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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.

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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 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 ± 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.

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