Risk/Benefit Profile of Arsenic Trioxide

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ABSTRACT

Approximately 20%-30% of patients with acute promyelocytic leukemia (APL) who are treated with the current standard all-trans retinoic acid and anthracycline-based chemotherapy regimen suffer relapse. In the mid-1990s, studies from China reported the effective use of arsenic trioxide in achieving complete remission in patients with APL. In the United States, a multicenter trial of this agent in 40 patients with relapsed APL following conventional therapy confirmed the positive safety and efficacy outcomes of a smaller 12-patient pilot study. Common adverse events were hyperleukocytosis, APL differentiation syndrome, prolonged QT interval on electrocardiogram, skin rash, and hyperglycemia. The Oncologist 2001;6(suppl 2):29-32

INTRODUCTION

Although arsenic has been used as a pharmaceutical agent since the first century BC, its association as a poison and its reported toxicities with chronic environmental exposure have given it a predominantly unfavorable reputation [1]. Arsenic is easily obtainable, lacks taste, and looks like sugar, and, thus, it was once a common source of accidental, homicidal, and suicidal poisoning, until federal restrictions limited its availability [1]. In many regions of the world, including Argentina, Chile [1], and Taiwan [2], arsenic toxicity associated with exposure to contaminated drinking water and industrial pollutants is a major health problem. In the United States, arsenic is found in concentrations higher than 10 mg/l in the water supply of several of the western states [3]. For example, in 24% of the U.S. counties where data were available, at least 10% of samples had arsenic concentrations exceeding 10 µg/l; the greatest frequencies were found in California, Idaho, Nevada, and Arizona (United States Geological Survey Fact Sheet 063-00; http://co.water.usgs.gov/trace/pubs/fs-063-00). The runoff from some geothermal power plants leaches arsenic from rock and soils, depositing it in the water supply. The smelting of ores and the combustion of coal also release arsenic into the environment as a by-product of these processes. Arsenical herbicides and pesticides (containing dimethylarsenic acid) carry the element into the air, soil, and water [4]. It may even be found in fruits and vegetables harvested for human consumption, as well as in poultry and livestock whose feed has been enhanced with arsenic to promote growth [1].

Arsenic has been reported to be a human carcinogen associated with malignancies of the lung, bladder, skin [5], liver, and prostate [2]. Although the mechanism is not yet understood, chronic exposure to high concentrations of arsenic may lead to carcinogenic effects owing to hypomethylation of DNA and the generation of deletion mutations [5, 6]. DNA hypomethylation induced by arsenic has been reported as an early event in aberrant gene expression that may be associated with carcinogenesis [5]. Although arsenic’s reputation is mostly one of toxicity and carcinogenesis, it is important to consider its therapeutic value in selected disease settings. Historically, formulations of arsenic have been used to treat a variety of illnesses. In traditional Chinese medicine, it is used to treat syphilis, rheumatoid arthritis, and psoriasis; and arsenic trioxide paste or arsenous acid is used as a devitalizing agent in tooth cavities before filling [7]. In Western medicine, before the development of penicillin, arsenic (the “silver bullet”) was used by Ehrlich to treat syphilis [8]. It was also the active agent in Fowler’s solution, which was commonly used to control the leukocytosis in patients with chronic myelocytic leukemia [9].

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The most common drug-related adverse events were those observed in the pilot study of 12 patients with APL, which decreased over time. The toxicities were not different from but generally self-limiting and reversible, tending to resolve in the majority of patients within 4-5 weeks of therapy. Toxicities were evaluated at each cycle and if the toxicity was not resolved, treatment was either delayed or dosing was adjusted. Treatment was discontinued if a treatment-emergent toxicity was noted that was manageable with supportive care alone.

In the 1990s, several studies reported the effective use of arsenic trioxide in patients with acute promyelocytic leukemia (APL) (Zhang et al., 52% CR, and Shen et al., 90% CR) [7, 10]. Conventional first-line treatment is all-trans retinoic acid (ATRA) and anthracycline chemotherapy. However, approximately 20%-30% of patients relapse and often are refractory to retreatment with ATRA [11].

Investigators have reported that arsenic trioxide induces partial cytodifferentiation [12, 13] and also triggers apoptosis of the leukemia cells, leading to high clinical and molecular remission rates in patients with relapsed APL [14]. To establish a risk/benefit profile for arsenic trioxide, we examined its safety and efficacy in two recent Western clinical studies. These clinical studies entail 12 patients from a single institution pilot study and 40 patients with relapsed APL treated in a multicenter trial involving nine participating centers [12].

**Efficacy in Patients with APL**

In the multicenter clinical trial, 40 patients with relapsed APL were treated with daily infusions of arsenic trioxide at a dose of 0.15 mg/kg over 1-2 hours until visible leukemic cells were eliminated from the bone marrow. One additional treatment cycle, for a cumulative total of 25 days, was permitted for patients in CR. If patients remained in CR, then another four cycles could be administered as maintenance on continuing arsenic trioxide therapy alone, the leukocytosis syndrome resolved in the majority of patients within 4-5 weeks of therapy. Nine (22%) patients experienced one or more signs or symptoms suggestive of the APL differentiation syndrome (fluid retention, pulmonary infiltrates and/or pleural effusions, dyspnea, myalgias, arthralgias, fever, and weight gain) [17]. The syndrome was seen only in patients during remission induction and not during consolidation or maintenance therapy. Similar to the retinoic acid syndrome, APL differentiation syndrome is effectively managed by a short course of corticosteroids (e.g., oral or i.v. dexamethasone 10 mg twice daily for 3-5 days beginning with the first sign or symptom) [18-20]. QT prolongation with an interval greater than 500 msec in at least one tracing was observed on electrocardiography in 16 (40%) of 40 patients.

**Drug Interactions**

The methyltransferases responsible for metabolism of trivalent arsenic are not cytochrome P450 enzymes [21]. Caution is advised when administering arsenic trioxide with other agents that cause QT/QTc interval prolongation; electrocardiographic monitoring is recommended [21].

**Risk/Benefit Profile**

Considering the limited treatment options for patients with relapsed APL, a favorable risk/benefit ratio is supported by the high response rate observed with this agent in this patient population. At median follow-up of 18 months, 27 (68%) of 40 patients were alive and 23 (58%) remained in CR [16]. Responses were seen across gender and all ages tested (range, 5-74 years). Arsenic trioxide was found to be safe for administration in patients when appropriate guidelines are followed. The most serious adverse events associated with hyperleukocytosis (WBC ≥10,000/µl), APL differentiation syndrome, and prolonged QT interval. Many patients subsequently received additional cycles of arsenic trioxide on a maintenance study. Of interest, no cumulative toxicity has been reported. The most common treatment-emergent toxicities in patients with relapsed APL are listed in Table 1. Hyperleukocytosis was observed in 20 (50%) patients. However, with continuing arsenic trioxide therapy alone, the leukocytosis syndrome resolved in the majority of patients within 4-5 weeks of therapy. Nine (22%) patients experienced one or more signs or symptoms suggestive of the APL differentiation syndrome (fluid retention, pulmonary infiltrates and/or pleural effusions, dyspnea, myalgias, arthralgias, fever, and weight gain) [17]. The syndrome was seen only in patients during remission induction and not during consolidation or maintenance therapy. Similar to the retinoic acid syndrome, APL differentiation syndrome is effectively managed by a short course of corticosteroids (e.g., oral or i.v. dexamethasone 10 mg twice daily for 3-5 days beginning with the first sign or symptom) [18-20]. QT prolongation with an interval greater than 500 msec in at least one tracing was observed on electrocardiography in 16 (40%) of 40 patients.

**Table 1. Most common arsenic trioxide-related toxicities**

<table>
<thead>
<tr>
<th>Category</th>
<th>Toxicity</th>
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</thead>
<tbody>
<tr>
<td>Hematologic</td>
<td>Leukocytosis</td>
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<tr>
<td>Digestive</td>
<td>Nausea, vomiting, diarrhea</td>
</tr>
<tr>
<td>Nervous system</td>
<td>Headache, peripheral neuropathy</td>
</tr>
<tr>
<td>Metabolic</td>
<td>Hyperglycemia (mild), hypokalemia, hypomagnesemia</td>
</tr>
<tr>
<td>Dermatologic</td>
<td>Skin rash</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Tachycardia, QT prolongation</td>
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treatment, including hyperleukocytosis, APL differentiation syndrome, electrocardiographic abnormalities, and hyperglycemia, were manageable and self-limiting [21].

The expectation of clinical benefit is substantial in patients with relapsed APL. No reported increases in the incidence of secondary malignancies have been observed in up to 10 years of follow-up in APL patients who received arsenic trioxide in China [22]. Only equivocal results regarding carcinogenicity have been obtained from experiments in rodent models [23].

CONCLUSIONS

Although chronic or acute high-dose exposure with inorganic arsenic is toxic to humans, the potential toxicities can be minimized and managed when arsenic trioxide is given in lower doses, such as those used in these clinical studies. Myelosuppression following arsenic trioxide treatment is considerably lower than what is observed after standard cytotoxic therapies. Accumulating safety and efficacy data in patients with APL who had failed prior treatment suggest a favorable risk/benefit ratio.

Arsenic trioxide demonstrated a favorable safety profile in the heavily pretreated APL population in a combined pilot and multicenter population of 52 patients. Adverse events were common but generally self-limiting and reversible. The implication is that arsenic trioxide can be used in clinical settings in which conventional chemotherapy cannot be used.

REFERENCES


