Successful Treatment of a Case of Relapsed Acute Promyelocytic Leukemia with Arsenic Trioxide


Abstract

We report a patient with an initial relapse of acute promyelocytic leukemia (APL) who achieved a second complete remission (CR) after treatment with arsenic trioxide. The patient, a 66-year-old woman diagnosed as having relapsed APL, received arsenic trioxide intravenously at a dose of 10 mg/day. At day 36, the patient achieved a second CR. The side effects were slight neuralgia and mild skin erythematous changes, which improved following cessation of the drug. Although arsenic trioxide may be effective for relapsed APL, it should be used with caution because of various complications.

Introduction

All trans retinoic acid (ATRA), proven to be effective for de novo acute promyelocytic leukemia (APL), has been shown to induce a 90% complete remission (CR) rate and result in a 60% long-term survival rate. However, relapse occurs in about 30% of patents after the initial CR (1). For relapsed patients, it is difficult to obtain a second CR with ATRA alone or in combination with chemotherapy (1, 2).

In 1997, arsenic trioxide was introduced for treatment of patients with relapsed APL (3, 4) and its remarkable effectiveness was confirmed in subsequent studies (5, 6). However, reports on the use of arsenic trioxide in Japan are rare (7). Here, we describe a patient with APL who achieved a second CR following treatment with arsenic trioxide, with only mild side effects.

Case Report

A 66-year-old woman was admitted to our hospital because of relapsed APL in June 2000. She had a history of APL from 1993 and had obtained the first CR with administration of ATRA alone followed by 5 courses of consolidation chemotherapy. She was followed up as an outpatient from September 1995.

Laboratory data on admission showed mild anemia (red blood cell count 2.54x10¹²/l) with decreased white blood cell count (1.9x10⁹/l) and a platelet count (120x10⁹/l). Disseminated intravascular coagulation was not present. The marrow smears showed increased promyelocytes (26%) and decreased neutrophils (4%). The karyotype of the bone marrow cells showed t (15:17) in 25% of the cells. The proportion of promyelocytic leukemia-retinoic acid receptor alfa (PML-RARA) fusion transcript by fluorescent in situ hybridization (FISH) was 32%.

We recommended the patient to consider treatment with Am80 (8, 9), however the patient refused this therapy since there was no institution near our hospital capable of performing this treatment. Next, we considered administration of arsenic trioxide. We investigated the possibility of importing this drug from United States or China, but that proved to be impossible, so we considered to use research arsenic agent. The successful use of this research reagent had been reported in Japan in 2000 (7), supported our decision. The institutional review board of our hospital approved this arsenic therapy for this patient. We explained to the patient the optional strategy of first administering ATRA and chemotherapy and only resorting to arsenic trioxide if this initial therapy failed. However, the patient rejected this idea because the low possibility of a second CR by combination therapy, and instead opted for the treatment first by arsenic trioxide. We also explained the possibilities of various serious side effects. After obtaining written informed consent, we initiated the administration of arsenic trioxide. To prepare the reagent, 200 mg of arsenic trioxide (Wako Chemistries, Tokyo) was added to 150 ml of normal saline. Since arsenic dissolves under alkaline conditions 10 ml
of 1N NaOH was added to the mixture. The pH was adjusted by the addition of 10 ml of 1N HCl and the final volume was adjusted to 200 ml. The final solution (0.1% solution) was transferred to a 10 ml vial and autoclaved. Before administration, one vial of the solution was added to 500 ml normal saline solution. The administration of ten milligrams/day of arsenic trioxide as described by Chen et al. (3) was started on June 21, 2000 (Fig. 1). The percentage of bone marrow promyelocyte started to decrease on day 28. At this time, myelocyte-like cells, without azur granules and nucleic bodies, began to increase (Fig. 2). The proportion of promyelocytes reached 2% at day 36 and the administration was stopped. At this time the percentage of PML-RARA positive cells by FISH was 20%, thus positive cells morphologically lacking promyelocytes were thought to exist. At this time, fusion signal appeared in the cells with lobed nuclei, indicating the differentiation of APL cells by arsenic trioxide (Fig. 3). At day 54 FISH positive cells had decreased to 2%.

Lower abdominal skin erythematous changes appeared 10 days after the start of arsenic trioxide treatment, (Fig. 4), however, they diminished once administration of the drug was stopped. Mild neuralgia occurred after the arsenic administration and improved one week after treatment ended. Long-term toxicity has not been observed. After hematological recovery, idarbicin and Ara C were administered as consolidation therapy. PML-RARA mRNA was undetectable by reverse transcription polymerase chain reaction in the bone marrow cells after the first consolidation chemotherapy.

**Discussion**

Relapsed APL shows resistance to ATRA because of increased levels of cellular retinoic acid binding protein (CRABP), mutations in the retinoic acid receptor gene and additional genetic abnormalities. Recently, two new promising agents, Am80 and arsenic trioxide, have been introduced for treatment of relapsed APL.

The remarkable effect of arsenic trioxide for APL was first reported in 1997 by a Chinese group (3, 4) and it was confirmed by a study in the U.S. in 1998 (5). The two-year survival rate after arsenic therapy was reported to be 40% which is excellent in comparison with the combination of ATRA and chemotherapy for relapsed APL (6).

Previously reported side effects were skin eruption, liver dysfunction, nausea, vomiting, retinoic acid syndrome, cardiac dysfunction and pleural effusion. Fortunately, the present patient suffered only mild skin erythematous change and neuralgia, which resolved after cessation of arsenic trioxide (10, 11).

The efficacy of arsenic trioxide treatment and the mechanisms by which it induces apoptosis of APL cells has previ-
Previously been reported. The apoptosis of APL cells was induced by the high concentration of arsenic trioxide obtained immediately after administration (3, 12). Arsenic trioxide is thought to facilitate apoptosis of APL cells via a down regulation of bcl-2, induction of caspase and reduction of glutathione transferase. Degeneration of PML-RARA protein has also been observed with administration of low concentrations of arsenic trioxide. This degeneration is thought to induce differentiation of APL cells. The differentiation effect of arsenic is partial, so APL cells change their morphology to resemble that of myelocytes or metamyelocytes; but these cells did not differentiate to neutrophils.

In this case the proportion of APL cells started to decrease after 4 weeks of administration and only existed in 2% of the bone marrow cells at day 36, as determined by microscopic examination. At the same time PML-RARA positive cells constituted 20% of total cells. This phenomenon indicated the differentiation of APL cells by arsenic trioxide. In fact, segmented nuclear cells having positive fusion gene emerged at day 28.

A standard therapy after successfully achieving a second CR has not been established. The relapse rate after a second CR by a regimen of continued administration of arsenic alone
was reported to be as much as 80%, whereas the consolidation chemotherapy group after arsenic showed a relapse rate of only 30% (6), indicating, obviously, the benefit of the latter treatment following successful second CR. Moreover, a new synthetic retinoid, Am80 (4-[(5, 6, 7, 8-tetrahydro-5, 5, 8, 8-teramethyl-2-naphtalenyl) carbamoil] benxoic acid), has also been proven to produce beneficial effect in patients with relapsed APL (8, 9). The adverse effects of Am80 are milder than those of arsenic. In the future, Am80 may become the drug of choice, instead of arsenic, to treat relapsed APL, because the side effects are less severe.

Although arsenic therapy can be highly beneficial to patients with APL, a cautious approach to its use should be adopted because of several possible adverse effects.

References