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$_2$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 precautions.