Introduction: The History of Arsenic Trioxide in Cancer Therapy

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ABSTRACT

Although arsenic can be poisonous, and chronic arsenic exposure from industrial or natural sources can cause serious toxicity, arsenic has been used therapeutically for more than 2,400 years. Thomas Fowler's potassium bicarbonate-based solution of arsenic trioxide (As$_2$O$_3$) was used empirically to treat a variety of disorders, and in 1878, was reported to reduce white blood cell counts in two normal individuals and one with "leucocythemia." Salvarsan, an organic arsenical for treating syphilis and trypanosomiasis, was developed in 1910 by Paul Ehrlich. In the 1930s, arsenic was reported to be effective in chronic myelogenous leukemia. After a decline in the use of arsenic during the mid-20th century, reports from China described a high proportion of hematologic responses in patients with acute promyelocytic leukemia (APL) who were treated with arsenic trioxide. Randomized clinical trials in the U.S. led to FDA approval of arsenic trioxide for relapsed or refractory APL in September 2000. The Oncologist 2001;6(suppl 2):1-2

Because of its significant medicinal properties, arsenic has been used as a therapeutic agent for more than 2,400 years [1]. In the 15th century, William Withering, who discovered digitalis, was a strong proponent of arsenic-based therapies. He argued, "Poisons in small doses are the best medicines; and the best medicines in too large doses are poisonous" [2]. In the 18th century, Thomas Fowler compounded a potassium bicarbonate-based solution of arsenic trioxide (As$_2$O$_3$) that would bear his name. Following its introduction, Fowler's solution was used empirically to treat a variety of diseases during the 18th, 19th, and early 20th centuries [3]. Pharmacology texts of the 1880s describe the use of arsenical pastes for cancers of the skin and breast, and arsenous acid was used to treat hypertension, bleeding gastric ulcers, heartburn, and chronic rheumatism [2]. Arsenic's reputation as a therapeutic agent was enhanced in 1910 when Nobel laureate Paul Ehrlich developed salvarsan, an organic arsenical for treating syphilis and trypanosomiasis. However, as medicine evolved in the 20th century, enthusiasm for medicinal arsenic waned rapidly [2].

In modern times, arsenic acquired a reputation as a toxic compound and a poison. Chronic arsenic exposure is a serious public health problem in some parts of the world [4]. Intoxication by this heavy metal can result from breathing sawdust, workplace air, or smoke from arsenic-preserved wood, or from ingesting contaminated water, food, or soil [5]. Arsenic is present in high concentrations in well water in many parts of the western United States, South America, and Taiwan. In Bangladesh, the health of millions of people has been adversely affected by contamination of the groundwater by naturally occurring arsenic [6]. Widespread use of arsenic-containing herbicides and pesticides, its incorporation into feed as a substance to promote the growth of livestock and poultry, and its industrial use have caused the environmental dispersion of this compound. Furthermore, environmental arsenic is concentrated in many species of fish and shellfish. Consequently, the average daily human intake of arsenic is approximately 300 µg, virtually all of this ingested with food and water [1, 3].

Arsenic poisoning has been a common method of homicide since the Middle Ages. For example, Napoleon may have been poisoned by arsenic-tainted wine that was served to him in exile [7]. The odorless and tasteless properties of most arsenic compounds make them attractive poisons [5]. Unlike strychnine, which is bitter, and other detectable poisons, arsenic is not easily recognized, and victims are...
unaware of its presence. Furthermore, both acute and chronic poisoning results in symptoms that can be confused with a variety of other natural disorders, including hemorrhagic gastroenteritis, cardiac arrhythmias, and psychiatric disease.

Arsenic’s antileukemic activity was first reported in the late 1800s. In 1878, a report from Boston City Hospital described the effect of Fowler’s solution on the reduction of white blood cell counts in two normal people and one patient with “leucocythemia” [3, 8]. Subsequently, As$_2$O$_3$ was administered as a primary antileukemic agent until it was replaced by radiation therapy. However, the hematologic use of arsenic experienced a resurgence in popularity in the 1930s when its efficacy was reported in patients with chronic myelogenous leukemia (CML) [9]. Until supplanted by modern chemotherapy, arsenic trioxide after radiation was considered the most effective treatment for CML and other types of leukemia. Recently, reports from China have described the induction of clinical and hematologic responses by arsenic trioxide in patients with de novo and relapsed acute promyelocytic leukemia (APL) [10-12].

The activity of arsenic trioxide in patients with APL is an important observation, inasmuch as approximately 20% to 30% of patients with this form of acute myelogenous leukemia relapse despite treatment with all-trans retinoic acid and combination chemotherapy. In one report from China, arsenic trioxide monotherapy produced complete clinical responses in 9 of 10 patients with relapsed APL [12]. Treatment was not associated with bone marrow suppression and produced only limited side effects. The results of these observational studies have been confirmed in randomized clinical trials in the U.S. [13, 14]. Consequently, arsenic trioxide (Trisenox™) was approved for the treatment of relapsed or refractory APL by the U.S. Food and Drug Administration in September 2000.

This event prompted the convening of a closed roundtable meeting of experts in hematology/oncology, The Promise of Trisenox™: Charting an Appropriate Scientific and Clinical Course, in New York on July 19, 2000. The meeting participants were charged with the following: discuss the role of arsenic trioxide in the therapy of APL, other hematologic cancers, and solid tumors; clarify the risk/benefit profile of arsenic trioxide and discuss and interpret the results of the clinical trials of arsenic trioxide (Trisenox™) in hematologic malignancies. This supplement is based on the proceedings of that meeting.

**REFERENCES**