On arsenic trioxide in the clinical treatment of acute promyelocytic leukemia

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ABSTRACT

Arsenic is generally considered hypertoxic. However, it has been used in traditional Chinese medicine since ancient times, to treat serious illnesses. Recently, a single dose of arsenic trioxide (As_2O_3) has been found especially effective in treating acute promyelocytic leukemia (APL). Generally speaking, As_2O_3 is a more effective treatment of APL than other, newer medications and has less severe adverse reactions and greater safety.

Arsenic is widely dispersed throughout nature, and its toxic effect in humans, which focus mainly on somatic cells, as well known. Epidemiological research and in vitro testing have shown that long-term contact with arsenic can induce the formation of various neoplasms via cellular aberration or mutation, either directly or synergistically with other carcinogenic factors [1]. Despite arsenic's hypertoxicity, it is necessary for growth and reproduction in humans and lower animals [2], and it has been used as a traditional Chinese medicine to treat of serious illness [3]. Even in Western countries, arsenic has long been included in the medical armamentarium for the treatment of. tumors [4]. Since the first report published in 1995 on the clinical outcome and mechanisms of arsenic trioxide (As_2O_3) given as a single dose for the treatment of acute promyelocytic leukemia (APL) [5].

1. Indications for an As_2O_3 regimen

The following are clinical situations in which the use of an As_2O_3 regimen may be indicated [6–9]: 1) Previously untreated (or newly diagnosed) APL especially in patients who are positive for t(15;17) or the PML/RARα/PML-fusion gene, a key feature in more than 90% of such patients; 2) APL that is refractory to all-trans retinoic acid (RA) or combined chemotherapy, recurrent disease, or relapsed after bone marrow transplantation; 3) APL in patients for whom RA and combined chemotherapy are intolerable or inadvisable; 4) Maintenance treatment after CR from APL; and 5) CGL and certain acute nonlymphocytic leukemia subtypes as well as those with myelodysplastic syndromes (MDS), if these are accompanied by an excessive increase in the number of promyelocytes.

As_2O_3 treatment is not suitable for a first choice for some APL patients, such as positivity for either t(11;17),t(5;17) or for the PLZF/RARα fusion gene, moderate to severe liver or kidney dysfunction caused by conditions other than leukemia, relapse during continuous As_2O_3 maintenance treatment or long-term arsenic exposure [8,9].

2. Methods of treatment

2.1. Induction of remission

In adults with APL, a daily injection of 10 ml of As_2O_3 (1 g/L) is administered after over in 250–500 ml of glucose solution (50 g/L) or normal saline for intravenous over during 3–4 h. In children with APL, the daily dose is 6 mg/m^2 (approximately 0.16 mg/kg). The single treatment course spans 4 weeks, sometimes with a 5- to 7-day break at the midpoint.

Peripheral hyperleukocytosis (HLT) can be prevented by administering oral hydroxyurea (1.0–8.0 g/d in divided doses), or a small dose of homoharringtonine cytarabine, or both (by intravenous drip) when the white blood cell (WBC) count $\geq 10 \times 10^9$/L before treatment or after As_2O_3 treatment [7,9] fatal bleeding may be contraled by infusion of activated factor 7 (novoseven) which stopped hemorrhage [10].

2.2. Treatment after remission

The amount and type of consolidation therapy necessary for an individual APL patient may remain something of an open question and require risk-adapted protocols. In general, the author treats patients after remission in the following ways.

2.2.1. Consolidation treatment with As_2O_3

The routine dose of As_2O_3 is used for 2–3 weeks in a treatment course, with break of 1 month between courses in the first year, 2 months in the second year, 3–4 months in the third year, and 6 months after 3 years.

2.2.2. Use of As_2O_3 and chemotherapy alternatively

HA, DA, or Ara-C plus mitoxantrone or etoposide or another similar drug are used in rotation, with break between courses as described for the consolidation treatment. In consolidation treatment, Ara-C 1.0 g/day × x3 can be added to increase efficacy.

Because As_2O_3 is far less effective than conventional chemotherapy. for inhibiting APL cell proliferation, the author recommends the alternating use of As_2O_3 and conventional chemotherapy in patients after remission [9].

3. Pharmacokinetics of As_2O_3

Shen et al. [11]. administered As_2O_3 intravenously at a dose of 10 mg/day for the treatment of 8 patients with relapsed APL. The arsenic content was measured by gas-phase chromatography. The maximal plasma concentration was 0.94 ± 0.37 mg/L, the time to peak concentration was 4 h, the plasma distribution half-time was 0.89 ± 0.29 h, the elimination half-time was 12.13 ± 3.31 h, the a apparent distribution volume was 3.83 ± 0.45 L, the system clearance was 1.43 ± 0.17 L/h, and the area under the curve was 7.25 ± 0.97 L/h. The continuous administration of As_2O_3 did not alter its pharmacokinetic behavior. During As_2O_3 treatment, the 24-h arsenic content in urine accounted for 1–8% of the daily dose. The arsenic accumulation in the hair and nails increased continuously, with a peak concentration rose 5- to 7-fold higher than pretreatment levels. Importantly, the arsenic content of urine, hair, and nails declined gradually after drug withdrawal. No bone marrow suppression or severe organ impairment were observed. The researchers concluded that As_2O_3 is a relatively safe and effective for the treatment of patients with relapsed APL, despite the arsenic accumulation in some tissues.

Hu et al. [12]. found that arsenic content in the cerebrospinal fluid was 4.8 ± 0.4 μg/L in 40 healthy people, comparatively, the content in patients before and 12 h after treatment with a routine dose of As_2O_3 was 4.8 ± 0.3 μg/L and 5.2 ± 0.1 μg/L, respectively. Similarly, in 46 patients with APL, no significant difference was found between these groups (p > 0.05). However, 12 h after treatment, the arsenic content in peripheral blood (30.0 ± 5.0 μg/L) was significantly higher than that of cerebrospinal fluid (p < 0.01), suggesting that it is inadvisable to use intravenous As_2O_3 therapy for patients with central nervous system (CNS) leukemia.

4. A Retrospective study of As_2O_3 therapy for APL: efficacy and course

4.1. Study group

The comparative effectiveness of As_2O_3 therapy was evaluated in 242 patients with APL treated at HMU Hospital. The patients were divided into 4 groups, (Table 1). The response rates for previously untreated children and adults are listed in Table 2, and the average number of treatment days and total As_2O_3 doses used to achieve CR in each of the four groups are listed in Table 3 [8,9].

In our review of reports from other hospitals in China, CR was 89.7% (183/204) in patients with previously untreated (or newly diagnosed) APL, and 84.2% (287/341) in patients with relapsed APL after induction RA, chemotherapy, or both, or during maintenance therapy [11,13]. Camacho et al. [14] used As_2O_3 for remission induction in 26 patients with relapsed or refractory APL at daily doses that ranged from 0.06 to 0.17 mg/kg, and 23 patients (88.5%) achieved CR. Elsewhere. 12 patients with APL that had relapsed after extensive

Table 1
Curative effects of As_2O_3 in 242 patients.

Patients	N	CR (%)	PR (%)	NR (%)
PU Group	124	109(87.9)	8(6.5)	7(5.6)
Relapse Group A	20	12(60.0)	1(5.0)	7(35.0)
Relapse Group B	59	41(69.5)	9(15.3)	9(15.3)
Refractory Group	39	19(48.7)	6(15.4)	14(35.9)
Total	**242**	**181(74.8)**	**24(9.9)**	**37(15.3)**

Group A: Relapsed APL treated with As_2O_3 as post-CR consolidation treatment
Group B: Relapsed APL treated with chemotherapeutic or other medicines as post-CR consolidation treatment.
*PU = previously untreated; CR = complete remission; PR = partial remission; NR = no remission.

Table 2
Comparison of curative effects between children and adults in PU Group.

Patients	N	CR (%)	PR (%)	NR (%)
Children Group	23	16(69.6)	4(17.4)	3(13.0)
Adult Group	101	93(92.1)	4(4.0)	4(4.0)
P Value	< 0.01	< 0.05	> 0.05	

Table 3
Days to achieve CR and the total dose of As_2O_3 used.

Patients	N	Days to Achieve CR X ± SD	Total Dose of As_2O_3 used (mg) X ± SD
PU Group	93	30.26 ± 7.4	302.6 ± 74
Relapse Group A	12	37.65 ± 22.2	376.5 ± 222
Relapse Group B	41	32.08 ± 10.26	320.8 ± 102.6
Refractory Group	19	31.22 ± 17.99	31.22 ± 17.99

prior therapy were treated with As_2O_3, and 11 of them had CR. Eight of 11 patients who were initially found to be positive for the PML/RARα-fusion transcript by the a reverse transcriptase polymerase chain reaction(RT-PCR) assay later tested negative; 3 other patients who persistently tested positive had early relapses [15]. Shigeno et al. [16] used As_2O_3 to treat 34 patients whose disease had relapsed, or had become refractory to RA and conventional chemotherapy , and 31 (91.2%) had CR.Eighteen of 25 patients who achieved CR also lost the previously evident PML/RARα-fusion transcript, as shown by RT-PCR assay. Additionally, 10(90.9%) of 11 children with hypergranular type of APL achieved hematological remission after a mean duration of 48 days with all 10 patients achieving molecular remission after a median duration of 81days [17]. Ghavamzadeh et al. [10] reported that CR were achieved in 82 (86.3%) patients of 94 new cases of APL, and in 13(76.5%) of 17 patients with relapse APL by As_2O_3 treatment. 44cases of 48patients who were hematological remission found to be negative for the PML/RAR α-fusion transcript; 3 cases of 4 other patients who tested positive had relapse in clinical expressions after persistent CR for one year. Recently, Mathews et al. [18] observed that 62(86.1%)of 72 patients with newly diagnosed cases of APL achieved hematologic CR after As_2O_3 treatment. RT-PCR analysis for the PML/RARα-fusion transcript was available in 54 patients, and 11cases(20.4%) were negative at the end of induction. Of the 43 who were positive 30(69.8%) became negative after a drug-free interval 4 weeks. Shen et al. [19] reported on a low-dose (0.08 mg/kg d^{-1}, for 28 days) As_2O_3 treatment for relapsed APL. Of 20 patients treated, 16 (80.0%) achieved CR. The estimated 2-year OS and relapse-free survival were $61.6 \pm 15.8\%$ and 49.1 ± 15. 1%, respectively, and there was no difference compared with those values in patients treated with a conventional dose. The authors concluded that low-dose As_2O_3 had the same effect as the conventional dose, and the mechanism of low-dose arsenic seemed to be, primarily, the induction of differentiation in APL cells.

4.2. Relapse

In our series of 86 APL patients who were on post-CR maintenance treatment with As$_2$O$_3$, 5 (5.8%) had relapses within 1 year after CR,12(14.0%)within 2 years, and 23(26.7%) within 3years (range, of 5–37 months, average of 25.4 ± 12.9 months). The relapse rate within 3 years of CR was significantly higher in male patients (33.3%) than in females (13.8%) [9]. A test positive for the PML/RAR α-fusion transcript is a best method to judge CR patients with APL to be relapse in the near future.

4.3. Overall survival

Of 136 patients followed up after As$_2$O$_3$ treatment at HMU Hospital, 11 died within 5 years and 125 have lived for 5 or more years (i.e., a 5-year overall survival[OS] of 91.9%) [8,9].

5. Factors related to therapeutic effectiveness

Therapeutic effectiveness and prognosis have a positive correlation with the band-cell count of peripheral WBC, hemoglobin content, platelet count, and bone marrow normoblast count. We found a negative correlation with WBC count, peripheral juvenile blood cell count, myeloproliferation degree, and lactic dehydrogenase (LDH) activity [8,9].

6. Drug resistance

In clinical practice, there is no cross–drug-resistance between As$_2$O$_3$ and RA or other antileukemic agents. This may be explained by the non-liposoluble nature of As$_2$O$_3$, its small molecular weight, and its distinctive modes of action [20]. In our observation, primary As$_2$O$_3$ resistance was found in 35.9% of refractory patients, 15.3% of patients whose disease relapsed after nonarsenic induction and consolidation, and in 5.7% of newly diagnosed APL patients; the rate of acquired resistance to As$_2$O$_3$ was 26.7% (23/86). In the latter instance, an increased dose of As$_2$O$_3$ enabled more than half of resistant patients to regain CR, presumably through overcoming an "inertia" in arsenic receptor or signaling pathways [9]. Geng et al. [21] found cross–drug-resistance between As$_2$O$_3$ and cisplatin. An increased As$_2$O$_3$ dose or action time resulted in a decrease of multidrug resistance protein expression and reversed the resistance.

7. Toxicity and side effects

7.1. Hyperleukocytosis

Of 242 APL patients studied, hyperleukocytosis (HLS) occurred in 183 (75.6%). Most of the increased WBC count consisted of transitional cells (i.e., those between abnormal promyelocytes and myelocytes and fairly mature granulocytes) [8], these result from As$_2$O$_3$ induced differentiation of APL cells [20,22]. Of the 242 patients, 2 developed hydrothorax and ascites, with a WBC count of 198.5×10^9/L in one, and 123.0×10^9/L in the other. Four other patients in this group had significantly elevated aspartate aminotransferase (AST) and alanine aminotransferase levels(ALT); 2 had elevated blood urea nitrogen, and 3 had peripheral WBC counts $\geq 50\times10^9$/L [9]. Chen et al. [23] observed that 1 APL patient developed RA syndrome and an apparently related HLS during As$_2$O$_3$ treatment for relapse, after an RA-induced CR. Roberts et al. [24] observed that a patient with relapsed APL manifested a markedly increased WBC count and CNS infarction relative to HLS during induction therapy with As$_2$O$_3$. Moreover, after As$_2$O$_3$ treatment for APL, HLS with a WBC count $\geq 10\times10^9$/L occurred in 58.1% (25/43) of patients with relapsed [20] and in 74.1% (43/58) of those with newly diagnosed disease [25]. Of 26 patients with relapsed or refractory APL who were treated with As$_2$O$_3$ to induce

remission, 15 (57.7%) showed HLS, which resolved in all cases without the use of other cytotoxic therapy [14]. In studies by other investigators, HLS occurred in 58.6–100% of APL patients treated with As$_2$O$_3$ [10,13,26]. In our observation, HLS $\geq 50\times10^9$/L influenced the treatment of disseminated intravascular coagulation [9].

During a single dose of As$_2$O$_3$ treatment, a few patients with APL occurred APL differentiation syndrome(APLDS) because excessive HLS plus patient's constitution factors. APLDS(ATRA syndrome be longs also to APLDS) usually maifestde as palpitation, chest depression, accelerated respiration, edema of the whole body hydrothorax, ascites, hydropericarditis and even respiratory distress or fate terminated in pulmonary hemorrhage and respiratory failure. Control HlS is emphasis on the prevention of APLDS development by plus chemotherapy when WBC count is on the increase, near 10×10^9/L.The treatment of APLDS may use higher dose of dexamethosone plus chemotherapy and the treatment of some symptoms after As$_2$O$_3$ stopped.

7.2. Myelosuppression and changes in red cells

We found mild and transient myelosuppression in 2 children and 1 adult who were given a larger-than-usual dose of As$_2$O$_3$ [9,20]. Of the 242 patients who received conventional treatment, 15 (6.2%) after a mean 18.4 days, depressed hemogram and myelogram readings, including decreases in bone marrow karyocytes, peripheral leukopenia (with the lowest count of 0.2×10^9/L in some cases), and less significant oligochromemia and thrombocytopenia. The inhibition resolved after a mean 21.4 days, generally without requiring drug withdrawal and with only occasionally use of granulocyte colony-stimulating or granalocyte-macrophage colony-stimulating factor. The red cells from bone marrow had abnormalities such as binuclear early erythroblasts, megaloblasts, petal-shaped nuclei, Howell-Jolly bodies, basophilic stippled erythrocytes, karyokinesis, and irregular-sized mature red cells [9].

7.3. Other adverse events

As$_2$O$_3$ generally causes less severe adverse reactions (e.g; hemorrhage), and is considered comparatively safe for the treatment of APL. In the 242 patients described above, other adverse events, in order of frequency, included gastrointestinal such as, anorexia, abdominal discomfort, nausea, vomiting, diarrhea(24.0%); skin lesions, such as xerosis cutis, pigmentation, erythema(22.7%); changes of liver function (14.1%): elevated AST, ALT, alkaline phosphatase, gamma-glutamy1 transpeptidase and blood bilirubin. Infrequent manifestations included facial and limb edema, ulcerative stomatitis, headache, changes in cardiac activity (e,g;sinus tachycardia and changes in the ST segment and T wave on electrocardiogrophy), prolongation of the partial remission interval, toothache, hydrothorax, ascites, elevation of blood urea nitrogen, nosebleed, gingival bleeding, persecution complex, and agnosia [9]. Rust and Soignet [27] reported that a multicenter trial in the United States of As$_2$O$_3$ in 40 patients with APL that relapsed after conventional therapy, confirmed the positive safety and efficacy findings from of a smaller 12-patient pilot study. Common adverse events included HLS, APL differentiation syndrome, a prolonged QT interval on electrocardiography, skin rash, and hyperglycemia. The occurrence of some toxic events including gastrointestinal disturbance, facial edema, and cardiac toxicity seemed less severe in the group given low-dose As$_2$O$_3$, than in the standard-dose group [16].

As of July 2002, in clinical trials with Trisenox, an intravenous formulation of As$_2$O$_3$, 522 patients (224 with APL, 298 with other hematologic malignancies) have been treated in the United states and the Europe. The adverse events noted in postmarketing use of As$_2$O$_3$ are generally similar to those observed in clinical trials, and no deaths due to As$_2$O$_3$ related cardiac arrhythmia have been reported. This experience appears to confirm that As$_2$O$_3$ is generally well tolerated and that the observed adverse effects are manageable and reversible [28]. However, when 7 patients with refractory or relapsed APL were treated

with As$_2$O$_3$, 6 noted water retention (shown by weight gain, pleural and pericardial exudates); 2 of 3 patients on As$_2$O$_3$ maintenance therapy showed polyneuropathy related to chronic arsenic poisoning, and 1 of those 2 patients suffered myoatrophy of a limb end [29]. Individual differences in the response of APL patients to As$_2$O$_3$ treatment are related to the amount of arsenic accumulation, detoxification and excretion, susceptibility and tolerance, or distinctive interactions between the patient's physical condition and the toxic effects of arsenic [9]. Although arsenic, in consideration of its proposed mutagenicity, is suspected of having the capacity to induce a second tumor, few relevant clinical reports exist.

8. As$_2$O$_3$ and RA: modes of action and combined use

As$_2$O$_3$ treatment was recently proposed as an alternative therapy for APL, because it can induce CR in patients with either RA-sensitive or RA-resistant APL. Intriguingly, As$_2$O$_3$ was also induced degradation of PML/RARα chimeras and to reorganize PML nuclear bodies (PML-NBs) [30]. In APL patients, RA triggers differentiation, whereas As$_2$O$_3$ induces both a partial differentiation and apoptosis. Although their mechanisms of action are believed to be distinct, both drugs induce catabolism of the oncogenic PML/RARα-fusion protein. Although APL cell lines resistant to one of these agents are sensitive to the other, the benefit of combining RA and arsenic in cell culture remains controversial. Shao et al. [31] believe that As$_2$O$_3$ and RA inhibit each other ' s therapeutic effects.

Lallemand et al. [32] used syngeneic grafts of leukemic blasts from PML/RARα transgenic rats as a model for APL to establish that RA and As$_2$O$_3$ act synergistically in vivo, and encouraged using this combination for APL patients. This exemplifies how murine models of human leukemia can be used to design or optimize therapies. RA and As$_2$O$_3$ together also prolonged the survival of recipients mare than did either drug alone. In contrast, neither in promyelocytic zinc finger protein (PLZF)-RARα transgenic rats nor in nude rats that received transplanted of PML/RARα cells did any of the 3 regimens induce CR [33]. However, in a clinical trial, RA combined with As$_2$O$_3$ for de novo APL treatment, achieved CR in 29/31 (93.5%) patients. The PML/RARα-fusion gene that was positive in all 29 patients before treatment turned negative in only 3 of them (10.3%) by the time of CR, and 10/13 patients (76.9%) who were PML/RARα positive became negative after the consolidation treatment. However, the results were not significant compared with those for As$_2$O$_3$ and RA usage or chemotherapy at a single dosage to treat APL [34]. In the author ' s clinical practice, single-agent As$_2$O$_3$ or RA administration, rather than the combination, is used for induction therapy in newly diagnosed APL cases to prevent a possible aggravation of APLDS, or other adverse events. Nevertheless, As$_2$O$_3$ and RA in combination has been adopted in some instances involving refractory or resistant disease or multiple relapses. Clearly, both drugs are highly effective; they do not cause cross–drug-resistance, and they share the same principal mode of action, specifically the induction of differentiation [35].

Conflict of interest

The authors declared that they have no conflicts of interest to this work. I declare that I do not have any commercial or associative interest that represents a conflict of interest in connection with the work submitted.

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