trisenox treatment contributes to a better quality of life than patients commonly experience during conventional chemotherapy. Serious adverse events do occur with Trisenox but can be effectively managed with appropriate patient monitoring and proper diagnosis and treatment. Table 4 summarizes the monitoring required during the administration of Trisenox in this patient population (Cell Therapeutics, 2002).
Arsenic trioxide fulfills a previously unmet medical need through its ability to induce CR in a large proportion of patients with relapsed or refractory APL. The drug’s adverse effects generally are manageable and reversible and do not require interruption of therapy. Moreover, the adverse effects decline in incidence and severity with continued Trisenox therapy, giving Trisenox a favorable safety profile.

Based on the broad mechanisms of action proposed for ATO, clinical trials currently are under way to evaluate the effectiveness of Trisenox in the treatment of a variety of other hematologic malignancies and solid tumors.

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### Table 3. Arsenic Trioxide (ATO) Treatment History

<table>
<thead>
<tr>
<th>Relapse</th>
<th>Clinical Features</th>
<th>Cytogenetics</th>
<th>ATO Treatment/28-Day Cycle*</th>
<th>Total ATO/Cycle</th>
<th>Cumulative Dose of ATO</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fourth</td>
<td>ATO first used</td>
<td>t(15;17)</td>
<td>(I) 10 mg/d x 2</td>
<td>560 mg</td>
<td>1,400 mg</td>
<td>Developed central nervous system relapse 10 months into remission; treated with intrathecal cytarabine Remission longer than with previous interventions</td>
</tr>
<tr>
<td></td>
<td>Hematologic, cytologic, and molecular remission after two cycles</td>
<td>(C) 10 mg/d x 3</td>
<td>840 mg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hematologic relapse at seven months after last cycle of ATO consolidation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fifth</td>
<td>Complete cytogenetic (karyotypic/FISH) remission after two cycles</td>
<td>t(15;17)+8</td>
<td>(I) 15 mg/d x 1</td>
<td>420 mg</td>
<td>2,380 mg</td>
<td>Cytarabine (150 mg/m²/d x 4) was added as therapy for trisomy 8</td>
</tr>
<tr>
<td></td>
<td>Cytogenetic relapse three months after last cycle of ATO consolidation</td>
<td>(I) 10 mg/d x 1</td>
<td>280 mg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(C) 10 mg/d x 1</td>
<td>280 mg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sixth</td>
<td>Partial cytogenetic remission of t(15;17) after first cycle of ATO</td>
<td>t(15;17)+8</td>
<td>(I) 10–15 mg/d x 1†</td>
<td>280 mg†</td>
<td>2,940 mg†</td>
<td>Cytarabine added as therapy for trisomy 8</td>
</tr>
<tr>
<td></td>
<td>Complete cytogenetic relapse of both clones immediately following second cycle of ATO</td>
<td></td>
<td>(I) 10 mg/d x 1†</td>
<td>280 mg†</td>
<td></td>
<td>ATO increased to 15 mg/d in first cycle when marrow blast percent did not decrease</td>
</tr>
<tr>
<td>Seventh</td>
<td>Partial cytogenetic remissions of t(15;17) and +8 during treatment.</td>
<td>t(15;17)+8</td>
<td>(I) 15 mg/d x 3</td>
<td>1,260 mg†</td>
<td>4,200 mg†</td>
<td>Daunorubicin (50 mg/m² x 2 d) plus cytarabine (100 mg/m² x 3 d) added to ATO therapy Trisomy 6 clone appeared during course of combination chemotherapy</td>
</tr>
<tr>
<td></td>
<td>Patient died two months after last ATO cycle</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

† At least 4,200 mg. In the sixth relapse, the patient was started on 10 mg/d, but the dose was increased during the cycle to 15 mg/d; thus, the total amount of ATO administered exceeded 4.2 g.

‡ The dose of ATO was increased by 5 mg/d during the cycle; consequently, 280 mg is the low end of the ATO exposure during this first cycle.

I—induction; C—consolidation; FISH—fluorescence in situ hybridization

*The first ATO treatment cycle was followed by one month of rest. The rest interval was increased by an additional month with each subsequent ATO cycle.

### Table 4. Recommended Monitoring During Trisenox® Administration in Patients With Relapsed Acute Promyelocytic Leukemia

<table>
<thead>
<tr>
<th>Recommended Laboratory and Diagnostic Testing</th>
<th>Before Initiation of Therapy</th>
<th>Twice Weekly</th>
<th>Weekly</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Electrocardiogram</td>
<td>X</td>
<td>–</td>
<td>X</td>
<td>+ as needed for patients at risk of cardiac event</td>
</tr>
<tr>
<td>Clinical chemistry panel (including BUN, creatinine, glucose, and liver function tests)</td>
<td>X</td>
<td>–</td>
<td>X</td>
<td>+ as needed</td>
</tr>
<tr>
<td>Potassium and magnesium</td>
<td>X</td>
<td>X</td>
<td>–</td>
<td>+ as needed</td>
</tr>
<tr>
<td>Hematology profile</td>
<td>X</td>
<td>X</td>
<td>–</td>
<td>+ as needed</td>
</tr>
<tr>
<td>Coagulation profile</td>
<td>X</td>
<td>X</td>
<td>–</td>
<td>Until resolution of coagulopathy</td>
</tr>
</tbody>
</table>

BUN—blood urea nitrogen

Note: Based on information from Cell Therapeutics, Inc., 2002.

### References


Based on the results of clinical trials with arsenic trioxide (ATO) in the United States, the U.S. Food and Drug Administration approved ATO in September 2000 under the name Trisenox® (Cell Therapeutics, Inc., Seattle, WA) for use in patients with APL who are refractory to or have relapsed from retinoid and anthracycline chemotherapy.

Rapid Recap

Arsenic Trioxide as Effective Therapy for Relapsed Acute Promyelocytic Leukemia

- The current standard of treatment for patients with de novo acute promyelocytic leukemia (APL) is all-trans retinoic acid (ATRA) plus anthracycline-based cytotoxic chemotherapy, which is highly effective for remission induction. However, a significant proportion of treated patients relapse and require salvage therapy.

- Based on the results of clinical trials with arsenic trioxide (ATO) in the United States, the U.S. Food and Drug Administration approved ATO in September 2000 under the name Trisenox® (Cell Therapeutics, Inc., Seattle, WA) for use in patients with APL who are refractory to or have relapsed from retinoid and anthracycline chemotherapy.

- The side effects of Trisenox therapy are mostly mild to moderate and self-limiting. They include leukocytosis, gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea, abdominal pain), fatigue, edema, hyperglycemia, dyspnea, cough, QT prolongation, rash or itching, headaches, and dizziness. Serious adverse events, including hyperleukocytosis, electrocardiograph abnormalities, and APL differentiation syndrome, can occur, but they can be successfully prevented and managed with careful patient monitoring during treatment.

- No cross-resistance is known to exist between Trisenox and ATRA or other anticancer agents.