Herpes Zoster Infection Associated with Poor Peripheral Blood Hematopoietic Stem Cell Mobilization

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The efficacy of peripheral blood hematopoietic stem cell (PBSC) harvest is important for successful autologous transplantation. The impact of viral infection on PBSC mobilization has rarely been reported. Here, we report a patient with relapsed diffuse large B-cell lymphoma who experienced disseminated cutaneous herpes zoster infection during the neutropenic phase of PBSC mobilization. A markedly reduced number of PBSCs was initially harvested ($1.72 \times 10^6$/kg, 77.2% reduction), followed by a sufficient number ($7.55 \times 10^6$/kg) during remobilization with the same mobilization regimen when herpes zoster infection had subsided. Because of the temporal association, we suggest that herpes zoster infection is a risk factor for poor PBSC mobilization, and remobilization with the same regimen is feasible. [J Formos Med Assoc 2008;107(12):958–960]

Key Words: autologous peripheral blood stem cell transplantation, hematopoietic stem cell transplantation, herpes virus, mobilization

Mobilized peripheral blood hematopoietic stem cells (PBSCs) have become the main source for autologous and allogeneic hematopoietic stem cell transplantation in patients with various hematologic malignancies and solid tumors. However, a number of patients fail to yield sufficient PBSCs for successful engraftment. There is a significant correlation between the quantity of re-infused CD34+ cells and sustained engraftment. Many risk factors account for poor mobilization,1–6 but the influence of viral infection, which occurs especially in the neutropenic phase of mobilization chemotherapy, has rarely been reported. Here, we report a case of relapsed diffuse large B-cell lymphoma (DLBCL) with poor PBSC mobilization. This may have been associated with reactivation of herpes zoster virus during the neutropenic phase of mobilization chemotherapy. We obtained a sufficient number of PBSCs during remobilization using the same mobilization regimen.

Case Report

A 54-year-old man with primary extranodal DLBCL of the right tibia initially presented with painful swelling of the right lower leg and a right tibial osteolytic tumor. He showed complete remission after eight courses of standard CHOP (cyclophosphamide, doxorubicin, vincristine and prednisolone) chemotherapy and subsequent 6500 cGy radiotherapy. Relapsed DLBCL over the radius, ulna and sternum, without bone marrow involvement, was found 13 months later, and a...
partial response was noted after two courses of salvage chemotherapy with MINE (mitoxantrone, ifosfamide and etoposide). In preparation for high-dose chemotherapy with autologous PBSC transplantation, PBSCs were mobilized with a conventional regimen of cyclophosphamide (4 g/m²) and granulocyte colony-stimulating factor (G-CSF; 5 μg/kg/day since nadir white blood cell count [WBC]), 7 weeks after the latest chemotherapy regimen. However, 8 days after chemotherapy, during the neutropenic phase (WBC, 190/μL) of mobilization chemotherapy, he developed painful vesiculopapular eruptions on an erythematous base over the unilateral T10 dermatome. Skin biopsy revealed intraepidermal vesicles with intercellular edema, multinucleated giant keratinocytes with steel grey nuclei, and margination of chromatin. All cultures for bacteria and fungi were negative. Testing for herpes zoster virus IgM was positive when a skin rash developed. Herpes zoster and herpes simplex virus IgG levels were <1:4 and 1:32, respectively, when the skin rash developed. Both titers were 1:16 at the convalescent stage when skin lesions subsided. Intravenous acyclovir was initiated 10 days after chemotherapy and the skin lesions subsided gradually 3 weeks later.

PBSCs were harvested as scheduled by three apheresis procedures when WBC approached 1000/μL (11 days after cyclophosphamide). The total number of CD34⁺ cells was $7.55 \times 10^6$/kg. CD34⁺ cell percentages in peripheral blood were 0.36%, 0.62% and 0.56% on 3 consecutive days.

Compared with the recruited CD34⁺ cell amount, there was a 77.2% reduction in CD34⁺ cells ($1.72 \ vs. \ 7.55 \times 10^6$/kg) when the patient showed evidence of active herpes zoster infection. The characteristics of the two consecutive courses of PBSC harvest are shown in the Table.

**Discussion**

Autologous PBSC transplantation following myeloablative therapy is widely used for various hematologic malignancies and solid tumors. The goal of PBSC mobilization is to obtain at least $2 \times 10^6$/kg CD34⁺ cells to ensure rapid and sustained engraftment. There are many risk factors that are correlated with poor mobilization. Type of malignancy, different mobilization regimens, interval between diagnosis and mobilization, number of prior chemotherapy courses, prolonged exposure to alkylating agents, lower WBC and platelet count, old age, disease status, and the interval between recent chemotherapy and mobilization are known to influence PBSC yield.¹⁻⁶ In our case, the two harvests had a similar interval between the latest chemotherapy and mobilization chemotherapy (7 vs. 8 weeks) and a similar initial WBC and platelet count. However, the first

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<th>Comparison of peripheral blood hematopoietic stem cell (PBSC) harvests</th>
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<tr>
<td></td>
<td>First harvest</td>
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<td>Interval between latest chemotherapy and mobilization chemotherapy (wk)</td>
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<td>Time from CY to PBSC harvest (d)</td>
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<td>CD34⁺ cell percentage in peripheral blood during 3 consecutive days of apheresis</td>
<td>0.10/0.20/0.14</td>
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<tr>
<td>Total CD34⁺ cells ($\times 10^6$/kg)</td>
<td>1.72</td>
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*CY = cyclophosphamide; G-CSF = granulocyte colony-stimulating factor; WBC = white blood cell count.*
harvest was temporally associated with reactivation of herpes zoster virus. Therefore, we believe that the cause of poor PBSC mobilization in the first session may have been associated with viral reactivation.

The risk of viral infection or reactivation is high among patients with impaired cell-mediated immunity. However, most of the studies focus on post-transplant analysis, and the impact of viral infection on the efficacy of PBSC harvest is unknown. Viral infection may cause a variable degree of bone marrow suppression. The causes include a direct cytotoxic effect on marrow cells, stimulation of the immune response through activation of cytotoxic lymphocytes or expression of viral proteins, or an influence on marrow stromal cells to compromise the bone marrow microenvironment. Nevertheless, although the mechanism of PBSC mobilization is not fully understood, the complex interplay between adhesion molecules, chemokines, cytokines, proteolytic enzymes, and stromal cells is involved in PBSC mobilization. It is possible that the inflammatory cytokines with their negative effect on proliferation of hematopoietic stem cells play a role in poor mobilization at the time of herpes virus infection. Further study is necessary to explore the linkage between viral infection and its effect on PBSC mobilization.

To resolve the problem of poor mobilization, remobilization with marrow harvest, a higher dose of G-CSF, other chemotherapy or growth factor combination regimens, newly developed agents such as AMD3100, used alone or in combination with G-CSF or chemotherapy, has been reported. What to use for a repeat mobilization attempt for a specific patient and disease may be a complex decision. The interval between mobilization and remobilization is also crucial. Our experience suggests that remobilization with the same regimen (cyclophosphamide and G-CSF) is feasible when the cause of poor mobilization is associated with herpes zoster virus reactivation and, possibly, other viral infections.

In conclusion, we presented a case of poor PBSC mobilization that might have been associated with reactivation of herpes zoster virus during the neutropenic phase of mobilization chemotherapy, and showed the feasibility of remobilization with the same regimen. However, further study is necessary to examine the association between viral infection and PBSC mobilization.

References