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Letter to The Editor

Difficulty of Peripheral Blood Stem Cell Collection after Multiple Consolidation Therapy in Acute Myeloid Leukemia

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To the Editor

Autologous hematopoietic stem cell transplantation (auto-SCT) is one therapeutic option after complete remission of acute myeloid leukemia (AML). Due to ease of collection and rapid engraftment, peripheral blood stem cells (PBSC) are now preferred over bone marrow for the auto-SCT procedure. To minimize both the total body leukemia burden and the contamination of the PBSC product, a high-dose-cytarabine-based consolidation regimen prior to the collection of granulocyte colony-stimulating factor (G-CSF) mobilized PBSCs could prove useful for *in vivo* purging.[1] However, the optimal schedule for this consolidation therapy is unknown.

We conducted a PBSC harvest in four patients with AML who were hospitalized in Toyohashi Municipal Hospital between April and November 2004. After complete remission was achieved in the patient by a single course of induction therapy, with intermediate-risk or good-risk cytogenesis excluding t(15,17), we conducted a G-CSF mobilized PBSC harvest both after the first consolidation therapy (cytarabine 4 g/m^2/day x 4 days and daunorubicin 45 mg/m^2/day x 2 days) and after the second consolidation therapy cytarabine 200 g/m^2/day x 5 days and mitoxantrone 7 mg/m^2/day x 3 days). The patients received 5-10 μg/kg of lenograstim before PBSC harvest. Cytogenetic classification of risk grouping was done according to the previously described method.[2] If the CD34$^+$ dose in the PBSCs collected was > 2.0 x 10^6 CD34$^+$ cells/kg recipient body weight after each of the first and second consolidation therapy, we conducted autologous peripheral blood stem cell transplantation (auto-PBSCT). The PBSC product collected after the second consolidation therapy was infused into the patient, while the PBSC product collected after the first consolidation therapy was kept for "backup." Informed consent was obtained for all medical procedures. The goal of this study was to evaluate the effect of the second consolidation on the dose of CD34$^+$ cells collected.

The summary data for the four patients are shown in Table 1. In all cases in which two PBSC collections were performed (Patients 1, 2, and 4) the dose of collected CD34$^+$ cells after one cycle of consolidation therapy was higher than that after two cycles. Only in Patient 1 did the PBSCs collected after the second consolidation therapy contain > 2.0 x 10^6 CD34$^+$ cells/kg. This patient underwent auto-PBSCT. Prior to consolidation therapy, minimal residual disease (MRD) was found in this patient as evidenced by detection of AML1/MTG8 by real-time reverse transcriptase-polymerase chain reaction (RT-PCR).[3] Minimal residual disease could not be detected in the PBSC product that was collected after the first and second consolidation therapies, nor in the bone marrow samples collected after the first and second consolidation therapies. MRD was not evaluable in Patients 2-4, because they had AML with normal karyotype. Patients 2-4 did not undergo autologous transplantation. All four patients were alive in complete remission at median of 8.7 months (range, 6.0-13 months) after diagnosis.

The concentration of leukemia-contaminated cells in the collected PBSC product after multiple courses of consolidation therapy is presumably smaller than that after a single course of consolidation therapy. However, the collection of an adequate dose of PBSC after the second consolidation therapy was difficult. We did not use high dose cytarabine in the second cycle consolidation regimen, because we were uncertain of its efficacy as a preparative regimen for PBSC harvest. This difference between the first and second consolidation regimens may have affected the dose of the collected CD34$^+$ cells.

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Table 1. Summary of patient data

Patient No.	1	2	3	4
Sex	Female	Female	Male	Male
Age (years)	52	47	49	58
FAB type	M2	M2	M4	M2
First PBSC collection				
Day of PBSC collection (from initiation of the chemotherapy)	Days 17 and 18	Day 19	Days 20 - 22	Days 19 and 20
Amount of blood processed (first day/ second day/ third day) (Liters)	6/ 13	13	10/ 10/ 10	12/ 12
Collected CD 34^+ cell dose (x 10^6/ kg)	25. 5	15. 9	3. 0	24. 0
Second PBSC collection				
Day of PBSC collection (from initiation of the chemotherapy)	Days 17 and 18	Days 20 and 21	NA*	Day 19
Amount of blood processed (first day/ second day) (Liters)	10/ 11	13/ 13	NA*	12
Collected CD 34^+ cell dose (x 10^6/ kg)	2. 9	0. 6	NA*	0. 03

NA : not applicable

*PBSC (peripheral blood stem cell) harvest was not conducted due to the low cell dose after the first consolidation therapy.

Previous studies have cited multiple cycles of prior chemotherapy as a risk factor for poor mobilization in patients with breast cancer and malignant lymphoma.[4] This is consistent with our experience. However, more effective *in vivo* purging is necessary for AML patients, in whom PBSC products are more likely to be contaminated by tumor cells. We intended to perform *in vivo* purging using two cycles of consolidation therapy. However, our experience has shown the difficulty with this strategy.

High-dose cytarabine has been reported to have a potent anti-leukemia effect and to be useful as a prior regimen for PBSC harvest.[5] Interestingly, MRD was not detected in the PBSC product collected after the first consolidation therapy containing high-dose cytarabine in Patient 1. Auto-SCT using the PBSC product without detectable MRD might reduce the relapse rate in AML with good-risk cytogenesis.[6] This indicates that PBSC products collected after one cycle of high-dose cytarabine might not contain enough leukemia cells to increase the risk of relapse. However, careful long-term evaluation is need.

There are two useful strategies for collecting PBSC products with reduced leukemia cell contamination. The first strategy involves reducing the contaminating leukemia cells in the PBSC product collected after the first cycle of consolidation therapy. This strategy requires the establishment of an optimal prior therapy. The addition of monoclonal antibody might be useful here. The second involves the establishment of effective mobilization after the second consolidation therapy, for which the administration of higher doses of G-CSF might be useful.

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