Cord Blood Transplantation Following Reduced-intensity Conditioning for Adult-onset Inherited Hemophagocytic Lymphohistiocytosis

Takuro Kuriyama¹, Koji Kato¹, Keiji Sakamoto¹, Masayasu Hayashi¹, Shuichiro Takashima¹, Yasuo Mori¹, Katsuto Takenaka¹, Hiromi Iwasaki², Takanori Teshima², Naoki Harada¹, Koji Nagafuji¹, Toshihiro Miyamoto¹ and Koichi Akashi¹,²

Abstract

Inherited hemophagocytic lymphohistiocytosis (HLH) is a genetic anomaly disorder in which abnormally activated cytotoxic T lymphocytes cannot induce the apoptosis of target cells and antigen-presenting cells, leading to hemophagocytosis, pancytopenia, and a variety of symptoms such as a high fever. The present patient with adult-onset HLH developed refractory disease despite receiving immunosuppressive treatments. He underwent a reduced-intensity conditioning (RIC) regimen that comprised antithymocyte globulin (ATG) followed by cord blood transplantation (RIC-CBT). He achieved and maintained a complete donor type. The incorporation of ATG into RIC-CBT may prevent graft failure and control hemophagocytosis, however, further efforts are necessary to reduce infectious complications.

Key words: hemophagocytic lymphohistiocytosis, cord blood transplantation, antithymocyte globulin

(DOI: 10.2169/internalmedicine.55.5241)

Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a hyper-inflammatory disease characterized by various symptoms such as a high fever, pancytopenia, and splenomegaly that are consequent to uncontrolled hypercytokinemia involving cytokines, such as interferon gamma (IFN-γ), tumor necrosis factor alpha, and interleukin (IL)-6. HLH is classified as inherited or acquired HLH (1-4). Inherited HLH is known to be caused by mutations in genes such as PFR1 and STX11 (5, 6). Acquired HLH can be caused by various underlying diseases such as infection and malignant lymphoma. In inherited HLH, defective cytotoxic activation inhibits cytotoxic T cells (CTLs) from inducing apoptosis in antigen-presenting cells (APCs); accordingly, CTLs continue to proliferate in response to constant stimulation from APCs, unlike normally activated CTLs, which secrete cytokines (mainly IFN-γ) and simultaneously induce the apoptosis of both target cells and APCs via the perforin/granzyme pathway (7). Therefore, abnormal CTLs secrete excess cytokines that subsequently activate and upregulate the phagocytic capacities of macrophages (8). In acquired HLH, CTLs are normally activated in response to viral infection, malignant disorders, and autoimmune diseases and subsequently activate macrophages and induce hypercytokinemia (9).

Patients with inherited HLH and inflammatory symptoms are typically treated with immunosuppressive agents such as corticosteroids and cyclosporine A. Etoposide is also effective. Antithymocyte globulin (ATG) was used successfully in a monocentric study (10). Alemtuzumab, an antibody against CD52, which is present on both T cells and histiocytes, has been shown to be beneficial in patients with refractory HLH (11). In patients with refractory HLH, allogeneic he-

¹Department of Medicine and Biosystemic Science, Kyushu University Graduate School of Medical Sciences, Japan, ²Center for Cellular and Molecular Medicine, Kyushu University Graduate School of Medical Sciences, Japan and ³Division of Hematology and Oncology, Department of Medicine, Kurume University School of Medicine, Japan
Received for publication February 27, 2015; Accepted for publication June 18, 2015
Correspondence to Dr. Koji Kato, kojikato@intmed1.med.kyushu-u.ac.jp
matopoietic stem cell transplantation (allo-HSCT) has also been used to achieve a cure through the correction of immune deficiencies (12).

Inherited HLH nearly always develops during infancy and early childhood; however, there are a few reports of late-onset HLH. In a recent study of adult patients with HLH, gene mutations associated with inherited HLH were found in 14% of the patients (13). Elderly patients with HLH are unable to tolerate full-intensity conditioning (FIC) and may not have a suitable sibling donor. FIC also leads to a reportedly increased mortality even among young patients with HLH, and therefore, reduced-intensity conditioning (RIC) has been recently recommended because of its association with reduced toxicity and an increased survival (14). In addition, cord blood has been recently used as an alternative source of stem cells for treating patients when human leukocyte antigen-matched related and unrelated donors are unavailable. However, there have been few reports of patients with inherited HLH who were successfully treated using RIC followed by cord blood transplantation (RIC-CBT). RIC and CBT, as well as HLH itself, are risk factors for engraftment failure. We previously reported a case of adult-onset inherited HLH with a PRF1 mutation (familial hemophagocytic lymphohistiocytosis, type 2) in a 62-year-old man (15). He was initially followed up without treatment. Approximately 7 years after the initial diagnosis, however, he received RIC-CBT with ATG to treat the refractory disease.

Case Report

A 69-year-old Japanese man who was previously diagnosed with inherited HLH at 62 years of age was again hospitalized with a high fever (15). He had been followed up for 6 years without treatment after the initial diagnosis. However, his symptoms such as cytopenia and a fever had deteriorated, and he had begun immunosuppressive treatment with oral cyclosporine and prednisolone a year earlier. At the time of the recent admission, his body temperature was 38.8°C and he exhibited splenomegaly (Fig. 1). A blood examination revealed a hemoglobin level of 13.1 g/dL, platelet count of 58×10^9/L, white blood cell count of 6.3×10^9/L, and the following blood chemistry results: blood urea nitrogen, 25 mg/dL; creatinine, 1.2 mg/dL; total bilirubin, 1.3 mg/dL; aspartate aminotransferase, 55 U/L; alanine aminotransferase, 55 U/L; lactase dehydrogenase, 415 U/L; C-reactive protein, 6.33 mg/dL; ferritin, 1,821 ng/dL; and soluble IL-2 receptor, 3,680 U/mL. A bone marrow puncture revealed hemophagocytosis, indicating an HLH relapse (Fig. 2). The patient was treated according to the 2004 HLH protocol and his condition immediately improved following therapy initiation (16). However, his symptoms became exaggerated as the dexamethasone dose was tapered, and his ferritin level increased to >10,000 ng/dL. Despite restoring the dexamethasone dose, he developed febrile neutropenia with a neutrophil count of 100/µL, indicating a requirement for immediate allo-HSCT. The patient received RIC-CBT because he had no sibling donors and there was insufficient time to find an unrelated donor from the Japan Marrow Donor Program. The RIC regimen comprised fludarabine (25 mg/m², days -8--4), rabbit ATG (1.25 mg/kg, days -7--6), melphalan (40 mg/m², days -3--2) and 2 Gy of total body irradiation (day -1). Graft-versus-host disease (GVHD) prophylaxis comprised tacrolimus (0.03 mg/kg/day, starting on day -1) and methylprednisolone (1 mg/kg, starting on day -5). The umbilical cord blood (total nuclear cell count, 3.14×10^7 cells/kg; CD34+ cell count, 1.08×10^5 cells/kg both blood type- and gender-matched and HLA 2-loci mismatched) was subsequently infused. Levofloxacin, itraconazole, acyclovir, isoniazid and inhalation of pentamidine were used as infection prophylaxis. Neutrophil engraftment was achieved on day 27 (Fig. 3), and complete chimerism (>95% donor cells) was indicated by a short tandem repeat analysis of the patient’s bone marrow on day 21 (Fig. 4). The lymphocyte

Figure 1. Abdominal CT scans before and after RIC-CBT. Left: CT shows relapsed HLH with splenomegaly before RIC-CBT. Right: CT shows remission after RIC-CBT. CT: computed tomography, HLH: hemophagocytic lymphohistiocytosis, RIC-CBT: reduced-intensity conditioning cord blood transplantation.
subset in the peripheral blood on day 25 was as follows: 42.2% of CD3+ T cells, 1.1% of CD19+ B cells, and 56.7% of CD56+ NK cells. Despite tapering both the tacrolimus and methylprednisolone doses, no acute or chronic GVHD developed, and no HLH relapse was observed in a complete donor-type chimerism analysis on day 60. In this patient, the major complication following RIC-CBT was infection. He developed hemorrhagic cystitis due to adenovirus (ADV-HC) on day 10 and was treated with cidofovir and continuous bladder irrigation. He became febrile on day 20, and computed tomography (CT) revealed small nodular shadows in the right middle and left upper lobes of his lungs. Although the β-D-glucan and galactomannan tests were negative, liposomal amphotericin B was administered for a possible diagnosis of invasive fungal infection. The patient recovered from both infections after a 1-month treatment course. No Epstein-Barr virus viremia was detected via a quantitative polymerase chain reaction (PCR) analysis during the clinical course. On day 57, the patient experienced weakness of the left arm and leg. A CT scan revealed a chronic subdural hematoma and subarachnoid hemorrhage. He had no disturbance of consciousness and received conservative management under close blood pressure control. He also underwent rehabilitation and was discharged on day 141 after RIC-
out DLI was needed. Because alemtuzumab had not been plan for the achievement of complete donor chimerism with-

a risk factor for graft failure, which in such cases is induced DLI to treat mixed chimerism following CBT. HLH itself is the high incidence of graft failure and the lack of available the conditioning regimen should be carefully selected, given opened mixed chimerism and received donor lymphocyte infu-

tion, PCR: polymerase chain reaction

CBT: A bone marrow chimerism analysis revealed complete donor type maintenance until day 255 (Fig. 4). Unfortu-
nately, on day 260, the patient presented with a fever along with BK-viral HC and pneumonia caused by Toxoplasma gondii infection, which was later confirmed by an autopsy. He died from infection on day 281 after RIC-CBT without a relapse of HLH.

Discussion

The elimination of uncontrolled activated lymphocytes is a treatment goal for patients with HLH. Therefore, allo-

HSCT is recommended as a curative treatment for patients with refractory HLH. Recently, RIC has been recommended for patients with HLH. Marsh et al. reported encouraging outcomes following RIC with alemtuzumab in young patients; in that study, the 3-year overall survival rate of RIC-treated patients who exhibited a low incidence of transplant-related mortality was 92%, whereas that of FIC-treated patients was 43% (14). In nearly all previous reports of HLH, the stem cell source was either bone marrow or peripheral blood from HLA-matched related or unrelated donors. CBT has been recently used as an alternative option if a suitable bone marrow or peripheral blood stem cell source cannot be identified. However, to date, there have been few reports of patients with HLH who underwent CBT. In addition, Marsh et al. reported that 17 of 26 patients treated with RIC developed mixed chimerism and received donor lymphocyte infusion (DLI) or a stem cell boost after allo-HSCT (14). Thus, the conditioning regimen should be carefully selected, given the high incidence of graft failure and the lack of available DLI to treat mixed chimerism following CBT. HLH itself is a risk factor for graft failure, which in such cases is induced by the uncontrolled activation of residual recipient T cells. Therefore, in the present patient with RIC-CBT, a careful plan for the achievement of complete donor chimerism without DLI was needed. Because alemtuzumab had not been approved for use in Japan at that time, the use of ATG in the present patient was key; not only for GVHD prophylaxis via the suppression of the donor T cells, but also as part of the conditioning regimen via the suppression of the recipient’s activated T cells. In fact, alemtuzumab is administered proximal to HSCT if GVHD prophylaxis is emphasized and distal to HSCT if graft failure risk is emphasized. Patients who received alemtuzumab distal to allo-HSCT (days -22-

-19) were reported to exhibit a high incidence of GVHD, whereas patients treated proximal to allo-HSCT (days -12-

-9) had a high incidence of mixed chimerism development, suggesting that the timing of alemtuzumab administration affects the incidence of mixed chimerism; this likely occurs because of higher systemic levels of alemtuzumab at the time of graft infusion and resultant increased graft T-cell de-

pletion (14). Due to the need for immunosuppression of HLH and conditioning to reduce the risk of graft failure in patients with HLH and those treated with RIC-CBT with a low incidence of GVHD, the optimal timing range of ATG administration was considered to be days -10--7, according to our data indicating that the half-life of ATG in the blood was approximately 2 weeks. The present patient successfully achieved and maintained complete chimerism without severe GVHD or relapse of hemophagocytosis in the bone marrow.

Several treatment limitations associated with the present case should be discussed. Particularly, infectious complica-

tions after RIC-CBT represent a major issue in the present study. Before RIC-CBT, the patient was treated with long-

term oral cyclosporine and prednisolone, in addition to etoposide-based therapy, according to the HLH-2004 proto-

col (16). ATG use is a strong risk factor for EBV reactiva-

tion, which may develop into a post-transplantation lymphoproliferative disorder. In the present patient, EBV vire-

mia was not detected by a quantitative PCR analysis until day 270. However, many infectious complications such as ADV-HC, fungal pneumonia, and Toxoplasma gondii infec-

tion are problematic. We should reconsider the timing and dosage of ATG in the setting of RIC-CBT.

In the report by Marsh et al., the symptoms of pediatric patients with HLH did not relapse despite the occurrence of mixed chimerism after allo-HSCT, suggesting that donor T cells are functionally dominant over residual activated recipient T cells, even in mixed chimerism (14). Accordingly, the necessity of achieving complete chimerism after allo-

HSCT is questionable. Therefore, a chimerism analysis of the T cell and NK cell populations in peripheral blood, rather than that of whole cells in the bone marrow, should be carefully examined, although the evaluation may be diffi-
cult to routinely conduct in clinical practice.

In conclusion, RIC-CBT with ATG may have prevented graft failure and controlled hemophagocytosis in the present patient. However, potential limitations associated with this study may be the single case and the short observation pe-

riod. Studies on adequate ATG use and donor selection are needed to reduce infectious complications, and a greater ac-
cumulation of clinical cases is necessary to establish an opti-
mal treatment strategy for adult-onset inherited HLH.

The authors state that they have no Conflict of Interest (COI).

Financial Support
This work was supported in part by a MEXT KAKENHI grant (number 25461453) to K. Kato.

References

© 2016 The Japanese Society of Internal Medicine
http://www.naika.or.jp/imonline/index.html