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Successful mobilization of peripheral blood stem cells in children with cancer using plerixafor (Mozobil™) and granulocyte-colony stimulating factor

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Abstract: This paper describes the successful mobilization of peripheral blood stem cells for autologous transplantation in three children with malignant diseases by using plerixafor (Mozobil™; Genzyme Corporation, Cambridge, MA) and granulocyte-colony stimulating factor (G-CSF) after failed previous mobilizations. A median sixfold increase in the number of circulating CD34+ cells after plerixafor treatment as compared with the baseline level was observed. An optimal CD34+ cell count for transplantation with one or two leukapheresis sessions was achieved. Mobilization using plerixafor was found to be safe with no adverse events. Therefore, the combination of G-CSF and plerixafor in children results in effective increases in peripheral CD34+ cell counts and reduces the risk of mobilization failure.

Keywords: stem cells, mobilization, plerixafor, children, G-CSF

Introduction

High-dose chemotherapy followed by autologous peripheral blood stem cell (PBSC) support is a salvage treatment option for patients with relapsed or refractory malignant diseases such as lymphomas, multiple myeloma (MM), and solid tumors.[1] The minimum dose of hemopoietic stem cells necessary for a prompt and durable engraftment is 2×10^6 CD34+ cells/kg body weight.[2] Unfortunately, this required minimum count is not achieved in approximately 20%–40% of patients undergoing mobilization, who are considered "poor mobilizers".[3] Mobilization of adequate numbers of PBSCs for myeloablative chemotherapy can be challenging in children and adults, although less frequently in the latter.[4] There is limited information about the frequency of unsuccessful mobilizations in children. Our experience revealed that approximately 11% of children and 21% of adults are poor mobilizers. Most of the children considered poor mobilizers either have Hodgkin's disease (HD) and solid tumors, or received large-volume chemotherapy and radiotherapy before attempted mobilization, or both.

Plerixafor (Mozobil™; Genzyme Corporation, Cambridge, MA) is a selective and reversible CXC chemokine receptor type 4 (CXCR4) antagonist and interrupts interaction of CXCR4 with stromal cell-derived factor-1 (SDF-1), thus resulting in rapid mobilization of stem cells in peripheral blood. In combination with granulocyte-colony stimulating factor (G-CSF), plerixafor leads to successful mobilization in approximately 70% of adult patients with non-Hodgkin's lymphoma, HD, and MM who failed a previous mobilization with G-CSF alone or in combination with chemotherapy.[5] Data on the use of plerixafor in stem cell mobilization in children are very limited.[3,4,6,7]

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Therefore, the experience, although limited, of our institution in the use of plerixafor for PBSC mobilization in children with cancer is presented here.

Methods

The patients are three boys, aged 8 years (Patient 1), 17 years (Patient 2), and 7 years (Patient 3) (Table 1). Two patients have HD with extranodal localizations (lung and bone), and one patient has a metastatic germ cell tumor. They all have refractory disease, had exhibited partial remission after second-line treatment, and consented to receive myeloablative chemotherapy and autologous PBSC transplantation as a salvage therapy. All three patients failed an earlier mobilization with chemotherapy and G-CSF, and Patient 1 failed a second mobilization with G-CSF alone (CD34+ cell count below 10 cells/μL in peripheral blood measured before apheresis). The patients with HD were mobilized using cyclophosphamide and G-CSF, and the patient with the germ cell tumor was mobilized using cyclophosphamide, etoposide (VP-16), and G-CSF.

After a discussion within the institution, it was decided that mobilization would be performed in each of these patients using a protocol for plerixafor and G-CSF. Plerixafor was obtained on a compassionate basis from Genzyme Bulgaria (Sofia). Written informed consent was obtained from the parents of the patients before therapy. Mobilization not including chemotherapy was started during each patient's hematological steady state with a 4-day subcutaneous administration of nonpegylated G-CSF at 10 μg/kg once daily in the morning. In the evening of the fourth day, at 11 hours before apheresis, plerixafor at 240 μg/kg was subcutaneously administered. G-CSF was given on the fifth day at 1 hour before apheresis. Patient 1 underwent one apheresis session with a very high yield of CD34+ cells, whereas the other two patients required two days for collections. In Patients 2 and 3, the session of plerixafor was repeated. PBSC collections began when the circulating CD34+ cell count exceeded 15 cells/μL after plerixafor administration. Double-volume leukapheresis was performed according to institutional guidelines. Harvesting was performed using the Fresenius Kabi AG (Bad Homburg, Germany) COM.TEC apheresis system. Apheresis product processing and storage were performed as per standardized procedures. According to institutional guidelines, the stem cell products were tested for bacterial and fungal contamination but not for tumor cell contamination (the protocol makes no provision for tumor cells). All products tested negative for microbial contamination.

Results

In all three patients, the peripheral blood CD34+ cell counts increased 3–13-fold (176, 31, and 75 cells/μL in Patients 1, 2, and 3, respectively) (Figure 1) at 11 hours following first plerixafor application. The total number of white blood cells also increased but less markedly. Successful total CD34+ cell yields above the margin of 2×10^6 cells/kg (11.3×10^6, 3.27×10^6, and 4.76×10^6 cells/kg) after one or two apheresis sessions was obtained. The patients did not experience any local or systemic adverse effects attributed to plerixafor such as diarrhea, nausea, injection site reactions, fatigue, headache, hypersensitivity, muscular pain, dizziness, arthralgia, or less common adverse effects such as dyspnea, increased fibrin D-dimers, anemia, hypotension, pulmonary embolism, and spleen

Table 1 Patient characteristics

Characteristic	Patient 1	Patient 2	Patient 3
Age (years)	8	17	7
Sex	Male	Male	Male
Body weight (kg)	25	50	33
Diagnosis	HD	Germ cell tumor	HD
Disease status at the time of PBSC mobilization	PR	PR	PR
Previous mobilization (n/type)	2/ch + G-CSF; G-CSF	1/ch + G-CSF	1/ch + G-CSF
Previous radiotherapy	Yes	No	No
Number of previous chemotherapy cycles	12	8	8
Number of plerixafor injections	1	2	2
Daily dose of plerixafor (mg)	6	12	8
WBC at baseline (/μL)	42×10^3	39×10^3	24.9×10^3
WBC at 11 hours after plerixafor (/μL)	58.8×10^3	63×10^3	57.4×10^3
CD34+ at baseline (/μL)	13	11	7
CD34+ at 11 hours after plerixafor (/μL)	176	31	75
-fold – increase CD34+ count	13.5	2.8	10.7
Total number of collected CD34+ cells ($\times 10^6$/kg)	11.3	3.27	4.76
Total number of aphereses per patient	1	2	2

Abbreviations: Ch, chemotherapy; G-CSF, granulocyte-colony stimulating factor; HD, Hodgkin's disease; PBSC, peripheral blood stem cell; PR, partial remission; WBC, white blood cells.

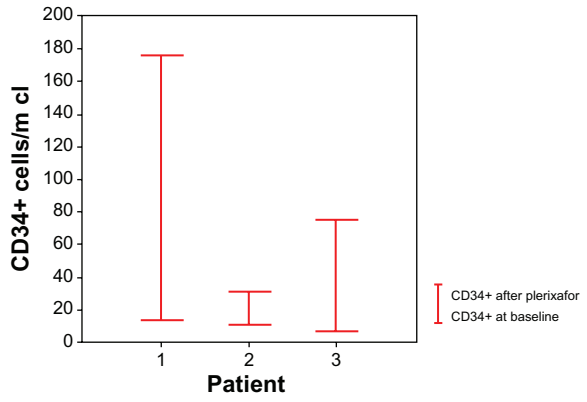

Figure 1 Sharp increase of patient's peripheral blood CD34+ cell counts 11 hours after the application of plerixafor (day 5, morning).
Abbreviations: HD, Hodgkin's disease; PBSC, peripheral blood stem cell; G-CSF, granulocyte-colony stimulating factor; WBC, white blood cells.

rupture. All patients received myeloablative chemotherapy for their specific diseases followed by the infusion of collected CD34+ cells. Hematological recovery (absolute neutrophil count, >500 cells/μL; platelet count, >20,000 cells/μL) occurred on days 9 and 11, 11 and 15, and 10 and 13 after the treatment for patients 1, 2, and 3, respectively. All patients had no transplant-related infections or other comorbidities.

Discussion

In adults with lymphomas and MM, the success of stem cell mobilization induced by plerixafor and G-CSF is well established. Although a number of studies from different centers and countries have demonstrated the efficacy of this combination in adults, studies in children are limited.[3,4,6,7] It should be noted that most of the described children have solid tumors.[4,6,7] This is mainly because the current treatment strategy in this age group involves single or tandem myeloablative chemotherapy with autologous PBSC transplantation for relapsed or conventional chemotherapy-resistant brain tumors, neuroblastomas, Ewing sarcomas, germ cell tumors, and other malignancies. These patients are often heavily pretreated and have difficulties in mobilizing the minimal number of CD34+ cells for transplantation. Most of these patients require more than two mobilization attempts or bone marrow harvesting, with all its known unfavorable effects, and delays in the administration of high-dose chemotherapy.[4]

The results of the present study show that the combination of G-CSF and plerixafor in children results in a higher increase in the peripheral CD34+ cell counts, provides sufficient numbers of PBSCs for transplantation with fewer apheresis sessions, ensures a faster progression to high-dose chemotherapy, and reduces the risk of mobilization failure with an acceptable safety profile and time periods to engraftment.[3,4]

Conclusion

On the basis of this report and the reviewed literature, G-CSF and plerixafor can be considered a suitable combination for PBSC mobilization in children with malignant diseases and failures in previous conventional mobilization attempts. Standard guidelines for the use of plerixafor in stem cell mobilization in pediatric patients based on multicenter studies will obviously be needed.

Disclosure

The authors declare no conflicts of interest in relation to this paper.

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