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Studies on the clinical efficacy and pharmacokinetics of low-dose arsenic trioxide in the treatment of relapsed acute promyelocytic leukemia: a comparison with conventional dosage

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Twenty cases of patients with relapsed acute promyelocytic leukemia (APL) were entered into this study for evaluating the clinical efficacy and pharmacokinetics of low-dose arsenic trioxide (As_2O_3). As_2O_3 was given at a daily dose of 0.08 mg/kg intravenously for 28 days. Pharmacokinetic study was carried out in eight patients. 16/20 (80%) patients achieved CR. The occurrence of some toxic events including gastrointestinal disturbance, facial edema and cardiac toxicity seemed reduced in the low-dose group than those in the standard-dose group. Differentiation changes were observed in peripheral blood, as well as in bone marrow (BM). Pharmacokinetic study showed that the plasma concentration increased soon after administration of As_2O_3 with the peak values of 1.535–3.424 μmol/l. After infusion, the plasma concentration was around 0.1–0.5 μmol/l. The arsenic concentration of the plasma of BM aspirates 24 h after administration in five patients was close to the level needed for differentiation-inducing effect. The estimated 2-year OS and RFS were 61.55 ± 15.79% and 49.11 ± 15.09% respectively, with no difference as compared with those in patients treated with conventional dose (P = 0.2865 and 0.7146, respectively). In conclusion, we demonstrated that low-dose As_2O_3 had the same effect as the conventional dosage and the mechanism of low-dose arsenic seemed to primarily induce differentiation of APL cells. *Leukemia* (2001) **15,** 735–741.
Keywords: acute promyelocytic leukemia; arsenic trioxide; pharmacokinetics; survival; differentiation; apoptosis

Introduction

Acute promyelocytic leukemia (APL) is a special subtype of acute myeloid leukemia (AML), with the characteristic chromosomal translocation t(15;17), leading to the formation of PML-RARα fusion gene and its related protein.[1–3] The clinical efficacy of As_2O_3 in APL was confirmed by several centers, with the CR rate varying from 63.8% to 93%.[4–8]

Although As_2O_3 is effective in the treatment of APL, it is a toxic agent known for centuries. Severe toxic events associated with the arsenic therapy such as impairment of liver function and cardiac toxicity were reported. How to minimize the side-effects deserves further study. As we have previously reported, As_2O_3 exerts dual effect on APL cells: induction of apoptosis (1–2 μmol/l); and differentiation (0.1–0.5 μmol/l).[9,10] The conventional dose (0.16 mg/kg) can reach a peak concentration of 6–8 μmol/l in the plasma[4] which exceeds two- to three-fold the level for inducing apoptosis. The purpose of this study is to evaluate clinical efficacy and toxic effect with a reduced dose to 0.08 mg/kg/day, 50% of the conventional dosage (0.16 mg/kg/day).

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Patients and methods

Patients

Twenty cases of relapsed APL (first relapse, R1) were entered into this study in our institute from 1997 to 1999. The diagnosis was established according to the FAB criteria. All patients had good performance status (ECOG <3), and had no arsenic pretreatment. Nineteen patients were found to have chromosomal translocation t(15;17) and/or PML-RARα expression. The twentieth patient was t(15;17) and PML-RARα-negative. No complex karyotype was observed in this group. The clinical data of the patients are summarized in Table 1. The control group consisted of hospitalized relapsed APL patients during 1994–1998, including 43 in R1, two in R2 and two in R3. They received conventional doses of As_2O_3. Among them, karyotyping was performed successfully in 22 patients at diagnosis of relapse. 19/22 were proved to have t(15;17), while three patients had normal karyotype. In addition, a complex karyotype, 46,XY, t(5;15)(q14;q22), t(15;17)(q22;q11-21), ins(16;17)(p11p12;q?), was observed in a patient at the diagnosis of relapse, which is confirmed by dual-color painting with WCP probes for chromosome 5, 15, 16 and 17. Twenty-seven out of 29 cases examined showed a positive RT-PCR result for PML-RARα. One patient was PML-RARα-negative and the other was proved to be AML1-ETO-positive at the time of relapse. They received ATRA during the disease presenting and achieved first remission.

Therapy

Low-dose group: As_2O_3 solution was prepared by the Pharmacy of Traditional Chinese Medicine in the First Hospital affiliated to Harbin Medical University of China. As_2O_3 0.08 mg/kg was diluted into 5% glucose-normal saline solution for intravenous drip over 2 h per day, for successive 28 days. If necessary, a second course was carried out after an interval of 14 days. The patients failed to reach CR after two courses were considered as non-responders and were treated with chemotherapy.

Conventional dose group: The regimen for the control group was to administer As_2O_3 with a daily dose of 0.16 mg/kg and each course lasted for almost 6 weeks.

Laboratory examination

Total blood cell count (every other day), bone marrow cytology (every 2 weeks), hepatorenal functions (every week) were performed during As_2O_3 therapy. Hydroxyurea (HU) or

Table 1 Patients' clinical data at diagnosis

Patient No.	*Age/Sex*	*WBC (10^9)*	*Platelet (10^9)*	*Hb (g/l)*	*APL cell % in BM*	*t(15;17)/PML-RARα*	*CR induction*	*Maintenance therapy*
1	M/21	3.4	70	142	71.5	t(15;17)/PML-RARα+	ATRA+CT	ATRA+CT
2	M/34	11.6	46	104	81	PML-RARα+	ATRA+CT	CT
3	F/53	1.2	45	118	54	t(15;17)/PML-RARα+	ATRA+CT	ATRA+CT
4	M/34	1.3	45	56	51.5	t(15;17)+	ATRA+CT	CT
5	M/20	46.2	16	142	91.5	PML-RARα+	ATRA+CT	ATRA+CT
6	M/28	1.1	46	98	84.5	t(15;17)/PML-RARα+	ATRA+CT	ATRA+CT
7	F/31	5.5	27	78	39	t(15;17)+	ATRA+CT	ATRA+CT
8	M/37	83.6	26	111	32	t(15;17)+	ATRA+CT	ATRA+CT
9	F/51	1.9	12	71	52	t(15;17)–/PML-RARα+	ATRA+CT	ATRA+CT
10	M/41	3.7	81	110	22.5	t(15;17)+	ATRA+CT	ATRA+CT
11	F/55	1.4	46	131	64.5	t(15;17)+	ATRA+CT	ATRA+CT
12	M/24	5.8	23	105	40.5	t(15;17)+	ATRA+CT	ATRA+CT
13	M/34	3.3	17	130	76.5	t(15;17)/PML-RARα+	ATRA+CT	ATRA+CT
14	F/28	1.3	48	62	73	t(15;17)/PML-RARα+	ATRA+CT	ATRA+CT
15	F/45	1.1	110	104	85.5	t(15;17)/PML-RARα+	ATRA+CT	ATRA+CT
16	M/18	4.4	172	180	14.5	t(15;17)/PML-RARα+	CT	CT
17	M/36	3.4	13	83	18	t(15;17)/PML-RARα+	ATRA+CT	ATRA+CT
18	F/23	3.4	45	125	40	t(15;17)+	ATRA+CT	ATRA+CT
19	M/6	6.0	76	58	75	PML-RARα+	ATRA+CT	CT
20	M/7	5.1	186	96	19.5	—	ATRA+CT	CT

CT, chemotherapy; +, positive; –, negative.

low-dose combined chemotherapy was given when hyperleukocytosis (WBC $\geqslant 10 \times 10^9$/l) occurred before or during arsenic treatment. G(M)-CSF (150–300 μg/day) was given if there was neutropenia.

Coagulation parameters, including plasma fibrinogen, D-dimers, fibrin degradation product (FDP), prothrombin time (PT), and activated partial thromboplastin time (APTT) were performed every week. Coagulopathy was corrected with platelet and fresh plasma transfusion; low-dose heparin was administered in the cases with obvious biochemical DIC.

Toxicity grading was established according to NCI criteria. As_2O_3 was withdrawn permanently when it exceeds degree III.

Pharmacokinetic studies

Plasma pharmacokinetics studies were performed in eight patients. The blood samples were collected into heparinized tubes during the first day of arsenic therapy, at 0 and 0.5, 1, 2, 3, 4, 6, 8, 12, 24 h after infusion. In five patients bone marrow aspiration was performed at day 14. The concentration of arsenic in supernatant plasma of peripheral blood and BM was measured with Gas-phase chromatography (GC-14B), ^{63}Ni ECD monitor according to the method as we previously reported.[1]

Pharmacokinetic parameters were calculated with software SP97 authorized by the Ministry of Public Health (MOPH) of China.

Definition of outcome

Complete remission (CR) was defined as followed: No APL clinical symptoms; untransfused hemoglobin greater than 100 g/dl, WBC greater than 1.5×10^9/l, platelet greater than 100×10^9/l; BM normocellular or moderately hypocellular less than 5% promyelocytes, and absence of leukemia cell or cytoplasmic Auer rods.

Observation of toxicity

Toxic effects were examined both clinically and paraclinically.[4,11] Hepatorenal function and ECG were assayed once a week.

Follow-up

After CR was achieved, all the patients were treated with continuation and consolidation therapy. The consolidation regimen mainly consisted of DA chemotherapy, but the dose and courses varied in different patients. The impact of continuation and consolidation therapy on the survival is not included in this study. The terminal line of follow-up was 31 May 2000.

Relapse-free survival (RFS) and overall survival (OS) was defined as the duration from complete remission to relapse or censored and death from any causes or censored, respectively (Figures 1 and 2). They were calculated from the day the patients achieved a second remission.

Statistical analysis

All the data in this study were analyzed by STAT 8.0 for windows and SAS 6.12 for windows software.

Results

Clinical response

Low-dose group: Sixteen of 20 (80%) reached CR after one course. Two of 20 died from intracranial hemorrhage due to thrombocytopenia during the early phase of therapy, at day 3 and day 8, respectively (cases 8 and 11). Two patients did not respond to arsenic treatment after two courses of therapy.

Between them, one was PML-RARα and t(15;17)-negative at the time of relapse (but he was proved to be PML-RARα-positive at initial disease presentation). The median dosage of As_2O_3 to reach CR was 140 mg. We observed the dynamic change of peripheral blood cell count. Hyperleukocytosis developed in eight of 20 cases (40%) with the peak value of 11.2–96.9 × 10^9/l. Of interest, all the patients who developed hyperleukocytosis achieved CRs. They received HU (40–50 mg/kg, four patients) or mild to moderate DA regimen (daunorubicin 30–40 mg/m^2 × 3 days, Ara-c 50–100 mg/m^2 × 5 days, four patients) when the WBC count exceeded 10 × 10^9/l during the therapy for the purpose of prevention of the complication of high WBC which is similar to ATRA syndrome. The patients with 'higher' WBC tend to receive DA. The interval between initiation of therapy and peak value varied from 4 to 20 days, with a median of 13.5 days. The clinical events are summarized in Table 2.

Conventional-dose group: The CR rate was 85.1% (40/47). Twenty-six of 31 cases receiving As_2O_3 alone achieved CR. Four patients died early from intracranial hemorrhage (three cases) or central infiltration (one case) by leukemia cells, which was confirmed by the clinical manifestation and CT scan. Central infiltration is rare in APL. One patient was confirmed with leukemia cell infiltration in the central nervous system. He manifested delirium, coma, neurological signs and the diagnosis was made by CT scan on the second day. Three patients did not respond to arsenic therapy. Among them, one was AML1-ETO positive at the time of relapse, one was PML-RARα-negative. In another non-responder, RT-PCR analysis was not obtained due to lack of material. The median time to reach CR was 31 days; median total dosage was 310 mg.[12] There was no significant difference between the two groups in terms of CR rate (P = 0.886, see Table 2).

Cytogenetic response

Low-dose group: Six patients in the low-dose group were assayed for PML-RARα by RT-PCR after achieving complete remission. None of them was converted to negative.

Conventional-dose group: Fifteen patients in this group underwent RT-PCR examination as soon as complete remission was obtained, the PML-RARα transcripts remained positive in all but one case. Among them, two cases received long-term As_2O_3 maintenance therapy (0.16 mg/kg/day, for 28 days, every other month), the cytogenetic remission was achieved after 41 and 37 months after the treatment.

Result of follow-up

Among 16 patients who achieved a second remission, 14 cases were followed up for over 7 to 33 months (median 15.5 months). The median overall survival (OS) and relapse-free survival (RFS) were not reached. The Kaplan–Meier estimated RFS at 12 months and 24 months were 78.57 ± 10.97% and 49.11 ± 15.09%, respectively. The estimated OS at 12 months and 24 months were 92.86 ± 6.88% and 61.55 ± 15.79% (Figures 1 and 2).

In terms of 2-year OS and DFS, there is no difference between the conventional- and low-dose groups, being 50.24 ± 10.25% *vs* 61.55 ± 15.79% and 41.62 ± 9.95% *vs* 49.11 ± 15.09%,[12] respectively, (P = 0.2865 and P = 0.7146, respectively).

Table 2 Major clinical events associated with the therapy

Patient No.	*Change of WBC*	*Related therapy*	*Maximal value (×10^9)*	*Outcome*	*Toxic effect*
1	—	—	—	CR	N
2	Increase	DA	87.3	CR	N
3	Increase	Hu	28.1	CR	N
4	Increase	DA	96.9	CR	Liver function/oral ulcer
5	Increase	DA	49.9	CR	Oral ulcer
6	Increase[a]	—	7.5	CR	Liver function
7	—	—	—	CR	N
8	—	—	—	ED	N
9	Increase	Hu	19.8	CR	N
10	—	—	—	CR	Liver function
11	—	—	—	CR	N
12	Decrease	—	—	NR	Skin reaction
13	—	—	—	ED	N
14	Increase	Hu	11.2	CR	N
15	—	—	—	CR	Skin reaction
16	—	—	—	CR	Liver function
17	Decrease	—	—	NR	N
18	Increase	DA	48.7	CR	N
19	Increase	Hu	28.3	CR	N
20	—	—	—	CR	N

—, No obvious change; N, no toxic effect; ED, early death; CR, complete remission; NR, non-remission.
[a]Not regarded as leukocytosis.

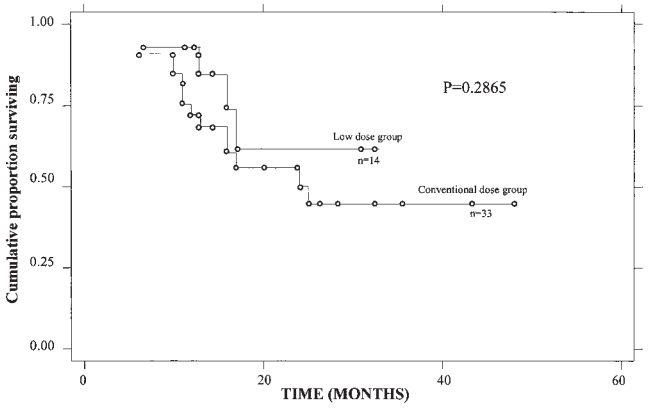

Figure 1 Kaplan–Meier survival estimates of OS.

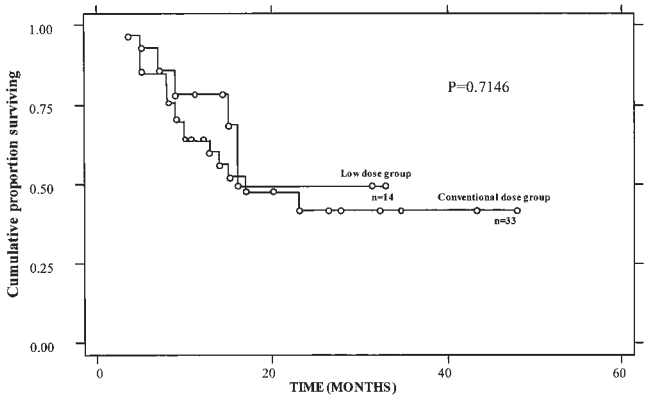

Figure 2 Kaplan–Meier survival estimates of RFS.

Morphological observation

Low-dose group: Peripheral blood was systematically examined in five patients of the low-dose group every other day, and morphological examination by Wright's stain was performed. The change similar to differentiation was observed in all these patients. We noticed that the percentage of abnormal promyelocytes decreased with the therapy. Concurrently, the myelocytes increased gradually and reached a climax (40–69%) after 11–21 days of As_2O_3 therapy. However, terminally differentiated cells such as polynuclear granulocytes did not increase. Bone marrow morphological change was observed at day 14 and 28 of the therapy. The percentage of myelocytes was found to be increased in the BM smear at day 14, while the promyelocytes decreased to a low level. This phenomenon was especially obvious in the BM smear at day 28. Table 3 demonstrates the morphological change of peripheral blood and BM during the therapy in one patient.

Conventional-dose group: Differentiation changes were also observed in the patients of this group.[12] The percentage of promyelocytes in BM declined gradually in all five cases during As_2O_3 treatment. In contrast, after 15–20 days' treatment, increased number of myelocytes and many degenerative cells bearing condensed or coarse nuclei with scanty cytoplasm ('nude' nucleus) were found in both BM and peripheral blood. The percentage of myelocytes in bone marrow was highest 20–25 days after the initiation of As_2O_3 treatment.

Toxic effects

Low-dose group: The main toxicity observed in both groups is the impairment of hepatic function, reflected by the increased transaminases (4/20, 20%). However, all these adverse effects were mild (NCI I degree), transminases can be reduced to normal level with supportive therapy, without suspending the treatment. Other associated adverse effects include: Two cases with oral ulcer (I degree): two cases with skin rash (I degree). The detailed data are listed in Table 4.

Conventional-dose group: Among 47 cases, 15 cases (31.9%) had experienced I–II degree hepatic dysfunction. Miscellaneous side-effects include: skin rash ($n = 12$); GI disturbance ($n = 5$); cardiotoxicity ($n = 8$); facial edema ($n = 5$); neurotoxicity ($n = 1$). The cardiac toxicity mainly restrained in mild A-V block (I degree) and arrhythmia, which was asymptomatic and needed no therapy. Facial edema was caused by the fluid retention in the body. One patient manifested neurological toxicity. He felt glove and stock-like sensory loss. However, we could not confirm whether it was related to arsenic therapy. One patient developed ARDS on day 22 of As_2O_3 treatment when the WBC count was 67.0×10^9/l.

We found that some side-effects occurred during conventional dose As_2O_3 therapy were not observed in the low-dose group such as GI disturbance and cardiotoxicity (Fisher's exact P value of 0.048). It seems that the incidence of liver function damage was lower in the low-dose group (20% *vs* 30%), but there was no statistical significance (Fisher's exact P value of 0.247). Transaminases levels in the patients with liver impairment is summarized in Table 5.

Pharmacokinetics

Plasma arsenic concentration rapidly reached peak levels after 2 h of infusion, with the mean peak concentration (Cpmax) of 2.628 ± 0.192 μmol/l (range 1.535–3.424), time to peak concentration was 2–3 h. Compared to the results in a previous study with 0.16 mg/kg As_2O_3,[4] Cpmax was nearly half

Table 3 The morphological change of peripheral blood and BM

	Peripheral blood			*Bone marrow*		
	Promyelocytes	*Myelocytes*	*Metamyelocytes*	*Promyelocytes*	*Myelocytes*	*Metamyelocytes*
1 w	51%	2%	N	73%	5.5%	1.5%
2 Ws	52%	24%	N	53.5%	35%	5%
3 Ws	8%	69%	9%	—	ND	—
4 Ws	5%	35%	N	5.5%	36%	28.5%

N, not seen; ND, not done.

Table 4 Comparison of adverse effects in both arms

	Low-dose arm (n = 20)				Traditional-dose arm (n = 47)				Fisher's exact P
NCI toxicity grading[a]	I	II	III	IV	I	II	III	IV	
Liver injury	4	0	0	0	^14	1	0	0	0.247
Skin reaction	2	0	0	0	8	4	0	0	0.372
GI disturbance	0	0	0	0	8	0	0	0	0.048
Facial edema	0	0	0	0	5	0	0	0	0.159
Neurotoxicity	0	0	0	0	1	0	0	0	0.701
Cardiotoxicity	0	0	0	0	8	0	0	0	0.048

[a]NCI toxicity grading: GI disturbance: nausea: grade I, able to eat, reasonable intake; grade II, intake significantly decreased, but can still eat; grade III, no significant intake. Vomiting: grade I, one episode in 24 h; grade II 2–5 episodes in 24 h; grade III, 6–10 episodes in 24 h; grade IV, more than 10 episodes in 24 h, or requiring parenteral support. Diarrhea and stomatitis are not seen.
Liver injury: transminases: grade I, ⩽2.5 normal upper limit (XN); grade II, 2.6–5.0 XN; grade III, 5.1–20.0 XN; grade IV, >20.0 XN. Bilirubin: grade II, <1.5 XN; grade II, 1.5–3.0 XN; grade III, >3.0 XN.
Cardiotoxicity: mainly with arrhythmia or A-V block, grade I, asymptomatic, transient, requiring no therapy; grade II, recurrent or persistent, no therapy required; grade III, require treatment; grade IV, require monitoring, hypotension, ventricular tachycardia or fibrillation.
Skin reaction: grade I, scattered macular or popular eruption, asymptomatic; grade II, scattered macular or popular eruption with pruritus or other associated symptoms; grade III, generalized symptomatic macular, popular or vesicular eruption; grade IV, exfoliative dermatitis or ulcering dermatitis.
Facial edema: refers to the NCI weight gain/loss grading, grade I, 5.0–9.9%; grade II, 10.0–19.9%; grade III, ⩾20.0.
Neurotoxicity: manifested with polyneuropathy, grade I, mild paresthesia; grade II, mild or moderate objective sensory loss; grade III, severe objective sensory loss.

Table 5 The height of transaminase in patients with liver injury

Patient	Low-dose group		Conventional-dose group	
	The height of GPT* (IU/l)	WHO grade	The height of GPT[a] (IU/l)	WHO grade
1	121	I	151	I
2	150	I	102	I
3	141	I	120	I
4	116	I	144	I
5			156	I
6			140	I
7			109	I
8			96	I
9			112	I
10			122	I
11			98	I
12			102	I
13			210	II
14			146	I
15			132	I

[a]The upper limit of GPT is 65 IU/l in our center.

Table 6 Cpmax of arsenic concentration in two studies

Case No.	Arsenic 5 mg/day Cpmax (μmol/l)	Arsenic 10 mg/day Cpmax (μmol/l)
1	1.535	6.01
2	2.283	8.18
3	2.808	6.22
4	2.768	7.70
5	2.848	6.82
6	2.616	5.54
7	3.424	6.62
8	2.742	7.30
X ± s	2.628 ± 0.192	6.799 ± 0.314

Table 7 Pharmacokinetic parameters after intravenous drip of low-dose As_2O_3 in relapsed APL patients

Patient No.	Cpmax (μmol/l)	t1/2α (h)	t1/2β (h)	CL(s) (l/h)	AUC (μmol/h/l)
1	1.535	2.705	7.360	2.575	9.808
2	2.283	2.770	9.199	1.606	15.722
3	2.808	1.470	6.227	2.078	12.152
4	2.768	1.567	14.900	2.073	12.182
6	2.616	1.729	11.201	2.762	9.141
8	2.742	1.200	11.486	2.223	11.359
Mean	2.636	1.413	9.411	1.987	12.706

of that before. The detailed data and pharmacokinetic parameters for each patient are shown in Tables 6 and 7.

Most of the time, the plasma concentration was maintained in the range of 0.1–0.5 μmol/l (concentration for differentiation *in vitro*). The concentration for apoptosis was only achieved 1–4 h after the infusion.

Arsenic concentration in the plasma of BM aspirates assayed in five patients was close to that for inducing differentiation in study *in vitro* (0.490, 0.106, 0.328, 0.061 and 0.051 μmol/l).

Discussion

The application of ATRA in the treatment of APL has been proved safe and can yield a high remission rate. However, when the relapse occurs, all patients who have recent exposure to retinoic acid are resistant to ATRA treatment.[4,8] The As_2O_3 was proved efficient in relapsed APL in many clinical studies,[4–8,13] being able to achieve a high CR rate and alleviate the abnormal coagulopathy.[14,15] *In vitro* study demonstrated that As_2O_3 exerted dual effects on APL cells: with induction of apoptosis at higher concentration (1–2 μmol/l) and partial differentiation at lower concentrations (0.1–0.5 μmol/l).[9,16,22] The mechanism involved in inducing apoptosis

has been clarified,[8,17–21] but that of the differentiation effect is not well known.[16]

Previously, we found that As_2O_3 (0.16 mg/kg) can reach a concentration much higher than that needed for inducing apoptosis *in vitro*,[4] by calculation, a lower dose of As_2O_3 (0.08 mg/kg) could also reach a concentration necessary for achieving a therapeutic effect. In addition, it was reported that As_2O_3 at a dose of 10 mg/day could cause severe toxic effect, particularly in the treatment of *de novo* cases, leading to liver function failure. Huang *et al*[11] reported severe acute side-effects including pleural effusion (5/7), pericardial effusion (4/7), and some chronic arsenic toxicity. We conducted this study for the purpose of investigating the clinical efficacy of low-dose As_2O_3 and its possible reduction of side-effects.

The results of this study have shown that in relapsed APL patients, low dose As_2O_3 (0.08 mg/kg) could yield a similar remission rate (80%) as compared with the conventional dose. Besides, the follow-up data also show similar outcome of the patients receiving different doses of arsenic. There was no cytogenetic response in the both dosages of As_2O_3, nearly all the patients did not have an immediate cytogenetic response after arsenic reinduction therapy. Soignet *et al*[7] reported that better cytogenetic response (66.7%) could be achieved when As_2O_3 was used after As_2O_3 maintenance therapy. In our previous report, two patients obtained cytogenetic remission 41 and 37 months after As_2O_3 treatment. This proves that at lower doses of As_2O_3 cytogenetic examination could be converted to negative after long-term treatment with the drug.

The main mechanism of low-dose As_2O_3 seems to induce partial differentiation apart from induction of apoptosis. In this study, we have noticed that WBC increased in half the patients. Differentiation changes were observed in the peripheral blood, as well as BM similar to ATRA therapy with increasing of myelocyte-like cells, but without terminal differentiation. The pharmacokinetic data shows that the concentration needed for apoptosis (1–2 μmol/l) can only be maintained in a short duration (1–4 h after As_2O_3 infusion). Most of the time, As_2O_3 exerts its differentiation effect at a concentration of 0.1–0.5 μmol/l.

We found that the toxicity of low-dose arsenic was reduced. Although the incidence of liver damage was not reduced to a statistically significant extent, its severity seems to be milder.

In conclusion, low-dose As_2O_3 is as effective as conventional dosage in remission induction with reduction of toxic effects. Its efficacy and toxicity need further observation and study.

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