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Arsenic trioxide

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Background: The ancient drug, arsenic, has remarkable efficacy in the treatment of relapsed acute promyelocytic leukemia (APL) and this success has led to exploration of its use in other malignancies. *Objective*: To provide an overview of the mechanism of action of arsenic and summarize its development in the treatment of APL and other malignant disorders. *Methods*: A 20-year search of MEDLINE, EMBASE and Web of Science was conducted. *Results/conclusions*: A series of clinical trials with arsenic trioxide has confirmed its benefit in the therapy of APL. Its role in the treatment of other malignancies remains to be determined. Careful attention to the clinical management of patients on arsenic trioxide therapy can significantly lessen the risk of major side effects.

Keywords: acute promyelocytic leukemia, apoptosis, arsenic trioxide, differentiation

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1. Introduction

'Well, Mortimer, for a gallon of elderberry wine, I take a teaspoonful of arsenic, and add a half-teaspoon of strychnine, and then just a pinch of cyanide' [1]. With these words, Aunt Martha describes to her nephew Mortimer how she and her sister Abby murdered lonely, elderly men in the famous play *Arsenic and Old Lace*. This famous drama and arsenic's storied history as a poisonous, homicidal agent, as well as the widespread health problems associated with chronic exposure to arsenic, have led to largely negative perceptions of it within the general public. However, arsenic also has a positive history as one of the oldest medicinal agents in the world, dating back to the time of Hippocrates [2-5].

Its modern history begins in the 1970s with studies in China using arsenic trioxide (As_2O_3), which demonstrated achievement of clinical remissions in patients with acute promyelocytic leukemia (APL). Subsequent studies confirmed the remarkable efficacy of arsenic trioxide (AT) in the treatment of APL [3]. This review will discuss the mechanisms of action of AT, its pharmacology, its clinical efficacy in APL and other malignancies and its toxicities and their management. Hopefully, the reader will see beyond what has been described as 'the duplicitous nature of inorganic arsenic' and realize the tremendous potential of this agent [6].

2. Disease biology relevant to arsenic trioxide: acute promyelocytic leukemia

Acute promyelocytic leukemia was first recognized as a unique subtype of acute leukemia by the Swedish physician, Leif Hillestad, when he reported three patients who had a rapidly fatal course over several weeks' duration, with disease features of a white blood cell morphology dominated by promyelocytes and a severe bleeding tendency secondary to thrombocytopenia and fibrinolysis [7]. In 1976, the French-American-British (FAB) group designated APL as the M3 subtype of acute myeloid leukemia (AML) [8].

At approximately the same time, a balanced reciprocal translocation between the long arms of chromosomes 15 and 17 [t(15;17) (q22;q21)] was reported

by Rowley [9]. This translocation was shown to disrupt the promyelocytic (PML) gene on chromosome 15 and the retinoic acid receptor-α (RARα) gene on chromosome 17 and resulted in the formation of two chimeric proteins, PML-RARα and RARα-PML [10-12]. A subset of patients who have APL but lack the t(15;17) have been identified. In the majority of these cases, the 17q21 breakpoint in RARα is disrupted and fused to alternative genes [13]. Thus, the 17q21 locus appears to be crucial for the pathogenesis of APL.

The unique clinical feature of APL is the fatal bleeding and thrombosis that can occur early in the course of the disease and its treatment. Although the pathogenesis of the coagulopathy is complex, it appears to be related to a diffuse activation of coagulation with hyperfibrinolysis and proteolytic activity related to the hypergranular cytoplasm of the malignant promyelocytes [14].

The introduction of modern chemotherapy for the treatment of AML in the 1970s and 1980s led to the achievement of complete remissions (CR) in patients with APL, though only a third of patients were cured. The remainder died of hemorrhage or relapse. However, it was noted as early as 1973 that APL cells were quite sensitive to anthracycline chemotherapy drugs [15,16].

A major breakthrough in the treatment of APL came in the 1980s, when it was shown that oral treatment with all-*trans*-retinoic acid (ATRA) could put over 90% of patients into complete remission without development of bone marrow hypoplasia or aggravation of the bleeding diathesis [17]. *In vitro* studies confirmed that the leukemic cells underwent differentiation and morphologic maturation in response to ATRA. However, most patients subsequently relapsed. Randomized trials combining ATRA with chemotherapy demonstrated the ability to induce CR in over 90% of patients and produce long-term disease-free survival rates of 70% or more [18].

A unique feature of ATRA therapy was development of the retinoic acid (RA) syndrome. This syndrome can also be seen with arsenic trioxide therapy and is now more appropriately termed the APL differentiation syndrome. Early in the course of therapy with ATRA, some patients develop fever, weight gain, respiratory distress, pleural or pericardial effusions, interstitial pulmonary infiltrates, hypotension, and acute renal failure. Although the disorder can be fatal, prompt discontinuation of ATRA and institution of steroid therapy in the form of intravenous dexamethasone (10 mg twice daily) can reverse many cases [19].

3. Introduction to arsenic trioxide

3.1 Chemistry

The chemical element arsenic has an atomic number of 33 but is never found in its pure elemental state. Instead, it forms arsenates of potassium, sodium or calcium, or sulfides and oxides, which are toxic and chemically unstable. The three inorganic forms of arsenic are red arsenic (arsenic disulfide, As_2S_2, known as realgar or sandaraca), yellow arsenic (arsenic trisulfide, As_2S_3, known as arsenicum, aurum pigmentum, or orpiment), and white arsenic (arsenic trioxide, As_2O_3). Organic arsenicals exist in a trivalent or pentavalent state and are linked covalently to a carbon atom [2].

After initial reports that an impure preparation of arsenic could induce remissions in APL, a purified form of inorganic arsenic (arsenic trioxide) was developed, and its efficacy in relapsed and refractory APL led to its approval by the Food and Drug Administration (FDA) in 2000 (Trisenox®, Cephalon).

3.2 Pharmacokinetics of intravenous arsenic trioxide

Intravenous AT has usually been given either in doses of 10 mg infused intravenously over 2 – 3 h once a day in Chinese studies, or in the FDA-approved dose of 0.15 mg/kg in 100 – 250 ml of 5% dextrose in water or 0.9% sodium chloride solution and infused over 1 – 2 h daily.

In some initial studies where 10 mg/day was infused, the peak level achieved in a study of 8 patients with relapsed APL was 5.54 – 7.3 μmol/l. Plasma arsenic was rapidly eliminated and 1 – 8% of the total daily dose was excreted in the urine [20].

A study utilizing a dose of 0.15 mg/kg found plasma concentrations of sodium arsenite and sodium arsenate with similar C_{max} values of 12.4 ± 8.4 and 10.2 ± 3.9 ng/ml, respectively, immediately after completion of administration, followed by a biphasic elimination. Steady-state plasma concentrations of inorganic arsenic were achieved with repeated administration. On Day 1, 20% of the daily dose was excreted in the urine; this figure was as high as 60% of the daily dose during subsequent weeks [21]. These and other studies suggest that other pathways of excretion such as through the bile may play a part in the elimination of arsenic [22].

Pharmacokinetics of oral AT was assessed in a comparative study that suggested that the systemic bioavailability of arsenic was similar whether it was given orally or intravenously [23]. Little or no data exist on the ability of AT to enter the cerebrospinal fluid (CSF). A man with APL in third relapse developed a severe headache with meningeal involvement with APL cells. He was treated with multimodality therapy including oral AT. Elemental arsenic levels were measured in the CSF and peripheral blood by mass spectroscopy and significant penetration of arsenic into the CSF in correlation with plasma levels was noted [24].

3.3 Mechanism of action

Arsenic trioxide has been described as an 'anticancer missile with multiple warheads', referring to its complex and multifaceted mechanism of action (**Figure 1**) [25]. With the discovery of its activity in APL, studies began in earnest to elucidate the mechanism of action of AT. An important study indicated dose-dependent dual effects, with preferential apoptosis at higher concentrations and partial differentiation at lower concentrations. The degradation and rapid

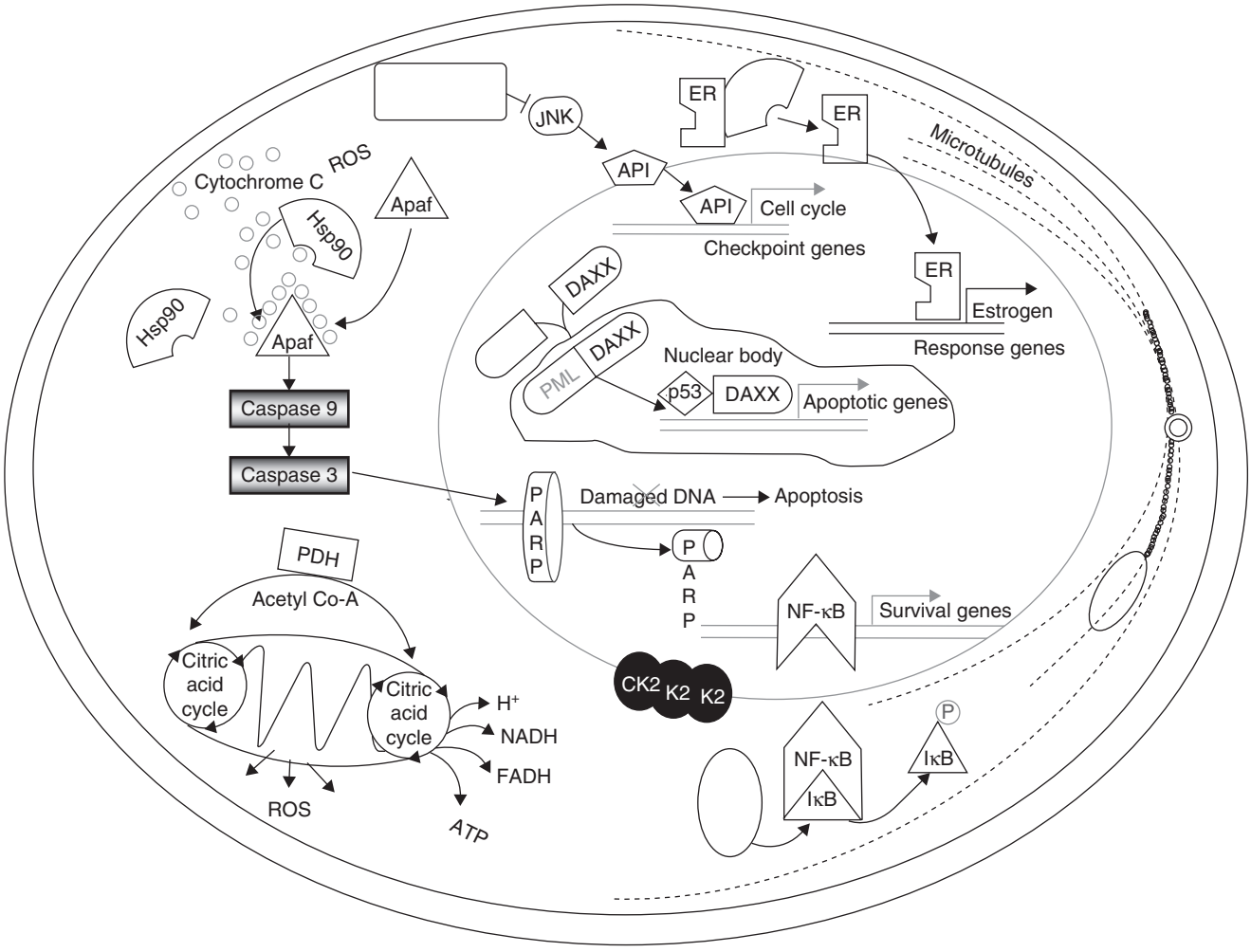

Figure 1. Cellular targets of arsenic trioxide. Arsenic trioxide targets multiple pathways in malignant cells, resulting in apoptosis or in the promotion of the differentiation program. Objects highlighted in gray are potential molecular targets for arsenic trioxide and arsenite.

Reproduced with permission [46].

modulation of PML-RARα proteins was thought to contribute to both of these effects [26]. This degradation and modulation appears to occur, in part, via phosphorylation of PML by mitogen-activated protein kinases (MAPK) with subsequent increased sumoylation of PML and increased PML-mediated apoptosis [27,28].

The intracellular content of glutathione has a significant effect on AT-induced apoptosis, with cells with the lowest glutathione content appearing to be most sensitive to AT [29-31]. It appears that the apoptotic effect of AT occurs predominantly in the G_2M phase of the cell cycle with significant activation of caspases and poly ADP ribose polymerase (PARP) cleavage [32].

Another mechanism by which AT can induce apoptosis is through induction of intracellular reactive oxygen species (ROS); these ROS can, in turn, potentiate arsenic trioxide-induced apoptosis by other mechanisms [33,34]. This effect can be attenuated by glutathione; thus, lower glutathione content as noted above can potentiate this effect. One study suggested that AT could inhibit vascular endothelial growth factor (VEGF) production and angiogenesis and also cause apoptosis of endothelial cells, which, when activated, can release cytokines such as VEGF that stimulate leukemic cell growth [35].

Arsenic trioxide is known to induce activation of multiple kinases, which can induce apoptosis in APL and other leukemia cell lines. Some of these kinases include c-jun *N*-terminal kinase (JNK) [36,37] and RAS-MAPK [38-40].

Arsenic trioxide's broad effects on protein degradation can also be manifested by downregulation of telomerase, with subsequent telomere shortening and cell death [41] and downregulation of Wilms' tumor gene (*wt-1*), which is upregulated in many subtypes of AML [42].

AT has been shown to downregulate B-cell lymphoma (BCL)-2 gene expression at the mRNA and protein levels [43], and this can be enhanced by using antisense

oligodeoxynucleotides to BCL-2 to increase the sensitivity of leukemic cells to AT [44].

The transcription factor NF-κB has antiapoptotic effects and ATRA-induced NF-κB activation in APL cells can prolong the lifespan of mature cells. Investigators have shown that AT can overcome the antiapoptotic effect of ATRA-induced NF-κB activity [45].

An extensive literature documents engagement of AT in the activation of caspases. This is summarized in a review by Miller *et al.* [46]. Arsenic trioxide also appears able to inhibit *p*-glycoprotein (PGP) expression in multidrug-resistant (MDR) human leukemia cell lines that overexpress the MDR1 gene by downregulating PGP expression, and thus can exert a synergistic effect in combination with adriamycin [47,48].

Additionally, AT has been shown to cause changes in the cellular microtubular network and caused formation of polymerized microtubules. This potentiation of tubulin polymerization may assist in arresting cell cycle at mitosis and inducing apoptosis [49].

ATRA can also amplify AT-induced phosphorylation of the retinoid receptor RXRα [50]. The literature on the differentiating effects of AT is relatively sparse, but such effects have been suggested by data presented by Chen *et al.* [26] and confirmed by Rojewski and colleagues [51]. AT may also inhibit proliferation of various cell lines. One study suggested that low concentrations of AT synergize with cyclic adenosine monophosphate in inducing differentiation of APL cells [52].

Arsenic trioxide thus works through multiple mechanisms of apoptosis induction:

- glutathione depletion
- induction of intracellular reactive oxygen species
- activation of kinases (e.g., c-jun *N*-terminal kinase)
- downregulation of telomerases wt-1 and BCL-2
- inhibition of NF-κB
- caspase activation
- inhibition of *p*-glycoprotein
- potentiation of tubulin polymerization.

The predominant activity of AT is inducing apoptosis via a variety of pathways in malignant cells. AT has cytotoxic activity *in vitro* against a large variety of cancer cells of both solid-tumor and hematologic origin, and Gazitt and Akay have suggested that it may be a 'universal anticancer drug' [25].

4. Clinical efficacy

There are several diseases in which arsenic trioxide has been studied *in vitro* or in clinical trials. Hematologic malignancies studied include:

- acute promyelocytic leukemia (definite efficacy)
- multiple myeloma (possible efficacy)
- acute myeloid leukemia (possible efficacy)
- acute lymphoblastic leukemia (unknown efficacy)
- adult T-cell leukemia/lymphoma (possible efficacy)
- myelodysplastic syndrome (possible efficacy)
- non-Hodgkin lymphoma (possible efficacy)
- chronic myeloid leukemia (possible efficacy).

Solid-tumor malignancies studied (all with unknown efficacy) include:

- gastrointestinal malignancies
- hepatocellular carcinoma
- ovarian carcinoma
- cervical carcinoma
- neuroblastoma
- sarcoma
- malignant glioma
- breast cancer
- renal cell carcinoma
- head and neck carcinoma
- nasopharyngeal carcinoma
- transitional cell carcinoma
- lung carcinoma
- prostate carcinoma
- germ-cell malignancies
- malignant melanoma.

4.1 Phase I trials

Only one Phase I trial of AT has been conducted. Cycles lasting 25 days every 3 – 5 weeks for patients with advanced hematologic malignancies demonstrated that doses up to 0.25 mg/kg/day were well-tolerated [53].

4.2 Acute promyelocytic leukemia

In 1992, Chinese investigators demonstrated that an intravenous infusion of 'Ailing-1', which was a crude solution made up of 1% AT with a trace amount of mercury chloride, induced CR in approximately two-thirds of patients with APL, with a 10-year survival rate of 30% [54]. With the recognition that AT was the active agent in this treatment, a purified form administered intravenously at a dose of 10 mg daily was given to 15 APL patients in relapse; 9 of the 10 patients treated with AT alone and all 5 of the remaining patients treated with a combination of AT and low-dose chemotherapy or ATRA achieved a clinical CR [20].

This led to a pilot trial in the United States where 12 heavily pretreated patients with APL received AT, initially 10 or 15 mg/day intravenously and with subsequent use of a 0.15 mg/kg/day dose to adjust for use in children. In this trial 11 of the 12 patients achieved a CR, with 8 of these 11 testing negative for PML/RARα by reverse transcriptase polymerase chain reaction (RT-PCR) assay [55].

A subsequent United States multicenter study in 40 patients in first (n = 21) or ≥ second (n = 19) relapse gave AT for up to 60 doses. After one consolidation course of 25 doses, patients could receive up to four additional maintenance courses. In this study 85% achieved CR with

31 achieving a cytogenetic remission, and 86% of the patients were negative by RT-PCR. The 18-month overall and relapse-free survivals were 66% and 56%, respectively. This study indicated that AT can induce the APL differentiation syndrome; the 10 patients who developed the syndrome responded to dexamethasone [56]. Another study showed that the incidence of the APL differentiation syndrome following treatment of APL with AT was 31% [57].

AT has also been utilized in newly diagnosed patients with APL. A study from Iran of 94 newly diagnosed patients and 17 relapsed patients demonstrated a CR rate of 86%, with 1-year and 2-year disease-free survivals of 88% and 64%, respectively [58]. A study from the MD Anderson Cancer Center combining ATRA and AT alone in 25 patients with low-risk disease (white blood count $< 10 \times 10^9$/l) and in combination with gemtuzumab ozogamicin (GO) on Day 1 of induction in high-risk patients induced a CR in 24 of 25 low-risk patients and 15 of 19 high-risk patients. Three high-risk patients had recurrent disease but the other 36 patients alive in first remission remained PCR-negative at last follow-up [59].

This apparent success of AT therapy as a single agent and the known efficacy of ATRA in APL led to studies combining the two agents. A trial from China treated 80 newly diagnosed and 28 relapsed patients with a combination of AT and low-dose ATRA. The results were compared to patients who had previously received AT or ATRA alone. Outcomes with AT plus ATRA were similar to AT alone and better than ATRA alone in terms of early mortality and complete remission rate. Days to CR were shorter with the combination therapy than with either ATRA or AT alone, and overall, it was felt that the combination was superior without an increase in side effects [60].

A small prospective trial from Shanghai comparing ATRA alone to AT alone or to the combination showed similar high CR rates of 90% or more, with a median number of days to CR of 25 with the combination compared to 31 with AT alone and 40 with ATRA alone. All 20 cases that received AT plus ATRA remained in remission at the time of the report, whereas 7 of the 37 patients receiving either ATRA or AT had relapsed [61].

The first large randomized trial addressing the use of AT in the treatment of APL was the United States Intergroup Trial, which was reported in 2007. All patients received an initial induction with ATRA, daunorubicin and cytarabine. They were then randomized to receive or not receive two courses of AT at 0.15 mg/kg/day for 5 days/week for 5 weeks. Subsequently, all patients received two consolidation courses of ATRA and daunorubicin, and patients in complete remission were then randomized to two different maintenance schedules. Event-free survival in the AT arm was 77% at 3 years compared to 59% in patients who did not receive AT ($p = 0.0013$). Overall survival was 86% at 3 years for the AT group and 77% for the standard group ($p = 0.029$) [62]. Randomized trials of AT plus ATRA vs ATRA plus chemotherapy in induction therapy are planned.

Traditionally, patients with APL who relapse are offered autologous or allogeneic blood or marrow transplantation (BMT) after reinduction therapy. Whether the results with AT are sufficiently good to allow patients not to receive transplants is not clear, based on retrospective studies. A study from China found the actuarial overall survival at 2 years for AT therapy alone was 82%, being 43% for BMT and 23% for chemotherapy ($p = 0.0004$) [63]. However, a retrospective comparison of US patients shows that 86% of patients following AT therapy and BMT remain alive and in complete remission compared to 41% who received AT alone [64]. At the present time, most investigators would still favor offering transplants to patients who have relapsed. Autologous transplant can be considered for patients who achieve molecular remission after reinduction with AT or other therapy, whereas allogeneic transplant should be considered for patients with persistent hematologic disease or molecular disease after salvage therapy [65].

Thus, AT has emerged as an important therapy in the treatment of APL and will probably have an increasing role in front-line therapy. Most patients receiving ATRA alone suffer a subsequent relapse, and thus in the past it has been essential to combine chemotherapy with ATRA to maximize outcome. AT will likely serve a similar function to chemotherapy, and this is probably related to the ability of AT to affect the leukemic stem cells in APL [66].

4.3 Multiple myeloma

The success of treatment of APL with AT as well as the broad mechanism of action of the drug has led to interest in treating other malignancies with AT. In multiple myeloma, preclinical trials have demonstrated that AT has similar mechanisms of action leading to cytotoxicity of myeloma cells as described in APL and other disorders [67,68]. In particular, *in vitro* studies have shown that ascorbic acid depletes intracellular glutathione and enhances the efficacy of AT [69]. Therefore, it has been combined with AT in clinical trials in several different diseases.

These observations led to clinical trials of AT in relapsed multiple myeloma. A Phase II trial of single-agent AT in relapsed multiple myeloma produced reductions in serum M-protein levels of 25% or more in 8 of 24 patients, and an additional 6 patients had stable disease. The median duration of response was nearly 20 weeks [70].

A combination of AT, melphalan and ascorbic acid was used to treat 10 patients. All 10 patients responded with reductions in serum M-protein levels, and 6 of 10 patients exhibited a sustained response [71]. A subsequent Phase II trial in 65 patients who had failed two prior regimens with a twice-weekly schedule of AT and ascorbic acid combined with melphalan achieved objective responses in 31 of 65 patients (48%) including 2 complete, 15 partial, and 14 minor responses [72]. A trial of AT with ascorbic acid

and high-dose melphalan with autologous hematopoietic stem-cell support randomized patients to high-dose melphalan alone or with the addition of two different doses of AT (0.15 or 0.25 mg/kg) on Days – 9 to – 3. Outcomes were similar in the three arms [73].

AT has also been combined with the new proteasome inhibitor bortezomib in combination with ascorbic acid *in vitro* and *in vivo* in a mouse model with apparent synergy [74]. This led to a Phase I/II study of this combination in 22 patients who had failed a median of four prior regimens. Two partial and four minor responses were seen in 22 patients (27%), with a progression-free survival of 5 months [75].

It thus appears that AT has activity in multiple myeloma, though its exact role in the therapy of the disease remains uncertain at this time.

4.4 Non-APL acute myeloid leukemia

Based on the success of AT in APL, *in vitro* studies demonstrated the induction of apoptosis in non-APL acute myeloid leukemia [76]. Several studies have assessed the efficacy of AT on acute megakaryocytic leukemia cell lines and demonstrated cytotoxicity [77,78].

In a Phase II trial of AT in relapsed and elderly patients with AML, 11 patients (median age 77) were treated with AT at a dose of 0.25 mg/kg daily up to a maximum of 60 days. All patients progressed and the median survival was 2.25 months [79]. A trial of the same dose of AT combined with ascorbic acid was tested in 11 patients. Complete remission or CR without full platelet recovery (CRp) was attained in 2 patients, with a bone marrow response in 1 patient [80].

A Phase I/II study of AT 0.25 mg/kg, given on Days 1 – 5 and 8 – 12, combined with low-dose cytarabine, 5 or 10 mg/m^2 subcutaneously on Days 1 – 14, with addition of ascorbic acid if there was a suboptimal response to the first cycle of therapy, was carried out in 57 patients with high-risk myelodysplastic syndrome (MDS) or poor-risk AML. Complete remission was achieved in 40% of the AML patients and 25% of the MDS patients. These results are encouraging but the exact role of AT in the responses is unclear [81]. Based on these limited studies, the role of AT in non-APL AML remains uncertain.

4.5 Acute lymphoblastic leukemia

In vitro studies suggested that AT may have efficacy against acute lymphoblastic leukemia (ALL) cell lines or sensitize leukemic cells to other agents such as dexamethasone [82-84]. However, a Phase II trial of AT at a dose of 0.25 mg/kg/day for 11 patients with relapsed or refractory ALL did not show any evidence of response, and AT probably has little role to play in the therapy of ALL [85].

4.6 Adult T-cell leukemia/lymphoma

Adult T-cell leukemia/lymphoma (ATL) caused by the human T-cell lymphotropic virus type I (HTLV-I) is an aggressive neoplasm of mature activated T cells that is not usually responsive to conventional therapy. TAX, an HTLV-I transcriptional activator with transforming potential, appears to specifically delocalize the PML-associated protein Int-6, and this prompted studies to examine the effects of AT with or without interferon on ATL cells. *In vitro* studies demonstrated synergy between AT and interferon-α in inducing cell-cycle arrest and apoptosis in HTLV-I cell lines [86].

A study of AT given with or without interferon-α to 4 patients with relapsed ATL showed responses in the 2 patients who received the two drugs, with a partial remission (PR) and improvement in thrombocytopenia, respectively [87]. A Phase II trial of this combination in 7 patients with relapsed or refractory ATL demonstrated 1 CR and 3 PRs, with 1 patient remaining alive and disease-free at 32 months [88]. Further studies of AT and interferon are warranted in this disease.

4.7 Myelodysplastic syndromes

There are some limited preclinical data justifying the use of AT in myelodysplastic syndromes [89]. A clinical trial combining AT with thalidomide in 28 MDS patients led to responses in 7 of 28 patients, including 1 complete hematologic and cytogenetic response and 1 patient with regression in spleen size [90]. Two Phase II multicenter trials of AT and MDS, one in the United States and one in Europe, demonstrated hematologic improvement rates of 39% in low-risk patients and 9% in high-risk patients in the United States and 26% in low-risk patients and 17% in high-risk patients in the European trial [91,92]. Based on these relatively limited data, the role of AT in MDS remains investigational.

4.8 Non-Hodgkin lymphoma

As noted previously, AT has *in vitro* activity against malignant lymphocytes [82,83]. Oral AT in combination with ascorbic acid and chlorambucil produced CR in two mantle-cell lymphoma cases and PR in two cases [93]. A case report of disease improvement in a Burkitt-like lymphoma patient has also been reported [94]. The role of AT in lymphoma remains uncertain at this time.

4.9 Chronic myelogenous leukemia

The activity of AT in chronic myelogenous leukemia (CML) is largely based on *in vitro* studies suggesting that AT inhibits translation of the mRNA of BCR-ABL, resulting in apoptosis [95]. This has suggested a rationale for combining AT with imatinib mesilate [96]. However, given the plethora of drugs approved and in development that are specific for BCR-ABL, it is unlikely that AT will play a significant role in the treatment of this disease despite the historical role it has played in the past.

5. Clinical efficacy in solid-tumor malignancies

In vitro studies have demonstrated that AT induces apoptosis and inhibits telomerase activity and can inhibit

vascular endothelial growth factor in a variety of solid-tumor malignancies. Clinical experience has been extremely limited, with only small trials reported in metastatic colorectal cancer [97], hepatocellular carcinoma [98], osteosarcoma and Ewing sarcoma [99], renal cell carcinoma [100], head and neck cancer [101], germ cell tumors [102] and malignant melanoma [103].

6. Safety and tolerability

The most immediate side effect of AT therapy in APL is the APL differentiation syndrome, described earlier, which can occur with ATRA or AT [19,57]. The etiology of the differentiation syndrome is not entirely elucidated. Differentiation of the APL blast does increase integrin expression on the cell surface and may cause increased extravascular extravasation of leucocytes [104]. It also increases cytokine expression, as reviewed in an article by Camacho *et al.* [57].

The other feared complication of AT therapy is cardiac arrhythmias. These can take the form of ventricular tachycardia, including torsade de pointes, and are related to frequent prolongation of the QT interval [105-107]. In a series by Barbey *et al.*, prolonged QT intervals developed in 38 of 99 patients treated with AT [105]. The degree of prolongation was higher in men than in women and in patients with hypokalemia. In the Ohnishi study [106], 8 patients all had prolonged QT intervals; 4 patients developed non-sustained ventricular tachycardia and required treatment with antiarrhythmic agents. Sui and colleagues studied 16 patients with electrocardiography and 24-h Holter monitoring at baseline and during and after oral AT therapy. The QT and QT_c intervals were significantly longer during AT therapy. No ventricular arrhythmias were observed [108].

The mechanism of QT prolongation with AT is not clearly worked out, although studies in guinea-pig papillary muscle have shown a prolongation of action potential duration, suggesting that AT has a direct effect on cardiac repolarization [109]. In a series from the MD Anderson Cancer Center, atrial and ventricular arrhythmias were observed in 4 of 77 patients. Three of four African-Americans given AT developed arrhythmias, versus only 1 of 73 non-African-American patients. The mechanism as to why African-Americans had an increased susceptibility to AT-induced cardiac arrhythmias is unclear [110].

Prior to commencing AT therapy, electrolyte measurements and ECG should be performed and any pre-existing electrolyte abnormalities should be corrected. Drugs known to prolong the QT interval should be withheld. Electrocardiograms should be performed every 1 – 2 weeks. Serum potassium and magnesium levels should be measured and corrected at least once a week. If the QT interval rises above normal, attempts should be made to increase potassium and magnesium concentrations into the high normal range. AT should be discontinued if the QT interval is > 500 ms [111].

Myelosuppression can occur with AT but is relatively infrequent, with grade 3 or 4 neutropenia or thrombocytopenia occurring in only 10 – 15% of patients and grade 3 or 4 anemia in 5% [56,112].

The list of toxicities associated with AT in the Trisenox packaging insert extends over several pages and involves nearly every organ system. These include constitutional symptoms, gastrointestinal disorders, electrolyte abnormalities, respiratory complaints, nervous system disorders, musculoskeletal pain, psychiatric disorders, ocular disorders, and renal and urinary disorders, among others (Trisenox packaging insert, Micromedex) [112].

Chronic arsenic exposure can result in a variety of skin manifestations including hyperpigmentation, keratosis, squamous cell carcinoma, and bowenoid lesions [113].

Liver function test abnormalities can commonly occur and typically cause hepatitis, with increases in aminotransferases (rarely greater than five times normal) beginning about 5 – 10 days after drug administration [114,115]. Peripheral neuropathy in a 'glove and stocking' distribution can occur in up to 10% of patients [116].

Interestingly, AT therapy has been associated with frequent varicella zoster reactivation, which developed in 26% of patients within a year of treatment with no preferential dermatomal involvement or systemic spread [117]. Another study reported an increased incidence of herpes simplex infection after AT therapy [118]. This increased incidence of viral infections is thought to be related to apoptosis of T-helper lymphocytes by AT.

Finally, there is concern that chronic exposure to arsenic could increase the risk of secondary malignancies as a result of DNA damage. An increased number of structural chromosomal abnormalities have been seen in rats chronically exposed to arsenic [119]. A report of solid tumors, including nasopharyngeal carcinoma and colonic adenocarcinoma, developing after treatment with AT has elevated this concern, although retrospective analysis suggested that these cancers may have been present prior to or shortly after the start of AT therapy [120].

7. Regulatory affairs

Arsenic trioxide (Trisenox) was approved by the FDA in 2000 for induction of remission and consolidation in patients with APL refractory to or relapsed from retinoid and anthracycline chemotherapy. Total development time for this indication was only 3 years, and the drug was approved as a priority and as an orphan drug in a 6-month timeframe.

8. Ongoing and future clinical development

8.1 Acute promyelocytic leukemia

In a randomized trial, APL was shown to be of benefit in the consolidative treatment of newly diagnosed APL [62]. It

has been used in the treatment of newly diagnosed patients with APL in small Phase II studies in combination with ATRA and gemtuzumab ozogamicin. The Southwestern Oncology Group will be leading an intergroup study of high-risk APL patients (white blood count > 10×10^9/l), to be known as S0535, which will combine ATRA with gemtuzumab ozogamicin and arsenic for induction therapy followed by consolidation and maintenance therapy. Studies are also being planned to compare AT plus ATRA to ATRA plus chemotherapy for induction treatment of newly diagnosed patients with APL.

8.2 Multiple myeloma

Studies remain in progress combining AT with ascorbic acid, dexamethasone, thalidomide and other agents to investigate its efficacy in this disorder. Its role in this setting remains investigational.

8.3 Other malignancies

Clinical trials are in progress to assess the role of AT combined with low-dose cytarabine for the treatment of elderly patients with AML. A Phase I/II study is assessing its role in combination with azacytidine for the treatment of patients with myelodysplastic syndrome. A combination study of AT with temozolomide and concurrent radiotherapy in patients with malignant glioma is underway. A combination of AT-targeted radiotherapy using ^{131}I-*meta*-iodobenzylguanidine combined with AT in patients with recurrent neuroblastoma or malignant chromaffin cell tumors is also being performed.

8.4 Arsenic derivatives

A large number of arsenic derivatives are in various phases of clinical development, including several oral formulations [121]. Oral AT has been studied in a small number of patients and led to complete hematologic and morphologic remissions in many of these patients. Tetra-arsenic tetrasulfide is an oral formulation that achieves high rates of remission and disease-free survival in APL [122,123].

9. Conclusion

AT has had a remarkable resurgence in the treatment of malignant disease, particularly in the setting of APL, where it has shown significant benefit in establishing durable clinical and molecular remissions in relapsed and newly diagnosed APL patients. Its role in consolidation therapy of newly diagnosed APL has recently been established, and its role in induction therapy of newly diagnosed APL patients is being defined. It is likely that it will play an ever-increasing role in the treatment of this disorder, which was once highly fatal but now appears to be highly curable.

The role of AT in the treatment of other malignancies and hematologic disorders is much less clear but continues to be explored in combination with other modalities of therapy. In parallel, the complex mechanism of action of AT continues to be unravelled.

10. Expert opinion

A role for AT in the treatment of APL is clearly established, and it is highly likely that a regimen for treatment of APL that does not require any traditional chemotherapy drugs will be developed in the future. The administration of AT can be done safely if careful attention to electrolyte abnormalities and electrocardiographic monitoring is undertaken. What role it will play in the treatment of other malignancies remains to be determined.

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Declaration of interest

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Bibliography

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Richards S. Arsenic and old lace. In: The most popular plays of the American theatre: ten of Broadway's longest-running plays. Stein and Day/Scarborough House, New York; 1979. p. 452
2. Waxman S, Anderson KC. History of the development of arsenic derivatives in cancer therapy. Oncologist 2001;6(Suppl 2):3-10
3. Zhu J, Chen Z, Lallemand-Breitenbach V, De The H. How acute promyelocytic leukaemia revived arsenic. Nat Rev 2002;2(9):705-13
4. Antman KH. Introduction: the history of arsenic trioxide in cancer therapy. Oncologist 2001;6(Suppl 2):1-2
5. Bonati A, Rizzoli V, Lunghi P. Arsenic trioxide in hematological malignancies: the new discovery of an ancient drug. Curr Pharm Biotech 2006;7(6):397-405

• **An excellent overview of the mechanisms of action of arsenic and its clinical uses.**

6. Scheindlin S. The duplicitous nature of inorganic arsenic. Mol Intervent 2005;5(2):60-4
7. Hillestad LK. Acute promyelocytic leukemia. Acta Med Scand 1957;159(3):189-94
8. Bennett JM, Catovsky D, Daniel MT, et al. Proposals for the classification of the acute leukaemias. French-American-British (FAB) co-operative group. Br J Haematol 1976;33(4):451-8
9. Rowley JD, Golomb HM, Dougherty C. 15/17 translocation, a consistent chromosomal change in acute promyelocytic leukaemia. Lancet 1977;1(8010):549-50
10. Kakizuka A, Miller WH Jr, Umesono K, et al. Chromosomal translocation t(15;17) in human acute promyelocytic leukemia fuses RAR alpha with a novel putative transcription factor, PML. Cell 1991;66(4):663-74
11. De The H, Chomienne C, Lanotte M, et al. The t(15;17) translocation of acute promyelocytic leukaemia fuses the retinoic acid receptor alpha gene to a novel transcribed locus. Nature 1990;347(6293):558-61
12. Borrow J, Goddard AD, Sheer D, Solomon E. Molecular analysis of acute promyelocytic leukemia breakpoint cluster region on chromosome 17. Science 1990;249(4976):1577-80
13. Grimwade D, Biondi A, Mozziconacci MJ, et al. Characterization of acute promyelocytic leukemia cases lacking the classic t(15;17): results of the European Working Party. Groupe Francais de Cytogenetique Hematologique, Groupe de Francais d'Hematologie Cellulaire, UK Cancer Cytogenetics Group and BIOMED 1 European Community-Concerted Action 'Molecular Cytogenetic Diagnosis in Haematological Malignancies'. Blood 2000;96(4):1297-308
14. Tallman MS, Brenner B, Serna Jdel, et al. Meeting report. Acute promyelocytic leukemia-associated coagulopathy, 21 January 2004, London, United Kingdom. Leuk Res 2005;29(3):347-51
15. Bernard J, Weil M, Boiron M, et al. Acute promyelocytic leukemia: results of treatment by daunorubicin. Blood 1973;41(4):489-96
16. Zhou GB, Chen SJ, Chen Z. Acute promyelocytic leukemia: a model of molecular target based therapy. Hematology (Amsterdam) 2005;10(Suppl 1):270-80
17. Huang ME, Ye YC, Chen SR, et al. Use of all-trans retinoic acid in the treatment of acute promyelocytic leukemia. Blood 1988;72(2):567-72

• **One of the first reports of the efficacy of ATRA in APL.**

18. Slack JL, Waxman S, Tricot G, et al. Advances in the management of acute promyelocytic leukemia and other hematologic malignancies with arsenic trioxide. Oncologist 2002;7(Suppl 1):1-13
19. De Botton S, Dombret H, Sanz M, et al. Incidence, clinical features, and outcome of all trans-retinoic acid syndrome in 413 cases of newly diagnosed acute promyelocytic leukemia. The European APL Group. Blood 1998;92(8):2712-8
20. Shen ZX, Chen GQ, Ni JH, et al. Use of arsenic trioxide (As2O3) in the treatment of acute promyelocytic leukemia (APL): II. Clinical efficacy and pharmacokinetics in relapsed patients. Blood 1997;89(9):3354-60
21. Fujisawa S, Ohno R, Shigeno K, et al. Pharmacokinetics of arsenic species in Japanese patients with relapsed or refractory acute promyelocytic leukemia treated with arsenic trioxide. Cancer Chemother Pharmacol 2007;59(4):485-93
22. Wang Z, Zhou J, Lu X, et al. Arsenic speciation in urine from acute promyelocytic leukemia patients undergoing arsenic trioxide treatment. Chem Res Toxicol 2004;17(1):95-103
23. Kumana CR, Au WY, Lee NS, et al. Systemic availability of arsenic from oral arsenic-trioxide used to treat patients with hematological malignancies. Eur J Clin Pharmacol 2002;58(8):521-6
24. Au WY, Tam S, Fong BM, Kwong YL. Elemental arsenic entered the cerebrospinal fluid during oral arsenic trioxide treatment of meningeal relapse of acute promyelocytic leukemia. Blood 2006;107(7):3012-3
25. Gazitt Y, Akay C. Arsenic trioxide: an anticancer missile with multiple warheads. Hematology (Amsterdam) 2005;10(3):205-13
26. Chen GQ, Shi XG, Tang W, et al. Use of arsenic trioxide (As2O3) in the treatment of acute promyelocytic leukemia (APL): I. As2O3 exerts dose-dependent dual effects on APL cells. Blood 1997;89(9):3345-53

•• **An initial seminal report addressing mechanism of action of AT in APL.**

27. Hayakawa F, Privalsky M. Phosphorylation of PML by mitogen-activated protein kinases plays a key role in arsenic trioxide-mediated apoptosis. Cancer Cell 2005;5(4):389-401
28. Zhu J, Zhou J, Peres L, et al. A sumoylation site in PML/RARA is essential for leukemic transformation. Cancer Cell 2005;7(2):143-53
29. Dai J, Weinberg RS, Waxman S, Jing Y. Malignant cells can be sensitized to undergo growth inhibition and apoptosis by arsenic trioxide through modulation of the glutathione redox system. Blood 1999;93(1):268-77
30. Davison K, Cote S, Mader S, Miller WH. Glutathione depletion overcomes resistance to arsenic trioxide in arsenic-resistant cell lines. Leukemia 2003;17(5):931-40
31. Yang CH, Kuo ML, Chen JC, Chen YC. Arsenic trioxide sensitivity is associated with low level of glutathione in cancer cells. Br J Cancer 1999;81(5):796-9

32. Halicka HD, Smolewski P, Darzynkiewicz Z, et al. Arsenic trioxide arrests cells early in mitosis leading to apoptosis. Cell Cycle (Georgetown TX) 2002;1(3):201-9

33. Woo SH, Park IC, Park MJ, et al. Arsenic trioxide induces apoptosis through a reactive oxygen species-dependent pathway and loss of mitochondrial membrane potential in HeLa cells. Int J Oncol 2002;21(1):57-63

34. Yi J, Yang J, He R, et al. Emodin enhances arsenic trioxide-induced apoptosis via generation of reactive oxygen species and inhibition of survival signaling. Cancer Res 2004;64(1):108-16

35. Roboz G, Dias S, Lam G, et al. Arsenic trioxide induces dose- and time-dependent apoptosis of endothelium and may exert an antileukemic effect via inhibition of angiogenesis. Blood 2000;96(4):1525-30

36. Davison K, Mann KK, Waxman S, Miller WH Jr. JNK activation is a mediator of arsenic trioxide-induced apoptosis in acute promyelocytic leukemia cells. Blood 2004;103(9):3496-502

37. Kajiguchi T, Yamamoto K, Hossain K, et al. Sustained activation of c-jun-terminal kinase (JNK) is closely related to arsenic trioxide-induced apoptosis in an acute myeloid leukemia (M2)-derived cell line, NKM-1. Leukemia 2003;17(11):2189-95

38. Lunghi P, Tabilio A, Lo-Coco F, et al. Arsenic trioxide (ATO) and MEK1 inhibition synergize to induce apoptosis in acute promyelocytic leukemia cells. Leukemia 2005;19(2):234-44

39. Lunghi P, Costanzo A, Levrero M, Bonati A. Treatment with arsenic trioxide (ATO) and MEK1 inhibitor activates the p73-p53AIP1 apoptotic pathway in leukemia cells. Blood 2004;104(2):519-25

40. Giafis N, Katsoulidis E, Sassano A, et al. Role of the p38 mitogen-activated protein kinase pathway in the generation of arsenic trioxide-dependent cellular responses. Cancer Res 2006;66(13):6763-71

41. Tarkanyi I, Dudognon C, Hillion J, et al. Retinoid/arsenic combination therapy of promyelocytic leukemia: induction of telomerase-dependent cell death. Leukemia 2005;19(10):1806-11

42. Glienke W, Chow K, Bauer N, Bergmann L. Down-regulation of wt1 expression in leukemia cell lines as part of apoptotic effect in arsenic treatment using two compounds. Leuk Lymphoma 2006;47(8):1629-38

43. Chen GQ, Zhu J, Shi XG, et al. In vitro studies on cellular and molecular mechanisms of arsenic trioxide (As2O3) in the treatment of acute promyelocytic leukemia: As2O3 induces NB4 cell apoptosis with downregulation of Bcl-2 expression and modulation of PML-RAR alpha/PML proteins. Blood 1996;88(3):1052-61

44. Zhang Y, Shen WL. Bcl-2 antisense oligodeoxynucleotide increases the sensitivity of leukemic cells to arsenic trioxide. Cell Biol Int 2003;27(12):953-8

45. Mathieu J, Besancon F. Arsenic trioxide represses NF-kappaB activation and increases apoptosis in ATRA-treated APL cells. Ann NY Acad Sci 2006;1090:203-8

46. Miller WH Jr, Schipper HM, Lee JS, et al. Mechanisms of action of arsenic trioxide. Cancer Res 2002;62(14):3893-903

• **An excellent overview of the mechanisms of action of AT.**

47. Hulai W, Haixiang S, Decheng B. Arsenic trioxide inhibits p-glycoprotein expression in multidrug-resistant human leukemia cells that overexpress the MDR1 gene. Chinese Med J 2003;116:1644-8

48. Seo T, Urasaki Y, Takemura H, Ueda T. Arsenic trioxide circumvents multidrug resistance based on different mechanisms in human leukemia cell lines. Anticancer Res 2005;25(2A):991-8

49. Ling YH, Jiang JD, Holland JF, Perez-Soler R. Arsenic trioxide produces polymerization of microtubules and mitotic arrest before apoptosis in human tumor cell lines. Mol Pharmacol 2002;62(3):529-38

50. Tarrade A, Bastien J, Bruck N, et al. Retinoic acid and arsenic trioxide cooperate for apoptosis through phosphorylated RXR alpha. Oncogene 2005;24(14):2277-88

51. Rojewski MT, Baldus C, Knauf W, et al. Dual effects of arsenic trioxide (As2O3) on non-acute promyelocytic leukaemia myeloid cell lines: induction of apoptosis and inhibition of proliferation. Br J Haematol 2002;116(3):555-63

52. Zhu Q, Zhang J, Zhu H, et al. Synergic effects of arsenic trioxide and cAMP during acute promyelocytic leukemia cell maturation subtends a novel signaling cross-talk. Blood 2002;99(3):1014-22

53. Soignet S, Wang ZG, Nagy J. Dose ranging study of arsenic trioxide in advanced hematologic cancers: clinical pharmacokinetic and biological effects. Blood 1998;92:598A

54. Sun HD, Ma L, Hu XC, Zhang TD. Ai-lin 1 treated 32 cases of acute promyelocytic leukemia. Chin J Integr Chin West Med 1992;12:170-1

55. Soignet SL, Maslak P, Wang ZG, et al. Complete remission after treatment of acute promyelocytic leukemia with arsenic trioxide. N Engl J Med 1998;339(19):1341-8

• **First US report of the outstanding efficacy of AT in APL.**

56. Soignet SL, Frankel SR, Douer D, et al. United States multicenter study of arsenic trioxide in relapsed acute promyelocytic leukemia. J Clin Oncol 2001;19(18):3852-60

57. Camacho LH, Soignet SL, Chanel S, et al. Leukocytosis and the retinoic acid syndrome in patients with acute promyelocytic leukemia treated with arsenic trioxide. J Clin Oncol 2000;18(13):2620-5

• **A report highlighting the APL differentiation syndrome occurring with AT.**

58. Ghavamzadeh A, Alimoghaddam K, Ghaffari SH, et al. Treatment of acute promyelocytic leukemia with arsenic trioxide without ATRA and/or chemotherapy. Ann Oncol 2006;17(1):131-4

59. Estey E, Garcia-Manero G, Ferrajoli A, et al. Use of all-trans retinoic acid plus arsenic trioxide as an alternative to chemotherapy in untreated acute promyelocytic leukemia. Blood 2006;107(9):3469-73

60. Wang G, Li W, Cui J, et al. An efficient therapeutic approach to patients with acute promyelocytic leukemia using a combination of arsenic trioxide with low-dose all-trans retinoic acid. Hematol Oncol 2004;22(2):63-71

61. Shen ZX, Shi ZZ, Fang J, et al. All-trans retinoic acid/As2O3 combination yields a high quality remission and survival in newly diagnosed acute promyelocytic leukemia. Proc Natl Acad Sci USA 2004;101(15):5328-35

•• **A report highlighting the novel combination of ATRA plus AT and its high efficacy in APL.**

62. Powell BL, Moser B, Stock W, et al. Effect of consolidation with arsenic trioxide

(AS2O3) on event-free survival (EFS) and overall survival (OS) among patients with newly diagnosed acute promyelocytic leukemia (APL): North American Intergroup Protocol C9710. J Clin Oncol 2007;25(18S):2

- **The first randomized trial (reported in abstract form) demonstrating the efficacy of AT in the consolidation therapy of APL.**

63. Au WY, Lie AK, Chim CS, et al. Arsenic trioxide in comparison with chemotherapy and bone marrow transplantation for the treatment of relapsed acute promyelocytic leukaemia. Ann Oncol 2003;14(5):752-7
64. Douer D, Hu W, Giralt S, et al. Arsenic trioxide (Trisenox) therapy for acute promyelocytic leukemia in the setting of hematopoietic stem cell transplantation. Oncologist 2003;8(2):132-40
65. Kharfan-Dabaja MA, Abou Mourad YR, Fernandez HF, et al. Hematopoietic cell transplantation in acute promyelocytic leukemia: a comprehensive review. Biol Blood Marrow Transplant 2007;13(9):997-1004
66. Zheng X, Seshire A, Ruster B, et al. Arsenic but not all-trans retinoic acid overcomes the aberrant stem cell capacity of PML/RARalpha-positive leukemic stem cells. Haematologica 2007;92(3):323-31
67. Kalmadi SR, Hussein MA. The emerging role of arsenic trioxide as an immunomodulatory agent in the management of multiple myeloma. Acta Haematol 2006;116(1):1-7
68. Ravandi F. Arsenic trioxide: expanding roles for an ancient drug? Leukemia 2004;18(9):1457-9
69. Bahlis NJ, Mccafferty-Grad J, Jordan-Mcmurry I, et al. Feasibility and correlates of arsenic trioxide combined with ascorbic acid-mediated depletion of intracellular glutathione for the treatment of relapsed/refractory multiple myeloma. Clin Cancer Res 2002;8(12):3658-68
70. Hussein MA, Saleh M, Ravandi F, et al. Phase 2 study of arsenic trioxide in patients with relapsed or refractory multiple myeloma. Br J Haematol 2004;125(4):470-6
71. Borad MJ, Swift R, Berenson JR. Efficacy of melphalan, arsenic trioxide, and ascorbic acid combination therapy (MAC) in relapsed and refractory multiple myeloma. Leukemia 2005;19(1):154-6
72. Berenson JR, Boccia R, Siegel D, et al. Efficacy and safety of melphalan, arsenic trioxide and ascorbic acid combination therapy in patients with relapsed or refractory multiple myeloma: a prospective, multicentre, phase II, single-arm study. Br J Haematol 2006;135(2):174-83
73. Qazilbash MH, Saliba RM, Davis MS, et al. Arsenic trioxide with ascorbic acid and high-dose melphalan for autologous hematopoietic stem cell transplantation for multiple myeloma [abstract 3090]. Blood 2006;108:881A
74. Campbell RA, Sanchez E, Steinberg JA, et al. Antimyeloma effects of arsenic trioxide are enhanced by melphalan, bortezomib and ascorbic acid. Br J Haematol 2007;138(4):467-78
75. Berenson JR, Matous J, Swift RA, et al. A phase I/II study of arsenic trioxide/bortezomib/ascorbic acid combination therapy for the treatment of relapsed or refractory multiple myeloma. Clin Cancer Res 2007;13(6):1762-8
76. Lehmann S, Bengtzen S, Paul A, et al. Effects of arsenic trioxide (As2O3) on leukemic cells from patients with non-M3 acute myelogenous leukemia: studies of cytotoxicity, apoptosis and the pattern of resistance. Eur J Haematol 2001;66(6):357-64
77. Lu M, Levin J, Sulpice E, et al. Effect of arsenic trioxide on viability, proliferation, and apoptosis in human megakaryocytic leukemia cell lines. Exp Hematol 1999;27(5):845-52
78. Lam HK, Li K, Chik KW, et al. Arsenic trioxide mediates intrinsic and extrinsic pathways of apoptosis and cell cycle arrest in acute megakaryocytic leukemia. Int J Oncol 2005;27(2):537-45
79. Parmar S, Rundhaugen LM, Boehlke L, et al. Phase II trial of arsenic trioxide in relapsed and refractory acute myeloid leukemia, secondary leukemia and/or newly diagnosed patients at least 65 years old. Leukemia Res 2004;28(9):909-19
80. Douer D, Watkins K, Louie R, et al. Treatment of non-APL acute myelogenous leukemia with intravenous arsenic trioxide plus ascorbic acid [abstract 1959]. Blood 2006;108(11):554A
81. Roboz G, Ritchie E, Allen-Bard S, et al. Arsenic trioxide is safe and effective in combination with low-dose Ara-c for the treatment of IPSS-2 myelodysplastic syndrome and poor-prognosis acute myeloid leukemia in elderly patients. Blood 2005;106:786A
82. Bornhauser BC, Bonapace L, Lindholm D, et al. Low-dose arsenic trioxide sensitizes glucocorticoid-resistant acute lymphoblastic leukemia cells to dexamethasone via an Akt-dependent pathway. Blood 2007;110(6):2084-91
83. Hu XM, Hirano T, Oka K. Arsenic trioxide induces apoptosis equally in T lymphoblastoid leukemia MOLT-4 cells and P-gp-expressing daunorubicin-resistant MOLT-4 cells. Cancer Chemother Pharmacol 2003;51(2):119-26
84. Zhu XH, Shen YL, Jing YK, et al. Apoptosis and growth inhibition in malignant lymphocytes after treatment with arsenic trioxide at clinically achievable concentrations. J Nat Cancer Inst 1999;91(9):772-8
85. Litzow MR, Lee S, Bennett JM, et al. A phase II trial of arsenic trioxide for relapsed and refractory acute lymphoblastic leukemia. Haematologica 2006;91(8):1105-8
86. Bazarbachi A, EL-Sabban ME, Nasr R, et al. Arsenic trioxide and interferon-alpha synergize to induce cell cycle arrest and apoptosis in human T-cell lymphotropic virus type I-transformed cells. Blood 1999;93(1):278-83
87. Ishitsuka K, Suzumiya J, Aoki M, et al. Therapeutic potential of arsenic trioxide with or without interferon-alpha for relapsed/refractory adult T-cell leukemia/lymphoma. Haematologica 2007;92(5):719-20
88. Hermine O, Dombret H, Poupon J, et al. Phase II trial of arsenic trioxide and alpha interferon in patients with relapsed/refractory adult T-cell leukemia/lymphoma. Hematol J 2004;5(2):130-4
89. Kerbauy DM, Lesnikov V, Abbasi N, et al. NF-kappa B and FLIP in arsenic trioxide (ATO)-induced apoptosis in myelodysplastic syndromes (MDSs). Blood 2005;106(12):3917-25
90. Raza A, Buonamici S, Lisak L, et al. Arsenic trioxide and thalidomide combination produces multi-lineage hematological responses in myelodysplastic syndromes patients, particularly in those

with high pre-therapy EVI1 expression. Leukemia Res 2004;28(8):791-803

91. Schiller GJ, Slack J, Hainsworth JD, et al. Phase II multicenter study of arsenic trioxide in patients with myelodysplastic syndromes. J Clin Oncol 2006;24(16):2456-64
- **This is an important report on the potential efficacy of AT in the myelodysplastic syndromes.**

92. Vey N, Bosly A, Guerci A, et al. Arsenic trioxide in patients with myelodysplastic syndromes: a phase II multicenter study. J Clin Oncol 2006;24(16):2465-71
- **Another important paper on the potential efficacy of AT in the myelodysplastic syndromes.**

93. Au WY, Kumana CR, Liang R, Kwong YL. Preliminary experience of oral arsenic trioxide based therapy in the treatment of refractory mantle cell lymphoma [abstract 338]. Ann Oncol 2005;16:136

94. Ravandi F, Van Besien K. Clinical activity of arsenic trioxide in Burkitt-like lymphoma. Leukemia 2003;17(1):271-2

95. Nimmanapalli R, Bali P, O'Bryan E, et al. Arsenic trioxide inhibits translation of mRNA of bcr-abl, resulting in attenuation of Bcr-Abl levels and apoptosis of human leukemia cells. Cancer Res 2003;63(22):7950-8

96. La Rosee P, Johnson K, O'dwyer ME, Druker BJ. In vitro studies of the combination of imatinib mesylate (Gleevec) and arsenic trioxide (Trisenox) in chronic myelogenous leukemia. Exp Hematol 2002;30(7):729-37

97. Subbarayan PR, Lima M, Ardalan B: Arsenic trioxide/ascorbic acid therapy in patients with refractory metastatic colorectal carcinoma: a clinical experience. Acta Oncologica (Stockholm) 2007;46(4):557-61

98. Lin CC, Hsu C, Hsu CH, et al. Arsenic trioxide in patients with hepatocellular carcinoma: a phase II trial. Investig New Drugs 2007;25(1):77-84

99. Guo W, Tang XD, Tang S, Yang Y. Preliminary report of combination chemotherapy including arsenic trioxide for stage III osteosarcoma and Ewing sarcoma. Chinese J Surg 2006;44(12):805-8

100. Vuky J, Yu R, Schwartz L, Motzer RJ. Phase II trial of arsenic trioxide in patients with metastatic renal cell carcinoma. Investig New Drugs 2002;20(3):327-30

101. Huilgol NG. A phase I study to study arsenic trioxide with radiation and hyperthermia in advanced head and neck cancer. Int J Hyperthermia 2006;22(5):391-7

102. Beer TM, Tangen CM, Nichols CR, et al. Southwest Oncology Group phase II study of arsenic trioxide in patients with refractory germ cell malignancies. Cancer 2006;106(12):2624-9

103. Kim KB, Bedikian AY, Camacho LH, et al. A phase II trial of arsenic trioxide in patients with metastatic melanoma. Cancer 2005;104(8):1687-92

104. Cunha De Santis G, De Barros Tamarozzi M, Sousa RB, et al. Adhesion molecules and differentiation syndrome: phenotypic and functional analysis of the effect of ATRA, As2O3, phenylbutyrate, and G-CSF in acute promyelocytic leukemia. Haematologica 2007;92(12):1615-22

105. Barbey JT, Pezzullo JC, Soignet SL. Effect of arsenic trioxide on QT interval in patients with advanced malignancies. J Clin Oncol 2003;21(19):3609-15
- **An important report on the effect of AT on QT interval in a large series of patients.**

106. Ohnishi K, Yoshida H, Shigeno K, et al. Prolongation of the QT interval and ventricular tachycardia in patients treated with arsenic trioxide for acute promyelocytic leukemia. Ann Intern Med 2000;133(11):881-5

107. Unnikrishnan D, Dutcher JP, Varshneya N, et al. Torsades de pointes in 3 patients with leukemia treated with arsenic trioxide. Blood 2001;97(5):1514-6

108. Siu CW, Au WY, Yung C, et al. Effects of oral arsenic trioxide therapy on QT intervals in patients with acute promyelocytic leukemia: implications for long-term cardiac safety. Blood 2006;108(1):103-6

109. Chiang CE, Luk HN, Wang TM, Ding PY. Prolongation of cardiac repolarization by arsenic trioxide. Blood 2002;100(6):2249-52

110. Patel SP, Garcia-Manero G, Ferrajoli A, et al. Cardiotoxicity in African-American patients treated with arsenic trioxide for acute promyelocytic leukemia. Leukemia Res 2006;30(3):362-3

111. Jones RL, Ewer MS. Cardiac and cardiovascular toxicity of nonanthracycline anticancer drugs. Exp Rev Anticancer Ther 2006;6(9):1249-69

112. Trisenox injection. Micromedex, 2007. Available from: http://mdx2.mayo.edu/hcs/librarian/ND_PR/Main/SBK/2/PFPUI/FW5UMjA2eGpEHa/ND_PG/PRIH/CS/93FBB8/ND_T/HCS/ND_P/Main/DUPLICATIONSHIELDSYNC/6A6A6F/ND_B/HCS/PFActionId/hcs.common.RetrieveDocumentCommon/DocId/14810500/ContentSetId/58/SearchTerm/trisenox/SearchOption/BeginWith

113. Mazumder DN, Das Gupta J, Santra A, et al. Chronic arsenic toxicity in west Bengal: the worst calamity in the world. J Indian Med Assoc 1998;96(1):4-7,18

114. Au WY, Kumana CR, Kou M, et al. Oral arsenic trioxide in the treatment of relapsed acute promyelocytic leukemia. Blood 2003;102(1):407-8

115. Mathews V, Desire S, George B, et al. Hepatotoxicity profile of single agent arsenic trioxide in the treatment of newly diagnosed acute promyelocytic leukemia, its impact on clinical outcome and the effect of genetic polymorphisms on the incidence of hepatotoxicity. Leukemia 2006;20(5):881-3

116. Lazo G, Kantarjian H, Estey E, et al. Use of arsenic trioxide (As2O3) in the treatment of patients with acute promyelocytic leukemia: the MD. Anderson experience. Cancer 2003;97(9):2218-24

117. Au WY, Kwong YL. Frequent varicella zoster reactivation associated with therapeutic use of arsenic trioxide: portents of an old scourge. J Am Acad Dermatol 2005;53(5):890-2

118. Nouri K, Ricotti CA, JR, Bouzari N, et al. The incidence of recurrent herpes simplex and herpes zoster infection during treatment with arsenic trioxide. J Drugs Dermatol 2006;5(2):182-5

119. Patlolla AK, Tchounwou PB. Cytogenetic evaluation of arsenic trioxide toxicity in Sprague-Dawley rats. Mutation Res 2005;587(1-2):126-33

120. Au WY, Kumana CR, Lam CW, et al. Solid tumors subsequent to arsenic trioxide treatment for acute promyelocytic leukemia. Leukemia Res 2007;31(1):105-8

121. Verstovsek S, Estrov Z. Arsenic derivatives as therapeutic agents for hematologic malignancies. Leukemia Res 2004;28(9):901-3
- **A review of other forms of arsenic as therapeutic agents for hematologic malignancies.**

122. Lu DP, Qiu JY, Jiang B, et al. Tetra-arsenic tetra-sulfide for the treatment of acute promyelocytic leukemia: a pilot report. Blood 2002;99(9):3136-43

123. Wu T, Zhao J, Jiang B, et al. Tetra-arsenic tetra-sulfide containing triple-agent regimen as the first line therapy for acute promyelocytic leukemia: expeditiously consecutive complete remission and improved disease-free survival [abstract 591]. Blood 2007;110:182a

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