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ORIGINAL PAPER

Delayed Hematological Recovery Following Autologous Transplantation Utilizing Peripheral Blood Stem Cells Harvested After Treatment with Arsenic Trioxide

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Abstract We describe herein two cases of delayed hematological recovery (DHR) following autologous peripheral blood stem cell transplantation (auto-PBSCT) using cells harvested during second molecular remission after treatment with arsenic trioxide (As_2O_3). Current therapeutic strategies with As_2O_3 plus auto-PBSCT might be hampered by potential mechanisms of DHR. Our observations highlight the need for study of the real effects of As_2O_3 on the kinetics of normal hematopoietic engraftment following auto-PBSCT.

Keywords Arsenic trioxide · Acute promyelocytic leukemia · Delayed hematological recovery · Autologous PBSCT

Abbreviations

Bu	busulfan
Cy	cyclophosphamide
Mel	melphalan
TBI	total body irradiation
Auto-SCT	autologous stem cell transplantation
G-CSF	granulocyte-colony stimulating factor
BMA	bone marrow aspiration
RBC	stored red blood cells
PC	stored platelet concentrate

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Introduction

Most patients with acute promyelocytic leukemia (APL) well respond to all-*trans* retinoic acid (ATRA) combined with chemotherapy, but a significant number eventually relapse. Arsenic trioxide (As_2O_3) is reported remarkably effective in patients with relapsed APL, including those apparently resistant to ATRA, with some patients even achieving molecular remission (molecular CR) after treatment [1, 2]. Although optimal therapeutic strategies after achieving remission using As_2O_3 have not been firmly established, recent studies with good outcome and low transplant-related mortality suggest the use of autologous transplantation, particularly in the absence of minimal residual disease (MRD), in patients with second remission [3, 4]. However, little information is available regarding the quality and quantity of hematopoietic stem cells harvested after As_2O_3 treatment. We have recently encountered two cases of delayed hematological recovery following autologous transplantation using peripheral blood stem cells harvested during second molecular remission after treatment with As_2O_3. These cases suggest the possibility of hematopoietic stem cell damage resulting from As_2O_3 administration.

Case Report and Discussion

Case 1

In July 2002, a 37-year-old man was diagnosed with APL characterized by t(15;17)(q22;q11-21) with PML/RARα transcript. Treatment with ATRA and subsequent anthracycline-based chemotherapy according to the APL protocol of the Japan Adult Leukemia Study Group (JALSG) [5] resulted in complete remission (CR). However, the patient relapsed in September 2004 and received As_2O_3 as a re-induction therapy at a dose of 0.15 mg/kg daily. After treatment for 45 consecutive days, the patient achieved second CR. Moreover, an additional two courses of treatment with As_2O_3 (accumulated dose, 950 mg total dose) resulted in molecular CR. No severe adverse effects were observed during As_2O_3 therapy. One month later, harvest of peripheral blood progenitor cells (PBPCs) was performed using a Cobe Spectra Cell Separator (Cobe BCT, Lakewood, CO, USA), following high-dose cytarabine (2 g/m^2 × 2 times/day × 4 days) and granulocyte-colony stimulating factor (G-CSF) mobilization. G-CSF (lenograstim) was given at a dose of 5 μg/kg/day until leukocytes increased 10,000/μl. A total of 11.2×10^7 CD34$^+$ cells (1.9×10^6/kg) was harvested. Additional studies using real time-PCR (RQ-PCR) methods on the harvested sample detected <50 copies of chimeric PML/RARαmRNA/μg of tRNA. In June 2005, at 134 days after last administration of As_2O_3, autologous MRD-negative PBPC transplantation was performed. The patient was conditioned with busulfan (4 mg/kg × 4 days) and cyclophosphamide (60 mg/kg × 2 days). The patient received G-CSF from day 1 and after an aplastic period of 14 days, displayed transient hematological recovery and became transfusion-independent. However, after discontinuation of G-CSF, the patient developed pancytopenia and again became transfusion dependent (Fig. 1). Bone marrow aspiration (BMA) performed on days 17, 35 and 44 consistently showed hypocellularity but normal morphology, with no metaphases showing any chromosome abnormalities. RQ-PCR assay also showed the absence of chimeric product. BMA on days 55 and 75 demonstrated recovery of myeloid and erythroid precursor cells, and even megakaryocytes. The patient remained transfusion-dependent for the next 5 months then gradually recovered from cytopenia without specific intervention (Fig. 1).

Case 2

In January 2002, a 50-year-old man with newly diagnosed PML/RARα-positive APL received ATRA combined chemotherapy according to the JALSG-APL protocol and attained CR. However, the patient relapsed 18 months later

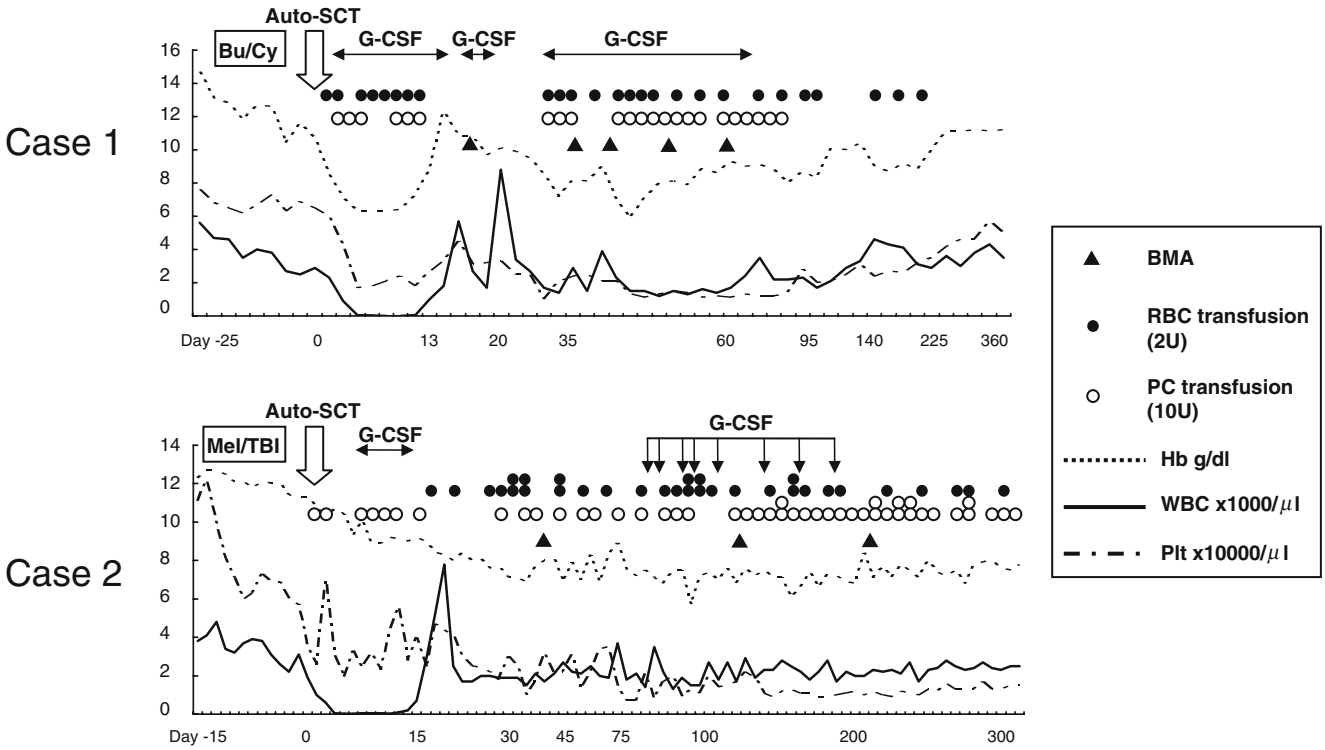

Fig. 1 Clinical course of two patients. Serial changes in levels of hemoglobin, white blood cells, platelets and required RBC and PC transfusions are shown

and underwent re-induction treatment using As_2O_3 at a daily dose of 0.15 mg/kg for 60 days, then achieved second CR. Despite an additional two courses of As_2O_3 therapy (accumulated dose, 1,100 mg total dose), the patient again experienced relapse of the central nerves system (CNS). Intrathecal administration of cytarabine and methotrexate was therefore initiated and successfully controlled CNS leukemia. Subsequently, the patient was treated using high-dose cytarabine, and MRD-negative autologous PBPCs were harvested during the recovery phase as applied in case 1. In July 2005, at 136 days after final As_2O_3 administration, a total of 8.2×10^7 $CD34^+$ cells (1.2×10^6/kg) was transplanted after conditioning with melphalan (160 mg/m^2) and total body irradiation (12 Gy). Use of radiation with melphalan has been previously evaluated in refractory or relapsed hematological malignancies, including CNS leukemia. In autologous settings, this combination has been shown to offer high response rates with minimum toxicity in patients with advanced acute leukemia, lymphoma or myeloma [6]. However, in this case, no full recovery of peripheral blood cells was observed after transplantation and bone marrow aspirates consistently indicated amegakaryocytic hypoplasia. Dependency on regular transfusion has not yet been reduced as of the time of writing, 10 months after transplantation (Fig. 1).

A striking aspect of our experience is that two cases of auto-transplantation following salvage treatment with As_2O_3 developed a delayed hematological recovery (DHR) such as prolonged pancytopenia. Although we have performed allogeneic bone marrow transplant after As_2O_3 therapy in two other cases to date [7], neither showed DHR after transplantation. Since both cases received >1.0×10^6/kg of $CD34^+$ cells [8], DHR might not be simply due to relatively lower numbers of $CD34^+$ cells in the graft. Although it could be speculated that As_2O_3 may have some effect on capability of mobilization of stem cell, there was no direct evidence to support this speculation. Alternatively, the possibility arises that As_2O_3 could interfere with the quality of harvested hematopoietic stem cells. We therefore checked cell surface markers to examine the possible impact of As_2O_3 on normal progenitor cell. The cellular profiles of $CD34^+$ cells obtained from the two patients differed from those of seven AML patients without previous history of As_2O_3 therapy with respect to a lower CD133 membranous expression (Table 1). CD133 is an antigen expressed on hematopoietic progenitor cells and interactions with local microenvironments in the bone marrow are thought to control homing, differentiation and self-renewal of the cells [9]. Low expression might thus contribute to the development of DHR. Although As_2O_3 has been noted to act on malignant hematopoietic cells, while sparing normal progenitors [10], our observations highlight the need to study of the real effects of As_2O_3 on the kinetics of hematopoietic

Table 1 Clinical characteristics of two patients who developed delayed hematological recovery after auto PBSCT

Age/sex	Diagnosis	ATRA/As2O3	Protocol for harvest	$CD34^+$ cell (10^6/kg)	% CD117	%CD133	%CD33	%CD38	HLA DR	Conditioning regimen for auto-transplant	Delayed hematological recovery
40/M	M3	Yes/yes	HDAC	1.9	2.46	79.96	97.46	99.30	90.36	Bu-Cy	Pancytopenia
54/M	M3	Yes/yes	HDAC	1.2	0.94 (2.82)[a]	74.56 (92.23)[a]	98.83 (92.10)[a]	99.43 (98.30)[a]	96.92 (95.50)[a]	Mel-TBI	Pancytopenia

[a] Phenotypes of $CD34^+$ cells harvested in patients without a previous history of AS_2O_3 therapy are indicated as a comparison; mean value of each antigen expression assayed in seven AML patients in our institution are in parentheses.

Abbreviation: ATRA, all trans retinoic acid; AS_2O_3, arsenic trioxide; HDAC, high dose cytarabine; Bu, busulfan; Cy, cyclophosphamide; Mel,melphalan; TBI, total body irradiation.

engraftment following autologous peripheral blood stem cell transplantation.

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