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Arsenic compounds as anticancer agents

Abstract In this paper the use of arsenic compounds as anticancer agents in clinical trials and in in vitro investigations is reviewed, including the experience at our institute. Treatment of newly diagnosed and relapsed patients with acute promyelocytic leukemia (APL) with arsenic trioxide (As_2O_3) has been found to result in complete remission (CR) rates of 85–93% when given by intravenous infusion for 2–3 h at a dose of 10 mg/day diluted in 5% glucose saline solution. Patients exhibit a response in 28–42 days. CR rates after administration of Composite Indigo Naturalis tablets containing arsenic sulfide and of pure tetraarsenic tetrasulfide reached 98% and 84.9%, respectively. At higher concentrations (1–2 μ*M*), arsenic induced apoptosis, while at lower concentrations (0.1–0.5 μ*M*), it triggered cell differentiation in vitro. As_2O_3-induced apoptosis has been observed in many cancer cell lines, including esophageal carcinoma, gastric cancer, neuroblastoma, lymphoid malignancies, and multiple myeloma. Its effectiveness was confirmed in the treatment of multiple myeloma. Arsenic compounds are effective agents in the treatment of APL and their activity against other types of cancer requires further investigation.

Keywords Acute promyelocytic leukemia · Apoptosis · Differentiation · Arsenic trioxide · Arsenic sulfide

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Introduction

Arsenic compounds have been used in the treatment of leukemia, particularly in chronic myeloid leukaemia (CML), erythremia, and Hodgkin's lymphoma since 1865 in the form of Fowler solution (potassium arsenite USP) [23]. An arsenic compound in the Ayurvedic pharmacopeia of India [21] was recognized as useful to control blood cell counts in patients with CML over 100 years ago. Two arsenic compounds have been utilized in Chinese traditional medicine for more than 500 years. One is *Pishang*, or white arsenic, essentially containing arsenic trioxide (As_2O_3), which was recorded in the *Compendium of Materia Medica* (edited by Li Shizhen, 1518–1593) and still used clinically in the treatment of certain skin diseases and asthma and to promote the healing of surgical wounds. The other compound is *Xiong-huang* (or realgar compound), which contains arsenic sulfide and was administered in the treatment of CML for more than 40 years. However, Fowler solution was abandoned in the treatment of CML due to their chronic toxicity with long-term use and the discovery of more effective chemotherapeutic agents.

Based on the principle in Chinese traditional medicine of "use a toxic agent against a toxic agent," in the early 1970s a group of clinical researchers at Harbin Medical University began to treat some types of cancer with white arsenic, which is known to be a toxin. Encouraging results have been observed in the treatment of esophageal carcinoma, malignant lymphoma, and leukemia, particularly CML and acute promyelocytic leukemia (APL). A solution of white arsenic containing As_2O_3 and a trace amount of mercury called *Ai-ling*-1 was used in a clinical trial in 1992 [20]. A pure solution of As_2O_3 has been used clinically since 1996 [24].

Huang et al. [6] first used the Chinese medicine Composite Indigo Naturalis tablets containing realgar, *Baphicanthus cusia*, *Radix salviae mithiorrhyzae*, *Radix pseudosatellariae*, and *Pulverata levis* in the treatment of

APL, achieving high complete remission (CR) rates. In 1999, Lu et al. [8] reported at the 1999 Annual Meeting of the American Society of Hematology that pure tetra-arsenic tetrasulfide (As_4S_4) is effective in the treatment of this type of acute leukemia. The high CR rate, particularly in relapsed APL patients, spurred further research on the mechanism of action and effectiveness of arsenic compounds in other malignancies. The use of As_2O_3 in the treatment of APL and other malignancies as well as its mechanism of action has been studied at our institute, in collaboration with researchers at Harbin Medical University, since 1994.

Use of arsenic compounds in APL

As_2O_3-induced CR rates

More than 400 APL patients worldwide have received arsenic treatment. The CR rate for newly diagnosed patients is 72–85% (Table 1). The highest CR rate was obtained with Composite Indigo Naturalis tablets [6], although further clinical trials are required. No cross-resistance was noted between As_2O_3 and all-*trans*-retinoic acid (ATRA). The CR rate was higher (85–93%) in relapsed APL patients treated with arsenic than in those newly diagnosed.

As_2O_3 is administered in the form of 1% solution at a dose of 0.16 mg/kg daily diluted with 5% glucose in normal saline given by intravenous drip for 2–3 h. Patients receive treatment for 28–44 days (rarely 60 days) to achieve CR [11, 14]. In a study conducted in our institute, the daily dose was reduced to 0.08 mg/kg, and of 29 patients, 80% achieved CR with fewer toxic effects. The lower dose is indicated in elderly patients and those who cannot tolerate the conventional dose.

Composite Indigo Naturalis is given orally at a dose of five tablets (0.25 g/tablet), three times daily. After 1 week, the daily dose is increased to 30 tablets. CR is achieved within 30–60 days [6]. Pure As_4S_4 0.5 g is administered orally, with the dose escalated to l.0 g three times daily. One treatment course is 2–4 weeks [8].

Toxic effects

Toxic effects [11, 14, 24] include skin dryness, itching, erythematous changes, and pigmentation in 25–30% of patients, headache during As_2O_3 infusion, arthralgia, or muscle pain in 14%, gastrointestinal side effects including nausea, vomiting, and diarrhea in 21–27%, peripheral neuropathy with numbness and distal muscle atrophy in 25%, and cardiac toxicity with EKG changes (low flat wave, tachycardia, grade I and rarely grade II atrioventricular block) in 7%. In 20–30% of the patients [11, 14], liver damage occurs, with elevation of alanine aminotransferase, aspartate aminotransferase, and glutamic pyruvic transaminase, glutamic oxaloacetic transaminase, and alkaline phosphatase levels, bilirubinemia and jaundice, and hepatic failure leading to death in severe cases. Interestingly, 50–60% of As_2O_3-treated patients develop hyperleukocytosis, with retinoic acid syndrome (RAS), accompanied by weight gain, pleural and pericardial effusion, and respiratory distress in 31% of patients [3]. Huang et al. [7] reported that six of seven As_2O_3-treated patients developed fluid retention with weight gain and pleural and pericardial effusion. Other side effects are enlargement of the salivary and thyroid glands, toothache, oral ulcers, and oral or nose bleeding [24].

Relapsed APL patients previously treated with chemotherapy and ATRA are more tolerant to As_2O_3 treatment. Among 11 newly diagnosed APL patients reported by Niu et al. [11], two patients developed severe liver damage resulting in death, although no severe hepatotoxic effects were observed in 47 relapsed patients treated with the same agent [11]. The reason remains to be elucidated.

Generally, the toxic effects are mild and respond to symptomatic treatment or resolve with dose reduction. Hyperleukocytosis can be prevented and treated with

Table 1 CR rates achieved in trials of arsenic compounds

Year	Compound	Disease status	No. of patients	CR rate (%)	Reference
1992	Ailing-1	De novo + relapse	32	85.5	20
1995	Composite Indigo	De novo + relapse	60	98	6
1996	As_2O_3	De novo	30	73.3	24
1996	As_2O_3	Relapse	42	52.4	24
1997	Ailing-1	Relapse	15	93	14
1998	As_2O_3	Relapse + refractory	12	92	17
1998	As_2O_3	Relapse + de novo	5	57	7
1998	As_2O_3	Relapse + de novo	98	87.1	9
1999	As_2O_3	De novo	11	72.7	11
1999	As_2O_3	Relapse	47	85.1	11
1999	As_2O_3	Relapse + refractory	40	85	18
1999	As_4S_4	De novo + relapse	100	84.9	8
2000	As_2O_3	De novo	124	87.9	25
2000	As_2O_3	De novo + relapse + refractory	242	74.8	25

cytotoxic agents. High-dose corticosteroids are effective in treating RAS. It should be noted that preexisting hemorrhagic manifestations are alleviated, with increased fibrinogen levels, gradual reductions in soluble fibrin-monomer and D-dimer levels, fibrinolysis activity, and tissue factor in the blood [27].

Postremission and long-term survival

Arsenic cannot eradicate leukemic clones after one course of As_2O_3 treatment. Of 15 patients in our series, 14 remained positive for promyelocytic leukemia (PML)-retinoic acid receptor α (RARα) immediately after achieving CR [14], but after two courses of As_2O_3 therapy, as in the study of Soignet et al. [17], 8 of 11 patients converted to PML-RARα-negative, indicating that a molecular remission is possible after consolidation therapy. With regard to long-term survival, in 33 patients entering CR and followed for 8–48 months in our series, estimated disease-free survival rates at 1 and 2 years were 63.6% and 41.6%, respectively [11]. Disease recurred in 12 of 18 patients treated with As_2O_3 alone, but in only 2 of 11 patients treated with As_2O_3 combined with chemotherapy.

Ma et al. [9] reported that 87.1% of APL patients treated with As_2O_3 achieved CR, and the overall 7-year survival rate was 58.6% with chemotherapy as consolidation therapy. Recently, Zhang et al. [25] have reported 5- and 7-year survival rates of 92.02% and 76.69%, respectively, in patients achieving CR and receiving As_2O_3 and/or chemotherapy as maintenance therapy.

Mechanism of action of As_2O_3

Induction of apoptosis

It has been reported that As_2O_3 has dual dose-dependent effects on NB4 cells [5]. At concentrations in the range 1–2 μM, As_2O_3 induces apoptosis, with formation of apoptotic bodies morphologically that are positive by in situ TdT labeling, show DNA laddering on gel electrophoresis, and exhibit an apoptotic peak in flow cytometry. Clinically, during As_2O_3 treatment, chromatin of leukemic cells becomes dense and coarse, and apoptotic bodies are seen.

Further studies on the mechanism of the apoptotic effect of As_2O_3 have revealed that it disrupts the mitochondrial transmembrane potential ($\Delta\Psi m$). This effect is enhanced by buthionine sulfoximine, which depletes the SH group in cells, and is partially inhibited by the SH group producer dithiothreitol. In addition, As_2O_3 enhances the reactive oxygen species (ROS) content and the activity of caspase 3 in NB4 cells, thus damaging the mitochondrial membrane. Investigation of the genes regulating the permeability of the mitochondrial membrane using Western blot analysis has revealed that As_2O_3 downregulates bcl-2 protein production without altering that of Bax [2, 4, 5]. It is important to point out that As_2O_3 is capable of rapidly degrading PML/PML-RARα protein and relocalizing PML onto nuclear bodies [2, 4].

Induction of partial differentiation

Between 10 and 15 days after treatment with As_2O_3, an increasing number of myelocyte-like cells appear in the peripheral blood of patients, cytoplasmic azurophil granules are transformed into neutrophils, and only a few metamyelocytes, but no clearly terminal-differentiated granulocytes, are seen [11, 14]. These findings reflect a partial differentiation effect of As_2O_3 on leukemic promyelocytes. In vitro investigation has shown that As_2O_3 increases the number of CD11b-positive but not NBT-positive cells [2]. Interestingly, low doses of As_2O_3 and ATRA produce similar gene expression profiles in APL cells, with upregulation of CD52 and Bfl-l, downregulation of RARα, no modulation of retinoic acid-induced gene E (RIG-E) and PreA-plasminogen activator inhibitor 2 (PAI-2), and synergistic effects in the regulation of protein kinase C (PKC) β-l, and small ubiquitin-related modifier 1 (SUMO-1) [2]. In addition, As_2O_3 at low concentrations gradually degrades PML-RARα protein and induces relocalization of PML into nuclear bodies [2].

It is well known that PML-RARα plays an important role in APL leukemogenesis by inhibiting differentiation of promyelocytes through a dominant-negative mechanism, and that normal PML protein plays a role in regulating cell proliferation [22]. Recently, it has been found in our laboratory that As_2O_3 induces acetylation of histones 3 and 4, resulting in transcriptional activation of downstream genes for differentiation. Strangely, As_2O_3 does not inhibit histone deacetylase. These findings require further investigation and remain to be confirmed.

Effects of arsenic compounds on other cancer cells

In vitro studies have demonstrated that As_2O_3 induces apoptosis in numerous cancer cell lines, including esophageal carcinoma [15], neuroblastoma [1], gastric cancer [16], lymphoid neoplasma [26], and myeloma [10, 12]. Seol et al. [13] have reported that As_2O_3 is able to reduce G_2/M arrest in head and neck cancer cell line PCI-1 with an increase in cyclin-dependent kinase (CDK) inhibitor p21 levels in a time-dependent manner and decreases in cdc2 and cyclin B levels, without altering levels of CDK2, CDK4, CDK6, cyclin D, cyclin E, and cyclin A. Zhang et al. [26] have reported that at a concentration of 1 μM, As_2O_3 markedly inhibits both proliferation and viability of NB4 cells, myeloma NOP-l cells, lymphoma NOL-3 cells, myeloid NKM-l cells, normal peripheral blood lymphocytes (PBLs),

non-Hodgkin's lymphoma (NHL) cells, and chronic lymphocytic leukemia (CLL) cells, but it reduces only viability in normal PBLs, CLL cells, and NHL cells. As_2O_3 induces apoptosis and downregulates Bcl-2 expression in NB4, NOP-l, and NKM-l cells. However, As_2O_3 at 1 μM only weakly inhibits proliferation, does not induce apoptosis or downregulate Bcl-2 expression, but arrests the cell cycle in the G_1 phase in myeloid HL-60 cells, lymphoblastoid Raji cells, and lymphoma Daudi cells.

Studies performed at our institute [28] have revealed that As_2O_3 markedly inhibits growth in a dose- and time-dependent manner in eight lymphoproliferative disease cell lines: pre-B acute lymphocytic leukemia (ALL) Nalm-6; Burkitt lymphoma Namalwa and Raji; B-cell lymphoma BJAB; follicular B cell lymphoma Su-DHL-4; T cell ALL Molt-4 and Jurkat; and CLL SKW-3. It induces apoptosis in a number of the cell lines, but not in Nalm-6, Namalwa, Raji, Su-DHL-4, and Jurkat cells. The apoptosis induced by As_2O_3 is associated with disruption of $\Delta\Psi m$ and caspase 3 activation. Degradation of PML protein also occurs, and there are no alterations in c-myc, Rb, CDK4, cyclin D1, p16, and p53. All these results indicate that As_2O_3 has distinct effects on a variety of cancer cells even when derived from the same type of malignancy.

Although As_2O_3 exhibits an anticancer effect against a broad spectrum of cancer cell lines, there have been few reports of its efficacy in clinical trials, apart from the high remission rate achieved in APL. Munshi et al. [10] treated nine patients with advanced refractory multiple myeloma with As_2O_3, of whom four completed >30 days of As_2O_3 infusion and two had a $>50\%$ reduction in myeloma paraprotein. Of the five patients who received infusion for <31 days, two had stable disease and disease progressed in three. Thus 23% (two of nine) responded to As_2O_3 therapy. Soignet et al. reported [19] the treatment with melarsoprol of eight patients with advanced leukemia at the dose used in the treatment of trypanosomiasis, but only a minor clinical response with regression of splenomegaly and lymphadenopathy was observed in one patient with CLL, although central nervous system toxicity was evident.

Conclusions

The results with arsenic compounds, particularly As_2O_3, in the treatment of APL indicate that cancer remission can be achieved through induction of apoptosis by a single agent formerly considered as a toxin. The mechanism of apoptosis induction by As_2O_3 at high concentrations is primarily through disruption of $\Delta\Psi m$ associated with an increase in ROS, caspase 3 activation, and downregulation of Bcl-2 expression. At lower concentrations it induces partial differentiation of cancer cells. However, the precise mechanism of action and the role of arsenic in the treatment of cancer should be clarified in further clinical trials.

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