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Umbilical Cord Blood Transplantation without Antithymocyte Globulin Results in Similar Survival but Better Quality of Life Compared with Unrelated Peripheral Blood Stem Cell Transplantation for the Treatment of Acute Leukemia—A Retrospective Study in China

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A B S T R A C T

Although previous studies have demonstrated improved outcomes in umbilical cord blood transplantation (UCBT) by omitting antithymocyte globulin (ATG) in the conditioning regimen, this approach has not been comparatively studied in unrelated peripheral blood stem cell transplantation (UPBSCT). To compare the risks and benefits between UCBT without ATG and UPBSCT in patients with acute leukemia (AL), we conducted a multicenter retrospective study of 79 patients who underwent UCBT (myeloablative conditioning without ATG) and 96 patients who underwent UPBSCT (myeloablative conditioning with ATG). The outcomes were graft failure, neutrophil engraftment, platelet engraftment, acute graft-versus-host disease (aGVHD), chronic graft-versus-host disease (cGVHD), transplantation-related mortality (TRM), relapse, overall survival (OS), and leukemia-free survival (LFS). Follow-up was censored on October 31, 2016. Engraftment was similar between the 2 groups but granulocyte and platelet recovery were slower in the UCBT group (both $P < .001$). The incidences of aGVHD, TRM, OS, and LFS were similar between the 2 groups (all $P > .05$). Without ATG, the UCBT group displayed less cGVHD and less moderate and severe cGVHD ($P < .001$ and $P = .004$). The incidences of Epstein-Barr virus viremia and post-transplantation lymphoproliferative disease were significantly lower in the UCBT group ($P < .001$ and $P = .037$). UCBT recipients had higher activity Karnofsky performance scores and 3-year GVHD-free/relapse-free survival than the UPBSCT group ($P = .03$ and $P = .04$). We observed similar survival when comparing UCBT without ATG and UPBSCT, but we also observed better quality of life in patients undergoing UCBT without ATG. We can therefore conclude that patients with primary AL for whom an appropriate HLA-matched sibling donor is not available could select either UCBT or UPBSCT.

INTRODUCTION

Umbilical cord blood transplantation (UCBT) is a recent approach for patients with hematological diseases and its use has made hematopoietic cell transplantation (HCT) available to additional patients [1]. Indeed, the increased level of HLA disparity that can be tolerated makes UCBT a very attractive alternative source of hematopoietic stem cells [1-3], but UCBT is associated with some drawbacks compared with unrelated bone marrow transplantation and unrelated peripheral blood stem cell transplantation (UPBSCT). The quantity of nucleated cells in umbilical cord blood is only

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about 10% of the number of nucleated cells in the peripheral blood stem cells or bone marrow. In addition, the T and B lymphocytes in umbilical cord blood are in their naïve state [4]. The limited number of cells and low immunogenicity of the nucleated cells could lead to engraftment failure and might slow hematopoietic and immune reconstitution, which could result in a high incidence of early opportunistic infections [5,6].

Therefore, how to increase the UCBT engraftment rate and reduce the incidence of infections are important areas of study. Some methods, including increasing the nucleated cell count and $CD34^+$ cell count and adjusting the conditioning regimen, were studied to address these problems. Starting in 2010, many physicians in China began to use intensive myeloablative conditioning regimens without antithymocyte globulin (ATG) for UCBT and cyclosporine combined with mycophenolate mofetil for graft-versus-host disease (GVHD) prophylaxis. Compared with UCBT with ATG, UCBT without ATG could significantly increase the engraftment rate; in addition, infection, transplantation-related mortality, and relapse rates were decreased, whereas the incidence of acute GVHD (aGVHD) and chronic GVHD (cGVHD) did not increase [7].

Although there are no randomized trials assessing the risks and benefits of UCBT compared with those of related and unrelated donors for patients with acute leukemia (AL), several retrospective studies have compared outcomes between UCBT and other sources of stem cells [8-13]. Recently, a study demonstrated that the graft-versus-leukemia effect effect of UCBT was better than that of HLA-matched or -mismatched unrelated donors and that UCBT could eventually be preferred to unrelated donors [13].

Because of the improvement of the therapeutic effect of UCBT after omitting ATG, we conducted a multicenter retrospective study to compare the risks and benefits between UCBT without ATG and UPBSCT. In addition, this is the first retrospective multicenter study in China to compare the results of UCBT and unrelated donors.

PATIENT AND METHODS

Study Design and Patients

This was a multicenter retrospective study of 175 consecutive patients with AL treated between January 2010 and December 2014 at the affiliated Anhui Provincial Hospital of Anhui Medical University, Nanfang Hospital affiliated with Southern Medical University, the Third Affiliated Hospital of Sun Yat-sen University, and the First Affiliated Hospital of Wannan Medical College. The inclusion criteria were as follows: (1) >14 years old, (2) diagnosed with AL, (3) no HLA-compatible related donors available, and (4) eligible for a single UCBT or UPBSCT that had not been depleted of T cells. Patients receiving UCBT and UPBSCT as a second transplantation after relapse after a first autologous or allogeneic transplantation were excluded.

All patients were fully informed of their disease status and treatment options. The transplantation protocol was approved by the Anhui Medical University, Southern Medical University, Sun Yat-sen University, and Wannan Medical College institutional review boards.

Grouping

The patients were grouped according to the treatment they received (UCBT versus UPBSCT). In addition, the patients were divided according to the first remission period (CR1), the > second complete remission period (≥CR2), and nonremission (including primary induction failure or no remission after relapse). The disease risk was based on the Disease Risk Index [14].

HLA Typing and Donor Selection

Alleles of the HLA-A, HLA-B, HAL-C, HLA-DRB1, and HLA-DQB1 were evaluated for UPBSCT donor-recipient pairs. Alleles of HLA-A, HLA-B, and HLA-DRB1 were evaluated for UCBT donor-recipient pairs. Genotyping was performed as described previously [15]. Serologic or antigen-level typing was performed with a standard 2-stage complement-dependent test of microcytotoxicity or low-resolution DNA-based typing [15].

Donor selection was based on the following: (1) if a suitable matched sibling donor (MSD) (ie, a sibling donor matching HLA 10/10) were available, the donor was chosen; (2) if a suitable MSD were unavailable, a suitably 10/10-matched unrelated donor (MUD) was selected. If a suitable MSD or HLA 10/10-matched MUD was unavailable, HLA 8/10 or 9/10 MUD and HLA ≥4/6 UCBT was selected; (3) if a suitable MSD or MUD were unavailable within the appropriate time frame for the patient (ie, high-risk patients achieved complete remission with 3 or 4 cycles of consolidation therapy; patients without remission urgently needed allogeneic HCT; patients in >CR2), HLA ≥4/6 UCBT was administered. Cord blood units were obtained through the Chinese Cord Blood Bank Network. Cord blood units matching at >4 of 6 HLA loci were selected. Preferred cord blood units contained a minimal cell count of $.3 \times 10^8$ nucleated cells/kg and $.15 \times 10^6$ $CD34^+$ cells/kg before freezing. Unrelated peripheral blood stem cells (PBSC) were obtained through the China Marrow Donor Program. PBSC were matched for HLA-A, HLA-B, and HLA-DRB1 loci; among HLA-A, HLA-B, HLA-C, HLA-DRB1, and HLA-DQB1, PBSC matching at >8 of 10 HLA loci was selected (among the patients who received PBSC, 39 patients matched at 10/10, 29 matched at 9/10, and 28 matched at 8/10). Preferred PBSC contained a minimal cell count of 3.0×10^8 nucleated cells/kg and 2.0×10^6 $CD34^+$ cells/kg.

Conditioning Regimen and GVHD Prophylaxis

UPBSCT patients received a total body irradiaton (TBI)/cyclophosphamide (CY_2) and busulfan (BU)/CY_2 myeloablative conditioning regimen plus fludarabine (FLU), etoposide, or cytarabine (Ara-c). GVHD prophylaxis regimens for UPBSCT were ATG, cyclosporine A, methotrexate, with or without mycophenolate mofetil.

The myeloablative conditioning regimen for UCBT was based on TBI/CY_2 and BU/CY2. Patients with poor physical status who could not tolerate TBI received conditioning regimens based on chemotherapy including BU/CY_2/FLU and BU/CY_2/Ara-c. Sixty-nine patients received TBI/CY_2/Ara-c (TBI 3 Gy two times each day on days -7 and -6; Ara-c 2 g/m^2 every 12 hours on days -5 and -4; CY 60 mg/kg days -3 and -2). The remaining 6 patients with acute lymphoblastic leukemia were treated with BU/CY_2 plus FLU (30 mg/m^2 days –8 to –5; BU 0.8 mg/kg every 6 hours days –7 to –4; CY 60 mg/kg days-3 and -2) and 4 patients with acute myeloid leukemia were treated with BU/CY_2 plus Ara-c (Ara-c 2 g/m^2 every 12 hours on days –9 to –8; BU .8 mg/kg every 6 hours on days –7 to –4; CY 60 mg/kg days -3 and -2). Twenty-four hours after the completion of conditioning, the patients received UCBT. GVHD prophylaxis regimens for UCBT included cyclosporine A and mycophenolate mofetil.

Outcomes

Follow-up was censored on October 31, 2016. *Primary graft failure* was defined as a profound persistent pancytopenia and marrow hypoplasia without donor-derived cells on day 42 or reconstitution with autologous cells. *Neutrophil engraftment* was defined as the first of 3 consecutive days with an absolute neutrophil count $.5 \times 10^9$/L. *Platelet engraftment* was defined as the first day when the platelet count was 20×10^9/L for 7 consecutive days without transfusion support.

aGVHD was diagnosed and graded according to the previously published criteria. [16] cGVHD was classified as mild, moderate, or severe according to the 2014 National Institutes of Health consensus criteria [17]. *Transplantation-related mortality* (TRM) was defined as death from any cause other than recurrent malignancy; time to TRM was defined as the number of days from transplantation to death without preceding relapse [18]. *Relapse* was defined by the morphologic evidence of disease in the peripheral blood, bone marrow, or extra medullary sites; *time to relapse* was defined as the number of days from transplantation to the first diagnosis of relapse [18]. *Overall survival* (OS) was defined as the number of days from transplantation to death of any cause. *Leukemia-free survival* (LFS) was defined as the number of days from transplantation to the first diagnosis of relapse or death [18]. The novel composite endpoint of *GVHD-free, relapse-free survival* (GRFS) after HCT was defined as patients without grade III or IV aGVHD, cGVHD requiring systemic treatment, relapse, or death [19]. The performance status observed in the patients surviving for 2 years was measured using the Karnofsky performance score (KPS) [20].

After transplantation, cytomegalovirus (CMV) DNA and Epstein-Barr virus (EBV) DNA were monitored twice every week during hospitalization. After discharge, CMV DNA and EBV DNA were monitored once every week for 3 months and then once every month for 1 year. In case of a positive result, the patient was monitored twice weekly during hospitalization and once weekly after discharge until the test became negative.

Immune Reconstitution

T ($CD3^+$, $CD3^+CD4^+$, $CD3^+CD8^+$), B ($CD19^+$), and natural killer (NK) ($CD3^-CD56^+$) cell numbers were prospectively measured during follow-up