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REVIEW

Swallowing a bitter pill–oral arsenic trioxide for acute promyelocytic leukemia

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ABSTRACT

Parenteral arsenic trioxide (ATO) has been firmly established as a standard therapy for acute promyelocytic leukemia (APL). Despite widespread use of oral arsenicals in medicine historically, they had disappeared from modern pharmacopeia until oral ATO was redeveloped in Hong Kong in 2000. Since then, over 200 patients with leukemia (predominantly APL) have been treated with oral ATO in Hong Kong and China. Oral arsenic trioxide and other formulations of arsenic appear to have a clinical efficacy comparable to that of IV formulations. These drugs given orally also appear to have a slightly better safety profile, lower operational costs and improved convenience for patients. The clinical experience with oral ATO has previously been reported piecemeal as case series, pilot studies or subgroup analyses rather than in a comprehensive cohort. In this report we attempt to synthesize the published English language literature on oral arsenicals and present the argument for further development of these compounds. Systematic study of this drug with well-designed randomized multi-center clinical trials is needed to accelerate its development and incorporation into clinical practice.

1. Introduction

Arsenic has been used medicinally for over 2000 years. Arsenic trioxide (As_2O_3, ATO), an industrial by-product of the many derivatives of naturally occurring arsenic, was first used in the 15th century [1]. In the 1700s, Dr. Thomas Fowler in Edinburgh created a 1% As_2O_3 solution in potassium bicarbonate (1% potassium arsenite, $KAsO_2$), popularly called the 'Fowler's solution" which was used empirically for the treatment of several infectious and malignant illnesses. Fowler's solution was noted to have leuco-reductive properties at the Boston City Hospital, in Massachusetts in 1878 which led to its use for treatment of leukemia [1]. Until the 1950s, As_2O_3 was considered second only to radiation for the treatment of chronic myeloid leukemia (CML); its use declined with the advent of cytotoxic chemotherapies.

Aside from sparse medicinal uses, the re-birth of ATO in modern medicine is attributed to the Chinese, who incorporated it into the treatment of acute promyelocytic leukemia (APL) in the 1970s, resulting in 10-year survival in up to one-third of treated patients [2]. Multiple follow-up studies established the benefit of intravenous (IV) ATO as part of APL induction and consolidation regimens [3–5] and suggested efficacy in other forms of acute myeloid leukemia (AML) [6,7]. Since long-term IV ATO use is resource-demanding due to the requirement for careful management of electrolytes and prolonged IV infusions, oral ATO is an attractive alternative (Table 1). It is easier to administer, can potentially decrease hospital cost [8], and improves upon the cardiac toxicity profile associated with IV ATO [9]. Since its redevelopment in 2000, over 200 patients with leukemia (predominantly APL) have been treated with oral ATO in Hong Kong and China. However so far, their clinical experience has been reported piecemeal as case series, pilot studies or subgroup analyses rather than a comprehensive cohort. In this review, we summarize the literature on oral ATO published to date in the English language and comment on its emerging role in the management of hematologic malignancies [10].

2. Mechanism of action

ATO is known to exert anti-leukemic cytotoxicity through various cellular effects [11]. It can promote tumor formation [12], or induce apoptosis, based on its concentration. At low concentrations, it induces myeloid maturation in APL cells via degradation of the promyelocytic leukemia/retinoic acid receptor-alpha (PML/RARα) fusion protein [13,14]. ATO targets the PML moiety of the PML/RARa fusion protein for sumoylation, leading to its localization to the nuclear matrix and subsequent degradation after recruitment of the proteasome. As PML/RARα is a potent repressor of myeloid maturation, its degradation results in differentiation of APL cells to mature granulocytes. At higher concentrations, arsenic targets the mitochondria, inducing collapse of the transmembrane potential, increased permeability, release of cytochrome C and activation of caspase which down-regulates BCL2 and the telomerase

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gene, inducing apoptosis [13]. Other cellular effects include activation of mitogen-activated protein kinases (MAPK) [15–17], and src-related kinases [15], as well as inhibition of Janus activated kinase (JAK) and signal transducer and activator of transcription (STAT) pathways [18,19]. Concentrations of arsenic ranging from 1 to 4 μM reduced STAT3 activation induced by JAKs in a dose-dependent manner, decreased JAK2 activation in the JAK^{V617F} expressing human erythroleukemia cell line (HEL) and induced cell death [19].

PML–RARα oncoprotein has been demonstrated to support leukemia initiating cell (LIC) self-renewal in vivo, providing a reservoir for relapse [20]. Arsenic has been shown to synergize with all-trans retinoic acid (ATRA) in eliminating LICs by enhancing catabolism of the PML–RARα fusion protein, hence leading to LIC eradication and long-term remission in mouse models of APL [21]. This activity against the LIC compartment may explain the marked clinical activity and low relapse rates observed with chemotherapy sparing differentiation therapy combining arsenic and ATRA [5,22].

3. Pharmacokinetics and development

Despite being used for centuries, no oral ATO formulation was available for clinical use until 2000 when Kumana and colleagues at the University of Hong Kong re-developed the drug for treatment of relapsed AML/APL [23]. Since pharmaceutical grade As_2O_3 was not available, the investigators suspended commercially available As_2O_3 (Sigma Chemical Company, St. Louis, Missouri, USA, minimum purity 99%) in water (500 mg aliquots of As_2O_3 powder in 150 ml sterile water) and solubilized the resulting As_2O_3 suspension drop-wise in 3 M sodium hydroxide, exploiting the alkaline solubility of arsenicals. When the powder was completely dissolved, further 250 ml sterile water was added, and the ensuing solution was adjusted to pH 8.0 by slow titration with 6 M hydrochloric acid (HCl). Subsequent adjustment of the pH to 7.2 was carried out with dilute HCl and sterile water to make up a final volume of 500 ml. The final product had an As_2O_3 concentration of 1 mg/ml and was adjusted to a neutral pH. The entire process was conducted in a pharmaceutical isolator without the addition of fungicidal agents. The shelf life of this oral formulation was determined to be at least 3 months.

In an initial pharmacokinetic study of this agent, oral ATO was administered to nine patients with refractory/relapsed AML or relapsed APL. This study was the first to demonstrate that oral ATO was more convenient, well tolerated, and exhibited similar systemic bioavailability as the IV formulation in humans [23]. Each patient was given 10 mg of IV ATO on the first day of treatment, followed by 10 mg of oral ATO on subsequent days. The oral drug was very well absorbed, with a rapid increase of elemental arsenic occurring within the first hour of administration. The AUC attributed to the oral dosing on day 2 was 99% in plasma and 87% in blood (compared to AUC due to IV dose on day 1). Concentrations of ATO after 48 h in the cellular fraction of blood were consistently higher (by about two- to three-fold) than the corresponding plasma concentrations in all but one patient. This individual had received interim blood transfusions which may have confounded the result. The peak plasma arsenic levels following oral ATO were lower (0.2–0.6 μmol/l) than the equivalent dose of intravenous ATO (0.5–2 μmol/l). However, oral ATO resulted in gradual intestinal absorption, producing a higher sustained plasma arsenic ATO level than that seen with IV administration. In fact, the total area under the curve (AUC) of drug exposure was effectively comparable between the intravenous and oral formulations, implying a similar degree of bioavailability between the two routes of administration. Oral ATO was predominantly excreted by the kidney.

Although intra-patient drug level variability was minimal, significant inter-patient variations in drug levels were noted with oral administration. ATO is metabolized by the liver into less active pentavalent metabolites. The assay used in this study measured total arsenic levels, which included all metabolites so first pass should not make a difference. Possible explanations for the observed inter-patient variability in drug levels could be problems with arsenic dosing or drug measurement levels, differences in volume of distribution among patients, dietary indiscretion by individual patients (consumption of seafood which may contain arsenic) and drug interactions [23].

Firkin and colleagues from Australia similarly prepared pharmaceutical grade ATO at a concentration of 1 mg/ml by obtaining As_2O_3 from Sigma Chemical Company, dissolving it in 1 mol/l sodium hydroxide (NaOH), and then adjusting the pH to 7.0 with 1 mol/l HCl [8]. Oral ATO 5 mg twice daily was substituted for IV ATO 10 mg daily for consolidation in five patients with APL (5 in CR1 and 1 in CR2) and for induction in two patients with accelerated phase chronic myeloid leukemia (APCML). Blood arsenic levels were monitored during oral and IV administration, and compared with levels drawn immediately prior to the first dose of the drug (nadir levels). Similar steady state arsenic concentrations were reached following both oral and IV dosing. Significant overlap was noted in three patients who received 10 mg per day of ATO by both routes with median values following IV versus oral ATO administration of 0.8 and 0.6, 1.0 and 1.3 and 2.0 and 2.6 μM, respectively in these patients. The rate of elimination of ATO from blood after oral or IV administration was the same at comparable steady state arsenic levels. Median blood arsenic levels in APL patients receiving oral ATO of 5 mg twice daily ranged from 0.6 to 2.6 μM. No tendency towards arsenic accumulation in blood was noted during continuous oral administration for up to 56 days. The authors of this study concluded that the pharmacokinetics of oral ATO were similar to IV ATO. Moreover, the oral formulation was well tolerated, with improved patient compliance due to the convenience [8].

To evaluate for possible accumulation of elemental arsenic after prolonged ATO therapy, Au et al. measured elemental arsenic levels in the plasma, white blood cell (WBC) and red blood cell (RBC) compartments of 26 APL patients and compared them with 12 controls [24]. Specimens were collected at 1 month (group 1), 2–12 months (group 2) and 24–41 months (group 3) after cessation of oral ATO treatment. The median cumulative dose of oral ATO was 1980 (560–3680 mg). Elemental arsenic levels in groups 2 and 3 i.e. after 2 months of cessation of oral ATO therapy were comparable to controls indicating that prolonged courses of ATO maintenance did not result in long-term arsenic accumulation.

Table 1
Comparison between oral and intravenous arsenic trioxide (ATO).

Advantages	Disadvantages
Ease of administration — no requirement for long-term iv access, outpatient management, quality of life	Uncertain compliance
Similar pharmacokinetics as IV formulation	Lack of data on effect of food and drug interactions on bioavailability
Decreased risk of infection (CLABSI)	No head-to-head comparison of efficacy with iv formulation
More economical/substantially decreased operational expenses	Paucity of clinical experience with oral ATO use
Improved cardiac toxicity profile	
Better tolerated in patients with renal insufficiency	

CLABSI- Central line associated blood stream infection.

4. Clinical efficacy

Oral ATO has never been compared head-to-head with the intravenous formulation in terms of efficacy. Although the initial study by Kumana et al. comparing oral to IV ATO showed that the pharmacokinetics of oral ATO were similar to those of the IV formulation, this comparison was not designed to assess efficacy. In this section, we summarize the studies utilizing oral ATO reported in the English language (Table 2). Further published data pertaining to oral ATO in the Chinese language alluded to in several reports were not available for review.