

Letter to the Editor

Therapy-related Myelodysplastic Syndrome after Autologous Stem Cell Transplantation Using Plerixafor for Mobilized Stem Cells in a Patient with Multiple Myeloma

Keywords: Plerixafor, peripheral blood stem cell harvest, autologous stem cell transplantation, graft failure, secondary myelodysplastic syndrome

TO THE EDITOR

Peripheral blood stem cell harvest (PBSCH) is an essential procedure for autologous stem cell transplantation (ASCT) in patients with multiple myeloma (MM). Safe engraftment was reported to require infusion of more than 2.0×10^6 CD34⁺ cells/kg of the recipient's weight.¹ Plerixafor is a selective inhibitor of C-X-C chemokine receptor type 4 (CXCR4), which blocks the interaction of CXCR4 with its ligand C-X-C motif chemokine 12 (CXCL12). As this interaction is needed to retain CD34⁺ cells in the bone marrow, plerixafor facilitates the rapid mobilization of CD34⁺ cells.² In patients with non-Hodgkin's lymphoma (NHL) and MM, plerixafor and granulocyte-colony stimulating factor (G-CSF) were reported to be well tolerated, resulting in a significantly higher number of patients from whom the optimal target number of CD34⁺ cells was able to be collected for transplantation than with G-CSF alone.^{3,4} Plerixafor is expected to facilitate the collection of CD34⁺ cells to perform ASCT even in patients without sufficient CD34⁺ cells. However, limited information is available regarding adverse events following ASCT using plerixafor for mobilized stem cells. Here, we present the case of a patient with refractory MM who developed secondary graft failure following ASCT with plerixafor for mobilized stem cells.

In 2014, a 63-year-old Japanese female developed left hip pain and was diagnosed with a sacral tumor. She was then referred to our hospital. Her medical history consisted of tonsil surgery at the age of 15 years and total resection of a uterine myoma at the age of 34 years. Her initial laboratory findings are shown in Table 1. Electrophoretic analysis of proteins revealed IgA lambda-type M-protein. Of note, Bence Jones protein was negative, and the free light-chain ratio was within the normal range. Bone marrow examination revealed that the hypocellular bone marrow consisted of 44% atypical plasma cells. Chromosomal analysis of bone marrow specimens using G-band staining was normal. However, bone marrow biopsy specimens demonstrated that the trabeculae were melting or thinning, and there was monotonous proliferation of small circular cells with eccentric nuclei and a perinuclear pale zone. These cells were positive for kappa and IgA, and negative for lambda, IgM,

and IgG. In February 2014, radiation therapy was performed for the sacral tumor, and bortezomib plus dexamethasone (BD) therapy comprising subcutaneous injection of bortezomib (1.3 mg/m²) and dexamethasone (20 mg/body weight) on days 1, 8, 15, and 22 was initiated for 5 weeks. After 4 courses of BD therapy, although the M-protein levels decreased, new subcutaneous nodules appeared on the forehead and outside the right orbit. In July 2014, PBSCH with 2 days of cyclophosphamide (CY; 2000 mg/m²) as the conditioning regimen and PBSCH with G-CSF alone were performed; however, the total collection yield from these 2 PBSCH cycles was only 1.1×10^6 CD34⁺ cells/kg of PBSCs. Following CY administration, the sacral tumor disappeared, the number of plasma cells in the bone marrow decreased to 0.4%, and the M-protein disappeared, as confirmed by protein electrophoresis. In April 2015, lenalidomide therapy of 25 mg per day on days 1–21 every 4 weeks was initiated because an extramedullary mass developed on the anterior chest and forehead. However, the lenalidomide dosage was decreased to 10 mg per day on days 1–21 every 4 weeks because of severe cytopenia. The extramedullary mass disappeared soon after the initiation of lenalidomide therapy, which lasted for 15 courses. In July 2016, although the

Table 1. Laboratory data at the first onset and admission

		At the first onset	At admission
White blood cell count	(/uL)	4,200	1,800
Red blood cell count	($\times 10^4$ /uL)	351	315
Hemoglobin	(g/dL)	10.8	10.1
Platelet count	($\times 10^4$ /uL)	201	9.4
Total protein	(g/dL)	9.0	6.5
Albumin	(g/dL)	3.9	4.2
Aspartate aminotransferase	(U/L)	34	24
Alanine aminotransferase	(U/L)	26	12
Lactate dehydrogenase	(U/L)	178	402
Serum creatinine	(mg/mL)	0.68	0.52
Corrected calcium	(mg/dL)	9.7	8.6
C-reactive protein	(mg/dL)	0.84	0.27
β 2 microglobulin	(mg/L)	2.6	2.3
immunoglobulin G	(mg/dL)	1476	895
immunoglobulin A	(mg/dL)	1877	96
immunoglobulin M	(mg/dL)	121	15

M-protein had disappeared, a cranial mass was detected, and was surgically excised and diagnosed as plasmacytoma by histological examination. Pomalidomide was administered, but intracranial plasmacytoma recurred, and was treated by local radiotherapy. In September 2016, the patient developed systemic plasmacytoma. Accordingly, 2 courses of CY/doxorubicin/vincristine/prednisone (CHOP) therapy (CY, 750 mg/m² on day 1; doxorubicin, 50 mg/m² on day 1; vincristine, 1.4 mg/m² on day 1; and prednisolone, 100 mg/body on days 1–5) and 4 courses of carfilzomib/lenalidomide/dexamethasone (KRd) therapy (carfilzomib, 40 mg on days 1, 2, 8, 9, 15, and 16; lenalidomide, 25 mg on days 1–21, and dexamethasone, 20 mg on days 1, 8, and 15) were administered. However, the lenalidomide dosage was also decreased to 10 mg per day due to severe cytopenia. As the plasmacytoma was gradually exacerbated, radiotherapy was performed for a mass on the left erector spinae muscles. In April 2017, her general malaise worsened and meal intake became poor, resulting in hospitalization.

Upon admission, her body temperature was 37.0°C, heart rate was 68 beats per min, and blood pressure was 95/62 mmHg. Physical examination revealed a palpable tumor from the right lower jaw angle to the clavicle. Laboratory findings at admission are also shown in Table 1. Bone marrow examination demonstrated hypocellular bone marrow with few megakaryocytes, no increase in plasma cells, and no finding suggestive of dysplasia in other cells (Fig. 1a, b). Moreover, there was no abnormal population suggesting myeloma cells by flow cytometry. Chromosomal analysis using G-band staining revealed 46,XX,del(20)(q1?) [10/20], 46,XX [10/20]. In addition, a left adrenal tumor (size, 41 mm) and multiple subcutaneous tumors (size, 5–16 mm)

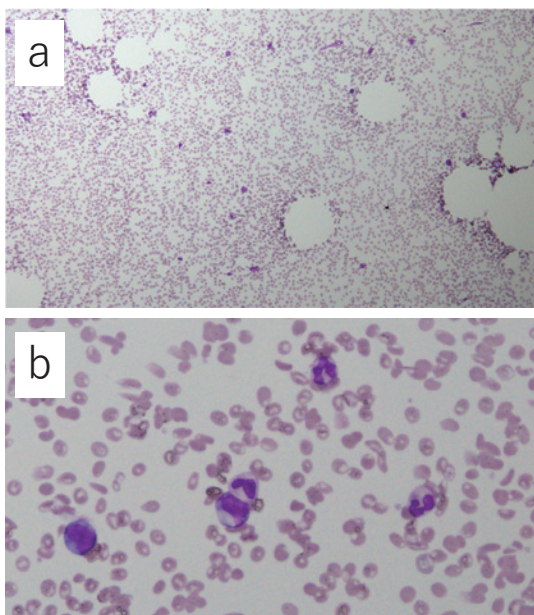


Fig. 1. Bone marrow examination at admission revealed hypocellular bone marrow with few megakaryocytes, no increase in plasma cells, and no findings suggestive of dysplasia in other cells (**a**: May-Giemsa staining $\times 100$, **b**: $\times 400$).

were noted on enhanced computed tomography (CT) with a signal equivalent to that of the soft tissue in the right neck, bilateral chest walls, right abdominal wall, right iliac lateral, and bilateral hips. PBSCH was performed with 2000 mg/m² of CY for 2 days as the conditioning regimen. In addition, 0.24 mg/kg of plerixafor was given one day before apheresis. Apheresis yielded 2.50×10^6 CD34⁺ cells/kg of PBSCs in 2 days. Furthermore, ASCT was performed with 100 mg/m² of melphalan for 2 days as the conditioning regimen. Although antibiotics were required for febrile neutropenia from day 6, engraftment was confirmed on day 14. However, G-CSF discontinuation reduced the neutrocyte level to below 0.5×10^9 cells/L. Conversely, platelet count did not increase over 100×10^9 cells/L. On day 40, hypocellular bone marrow with no megakaryocytes, a few granulocytes with pseudo Pelger-Huet anomaly, and no myeloma cells were observed on bone marrow examination (Fig 2a, b). Chromosomal analysis using G-band staining revealed 46,XX,t(5;13)(q31;q12) [3/20]; 47, idem, +18 [1/20]; 46,XX,del(20)(q11.2;q13.3) [4/20]; 46,XX [12/20]. Fewer megakaryocytes, megaloblastic change in erythrocytes, and few myeloma cells were observed in bone marrow biopsy specimens (Fig. 2c-f). On day 66, enhanced CT and magnetic resonance imaging performed due to the rapid exacerbation of lower back pain demonstrated multiple enhanced tumors in the intracranial, intraspinal, and epidural regions. Accordingly, palliative therapy was performed. The patient died on day 73 while dependent on G-CSF and platelet transfusion.

In the present case, as there was no treatment other than ASCT with high-dose melphalan therapy, we performed PBSCH with plerixafor despite the chromosomal abnormality typifying MDS. Plerixafor facilitated successful harvesting regardless of the insufficient stem cell collection in the early-stage treatment and subsequent treatments, including lenalidomide and cytotoxic chemotherapies. Thus, plerixafor significantly improved the treatment of refractory MM because it provided the treatment option of ASCT to a patient who had been impossible to treat thus far.

A previous study on plerixafor for patients with MM reported no graft failure in 149 patients who underwent ASCT with plerixafor for mobilized stem cells, except for 1 patient who died 10 days post-transplantation.⁴ In another study on plerixafor for patients with NHL, 2 graft failures were reported among 135 patients who underwent ASCT with plerixafor for mobilized stem cells.³ Of note, 1 of these 2 patients with graft failure had preexisting chromosomal abnormalities, and the graft failure was attributed to MDS. The secondary graft failure in our case may have been due to secondary MDS because of the chromosomal abnormality typifying MDS, which was confirmed at the second PBSCH, and dysplasia in erythrocytes, which was detected by bone marrow biopsy at the secondary graft failure. Although the diagnosis of secondary MDS before PBSCH was impossible because of the effects of lenalidomide and the absence of dysplasia in the bone marrow, MDS clones were likely present before PBSCH. Plerixafor blocks the interaction

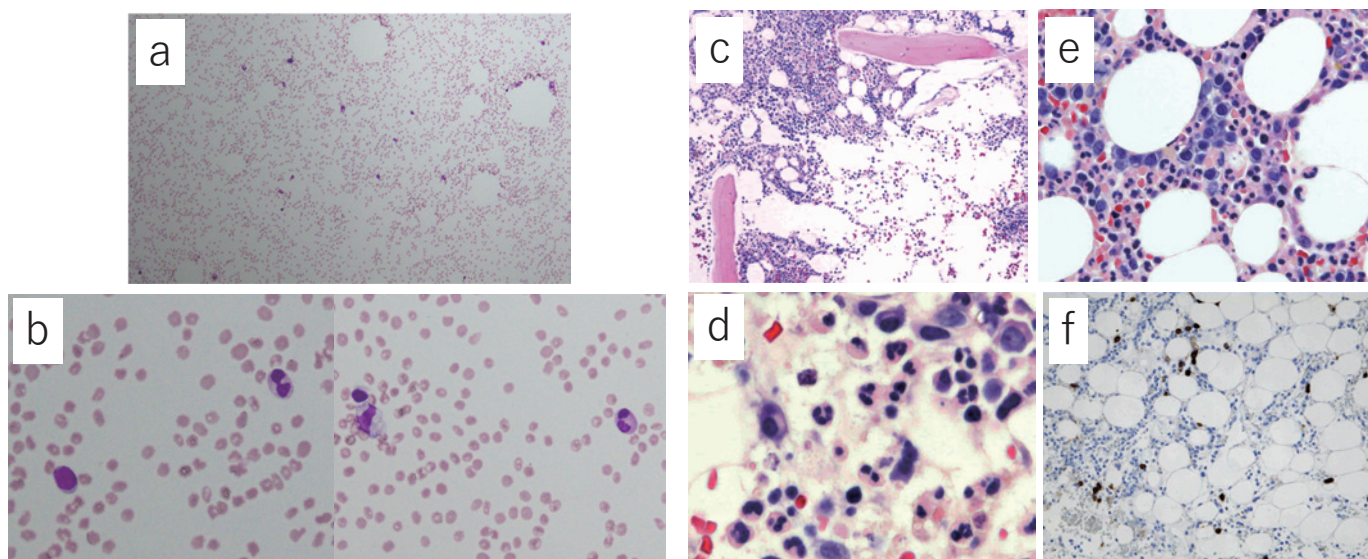


Fig. 2. Bone marrow examination on day 40 of autologous stem cell transplantation revealed hypocellular bone marrow with no megakaryocytes (*a*: $\times 100$), a few granulocytes with pseudo Pelger-Huet anomaly, and no myeloma cells (*b*: $\times 400$). Bone marrow biopsy specimens revealed fewer megakaryocytes (*c*: hematoxylin and eosin staining $\times 100$), megaloblastic change in erythrocytes (*d*: $\times 400$), and few myeloma cells (*e*: $\times 400$, *f*: CD138 immunochemistry staining $\times 400$).

between CD34⁺ cells or leukemic blasts and MDS clones, and can be used in combination with chemotherapy and the conditioning regimen for allogeneic transplantation.^{5,6} In the present case, preexisting MDS clones were mobilized together with CD34⁺ cells, which caused the secondary MDS after ASCT. Secondary MDS in patients undergoing MM treatment,⁷⁻¹¹ including ASCT, has been previously reported.⁹⁻¹¹ In the previously reported patients with MM, the overall diagnostic rate of therapy-related MDS and acute myeloid leukemia (AML) was 0.9%⁷ and 3.4%,⁸ respectively, and the median time for diagnosis was 52.7 months⁷ and 7 years,⁸ respectively. In patients with MM treated using ASCT, the reported 5-year cumulative incidence was 18%, and the median time from ASCT to diagnosis of MDS was 30.9 months.⁹ The median survival in these studies after the diagnosis of MDS/AML was 6.7 months,⁷ 6.3 months,⁸ and 18 months, respectively.⁹ In 49 reported patients who underwent ASCT with plerixafor for mobilized stem cells, the cumulative incidence of MDS/AML at 42 months was 17%.¹¹ The presence of cytogenetic abnormalities typifying MDS and collection of an inadequate number of PBSCs are factors that have been found to affect the development of secondary MDS following ASCT.^{10,12} Until the emergence of plerixafor, collecting a sufficient number of PBSCs from patients presenting with these factors was difficult, limiting ASCT. Thus, the increase in the development of secondary MDS following ASCT with plerixafor for mobilized stem cells may be attributed to an increase in the number of high-risk patients who can undergo ASCT with plerixafor.

A study on second ASCT for MM patients described that the sole use of PBSCs procured after the previous ASCT was for secondary MDS/AML, but the addition of PBSCs collected before ASCT neutralized the risk of MDS/AML.¹² PBSC should be attempted even if sufficient PBSC cannot

be collected. The risk of secondary MDS/AML after ASCT may be reduced by adding these insufficient PBSC to the PBSC collected later.

In conclusion, when performing PBSCH with plerixafor for patients with chromosomal abnormalities typifying MDS and poor mobilization, physicians should consider the possibility of graft failure because of secondary MDS following ASCT. Therefore, during PBSCH with plerixafor, physicians must check chromosomal abnormalities and dysplasia by bone marrow examination in addition to evaluating MM. This should also be kept in mind regardless of the use of plerixafor.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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Received: February 20, 2018.


Revised: July 6, 2018.

Accepted: July 10, 2018.

J-STAGE Advance Published: August 8, 2018

DOI:10.3960/jslrt.18005

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