

CLINICAL NOTE

Alemtuzumab-based reduced-intensity conditioning for XIAP deficiency

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Short running Title: Alem-containing RIC for XIAP deficiency

Key words: XIAP deficiency; allogenic hematopoietic cell transplantation; alemtuzumab; mixed chimerism

Number of text pages: 6

Number of words: 728

Number of reference pages: 1

Numbers of tables and figures: 1 figure and 0 tables

X-linked inhibitor of apoptosis protein (XIAP) deficiency is a rare inborn error of immunity characterized by hemophagocytic lymphohistiocytosis (HLH) triggered by Epstein-Barr virus (EBV) infection, early-onset inflammatory bowel disease (IBD), and lymphoproliferative disorder. XIAP deficiency is caused by a variant of the *XIAP/baculoviral inhibitor of apoptosis protein repeat-containing protein 4 (BIRC4)* gene.¹

Allogenic hematopoietic cell transplantation (HCT) is the curative treatment for patients with conventional treatment-resistant IBD and HLH. Myeloablative conditioning often leads to a poor prognosis due to severe transplant-related complications.² Anti-thymocyte globulin (ATG)-containing reduced-intensity conditionings (RICs) improved treatment results; however, high incidences of post-transplant HLH and acute graft-versus-host disease (GVHD) remain unresolved.³ Alemtuzumab is a CD52-targeting humanized monoclonal antibody that exerts long-term immunologic effects not only on T-lymphocytes, B-lymphocytes, and natural killer lymphocytes but also on monocytes/macrophages and dendritic cells. Due to its powerful immunosuppressive effect, alemtuzumab has been widely used to prevent GVHD in allogeneic HCT for non-malignant diseases, but not yet for XIAP deficiency in Japan. We performed allogeneic HCT for XIAP deficiency using an alemtuzumab-based conditioning. We obtained prior institutional committee approval for the off-label use of alemtuzumab in children.

Here, we report a 6-year-old boy with XIAP deficiency harboring a hemizygous variant of the *XIAP/BIRC4* gene (c.577_578insACCAAG,

p.Thr192_gly193insAspGln). He experienced HLH at the age of 2 and 4 years following EBV and cytomegalovirus (CMV) infection, respectively, which subsided following administration of prednisolone. At the age of 5 years, he developed IBD, which was refractory to conventional treatment. At the age of 6 years, he underwent bone marrow transplantation (BMT) with active IBD from a human leukocyte antigen 8/8 allele-matched unrelated donor using a conditioning regimen consisting of fludarabine (30 mg/m²/day, day -9 to -4), targeted doses of busulfan (cumulative area under the curve: 65 mg/L × h, day -7 to -4), and alemtuzumab (0.16 mg/kg/day, day -14 to -10). For fear of a higher risk of severe regimen-related gastrointestinal toxicity, the patient received busulfan, but not melphalan, as previously reported.^{2,3} GVHD prophylaxis consisted of tacrolimus (Tac) and short-term methotrexate.

The clinical course of allogenic BMT is shown in Fig. 1a. He experienced methicillin-resistant *Staphylococcus aureus* sepsis and BK virus-associated hemorrhagic cystitis on days -2 and 8, which were controllable with meropenem/teicoplanin and hydration, respectively. CMV antigenemia was detected on day 20 during letermovir prophylaxis, which soon became negative following ganciclovir treatment. EBV reactivation was not observed. Neutrophils (> 500/μL) engrafted on day 25. No significant post-transplant HLH or acute GVHD was observed. Higher than 90% donor chimerism was confirmed in whole bone marrow cells by the short tandem repeat method on days 31, 67, and 94. However, donor chimerism of CD3⁺ T-cells in peripheral blood was approximately 40% on day 94 and decreased to less than 20% thereafter, despite immediate discontinuation of Tac, while B-cell, monocyte, and

neutrophil donor chimerism was constantly higher than 95% (Fig. 1b). The serum interleukin (IL)-18 level, which significantly increased upon HLH recurrence,⁴ remained low after BMT (Fig. 1c). Moreover, the level of fecal calprotectin, a biomarker of IBD activity, also decreased (Fig. 1d). Because he was asymptomatic and no active IBD lesions were confirmed by colonoscopy (Fig. 1e), neither donor lymphocyte infusion nor second HCT was performed. He remained alive and free of disease-related symptoms 16 months after BMT.

Unlike allogeneic HCT using ATG-containing RICs,³ severe acute GVHD and post-transplant HLH are not frequently observed in allogeneic HCT using alemtuzumab-based RICs.² Thus, the post-transplant clinical course of the present case was uneventful and he did not develop GVHD or HLH, principally due to the powerful and sustained effects of alemtuzumab on various immunocompetent cells. However, alemtuzumab-containing RICs are associated with a high risk of low-level donor chimerism, which is largely influenced by the timing and dose of alemtuzumab. The present case developed low-level (~20%) T-cell donor chimerism without disease recurrence. Indeed, a previous report demonstrated that 20–30% T-cell donor chimerism is often sufficient to protect against disease recurrence.⁵ Alternatively, sustained high donor chimerism of monocytes and normalization of the serum IL-18 level, which are likely associated with high activity of HLH and IBD in patients with XIAP deficiency,^{1,4} might help to prevent disease reactivation.

In conclusion, an alemtuzumab-based conditioning is feasible for HCT in patients with XIAP deficiency to prevent post-transplant HLH and acute GVHD, although

further adjustment of the dosage and timing of alemtuzumab is required to reduce the risk of low-level donor chimerism.

ACKNOWLEDGEMENTS

We would like to thank Dr. Yoshitaka Honda for technical assistance with blood cell separation.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ETHICS STATEMENT

Informed consent for publication was obtained from the legal guardians of the patient.

AUTHOR CONTRIBUTIONS

H.Kobushi and K.U. wrote the paper. H.Kobushi, E.H., K.K., and M.S. collected the data. E.H., H.Kanegane, and J.T. assisted with interpretation of the data and provided insightful comments. All authors read and approved the final manuscript.

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Figure legend

Figure 1. (a) Clinical course of BMT. Black and dotted lines indicate neutrophil and lymphocyte counts, respectively. Glucocorticoid potency is shown as prednisolone equivalent dose (mg/kg/day). (b) Serial chimerism analyses of whole blood cells (black line) and CD3⁺ cells (dotted line) in peripheral blood. The data are presented as the measured value $\pm$ error range. (c) Serial analyses of serum IL-18 levels. (d) Serial analyses of fecal calprotectin levels. (e) Colonoscopic images 2 and 12 months after HCT. Alem, alemtuzumab; BKV, BK virus; Bu, busulfan; CMV, cytomegalovirus; Flu, fludarabine; GC, glucocorticoid; GCV, ganciclovir; HCT, hematopoietic cell transplantation; IBD, inflammatory bowel disease; IL, interleukin; LTV, letermovir; MEPM, meropenem; MRSA, methicillin-resistant *Staphylococcus aureus*; MTX, methotrexate; Tac, tacrolimus; TAZ/PIPC, tazobactam piperacillin; TEIC, teicoplanin; uBMT, unrelated bone marrow transplantation.