

## Arsenic Trioxide

**Trade Name(s):** Trisenox

**Type of Drug:** Arsenic trioxide is a chemotherapy drug.

### **How Drug Works:**

The action of arsenic trioxide is not completely understood. Arsenic trioxide appears to cause changes in cancer cells that make them die. It also appears to correct the gene responsible for making a flawed protein (called the PML-RAR fusion protein) that causes acute promyelocytic leukemia. It is used to treat acute pro-myelocytic leukemia that no longer responds to first-line chemotherapy and ATRA (All-Trans-Retinoic Acid).

### **How Drug Is Given:**

Arsenic trioxide is given by injection into a vein. The first set of treatments (induction) are given daily until the leukemic cells in the bone marrow disappear, up to 60 treatments. Then three to six weeks after induction, consolidation treatment is given five days a week for up to five weeks. The dose depends on your size.

*Read the following information. If you do not understand it or if any of it causes you special concern, check with your doctor.*

### **Before taking this drug, tell your doctor:**

\* If you are trying to become pregnant, are pregnant, or breastfeeding. This drug may cause birth defects if either the male or female is taking it at the time of conception or during pregnancy. Men and women who are taking this drug need to use some kind of birth control. However, do not use oral contraceptives (“the pill”) without checking with your doctor.

\* If you think you may want to have children in the future. Many chemotherapy drugs can cause sterility.

\* If you have any of the following medical problems: chickenpox or exposure to chickenpox, gout, heart disease, congestive heart failure, shingles, kidney stones, liver disease, or other forms of cancer.

\* If you are taking any other prescription or over-the-counter drugs, including vitamins and herbals.

### **Should I avoid any other medications, foods, alcohol, and/or activities?**

Your prescription and nonprescription medications may interact with other drugs, causing a harmful effect. Certain foods or alcohol can also interact with drug products. Never begin taking a new medication, prescription or nonprescription, without asking your doctor or nurse if it will interact with alcohol, foods or other medications. Some drug products can cause drowsiness and may affect activities such as driving.

**Precautions:**

Arsenic trioxide can increase the time it takes for the heartbeat impulse to pass through the heart. You will have a baseline electrocardiogram (EKG), and this may be repeated during the treatment. In addition, you will have blood tests to make sure that the blood electrolyte values and the kidney function tests are normal. If they are abnormal, or if the EKG shows changes, your treatment will be stopped and the abnormalities corrected.

Tell your doctor if you are taking any medicines for an irregular heartbeat or fluid pills.

If you have acute promyelocytic leukemia (APL), the drug may cause APL differentiation syndrome, with fever, difficulty breathing, weight gain, fluid in or around the lung, and death. You will be watched very closely and need to report any of these symptoms right away so that treatment of the syndrome can begin.

Tell all the doctors, dentists, and pharmacists you visit that you are taking this drug.

- \* Most of the following side effects probably will not occur.
- \* Your doctor or nurse will want to discuss specific care instructions with you.
- \* They can help you understand these side effects and help you deal with them.

**Side Effects:****More Common Side Effects:**

- \* Nausea
- \* Skin redness
- \* Vomiting
- \* Weight gain
- \* Diarrhea
- \* Itching
- \* Headaches
- \* Dizziness
- \* Fever, shaking chills (rigors), hives, difficulty breathing
- \* Constipation
- \* Low blood levels of potassium
- \* Poor appetite
- \* Low blood levels of magnesium
- \* Tiredness (fatigue)
- \* Difficulty sleeping
- \* High sugar level in the blood
- \* Cough
- \* High white blood cell count

- \* Skin inflammation

### **Less Common Side Effects:**

- \* Heartburn
- \* EKG changes, which can lead to slowing down of the heart
- \* Dry mouth
- \* Low red blood cell count with increased risk of anemia and tiredness (fatigue)
- \* Low platelet count with increased risk of bleeding
- \* Low white blood cell count with increased risk of infection
- \* Chest pain
- \* Pain, redness, and swelling at injection site
- \* Aching of muscles and bones
- \* High blood levels of potassium
- \* Low blood level of calcium
- \* Low blood sugar
- \* Increased blood levels of liver function tests
- \* Numbness or tingling of hands or feet
- \* Tremor
- \* Too little oxygen in the blood
- \* Fluid around the lungs or heart
- \* Wheezing
- \* Breathing problems

### **Rare Side Effects:**

- \* Fatal irregular heartbeats
- \* Abdominal distention or tenderness
- \* Seizures
- \* Coma
- \* Darkening of skin

### **Side Effects/Symptoms of the Drug:**

Call your doctor or nurse right away if you develop a rash, fever, chills, or difficulty breathing.

Report any bruising or bleeding, seizures, or chest pain immediately.

## **Arsenic Trioxide Questioned in Cancer Treatment Deaths Questions Are Raised About Drug Reaction**

A drug called arsenic trioxide is thought to help patients with acute promyelocytic leukemia (APL) achieve remission, but three out of 10 patients taking the drug died suddenly during the first cycle of treatment during a clinical trial, according to a report in the July 15th issue of *Blood* (Vol. 98, No. 2: 266-271).

Peter Westervelt, MD, PhD, who recently became assistant professor at the University of Massachusetts Medical School in Worcester, and his colleagues from the Washington University School of Medicine in St. Louis, report that autopsies on two of the patients did not identify a cause of death, though bleeding into the lungs was reported in one, and they suspect that cardiac arrhythmia (irregularity of heartbeat) may have played a role in their deaths. The third patient's heart stopped beating suddenly. The study was a phase I/II study in which Westervelt wanted to determine the greatest dose that people could take, the smallest dose that would achieve results, and any side effects associated with arsenic trioxide.

### **Remission Was Short Lived**

Despite the deaths, six out of the seven remaining patients in the trial went into complete remission; however, the researchers note that the "durability of remissions in our series was short-lived in most cases, and no patients remained in remission without further therapy." According to the researchers, several studies have documented the efficacy of arsenic trioxide in treating patients with APL, including patients who have relapsed or who have not been helped by other treatments. "Hematological remission rates of 85% to 90% have been reported...with most patients eventually achieving cytogenetic or molecular remission without additional chemotherapy," the researchers write. Most studies also have reported no treatment-related deaths. But another recent study in the same journal documented a potentially fatal rapid heartbeat in three patients after treatment with arsenic trioxide, resulting in two deaths. All these patients had progressive leukemia.

### **Formulation Used May Be Suspect**

Westervelt points out that problems in their trial may have been with the formulation of arsenic trioxide that they used. "Our observations should nonetheless raise a cautionary flag to practitioners regarding the potential for previously under-appreciated cardiac toxicity with this agent," Westervelt says.

### **Genetics May Play a Role**

The researchers also report that genetics may play a role in the effects of arsenic trioxide: "The fact that all three patients who died early in our study were of African American

descent raises the possibility of a genetic basis for differing susceptibilities to arsenic trioxide toxicity between individual patients."

According to the researchers, this study and other anecdotal evidence of "serious potentially arsenic-related cardiac toxicity presented here suggest that this agent, at the doses currently used for the treatment of APL, may have more significant toxicity than previously recognized."

Herman Kattlove, MD, a medical oncologist with the American Cancer Society (ACS) suggests that if a patient failed all other treatment, then this is still their best hope prior to a bone marrow transplant. But he says, "I would not recommend taking it as first-line therapy until the cause of these deaths have been worked out." Kattlove says he thinks the main issue raised is whether the formulation used in this study had any safety problems, because other studies of this drug with different formulations did not report any adverse effects. "But," Kattlove adds, "although earlier studies with the standard formulation did not lead to sudden deaths, arsenic is known to cause heart beat abnormalities and patients receiving this drug will need careful monitoring."

#### **ESSENCE OF ARTICLE**

"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 ( $\text{As}_2\text{O}_3$ ) 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."

#### **ARTICLE**

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Key Words. Acute promyelocytic leukemia • Arsenic trioxide chemotherapy • Cancer • Leukemia

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 ( $\text{As}_2\text{O}_3$ ) 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  $\mu\text{g}$ , 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<sub>2</sub>O<sub>3</sub> 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<sup>TM</sup>) 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<sup>TM</sup>: 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<sup>TM</sup>) in hematologic malignancies. This supplement is based on the proceedings of that meeting.

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***Induction of NKG2D Ligands and Subsequent Enhancement of NK Cell-mediated Lysis of Cancer Cells by Arsenic Trioxide.***

**Basic Studies**

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**ESSENCE OF ARTICLE**

“This study suggests that the immunomodulatory property of ATO would be an attractive strategy to improve the effectiveness of NK cell-based cancer immunotherapy.”

**Abstract:**

Natural killer (NK) cells are important effector cells in immune responses to tumor cells and the activation of NK cells is mediated through specific interactions between activating receptors and their cognate ligands. Recently, it has been demonstrated that induction of NKG2D ligands on tumor cells by various stresses render them more sensitive to NK cell-mediated killing. Therefore, in this study, it was investigated whether arsenic trioxide (ATO) could up-regulate NKG2D ligands on tumor cells and increase the susceptibility of cancer cells against NK cells. ATO increased transcription of NKG2D ligands, predominantly ULBP1, in various cancer cell lines, such as K562 chronic myelogenous leukemic cells, NB4 acute promyelocytic leukemic cells, and MCF7 breast cancer cells, and subsequently the surface expression of NKG2D ligands. These results were followed by increased susceptibility of cancer cells to NK cell-mediated cytotoxicity after treatment with ATO. This increase in cytotoxicity was abolished by addition of a blocking NKG2D monoclonal antibody, indicating that the increased susceptibility of ATO-treated cancer cells to cytotoxicity of NK cells was mediated through up-regulation of NKG2D ligands. In addition, abrogation of heat shock proteins induction with KNK437 would sensitize the ATO-treated MCF-7 cells to NK cell-mediated killing. This study suggests that the immunomodulatory property of ATO would be an attractive strategy to improve the effectiveness of NK cell-based cancer immunotherapy.