

Successful sequential therapy with rituximab and daratumumab for refractory post-transplant immune thrombocytopenic purpura

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LETTER TO THE EDITOR

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ABBREVIATIONS

BMT	Bone marrow transplantation
GVHD	Graft-versus-host disease
HCT	Hematopoietic cell transplantation
HLA	Human leukocyte antigen
ITP	Immune thrombocytopenic purpura
IMC	Immune-mediated cytopenia
IVIG	Intravenous immunoglobulin

BMT	Bone marrow transplantation
mAb	Monoclonal antibody
RIC	Reduced-intensity conditioning
TPO-RA	Thrombopoietin receptor agonist

To the Editor,

Immune-mediated cytopenias (IMCs), including immune thrombocytopenic purpura (ITP), autoimmune hemolytic anemia, and autoimmune neutropenia, have been newly highlighted as a significant complication after allogeneic hematopoietic cell transplantation (HCT), with a cumulative incidence of 2.1% to 52.6%.^{1,2} Major risk factors for post-transplant IMC include younger recipient age at HCT, non-malignant disease, cord blood transplantation, unrelated donor, and a reduced-intensity conditioning (RIC) regimen.^{1,2} Post-transplant IMCs are occasionally resistant to conventional first-line therapy, i.e., corticosteroid and/or intravenous immunoglobulin (IVIG) therapy in combination with supportive therapy, such as granulocyte colony-stimulating factor, thrombopoietin receptor agonist (TPO-RA), and transfusion. Rituximab, an anti-CD20 monoclonal antibody (mAb), mycophenolate mofetil, bortezomib, and daratumumab, an anti-CD38 mAb, have been used as second-line or subsequent therapies for refractory or recurrent cases.¹⁻⁵

A 17-year-old boy with adrenoleukodystrophy underwent allogeneic bone marrow transplantation (BMT) from a human leukocyte antigen (HLA) 7/8 allele-matched unrelated donor using a RIC regimen consisting of fludarabine (125 mg/m²), melphalan (140 mg/m²), rabbit anti-thymocyte globulin (5 mg/kg), and total body irradiation of 4 Gy. Tacrolimus and short-term methotrexate were administered as prophylaxis for graft-versus-host disease (GVHD). Myeloid lineage cell engraftment and complete chimerism were achieved on days 20 and 28, respectively. No significant GVHD was observed.

On day 118, he was readmitted to our hospital with oral bleeding and cutaneous purpura, and was diagnosed with ITP. The clinical course after onset of ITP is shown in the Figure. Soon after re-admission, frequent red blood cell and platelet transfusions were required to treat massive gastric mucosal bleeding. Since various treatments, such as IVIG, prednisolone, methylprednisolone, TPO-RAs (eltrombopag and romiplostim), and four courses of 375 mg/m²/week rituximab, failed to improve thrombocytopenia, he received one course of 16 mg/kg daratumumab on day 191, after the approval for use as an unapproved drug from the Patient Safety Unit of Kyoto University Hospital. His platelet counts soon exceeded 100×10⁹/L but suddenly decreased 7 months later while he was receiving romiplostim therapy. Since the effect of the three courses of daratumumab was transient and serial flow cytometric analyses demonstrated the reemergence of CD20+ B cells, which had disappeared after rituximab therapy, just before the recurrence of ITP, he received four courses of rituximab in combination with prednisolone (1 mg/kg/day) and romiplostim. His platelet counts gradually increased and reached more than 100×10⁹/L 1 month after initiation of the second rituximab treatment, while he was still undergoing therapy with prednisolone and romiplostim.

The pathophysiology of post-HCT IMCs is still poorly understood. However, it has been speculated that immune dysregulation caused by conditioning regimens, infections, GVHD, immunosuppressive agents, reduced and dysfunctional regulatory T cells, and/or HLA mismatched donor-derived naïve T cells trigger the development of post-HCT IMCs mainly via auto-antibody production to hematopoietic cells.^{1,2,6} High-throughput single-cell bioassay of antibody-secreting cells of ITP patients has recently demonstrated the existence and dissemination of autoreactive plasma cells in multiple hematopoiesis organs, such as spleen, bone marrow, and lymph nodes, which might reduce the efficacy of B cell depletion by rituximab.⁵ In the present case, CD38-targeting therapy using daratumumab quickly improved the first episode of rituximab-refractory ITP, suggesting the presence of autoreactive plasma cells. By contrast, additional rituximab therapy was effective in counteracting the recurrence of daratumumab-refractory ITP, implying the presence of remnant autoreactive B cells. Thus, sequential or combination therapy with rituximab and daratumumab appears to be a promising therapeutic option for refractory post-transplant IMCs, which might be caused by multiple antibody-secreting cell populations.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest associated with this manuscript.

REFERENCES

1. Michniacki TF, Ebens CL, Choi SW. Immune-mediated cytopenias after hematopoietic cell transplantation: pathophysiology, clinical manifestations, diagnosis, and treatment strategies. *Curr Oncol Rep* . 2019;21:87.
2. Gupta AO, Boelensbe JJ, Ebens CL, et al. Consensus opinion on immune-mediated cytopenias after hematopoietic cell transplant for inherited metabolic disorders. *Bone Marrow Transplant* . 2021;56:1238-1247.
3. Faraci M, Zecca M, Pillon M, et al. Autoimmune hematological diseases after allogeneic hematopoietic stem cell transplantation in children: an Italian multicenter experience. *Biol Blood Marrow Transplant* . 2014;20:272-278.
4. Driouk L, Schmitt R, Peters A, et al. Daratumumab therapy for post-HSCT immune-mediated cytopenia: experiences from two pediatric cases and review of literature. *Mol Cell Pediatr* . 2021;8:5.
5. Canales-Herrerias P, cricks E, Broketa M, et al. High-affinity autoreactive plasma cells disseminate through multiple organs in patients with immune thrombocytopenic purpura. *J Clin Invest* . 2022;132:e153580.
6. Kruizinga MD, van Tol MJD, Bekker V, et al. Risk factors, treatment, and immune dysregulation in autoimmune cytopenia after allogeneic hematopoietic stem cell transplantation in pediatric patients. *Biol Blood Marrow Transplant* . 2018;24:772-778.

FIGURE LEGEND

FIGURE. Clinical course of the present case after the first episode of ITP (A) and after the recurrence of ITP (B). Abbreviations: BMT, bone marrow transplantation; Hb, hemoglobin; IVIG, intravenous immunoglobulin; mPSL, methylprednisolone; PC, platelet concentrate; Plt, platelet; PSL, prednisolone; RCC, red cell concentrate.

