To the editor:

Oral arsenic trioxide in the treatment of relapsed acute promyelocytic leukemia

Oral potassium arsenite used to be an important antileukemic agent[1] until the 1950s, when it was surpassed by modern chemotherapeutic drugs. The use of arsenic resurged when its high efficacy was shown in acute promyelocytic leukemia (APL).[2,3] However, to date, only intravenous As_2O_3 has been used. We have recently redeveloped an oral preparation of As_2O_3,[4] which achieved total blood cell and plasma levels of elemental arsenic comparable with those of intravenous As_2O_3.

Treated with oral As_2O_3 were 12 consecutive unselected patients with relapsed APL (Table 1). The relapse was confirmed morphologically (> 30% blasts + abnormal promyelocytes in the marrow) and cytogenetically (presence of t(15;17), with none of the cases showing additional karyotyic aberrations) or molecularly (presence of *PML/RARA*). The treatment was given with informed consent, and the protocol was approved by the institutional review board of the University of Hong Kong. All patients had a pretreatment Karnofsky score higher than 80%. Routine monitoring included alternate daily blood counts and renal/liver function tests (LFTs), and electrocardiography (ECG) daily in the initial week, then weekly.

There were 8 patients in first relapse (R1) treated with oral As_2O_3 (10 mg/d) until complete remission (CR; < 5% of abnormal promyelocytes + blasts in the marrow), followed by consolidation with idarubicin (6 mg/m^2/d, 5 days in the first month, then 2 days per month for 2 months).[5] Cases 1, 2, 3, 5, and 7 received one day of intravenous As_2O_3 as part of the initial pharmacokinetic study.[4] All patients achieved CR2 with oral As_2O_3, given for a median of 37 days (range, 22-59 days). At a median follow-up of 14 months (range, 6-18 months), 7 patients were in continuous CR2.

In R2, 5 patients (including case 1, who relapsed after CR2) were treated with a combination of oral As_2O_3 (10 mg/d) and all-*trans* retinoic acid (ATRA; 45 mg/m^2/d) until remission,[6] followed by 6 consolidation courses with As_2O_3 and ATRA (As_2O_3: 10 mg/d; ATRA: 45 mg/m^2/d, for 2 weeks every 2 months). With oral As_2O_3/ATRA given for a median of 31 days (range, 28-37 days), 4 patients achieved CR3. At a median follow-up of 17 months (range, 14-19 months), all had remained in CR3. Patient 1 died of cerebral hemorrhage 76 days after treatment, without achieving CR3.

PML/RARA remained positive in all patients after As_2O_3-induced CR. However, *PML/RARA* became negative in 11 cases 3 to 6 months after remission, and remained negative until the latest bone marrow examination. Polymerase chain reaction (PCR) in patient 1 became positive shortly before R2.

Of the patients, 4 (cases 1, 4, 10, and 12) developed leucocytosis (median, 74 × 10^9/L [range, 62-120 × 10^9/L]) requiring idarubicin (6 mg/m^2/d × 5, given when white cell count > 15 × 10^9/L) for control. However, symptomatology similar to the ATRA syndrome[7] was not observed. Impairment of LFTs occurred in 5 patients, peaking at a median of 11 days (range, 5-21 days). LFTs

Table 1. Clinicopathologic features and outcome of 12 consecutive patients with relapsed-acute promyelocytic leukemia treated with oral As_2O_3

Patient no.	Sex/ age, y	Status	Previous induction treatment	Time from last CR, mo	Relapse: Hb, g/L	Relapse: WBC, × 10^9/L	Relapse: Plat, × 10^9/L	Oral As_2O_3 therapy: Duration, d	Oral As_2O_3 therapy: Additional Rx	Oral As_2O_3 therapy: Result	Consolidation	Latest PCR† (mo)	DFS, mo	Remarks
1*	M/23	R1	ATRA + Dauno	11	156	2.1	87	59	Ida	CR	Ida		13	—
		R2	IV As_2O_3 + Ida	10	140	2.5	25	76	ATRA	NR	—	+ (dead)		—
2*	M/33	R2	Dauno/IV As_2O_3 + Ida	25	134	2.1	20	32	ATRA	CR	As_2O_3 + ATRA	− (18)	19+	—
3*	F/13	R2	ATRA + IV As_2O_3	12	86	1.2	15	30	ATRA	CR	As_2O_3 + ATRA	− (18)	19+	—
4	M/54	R1	ATRA + Dauno	100	85	34.8	81	40	Ida	CR	Ida	− (18)	18+	Mother: AML
5*	M/32	R1	ATRA + Dauno + MP	22	145	2.4	177	33	NA	CR	Ida	− (18)	18+	—
6	F/32	R1	ATRA + Dauno	12	122	0.8	84	51	NA	CR	Ida	− (12)	18+	—
7*	F/45	R2	ATRA + Dauno/IV As_2O_3 + Ida	17	112	1.9	50	37	ATRA	CR	As_2O_3 + ATRA	− (14)	17+	—
8	F/65	R1	ATRA	16	72	2.8	141	28	NA	CR	As_2O_3 + ATRA	− (12)	15+	CRF due to DM on CAPD, Ida consolidation omitted due to CRF
9	F/18	R2	ATRA + Dauno/IV As_2O_3 + Ida	12	101	1.9	180	28	ATRA	CR	As_2O_3 + ATRA	− (12)	14+	—
10*	F/18	R1	ATRA + Dauno	12	82	12.6	54	44	Ida	CR	Ida	− (6)	9+	—
11*	M/45	R1	ATRA + Dauno	240	42	0.6	9	22	NA	CR	As_2O_3	− (3)	7+	Ida consolidation omitted due to high cumulative doses of anthracycline
12	F/40	R1	ATRA + Ara-c	23	85	6.5	39	28	Ida	CR	Ida	− (3)	6+	CRHD, double valve rep

DFS indicates disease-free survival; M, male; R1, first relapse; ATRA, all-*trans* retinoic acid; Dauno, daunorubicin; Ida, idarubicin; CR, complete remission; —, none; IV, intravenous; R2, second relapse; NR, nonremission; F, female; AML; acute myeloid leukemia; NA, no additional Rx; CRF, chronic renal failure; DM, diabetes mellitus; CAPD, continuous ambulatory peritoneal dialysis; Ara-c, cytosine arabinoside; CRHD, chronic rheumatic heart disease; and rep, replacement.

*Pharmacokinetic data of oral As_2O_3 have previously been reported.[4]

†PCR for *PML/RARA*. + indicates positive; −, negative, (time from initial diagnosis).

normalized after temporary cessation of treatment, and further oral As_2O_3 therapy was not compromised. Mild skin rashes (grade I) developed in 5 patients and subsided with symptomatic treatment. Headache developed in 2 patients on oral As_2O_3/ATRA, and subsided when the dose of ATRA was split. None of our patients showed ECG abnormalities of the types previously reported.[8]

Our preliminary results in this pilot study showed that oral As_2O_3 was highly active in relapsed APL, with an efficacy comparable with intravenous As_2O_3.[9] The side effects, including the frequency and severity of leucocytosis, LFT derangement, and skin rashes, were also comparable with intravenous As_2O_3.[2,3] Cardiac arrhythmias were not found, which was similar to a previous study of intravenous As_2O_3 in Chinese patients, where arrhythmia was seen in only 1 of 58 patients.[2]

It is important to note that only 4 patients received oral As_2O_3 as a single agent for CR induction, with the rest having received ATRA or idarubicin before CR was reached. With this limitation, our results showed that oral As_2O_3 had a short-term efficacy and safety profile similar to intravenous As_2O_3. A recent study also showed that oral tetra-arsenic tetrasulfide was highly efficacious in APL.[10] However, the long-term efficacy and safety of oral As_2O_3 compared with intravenous As_2O_3 will require longer follow-up. Finally, although oral or intravenous As_2O_3 and hematopoietic stem cell transplantation are effective treatment modalities for patients with relapsed APL, their relative merits are undefined, and further randomized trials will be needed to address this issue.

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The University of Hong Kong has filed a temporary patent for the use of oral arsenic trioxide in the treatment of acute promyelocytic leukemia.

References

1. Kwong YL, Todd D. Delicious poison: arsenic trioxide for the treatment of leukemia. Blood. 1997;89:3487-3488.
2. Niu C, Yan H, Yu T, et al. Studies on treatment of acute promyelocytic leukemia with arsenic trioxide: remission induction, follow-up, and molecular monitoring in 11 newly diagnosed and 47 relapsed acute promyelocytic leukemia patients. Blood. 1999;94:3315-3324.
3. 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: 3852-3860.
4. Kumana CR, Au WY, Lee NSL, Kou M, Lam CW, Kwong YL. Systemic availability of oral arsenic-trioxide used for treatment of patients with haematological malignancies. Eur J Clin Pharmacol. 2002;58:521-526.
5. Kwong YL, Au WY, Chim CS, Pang A, Suen C, Liang R. Arsenic trioxide- and idarubicin-induced remissions in relapsed acute promyelocytic leukaemia: clinicopathological and molecular features of a pilot study. Am J Hematol. 2001;66: 274-279.
6. Au WY, Chim CS, Lie AK, Liang R, Kwong YL. Combined arsenic trioxide and all-trans retinoic acid treatment for acute promyelocytic leukaemia recurring from previous relapses successfully treated using arsenic trioxide. Br J Haematol. 2002;117:130-132.
7. 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;18:2620-2625.
8. 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;133:881-885.
9. Tallman MS, Nabhan C, Feusner JH, Rowe JM. Acute promyelocytic leukemia: evolving therapeutic strategies. Blood. 2002;99:759-767.
10. Lu DP, Qiu JY, Jiang B, et al. Tetra-arsenic tetra-sulfide for the treatment of acute promyelocytic leukemia: a pilot report. Blood. 2002;99:3136-3143.

To the editor:

No clinical evidence for CD4$^+$ cell depletion caused by rituximab

In the recent letter "Pure red-cell aplasia due to parvovirus B19 infection in a patient treated with alemtuzumab"[1] Herbert et al inaccurately stated that "the severe CD4 lymphopenia induced by alemtuzumab and other monoclonal therapies such as rituximab for lymphoproliferative diseases is a risk factor for opportunistic infections." [1(p1654)]

Rituximab (Rituxan; IDEC Pharmaceuticals, San Diego, CA/ Genentech, South San Francisco, CA) is an FDA-approved therapeutic monoclonal antibody directed against CD20, an antigen expressed uniquely on cells of the B-lymphocyte lineage, but not on T lymphocytes. In contrast, CD4 is expressed on T lymphocytes, macrophages, and microglial cells, but not on B lymphocytes. Although parvovirus B19 infection has been reported in a patient treated with rituximab,[2] we are not aware of any data suggesting that administration of rituximab leads to a depletion of CD4$^+$ T cells. In fact, flow cytometry data from 166 patients treated with rituximab in a clinical trial showed no diminution of absolute numbers of CD3$^+$, CD4$^+$, CD8$^+$, or natural killer cells.[3]

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References

1. Herbert KE, Prince HM, Westerman DA. Pure red-cell aplasia due to parvovirus B19 infection in a patient treated with alemtuzumab [letter]. Blood. 2003;101: 1654.
2. Sharma VR, Fleming DR, Stone SP. Pure red cell aplasia due to parvovirus B19 in a patient treated with rituximab. Blood. 2000;96:1184-1186.
3. McLaughlin P, Grillo-López AJ, Link BK, et al. Rituximab chimeric anti-CD20 monoclonal antibody therapy for relapsed indolent lymphoma: half of patients respond to a four-dose treatment program. J Clin Oncol. 1998;16:2825-2833.

Response:

Pure red cell aplasia and alemtuzumab

Drs Saville and Multani point out an incorrect statement in our recent letter.[1] We had included this statement to highlight the similarity of our case of alemtuzumab-induced pure red cell aplasia (PRCA) to the recent reports of rituximab-associated PRCA (which have now climbed to 3 reports).[2-4] We agree that given the currently recognized mechanisms of action of rituximab, it would be unlikely