Successful Treatment With Third Stem Cell Transplant From an Allogeneic Donor for a Patient With Relapsed Diffuse Large B-Cell Lymphoma

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Abstract

High-dose chemotherapy with autologous stem cell transplant is commonly used for diffuse large B-cell lymphoma that recurs after successful salvage chemotherapy. However, in patients in whom the disease recurs again, the prognosis is poor. A 40-year-old woman who underwent allogeneic stem cell transplant 4 years after autologous stem cell transplant developed recurrent diffuse large B-cell lymphoma 3 years after the initial autologous stem cell transplant. She then underwent reduced-intensity hematopoietic stem cell transplant from a human leukocyte antigen-matched, unrelated donor who was not the previous autologous stem cell transplant donor. She achieved a long survival (328 days after the reduced-intensity hematopoietic stem cell transplant and 1844 days after the first allogeneic transplant). A second allogenic transplant may provide survival benefits in a proportion of patients with malignant lymphoma recurring after allogeneic transplant, although careful consideration is required because of the high risk of treatment-related mortality with second allogenic transplant.

Key words: Vasculopathy, Immunosuppression, Chronic rejection, Alloantibodies

Introduction

Standard therapy for diffuse large B-cell lymphoma (DLBCL) recurring after successful salvage chemotherapy is high-dose chemotherapy with autologous stem cell transplant (auto-SCT). However, if the disease recurs again after these therapies, the mean survival time of the patients is 7 to 8 months median survival duration.1,2 Standard therapy for such patients has not been established. Current treatments include chemotherapy with other drugs, a second trial of auto-SCT, and allogeneic stem cell transplant (allo-SCT). We report a patient who underwent allo-SCT 4 years after auto-SCT and developed recurrent DLBCL 3 years later. She then underwent reduced-intensity hematopoietic stem cell transplant (RIST) from an HLA-matched unrelated donor (HLA-MURD) who was not her previous allo-SCT donor, and she survived for a long time.

Case Report

A 40-year-old woman whose major complaint was pain in the left elbow visited a primary care doctor. A mass was found in the distal tip of the left humerus. Surgical removal of the lesion was performed in May 1993. Immunostaining revealed a diffuse proliferation of CD20-positive and CD79a-positive medium and large lymphoma cells. Based on these findings, DLBCL was diagnosed. Chromosome analysis showed a normal karyotype, and the clinical stage was IEA. The first remission was achieved after 3 courses of CHOP therapy plus local radiation therapy at 40 Gy. However, recurrent lesions were found in the left humerus in January 1998 and in the nasal cavity in July 2000. The recurrences were treated by salvage...
chemotherapy. A third recurrence followed by salvage chemotherapy and auto-SCT was performed in June 2002. A high-dose regimen of ranimustine 300 mg/m² on day 6, etoposide 200 mg/m² from days 5 to 2, Ara-C 2 g/m² from days 3 to 2, and melphalan 140 mg/m² on day 1 was administered.

In April 2006, she experienced a fourth relapse with bone metastases and bone marrow infiltration when she transferred to our hospital. At that time, multiple bone lesions and bone marrow infiltration were observed. Atypical cells in the bone marrow were CD19−, CD20−, and CD79a-positive, and CD3− and CD10-negative medium and large cells. Therefore, recurrent DLBCL was diagnosed. At that time, performance status was 0, lactate dehydrogenase was 196 IU/L, the clinical re-stage was stage IV EA, and the secondary international prognostic index was low-intermediate risk. After 3 courses of combination therapy of rituximab and ESHAP (ie, rituximab 375 mg/m² on day 1; etoposide 40 mg/m² from days 2 to 5; carboplatin 37.5 mg/m² from days 2 to 5; methylprednisolone 500 mg/body from days 2 to 6; and cytarabine 2000 mg/m² on day 6), partial remission was achieved. In October 2006, RIST from HLA-A, HLA-B, HLA-DR antigens from a matched unrelated donor was performed after a conditioning regimen with cyclophosphamide 750 mg/m² and fludarabine 25 mg/m² from days −5 to −3. Grade 2 acute graft-versus-host disease developed 17 days after transplant, and this was relieved using only topical steroids. After that, extensive-type chronic acute graft-versus-host disease was developed 17 days after transplant, and this was relieved using only topical steroids. After that, extensive-type chronic acute graft-versus-host disease was observed; however, spontaneous remission occurred. Bone marrow examination did not show infiltration of lymphoma cells, and a positron emission tomography-computed tomography scan showed a reduced accumulation in bone lesions; complete remission after allo-SCT was diagnosed. However, in November 2009, enlargement of the left precordial region was observed and, based on a biopsy of the site, recurrence of DLBCL was diagnosed. Immunosuppressive drugs were discontinued 6 months after transplant. Donor lymphocyte infusion was considered, but consent for donor lymphocyte infusion was not obtained from the donor. Therefore, 4 courses of combination therapy of rituximab and EPOCH (rituximab 375 mg/m² on day 1; etoposide 50 mg/m² from days 2 to 5; vincristine 0.4 mg/m² from days 2 to 5; Adriamycin 10 mg/m² from days 2 to 5; cyclophosphamide 750 mg/m² on day 6; and prednisolone 60 mg/m² from days 2 to 6) were performed. We selected a different unrelated donor for the second allo-SCT because we were able to find a suitable HLA-MURD for the second allo-SCT, while none were available for the first allo-SCT. The second RIST HLA-A, HLA-B, HLA-DR antigens matching an unrelated another donor was performed in January 2011 (fludarabine 25 mg/m² from days 8 to −4; melphalan 70 mg/m² from days −3 to −2; and total body irradiation at 4 Gy on day −1). Hematopoietic stem cell transplant comorbidity index (HCT-CI) before RIST was 0. She has been in complete remission without severe complications (including acute graft-versus-host disease) to the time of this writing, and she has been surviving for 6 years since she relapsed after the initial allo-SCT.

Discussion

In the Parma study, in which patients with salvage chemotherapy-sensitive, recurrent aggressive non-Hodgkin lymphoma, were randomly assigned to undergo auto-SCT or to continue chemotherapy, overall survival was significantly longer in the auto-SCT group; now auto-SCT is considered standard therapy for chemotherapy-sensitive, recurrent aggressive non-Hodgkin lymphoma. However, the 5-year overall survival and disease-free survival after auto-SCT in Parma study were 53% and 46%; the outcome was not sufficiently favorable. It was reported that the poor prognostic factors after auto-SCT included unresponsiveness to salvage chemotherapy, high risk of relapse on secondary international prognostic index, and high risk of relapse on HCT-CI. Standard therapy for recurrence after auto-SCT has not been established. In a small number of patients who have undergone a second auto-SCT, the response rates to the second auto-SCT were 20% to 40% and treatment-related mortality occurred in 10% to 20% of patients. Various problems were highlighted, such as a potential increased risk of secondary cancer and difficulty obtaining enough stem cells. Compared to auto-SCT, the advantages of allo-SCT are that there is no possibility of tumor cell contamination and that graft-versus-lymphoma effect is expected.

Freytes and associates reported that the 5-year overall survival, disease-free survival, and treatment-related mortality after auto-SCT were 24%, 5%, and 25% in 114 patients with malignant lymphoma who received myeloablative conditioning regimen for
recurrence after auto-SCT; and that poor prognostic factors included non-total body irradiation regimen and transplant in nonremission. On the other hand, it was reported that the 3-year overall survival, disease-free survival, and treatment-related mortality after RIST were 32%, 21%, and 44% in 263 patients with malignant lymphoma who underwent RIST for recurrence after auto-SCT, and that poor prognostic factors included non-total body irradiation regimen, transplant in nonremission, and poor performance status at transplant. In 101 patients with DLBCL who underwent allo-SCT (myeloablative conditioning regimen, n=37; RIST, n=64) for recurrence after auto-SCT, 3-year overall survival, progression-free survival, and treatment-related mortality were 54%, 42%, and 28% with no difference in outcome between pretransplant treatments. Poor prognostic factors included early relapse after auto-SCT, age 45 years or more, and transplant in nonremission. It is reported that RIST for malignant lymphoma recurring after auto-SCT may provide a similar outcome to myeloablative transplant; RIST did not always improve treatment-related mortality, so even when RIST is used, treatment-related mortality remains a problem.

This patient described here developed recurrent disease 4 years after auto-SCT and underwent RIST. Reduced-intensity hematopoietic stem cell transplant was selected, instead of a second auto-SCT, because the response to salvage therapy was only partial remission, HCT-CI before transplant was good, and cells from an HLA-MURD were available.

The patient again developed recurrent disease 3 years after the RIST. When recurrence occurs after allo-SCT, if severe acute graft-versus-host disease does not occur, immunosuppressive drugs are discontinued. Bishop and associates reported that the therapeutic effect of discontinuation of immunosuppressive drugs was observed in 60% of 15 patients with DLBCL recurring after allo-SCT; however, the long-term therapeutic effect is not known.

Wudhikarn and associates conducted a study in 72 patients with malignant lymphoma that recurred after allo-SCT and reported that the 3-year survival rate was 44%. Discontinuation of immunosuppressive drugs was selected as a primary therapy in 81% of the patients; however, complete remission was achieved in only 13.8%; the remaining patients received chemotherapy, radiation therapy, donor lymphocyte infusion, or second allo-SCT as a secondary therapy. Wudhikarn and associates reported that poor prognostic factors included early (<100 days) posttransplant relapse, a poor response to therapy after transplant, an advanced stage at relapse, and certain histologic types (Indolent [60%] vs Hodgkin [49%] vs DLBCL [46%] vs Mantle [43%] vs T/NK [39%] vs Burkitt [0%]; P = .05).

There have been no reports on second allo-SCT for recurrence of malignant lymphoma after allo-SCT alone. In patients with hematopoietic malignancy who underwent second allo-SCT after first allo-SCT, 5-year overall survival, disease-free survival, and treatment-related mortality were 26% to 28%, 25% to 28%, and 30% to 46%; it was reported that poor prognostic factors included early posttransplant relapse, non-total body irradiation regimen, and age 20 years or more at second allo-SCT. It has been suggested that the therapeutic effect of retransplant may be expected in some hematopoietic malignancy patients whose time from the first allo-SCT to relapse was longer. In our patient, a favorable outcome was achieved, probably because recurrence occurred 4 years after the first allo-SCT and because HCT-CI at second allo-SCT remained good. There are no confirmatory data about an advantage for the selection of a different donor for the second SCT, although there are reports about this selection, including a study showing that different donor has a trend toward better outcome.

In conclusion, we treated a patient with DLBCL recurring after autologous transplant and allo-SCT who underwent second allo-SCT and achieved a good therapeutic effect. Because the risk of treatment-related mortality in second allo-SCT is high, careful consideration is required when selecting patients for second allo-SCT. However, our experience suggests that second allo-SCT may provide a longer survival period in some patients with malignant lymphoma recurring after allo-SCT.

References


