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Umbilical Cord Blood as an Alternative Source of Reduced-Intensity Hematopoietic Stem Cell Transplantation for Chronic Epstein-Barr Virus–Associated T or Natural Killer Cell Lymphoproliferative Diseases

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A B S T R A C T

Chronic Epstein-Barr virus–associated T/natural killer cell lymphoproliferative diseases represented by chronic active Epstein-Barr virus infection are lethal but are curable with several courses of chemotherapy and allogeneic hematopoietic stem cell transplantation (HSCT). Recently, we reported that reduced-intensity conditioning (RIC) provided better outcomes than myeloablative conditioning because RIC was less toxic. However, it was unclear whether cord blood transplantation (CBT) works in the context of RIC. We retrospectively analyzed 17 patients who underwent RIC followed by bone marrow transplantation (RIC-BMT) and 15 patients who underwent RIC followed by CBT (RIC-CBT). The representative regimen was fludarabine and melphalan based. The overall survival rates with RIC-BMT and RIC-CBT were 92.9% ± 6.9% and 93.3% ± 6.4%, respectively ($P = .87$). One patient died of lung graft-versus-host disease after RIC-BMT, and 1 patient died of multiple viral infections after RIC-CBT. Although cytotoxic chemotherapy was also immunosuppressive and might contribute to better donor cell engraftment after RIC-HSCT, the rate of engraftment failure after RIC-CBT was still higher than that after RIC-BMT (not significant); however, patients who had experienced graft failure were successfully rescued with a second HSCT. Unrelated cord blood can be an alternative source for RIC-HSCT if a patient has no family donor.

INTRODUCTION

Epstein-Barr virus (EBV), also known as human herpesvirus 4, is a B cell lymphotropic and oncogenic virus and occasionally causes a variety of B cell lymphoproliferative diseases (LPDs) [1]. However, latent EBV infection can occur in T cells and/or natural killer cells (T/NK cells), resulting in T/NK cell LPDs [2,3]. Chronic EBV-associated T/NK cell LPDs (EBV$^+$ T/NK cell LPDs) are 1 of 3 distinct types of EBV$^+$ T/NK cell LPDs (acute type, chronic type, and malignant type) [1,4]. Chronic EBV$^+$ T/NK cell LPDs are represented by chronic active EBV infection (CAEBV) that is sometimes accompanied by hypersensitivity to mosquito bites or severe-type hydroa vacciniforme, but hypersensitivity to mosquito bites and severe-type hydroa vacciniforme also occur independently of CAEBV [5].

Chronic EBV$^+$ T/NK cell LPD is not a simple chronic disease, but its flare could result in a rapid, irreversible, and fatal clinical course. A study found that more than 60% of patients died over several years, mainly due to organ failure (such as liver and heart), hemophagocytic syndrome (HPS), and lymphoma [6]. Allogeneic hematopoietic stem cell transplantation (HSCT) is the only cure for the patients with chronic EBV$^+$ T/NK cell LPD [7], although rare exceptions were reported in which complete molecular remission was achieved with multidrug chemotherapy [8].

Reduced-intensity conditioning (RIC) and umbilical cord blood transplantation (CBT) were developed in the 2000s. RIC is less toxic than myeloablative conditioning in regard to reducing transplant-related mortality, allowing growth and development in children, and to retaining fertility in young adults [9]. In our previous report on chronic EBV$^+$ T/NK cell LPD, RIC followed by HSCT (RIC-HSCT) brought about better outcomes (survival rate > 90%) than myeloablative conditioning-HSCT, and we found that CBT, as well as bone marrow transplantation (BMT), might lead to a cure in these patients [10]. However, the number of cases of RIC-CBT was too small to discuss its efficacy in that report. Unrelated CBT is potentially promising because, as opposed to unrelated bone marrow, unrelated cord blood (CB) is immediately available. However, CB lymphocytes are naive and do not have specific immune memories to EBV, whereas most adult lymphocytes have been exposed to and are immune to EBV; it is possible that this difference can influence the post-transplant clinical courses and immune reconstruction to EBV. In addition, donor lymphocyte infusion is not available after CBT.

The aim of this retrospective analysis using our latest institutional registration and follow-up data was to clarify whether RIC-CBT could be an alternative treatment for the patients with chronic EBV$^+$ T/NK cell LPD if there is no family donor. This study was approved by the Research Ethics Committee of Osaka Medical Center and Research Institute for Maternal and Child Health.

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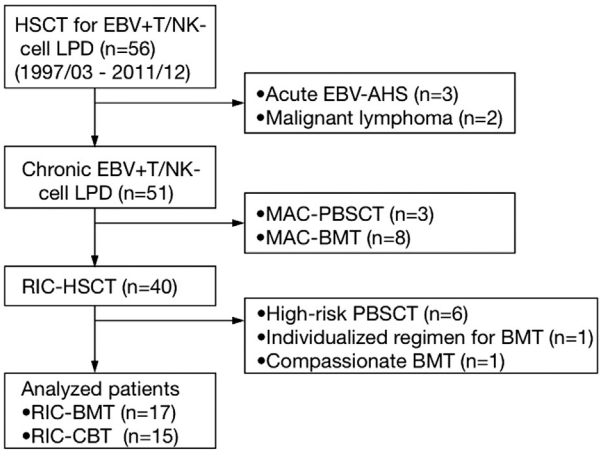

Figure 1. Patient selection. Fifty-six patients with EBV$^+$ T/NK cell LPD were treated with allogeneic HSCT at our institute. Selection criteria for the current study were chronic EBV$^+$ T/NK cell LPD, RIC, and BMT or CBT. Two patients who underwent RIC-BMT were also excluded because of individualized less-intensity conditioning for kidney dysfunction (n = 1) and compassionate transplantation for uncontrollable fulminant hemophagocytic lymphohistiocytosis (n = 1). EBV-AHS indicates EBV-associated hemophagocytic syndrome; MAC, myaloablative conditioning; PBSCT, peripheral blood stem cell transplantation.

METHODS

Patients

Patients with CAEBV met the criteria proposed in 2005 [11]. Fifty-six patients with EBV$^+$ T/NK cell LPD were treated with allogeneic HSCT between March 1997 and December 2011 at our institute (Figure 1). We excluded 5 patients from the analysis because their diagnoses were hemophagocytic lymphohistiocytosis as acute EBV infection (n = 3) or malignant lymphoma (n = 2). Of the 51 patients with chronic EBV$^+$ T/NK cell LPD, 44 had a diagnosis of CAEBV, 5 had a diagnosis of hypersensitivity to mosquito bites, and 2 had a diagnosis of severe-type hydroa vacciniforme without clinical manifestation of CAEBV.

Because all CBTs were performed after RIC and because the overall survival (OS) rate after myeloablative conditioning (median ± standard error, 54.5% ± 15.0%) was significantly inferior to that after RIC in regard to toxicity [10], patients who underwent myeloablative conditioning-HSCT (n = 11) were excluded from further analysis. There were 40 cases of RIC-HSCT. Six patients who underwent peripheral blood stem cell transplantation were excluded because peripheral blood stem cell transplantation tended to be used in patients with severe complications or other high-risk conditions: poorly controlled pneumonia with *Pseudomonas aeruginosa* (n = 1), severe heart dysfunction (n = 2), persistent HPS with febrile neutropenia (n = 1), and HLA 3/6 allele-mismatched HSCT (n = 2). The hematopoietic cell transplantation-specific comorbidity index (HCT-CI) of these 6 patients was a median of 1 (range, 0 to 4) [12].

Two additional patients were excluded: 1 was treated with individualized less-intensity conditioning for kidney dysfunction (including fludarabine [Flu] 100 mg/m^2 and melphalan [LPAM] 50 mg/m^2) and experienced donor-cell rejection after BMT (HCT-CI = 0), and 1 had uncontrolled fulminant CAEBV-associated HPS with adenovirus hemorrhagic cystitis at the initiation of RIC and died of progressive primary disease at 4 days after compassionate BMT (HCT-CI = 6). As a result, the analysis includes 17 patients who underwent RIC-BMT (related, n = 11; unrelated n = 6) and 15 patients who underwent unrelated RIC-CBT. The HCT-CI of these 17 and 15 patients were all 0.

Detection of EBV

Identification of EBV-infected cells and measurement of EBV load have been described elsewhere [10]. Briefly, for identification, the EBV genome was amplified by PCR in DNA extracted from each lymphocyte subset in peripheral blood, or EBV-encoded small ribonucleic acid (EBER) and surface

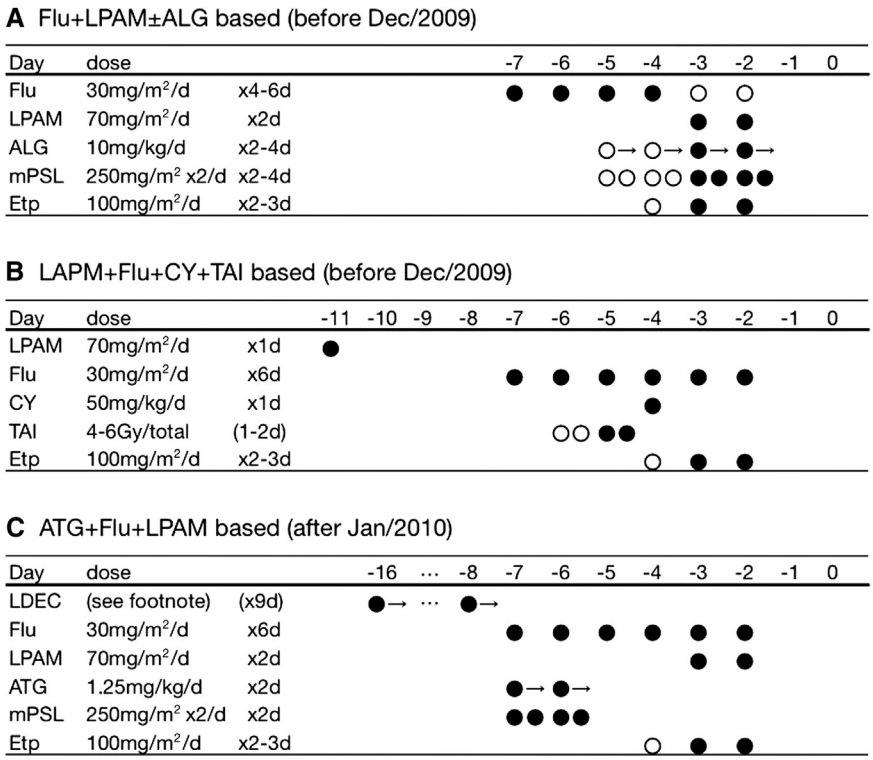

Figure 2. Conditioning regimen. Closed circles indicate fixed administration, and open circles indicate optional administration. (A) Standard conditioning regimen, which tended to be used for BMT. The problems were a high rate of EBV$^+$ post-transplant LPD at a total antilymphocyte globulin dose of 40 mg/kg in patients with variable diseases other than EBV$^+$ T/NK cell LPD and then no availability of antilymphocyte globulin afterward. (B) Conditioning regimen for high risk of rejection, which tended to be used for CBT. The problem was a usage of irradiation, which might induce a higher rate of subsequent neoplasms compared with drug administration. (C) Current regimen universally administered for BMT and CBT since January 2010. ALG indicates anti-lymphocyte globulin LDEC, low-dose Etp 30 mg/m^2/d and CA 20 mg/m^2/d were administered for 24 hours continuously for a median of 9 days (range, 4 to 14 days) just before RIC with Flu + LPAM; TAI, thoracoabdominal irradiation; mPSL, methylprednisolone; CY, cyclophosphamide.