History of the Development of Arsenic Derivatives in Cancer Therapy

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ABSTRACT

Arsenic is a natural substance that has been used medicinally for over 2,400 years. In the 19th century, it was the mainstay of the materia medica. A solution of potassium arsenite (Fowler’s solution) was used for a variety of systemic illnesses from the 18th until the 20th century. This multipurpose solution was also primary therapy for the treatment of chronic myelogenous leukemia until replaced by radiation and cytotoxic chemotherapy. The past 100 years have seen a precipitous decline in arsenic use and, by the mid-1990s, the only recognized indication was the treatment of trypanosomiasis. Much of this decline was due to concerns about the toxicity and potential carcinogenicity of chronic arsenic administration. The rebirth of arsenic therapy occurred in the 1970s when physicians in China began using arsenic trioxide as part of a treatment for acute promyelocytic leukemia (APL). Their accumulated experience showed that a stable solution of arsenic trioxide given by intravenous infusion was remarkably safe and effective both in patients with newly diagnosed APL leukemia and in those with refractory and relapsed APL. The mechanisms of action of arsenic derivatives in this disease and other malignancies are many and include induction of apoptosis, partial cytodifferentiation, inhibition of proliferation, and inhibition of angiogenesis. Molecular studies and ongoing clinical trials suggest that, as a chemotherapeutic agent, arsenic trioxide shows great promise in the treatment of malignant disease.

INTRODUCTION

Arsenic is a common, naturally occurring substance. In nature, it is rarely found in its pure elemental state [1]. Instead, it exists as highly toxic, chemically unstable sulfides, oxides, and arsenates of potassium, sodium, or calcium. There are three inorganic forms of arsenic: red, yellow, and white. Red arsenic (arsenic disulﬁde, As2S2, referred to as realgar or sandaraca) and yellow arsenic (arsenic trisulﬁde, As2S3, referred to as arsenikon, aurum pigmentum, or orpiment) are toxic, chemically unstable complex sulﬁdes [2]. White arsenic (arsenic trioxi- de, As2O3) is an industrial by-product produced by roasting arsenic-containing ores (realgar) and salvaging and purifying the smoke. The organic arsenicals consist of an arsenic atom in its trivalent or pentavalent state linked covalently to a carbon atom. Compared with the inorganic forms, the organic compounds are often more stable, less toxic, and excreted more rapidly. The past, present, and future of medicinal arsenic is a story of use, dishonor, and redemption.

The Past

Arsenic has been used as a therapeutic agent and poison for more than 2,400 years (Table 1) [3]. Hippocrates used the arsenic sulﬁdes realgar and orpiment to treat ulcers, and Dioscorides used the latter as a depilatory.

Many arsenic preparations were used therapeutically in the 18th century. In the 19th century, arsenic was the mainstay of the materia medica. Although pure metallic arsenic was without therapeutic indications, physicians of the time prescribed arsenides and arsenic salts as antiperiodics, antipyretics, antisepsics, antispasmodics, caustics, chol...
Table 1. Medicinal use of arsenic

<table>
<thead>
<tr>
<th>Action</th>
<th>Example Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>Used as a depilatory</td>
<td>Jean de Gorris used arsenic as a sudorific.</td>
</tr>
<tr>
<td>Used as a sedative</td>
<td>Angelus Salva used arsenic against the plague.</td>
</tr>
<tr>
<td>Used as a treatment</td>
<td>Lentilius and Friceus used arsenic as a treatment for malaria.</td>
</tr>
<tr>
<td>For asthma, chorea, eczema, pemphigus, and psoriasis</td>
<td>Fowler's solution (potassium arsenite) was praised for its success in treating asthma, chorea, eczema, Hodgkin's disease, pemphigus, and psoriasis.</td>
</tr>
</tbody>
</table>

In the 18th and 19th centuries, the art of arsenic therapy—often learned after trial and error—was to control its pharmacologic action while making it serve the therapeutic aims. Although some physicians recommended that arsenic preparations be administered in judicious amounts, exacting enough to cure, other practitioners believed that it could be given in large, heroic doses for variable periods. Proponents of the latter approach believed that timid doses were only homeopathic and not worthy of consideration. Therapeutic monitoring of heroic arsenic therapy consisted of closely observing the patient for signs of epithelial, neurological, or gastrointestinal toxicity. Advocates of arsenic therapy defended the medicine against prejudices by recommending that it be employed in a rational fashion with careful monitoring for an overdose. Evidence of healing activity was seen with increased heat and dryness of the skin, tachycardia, itchiness of the eyelids, conjunctivitis, gingivitis, salivation, gastrointestinal symptoms, and a dirt-brown or unwashed appearance of the skin [4].

In the 1700s, Thomas Fowler developed a solution of arsenic trioxide in potassium bicarbonate (1% w/v) that was used empirically for the treatment of a variety of diseases including asthma, chorea, eczema, pemphigus, and psoriasis [1, 5]. Following its introduction, Fowler’s solution became a standard remedy to treat anemia, Hodgkin’s disease, and leukemia [1, 6]. The activity of arsenic trioxide on leukocytes was first described in 1878, when it was reported that Fowler’s solution produced a slight decline in white blood cell counts in two normal individuals and a dramatic decline in a patient with chronic myelogenous leukemia (CML) treated with the preparation for 10 weeks. After discontinuation of treatment, the leukocyte count progressively increased until arsenic therapy was reinstituted [7]. Arsenic therapy subsequently became the mainstay of antileukemic treatment until its use was supplanted by radiation therapy in the early 20th century [5, 6]. It then experienced a brief resurgence in popularity following a report in 1951 of nine patients with CML who responded to arsenic trioxide therapy at Boston City Hospital. Laboratory and clinical changes included reduction in total white blood cell counts from several hundred thousand per cubic millimeter to an approximately normal, reduction in the size of enlarged livers and spleens, a return to apparently normal hematopoiesis in bone marrow biopsy specimens, and a sense of well-being [6]. Discontinuation of therapy was followed by clinical and hematologic relapse within weeks. However, Kandel et al. reported the development of chronic arsenic poisoning in five of six patients treated for CML and recommended careful patient monitoring with its use [8]. Thereafter, the use of Fowler’s solution progressively declined, and it was supplanted by radiotherapy and cytotoxic chemotherapy.

Early use of arsenic derivatives for infectious diseases was based on the work of Nobel laureate, physician, bacteriologist, and founder of chemotherapy Paul Ehrlich. During his time, 500 types of organic arsenic compounds were in clinical use. In 1910, Ehrlich introduced salvarsan, an organic arsenical that could cure syphilis and is still used today to treat trypanosomiasis [1].

The Present

In the 1960s, the efficacy of potassium arsenite was tested in a variety of animal malignancies [9]. Tumors were chosen because of their biologic characteristics and known response to certain antitumor drugs. Arsenic therapy was effective only in animals with Ehrlich ascites tumor, one of the eight tumor models studied. In a search for more cancer-selective cytotoxics, a group of sulfhydryl inhibitors including oxophenarsine was evaluated for anticancer activity by studying their effects on the metabolism of normal and cancer cells. Arsenic showed a preferential selectivity for malignant cells both clinically and in radioactive tracer studies [10]. However, despite this observation, arsenic and other sulfhydryl inhibitors were replaced by other anticancer agents in the early 1970s.
Much of the recent decline in the medical use of arsenic (other than limited use in parasitic infections) can be attributed to concerns about its toxicity and potential for carcinogenicity, particularly skin cancer [11, 12]. Environmentalists refer to arsenic as the number one carcinogen. In 1979, the International Agency for Research on Cancer introduced an overall classification system for carcinogens and placed arsenic and certain arsenic compounds in group 1, agents that are carcinogenic to humans [13].

Interestingly, arsenic has never been shown to be carcinogenic in animal models or responsible for an increase in solid tumors in humans. Furthermore, its long-term toxic effects remain unexplored [11-15]. Despite the hazards, the potential for adverse effects should not deter physicians from using arsenic trioxide to treat patients with life-threatening diseases. Many of the cancer chemotherapeutic agents in use today are genotoxic and carcinogenic. For example, chromosomal translocations, deletions, or losses followed by increases in monocytic leukemias are associated with epipodophylotoxin, anthracycline, and alkylating-agent therapies and radiation therapy for Hodgkin’s disease and other childhood cancers [16, 17]. Longer-term sequelae due to cytotoxic treatments include increases in thyroid cancer and breast cancer in young women [18, 19].

In 1994, Aronson described arsenic’s fall from therapeutic grace: “The magic is gone, and a collective embarrassment hides arsenic’s quiet departure from the clinical scene. Of course, many therapies have in time been rejected but few—beyond mercurials, blood-letting, and arsenic—had been first proclaimed as near panaceas before their downfall” [1]. However, at least in the field of clinical oncology, Aronson’s lament was premature, and the future of arsenic now seems certain.

**The Future**

The study of acute promyelocytic leukemia (APL) and the role of arsenic in its treatment are among the most exciting stories in clinical oncology. Despite dramatic advances in the therapy of this common subtype of acute leukemia with all-trans retinoic acid (ATRA) and combination chemotherapy, approximately 20%-30% of patients will relapse and die, unless rescued by bone marrow transplantation [20, 21].

A long tradition of arsenic use in Chinese medicine provided the basis for the formal introduction in the 1970s of “ailing-1,” a solution of crude arsenic trioxide and herbal extracts, for the treatment of patients with APL [3, 22-24]. Arsenous acid or arsenic trioxide paste is often used in China to devitalize the pulp of diseased teeth, and arsenic preparations have also been incorporated into therapeutic regimens for psoriasis, syphilis, and rheumatic diseases [25]. Initial studies at Harbin Medical University followed by a careful clinical trial at the Shanghai Second Medical University document remarkable clinical efficacy in patients with newly diagnosed and relapsed APL. Patients were treated daily with 10 mg of intravenous arsenic trioxide infused over 2 to 3 hours. This monotherapy produced complete remissions in six (85.7%) of seven patients presenting with de novo APL (Table 2) [24]. In addition, unlike ATRA therapy, long-term arsenic trioxide therapy was followed by molecular remissions in some patients. Although patients with relapsed APL generally do not fare well unless treated with bone marrow transplantation, studies from the same institution reported that arsenic trioxide was equally effective in such patients. Arsenic trioxide monotherapy produced complete remissions in 9 (90%) of 10 patients who initially had a complete response with ATRA and chemotherapy (Table 3) [25].

These studies provide evidence that arsenic can be used as a safe and effective single agent to induce complete remissions in patients with newly diagnosed and relapsed APL. Remission is produced without the myeloid suppression that accompanies induction and consolidation therapy with conventional chemotherapeutic agents. Extension of the pivotal Chinese studies by investigators in the United States has confirmed the activity of low-dose arsenic trioxide in patients with relapsed APL [21]. In this study, 11 of

<table>
<thead>
<tr>
<th>Group</th>
<th>Treatment</th>
<th>Patients</th>
<th>Patients with CR (%)</th>
<th>Days to CR (median)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newly diagnosed</td>
<td>As₂O₃</td>
<td>7</td>
<td>6 (85.7)</td>
<td>30–36 (35)</td>
</tr>
<tr>
<td></td>
<td>As₂O₃ + chemo</td>
<td>4</td>
<td>2 (50.0)</td>
<td>36–36 (36)</td>
</tr>
<tr>
<td>Relapsed</td>
<td>As₂O₃</td>
<td>31</td>
<td>26 (83.9)</td>
<td>17–76 (30)</td>
</tr>
<tr>
<td></td>
<td>As₂O₃ + chemo</td>
<td>11</td>
<td>9 (81.8)</td>
<td>25–63 (35)</td>
</tr>
<tr>
<td></td>
<td>As₂O₃ + ATRA</td>
<td>5</td>
<td>5 (100.0)</td>
<td>19–46 (39)</td>
</tr>
</tbody>
</table>

As₂O₃ = arsenic trioxide; ATRA = all-trans retinoic acid; chemo = chemotherapy; CR = complete remission.

Adapted with permission [24].
12 patients achieved complete remission after a few weeks of treatment, with relatively mild adverse effects. Immuno-fluorescence analysis showed that cells carrying the t(15;17) translocation expressed antigens that are characteristic of both immature and mature cells after treatment with arsenic trioxide. The presence of these cells after treatment and their progressive increase into the early phase of complete remission imply that arsenic trioxide induces differentiation of leukemic cells along the myeloid pathway. Arsenic trioxide treatment also induced the expression and/or activation of caspases, proteolytic enzymes that are involved in apoptosis. These results show that the clinical response in patients with APL is associated with the induction of incomplete cytodifferentiation and apoptosis.

**MECHANISMS OF ACTION AND FUTURE APPLICATIONS IN CANCER TREATMENT**

Although the precise mechanism of arsenic trioxide action is unknown, a variety of in vitro studies suggest that several mechanisms may contribute to its effectiveness in vivo (Fig. 1). As described above, these mechanisms include induction of apoptosis, partial cellular differentiation, degradation of specific APL fusion transcripts, antiproliferation, and inhibition of angiogenesis. Many of the studies that show specific activities for arsenic trioxide in APL have used NB4, a unique cell line that carries the t(15;17) translocation juxtaposing the PML and RARA genes and was derived from the bone marrow of an APL patient [26]. Studies in other model systems are extending many of these findings to other types of hematologic malignancies.

**Induction of Apoptosis**

Apoptosis, or programmed cell death, occurs during senescence of normal cells. Inhibition of this process can immortalize cells and occurs through several mechanisms including upregulation of bcl-2 activity, deletions of the retinoblastoma (RB) gene, p53 mutations, and overexpression of cyclin D2 [27]. Apoptosis proceeds through three phases: a premitochondrial initiation phase, a decision/effector phase, and a degradation phase.

![Figure 1. Possible mechanisms of action of arsenic trioxide (As$_2$O$_3$) in acute promyelocytic leukemia (APL).](http://theoncologist.alphamedpress.org/Downloaded from http://theoncologist.alphamedpress.org)
Premitochondrial Phase

The premitochondrial phase consists of the transduction of proapoptotic signals or activation of nonspecific damage pathways. Bcl-2 is an integral intracellular membrane protein that can protect cells from apoptosis induced by multiple insults in a variety of cell types. Bax, another member of the family, is proapoptotic. One of the mechanisms by which bcl-2 inhibits apoptosis is through heterodimerization with Bax. Studies of the APL cell line NB4 and other myeloid leukemia cell lines have shown that arsenic trioxide may downregulate the bcl-2 protein, thereby enhancing apoptosis [28, 29]. This activity was independent of PML and PML/RAR-α expression. Arsenic may also interfere with a large number of other processes (e.g., histone deacetylase activity, cell cycle progression, DNA repair, ubiquitination, tubulin polymerization, nitric oxide synthesis, and oncogene expression or activation) that may activate premitochondrial pathways inducing apoptosis [30, 31].

Decision/Effector Phase

Mitochondria are the major sites of action of Bax and other apoptotic regulatory proteins of the bcl-2 family [18, 19, 32]. Under pathologic conditions, apoptotic signals trigger progressive permeabilization of the mitochondrial membrane. This progressive process is principally secondary to action of the permeability transition pore complex (PTPC). The degree of pore opening is an important determinant of the degree of apoptosis. Interactions of the bcl-2/Bax complex at the PTPC make up a "life or death" process that determines the fate of the cell. These proteins control an amplification loop in the mitochondrial apoptotic signaling pathway. By downregulating bcl-2, arsenic trioxide shifts the balance toward apoptosis at the PTPC.

Generation of reactive oxygen species can cause loss of mitochondrial membrane potential with subsequent changes in membrane permeability [33]. The NB4 APL-derived cell line has relatively low levels of reduced glutathione, glutathione peroxidase, catalase, and glutathione-S-transferase, an arsenic trioxide cellular efflux transporter. This cell line also expresses constitutively higher levels of hydrogen peroxide than a monocytic leukemia cell line, U937 [33-35]. Arsenic trioxide further inhibits glutathione peroxidase and increases cellular hydrogen peroxide content. Ascorbic acid, by increasing intracellular hydrogen peroxide, enhances arsenic trioxide-induced apoptosis of lymphoma cells but not of normal bone marrow progenitor cells [34]. Figure 2 describes the consequences of this increase [36].

Degradation Phase

The degradation phase of apoptosis is characterized by condensation and fragmentation of nuclear chromatin, condensation of cytoplasmic organelles, dilatation of the endoplasmic reticulum, shrinkage of cells, and alterations in cell membranes that promote a phagocytic, rather than an inflammatory, reaction to the dying cell [37]. Ultrastructurally, the nuclear changes are preeminent with internucleosomal cleavage of DNA that is recognized on agarose gel electrophoresis as a "DNA ladder."

Caspases are aspartate-specific proteases that are synthesized as inactive proenzymes [37]. Their name is derived from "c,-" denoting a cysteine protease, plus "aspase," referring to their aspartic acid substrate. Individual family members, 1-10, are then referred to by the order in which they were first described in the literature. Caspases are activated in a cascade fashion, which plays a central role in the degradation phase of apoptosis. Although not all of the caspase substrates are known, caspases have been reported to cleave and inactivate poly (ADP-ribose) polymerase (PARP), a DNA repair and genome maintenance enzyme [38]. Mitochondrial damage during the decision/effecter phase

![Figure 2. Mechanism of arsenic trioxide (As$_2$O$_3$)-induced apoptosis. GSTπ = glutathione S transferase; As(GS)$_3$ = arsenic-glutathione conjugate; SOD = superoxide dismutase; GPx = glutathione peroxidase; ∆ψM = membrane potential. Adapted with permission [33].](http://theoncologist.alphamedpress.org/Downloaded from)
of apoptosis releases cytochrome C into the cytosol. This heme-containing protein triggers the activation of procaspase, which sequentially activates other members of the caspase family and produces the characteristic features of apoptosis [30].

One mechanism of arsenic-induced apoptosis is caspase activation. Studies of the APL-derived NB4 cell line confirm this property [38]. Subsequently, proteolysis of intracellular proteins including nuclear PARP completes the apoptotic process.

**Effects on Cellular Differentiation and PML/RAR-α**

The PML/RAR-α fusion gene encodes a chimeric protein that produces a maturation block at the promyelocyte stage of myeloid differentiation [39]. Consequently, the effects of arsenic trioxide on this oncogenic gene and its protein product would be expected to contribute to its mechanism of action. A phenotypic manifestation of its activity in cellular differentiation was observed in serial immunophenotypic studies of peripheral blood and bone marrow samples from patients with APL treated with arsenic trioxide [21]. At diagnosis, the leukemic cells express CD33, a primitive myeloid antigen. During the course of arsenic therapy, however, the proportion of cells that express this primitive antigen decreases, and the population of myeloid elements that express CD11b, a marker of mature myeloid cells, increases. These findings are immunophenotypic evidence of the clinical activity of arsenic in inducing remission of APL. Interestingly, arsenic therapy is also accompanied by the unexpected presence of a population of double-positive cells (CD33+/CD11b+). Early in complete remission, fluorescence in situ hybridization assays showed the presence of t(15;17). However, with the passage of time, only the normal pattern of fluorescence could be found in the double-positive population. This evidence suggests that arsenic trioxide induces partial cytodifferentiation of the leukemic cell population.

The effects of arsenic trioxide on PML/RAR-α have also been studied at a molecular level. The PML gene product is a growth suppressor that is localized on nuclear matrix-associated bodies [40]. In patients with APL, PML/RAR-α removes the growth inhibitory activity of PML by displacing PML and other antigens from nuclear bodies to nuclear microspeckles. This presumably causes the disappearance of the normal physiologic function of PML and the nuclear bodies. In APL cells, arsenic relocalizes PML and PML/RAR-α onto the nuclear bodies and also induces degradation of the proteins [40, 41]. However, the effects of arsenic are also independent of both PML and RAR-α. Studies with NB4-306 cells, a retinoic acid-resistant APL cell line that no longer expresses the intact PML-RAR-α fusion protein, indicate that arsenic trioxide inhibits growth and induces apoptosis independent of the presence of the chimeric gene product [41]. In addition, it also inhibits growth and induces apoptosis in PML+/α and PML+/α progenitors. These data indicate that its activity may extend to a variety of hematopoietic and solid tumors and suggest that combined ATRA and arsenic trioxide therapy may be synergistic [36].

**Antiproliferative Activity**

Studies conducted on human myeloma cells indicate that arsenic trioxide also exerts antiproliferative activity. At pharmacologic concentrations, arsenic trioxide produces a dose- and time-dependent inhibition of survival and growth in myeloma cell lines [42], an effect resembling that seen in APL. Interestingly, immunofluorescence studies of nonseparated bone marrow indicated that this arsenic derivative triggered apoptosis in myeloma cells while sparing most myeloid elements. Incubation of primary myeloma cells with interleukin-6 (IL-6), a myeloma growth factor, failed to prevent arsenic-induced cell death or inhibit proliferation of the malignant clone. Cell cycle analysis by flow cytometry of myeloma cells incubated with arsenic trioxide has supported these results. In a study of eight human myeloma cell lines, it produced a significant, dose-dependent inhibition of proliferation [43]. Cells treated with arsenic trioxide were prevented from cycling and arrested at either G1 or G2/M. This antiproliferative activity suggests a potential role for arsenic therapy in patients with multiple myeloma.

**Inhibition of Angiogenesis**

Angiogenesis plays a critical role in the growth of solid tumors and may also be important for the expansion of leukemic cell populations. Arsenic trioxide has inhibited angiogenesis in both systems. In experimental solid tumors, a single administration of arsenic trioxide produced preferential vascular shutdown in the tumor tissue with a resultant hemorrhagic necrosis [44]. This phenomenon was repeatable and without apparent toxic effects on the normal skin, muscle, or kidneys of the experimental animals. Studies of human umbilical vein endothelial cells treated with arsenic trioxide have revealed a series of events that may contribute to the ability of arsenic to exert antitumor activity. They include activation of endothelial cells, upregulation of endothelial cell adhesion molecules, prevention of capillary tube growth and branching vessels, apoptosis of endothelial cells, and inhibition of vascular endothelial growth factor production [45]. It is possible that release of vascular endothelial growth factor by the leukemic cells causes a positive feedback loop with the paracrine production of GM-CSF, IL-6, IL-7, and IL-10 by the stimulated, rapidly proliferating endothelial cells. These
cytokines then provide additional growth signals to the leukemic cell population, and a vicious cycle ensues. The ability of arsenic trioxide to interrupt this loop may contribute to its efficacy.

Activity in Other Malignancies

The apoptotic, antiproliferative, angioinhibitory activity of arsenic trioxide and its other properties may contribute to the ability of this agent to treat a variety of other tumors. Its antiproliferative effect on myeloma cell lines suggests a role in the treatment of multiple myeloma, and it has shown activity in chronic B-cell leukemia cell lines and an adult T-cell leukemia cell line [46, 47]. Experimental treatment of neuroblastoma cell lines indicates that arsenic trioxide is very effective in inducing apoptosis in this primitive neuroectodermal tumor [48]. Activity in this cell line is a function of the population’s intracellular level of reduced glutathione and underscores the importance of the cellular redox potential in the sensitivity of various tumor systems to arsenic therapy.

CONCLUSIONS

The medicinal use of arsenic has spanned more than 2,400 years. It was once considered a panacea for all types of ailments, including CML and Hodgkin’s disease. However, by the late 1900s, arsenic therapy was restricted to the treatment of trypanosomiasis. In fact, its obituary had already been written when researchers in China rediscovered the remarkable therapeutic efficacy of arsenic trioxide in patients with newly diagnosed and relapsed APL. This activity stems from distinct features of the leukemic cell population, in part dependent on the presence of the PML/RAR-α chimeric gene product, as well as from arsenic trioxide’s broad spectrum of biologic effects. These include its ability to induce apoptosis through multiple mechanisms and partial cytodifferentiation of leukemia cells, its ability to inhibit angiogenesis, and its antiproliferative activity.

Although chronic exposure to arsenic may have toxic effects, the recent literature is replete with evidence of the therapeutic efficacy of arsenic derivatives through acute exposure in patients with APL. Of particular importance, low doses of arsenic are clinically effective in this setting. The absence of myelosuppression with arsenic trioxide provides an advantage over conventional cytotoxic chemotherapeutic agents. The studies described in this supplement and ongoing clinical trials indicate that the future of arsenic therapy in malignant diseases is indeed promising.

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