A case of allogeneic hematopoietic stem cell transplantation for primary plasma cell leukemia after treatment with daratumumab

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Dear Editor,

Plasma cell leukemia (PCL) is a variant of multiple myeloma (MM), and it is defined by the presence of more than 20% of plasma cells in peripheral blood and an absolute plasma cell count greater than 2×10^9/l[1]. Because primary PCL (pPCL), a PCL subtype without evidence of previous MM, shows frequent early treatment failure and poor prognosis [2], hematopoietic stem cell transplantation (HCT) should be considered . However, although it is reported that autologous and/or allogeneic stem cell transplantation improves pPCL outcomes [3], an appropriate strategy of HCT for pPCL remains elusive.

Here, we report about a patient who underwent allogeneic HCT (allo-HCT) for pPCL that was treated using salvage chemotherapy with daratumumab. To our knowledge, this is the first report of allo-HCT after treatment with daratumumab.

A 47-year-old Japanese man presented with lower back pain and right vision deterioration, which was diagnosed as central retinal vein occlusion by an ophthalmologist, and he was referred to the previous hospital. He was diagnosed with immunoglobulin (Ig) A-kappa-type PCL based on the following laboratory data: white cell blood count, 22200/μl with 87.0% lymphocytes that were mostly abnormal plasmacytes; serum IgA level, 5904 mg/dl; and serum free kappa/lambda ratio, 166.47. Bone marrow aspiration showed 78.8% plasmacytes, and the karyotype was 46, inv (Y) (p11.2; q11.2). An interphase fluorescence in situ hybridization study revealed that t (11;14) was positive but t (4;14), t (14;16), del (13), and del (17) were negative. After four cycles of bortezomib, lenalidomide, and low-dose dexamethasone (VRd) by the previous doctor, he was referred to our hospital for HCT. Laboratory test results on admission were as follows: white blood cells, 3940/μl without abnormal plasmacytes;

hemoglobin, 13.7 g/dl; platelet count, 21.1 × 10^4/μl; IgG, 282 ml/dl; IgM, 25 mg/dl; IgA, 475 mg/dl; and serum free kappa/lambda ratio, 10.31. Bone marrow aspiration showed 1.8% plasmacytes, and complex karyotype with t (11;14) was noted (Fig 1).

After the patient's admission to our hospital, VRd therapy was continued. Because bone marrow aspiration after five cycles of VRd revealed an increase in abnormal plasmacytes, we concluded that the disease was refractory to VRd. Therefore, the chemotherapy regimen was changed to daratumumab, lenalidomide, and low-dose dexamethasone (DRd), following which the abnormal plasmacytes in the bone marrow decreased again. After two cycles of DRd, high-dose melphalan (100 mg/m^2 for 2 consecutive days) with autologous stem cell transplantation (ASCT) was performed, and a stringent complete remission was achieved. After ASCT, DRd therapy was continued for six cycles in total.

We decided to perform allo-HCT for three reasons: first, on stem cell mobilization, we harvested only 1.75×10^6/kg of CD34-positive cells that were not sufficient for tandem ASCT; second, a suitable human leukocyte antigen-matched unrelated donor was found; and finally, the patient's general state was good even after ASCT.

The patient underwent human leukocyte antigens 8/8 full-matched unrelated bone marrow transplantation with a conditioning regimen of fludarabine (25 mg/m^2 for 5 consecutive days), melphalan (70 mg/m^2 for 2 consecutive days), and 8-Gy total body irradiation. This treatment was based on a previous report that demonstrated the feasibility of a myeloablative-conditioning regimen for MM patients after ASCT [4]. For graft-versus-host disease (GVHD) prophylaxis, tacrolimus and methotrexate were used. The total nucleated cell count of bone marrow collection was 2.13×10^8/kg. Neutrophil engraftment was achieved on day 12, and chimerism analysis from bone marrow

aspiration revealed a complete donor chimerism on day 31. No acute GVHD symptoms appeared, and the patient was discharged on day 50. Primary PCL remained in stringent complete remission 18 months after allo-HCT.

Daratumumab is a human CD38 monoclonal antibody that targets CD38-expressing myeloma cells and has a high therapeutic effect in patients with myeloma [5]. In fact, in a POLLUX study, a phase 3 trial of combination with daratumumab therapy showed that DRd prolongs the progression-free survival of patients with relapsed or refractory MM compared with lenalidomide and DRd therapy [6]. However, the use of daratumumab as a consolidation or salvage therapy before allo-HCT has not yet been reported. Although a clinical trial of daratumumab-containing regimen for patients with newly diagnosed myeloma before ASCT has been reported [7], the safety and efficacy of allo-HCT after daratumumab therapy remains unclear.

CD38 is not only expressed by myeloma cells but also on normal myeloid progenitor cells and lymphocytes [8]. Therefore, in allo-HCT, daratumumab can kill CD38-positive myeloid cells and regulatory T cells from the donor's bone marrow [9-10], which can cause an increase in the rate of graft failure and acute GVHD. However, previous studies reported that daratumumab in vitro is not toxic to CD34- and CD38-positive cells mobilized from patients with myeloma [11], and daratumumab administered as a salvage therapy in patients with relapsed or refractory MM after allo-HCT does not increase the GVHD rate [12], and this supports the safety of using daratumumab before allo-HCT.

In conclusion, we described a case of pPCL that was successfully treated with allo-HCT after salvage therapy with daratumumab for the first time. Faster engraftment was achieved, and no acute GVHD was encountered, suggesting that daratumumab had no adverse effect on the prognosis of allo-HCT. To evaluate the efficacy and safety of

daratumumab before allo-HCT, further analysis with a larger number of patients must be conducted.

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Compliance with ehical standards

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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Informed consent: Informed consent was obtained from the patient included in the study.

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Figure legends

Figure 1. Clinical course until allogeneic hematopoietic stem cell transplantation

VRd: bortezomib, lenalidomide, and low-dose dexamethasone

DRd: daratumumab, lenalidomide, and low-dose dexamethasone