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ORIGINAL ARTICLE

Unrelated cord blood transplantation in CML: Japan Cord Blood Bank Network analysis

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We analysed 86 patients with CML who received unrelated cord blood transplantation (UCBT), identified through a registry of the Japan Cord Blood Bank Network. At transplantation, the median patient age was 39 years (range, 1–67 years); 38 patients were in chronic phase (CP), 13 in the accelerated phase (AP) and 35 in blast crisis (BC). Median duration from diagnosis to UCBT was 1.5 years (range, 0.2–14.6 years). A nucleated cell (NC) dose of more than 3.0×10^7 per kg was sufficient to achieve neutrophil (91%) and platelet recovery (86%), whereas the lower dose of NC achieved only 60 and 61%, respectively. The duration and type of pre-transplant treatment did not affect neutrophil or platelet recovery. Results of multivariate analysis indicated that older patients (>50 years) had a higher incidence of transplant-related mortality. Advanced-disease stage and lower doses of NCs were significantly associated with lower leukaemia-free and event-free survival. At 2-year survival for patients in CP, AP and BC was 71, 59 and 32%, respectively ($P = 0.0004$). A pre-transplant European Group for Blood and Marrow Transplantation scoring system was effective in predicting the outcome of UCBT. We conclude that UCBT is a reasonable alternative therapy for patients with CML.

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Introduction

Recent clinical research on unrelated cord blood transplantation (UCBT) has encouraged the use of human umbilical cord blood (CB) as a source of haematopoietic SCT (HSCT) in patients with haematopoietic malignancies.[1–5] In Japan, more than 3500 UCBTs have been performed through 11 CB banks in the Japan Cord Blood Bank Network (JCBBN). As a component of quality management and promotion, the JCBBN established a common registry for studying the results of UCBT. However, the clinical application of UCBT for CML has not been established because treatment with interferon (IFN)-α and molecular-targeting reagents, such as imatinib mesylate (imatinib), have induced complete cytogenetic remission and improved long-term survival without the need for allogeneic haematopoietic transplantation.[6–8] Imatinib has now replaced IFN as the first-line therapy for CML and induces a molecular remission (MR) as well as a complete cytogenetic response (CCyR) in the vast majority of patients newly diagnosed with CML who are in the chronic phase (CP) of the disease.[8–10] Imatinib induces complete haematological responses not only in patients in CP but also in those in the accelerated phase (AP) of the disease and in blastic crisis (BC).[11] Although its long-term

Brief report

Chronic graft-versus-host disease following umbilical cord blood transplantation: retrospective survey involving 1072 patients in Japan

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We have little information on chronic graft-versus-host disease (GVHD) after cord blood transplantation (CBT). We investigated its clinical features in 1072 Japanese patients with hematologic malignancies who received a transplant through the Japan Cord Blood Bank Network. The primary end point was to investigate the incidence of any chronic GVHD. Median age of the patients was 33 years (range, 0-79 years). The cumulative incidence of chronic GVHD 2 years after transplantation was 28%. Chronic GVHD was fatal in 29 patients. Multivariate analysis demonstrated that development of chronic GVHD was favorably associated with both overall survival and event-free survival. Multivariate analysis identified risk factors of chronic GVHD: higher patient body weight, higher number of mismatched antigens for GVHD direction, myeloablative preparative regimen, use of mycophenolate mofetil in GVHD prophylaxis, and development of grades II to IV acute GVHD. Although chronic GVHD is a significant problem after CBT, it is associated with improved survival, perhaps due to graft-versus-malignancy effects. (Blood. 2008;112:2579-2582)

Introduction

Chronic graft-versus-host disease (GVHD) is a significant concern in allogeneic hematopoietic stem cell transplantation (HSCT). Many studies have been published on clinical features of chronic GVHD following bone marrow transplantation (BMT) and peripheral blood stem cell transplantation (PBSCT). In contrast, we have limited information on chronic GVHD following cord blood transplantation (CBT).

Methods

Informed consent was obtained in accordance with the Declaration of Helsinki. According to local policy, the study was approved by Japan Cord Blood Bank Network. We had no direct contact with human subjects during our study; data on patients who underwent CBT were obtained from the Japan Cord Blood Bank Network. The primary end point of this study was to investigate the incidence of any chronic GVHD after CBT. Cord blood units are provided with written informed consent. Between June 1997 and August 2006, 2713 cord blood transplant recipients were registered with the Japan Cord Blood Bank Network. All recipients received a single cord blood unit. We included those with hematologic malignancies who underwent CBT without T-cell depletion. We excluded patients with a history of any type of allogeneic HSCT prior to CBT. A total of 2015 patients met the criteria. Of those, we excluded 943 with disease progression, death without progression, and graft failure within 100 days after transplantation. In this study, we retrospectively investigated clinical features of chronic GVHD in the remaining 1072 patients. Cytomegalovirus-seropositive cord blood unit was not provided to transplantation centers. Acute and chronic GVHD were diagnosed and graded according to standard criteria.[1,2] GVHD that developed after day 100 was defined as chronic GVHD. If the mode of presentation for chronic GVHD was progressive, the date of onset was defined as day 100. SAS version 9.1.3 (SAS Institute, Cary, NC) was used for all statistical analyses.

Results and discussion

The median age of the 1072 patients was 33 years (range, 0-79 years) and the median patient body weight was 50.0 kg (range, 4.0-96.1 kg). The median follow up of the surviving patients was 18.1 months (range, 3.3-110.1 months). Of the 1072 patients, 492 (46%) developed grades II to IV acute GVHD within 100 days of transplantation. Chronic GVHD was diagnosed in 312, and the cumulative incidence of chronic GVHD 2 years after transplantation was 28% (95% confidence interval [CI], 25%-31%; Figure 1).

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Unrelated Cord Blood Transplantation for Severe Aplastic Anemia

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ABSTRACT

In the present study we evaluated the feasibility of unrelated cord blood transplantation (UCBT) in patients with severe aplastic anemia (SAA). The outcome of 31 SAA patients (median age 28; range: 0.9-72.3 years old) who received UCBT was analyzed. The cumulative incidences of the neutrophil and platelet recovery after UCBT were 54.8 and 72.2%, respectively (95% confidence interval [CI] = 36.0%-70.3% and 51.3%-85.3%, respectively). The cumulative incidences of grade ≥II acute and chronic graft-versus-host disease (aGVHD, cGVHD) were 17.1% (95% CI = 6.2%-32.8%) and 19.7% (95% CI = 6.2%-38.8%), respectively. Currently, 13 patients are alive, having survived for 33.7 months (median; range: 6-77 months) after UCBT. The probability of overall survival (OS) at 2 years was 41.1% (95% CI = 23.8%-57.7%). A conditioning regimen that included low-dose total body irradiation (TBI) (2-5 Gy), fludarabine, and cyclophosphamide resulted in a favorable OS (80%; 95% CI = 20.4%-96.9%). This result suggests that UCBT using the optimal conditioning regimen can be a salvage treatment for patients without a suitable bone marrow donor and warrants evaluation in further prospective studies.

KEY WORDS
Unrelated cord blood transplantation • Severe aplastic anemia

INTRODUCTION

Over the last 2 decades, the outcome of patients with severe aplastic anemia (SAA) has dramatically improved regardless of whether patients received immunosuppressive therapy (IST) or bone marrow transplantation (BMT) [1-3]. BMT from an HLA-matched sibling is curative in the majority of younger patients with SAA, and is currently recommended as first-line treatment [4]. IST, with a combination of antithymocyte globulin (ATG) and cyclosporine (CSA), has been an alternative therapy for patients without an HLA-matched sibling. BMT from an unrelated donor (UD) is used as a salvage therapy for patients who fail to respond to IST or who experience a relapse of the disease. However, in general, the results of UD-BMT have been inferior to those achieved with an HLA-matched sibling.

The report the Center for International Blood and Marrow Transplant Research (CIBMTR) on UD-BMT (n = 231), for the period 1988-1998, showed that the overall survival (OS) rates for matched and mismatched UD-BMT in patients with SAA were 39% and 36%, respectively [5]. The Japan Marrow Donor Program (JMDP) reported a favorable outcome with 56% survival rate in 154 patients with SAA who received UD-BMT between 1993 and 2000 [6]. In

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Key Words. Cell cycle • Clonal assays • Hematopoietic stem cell transplantation • Long-term repopulation • Mesenchymal stem cells • Stem cell-microenvironment interactions • Human hematopoietic stem cells • Severe combined immunodeficient repopulating cell

ABSTRACT

Hematopoiesis is a dynamic and strictly regulated process orchestrated by self-renewing hematopoietic stem cells (HSCs) and the supporting microenvironment. However, the exact mechanisms by which individual human HSCs sustain hematopoietic homeostasis remain to be clarified. To understand how the long-term repopulating cell (LTRC) activity of individual human HSCs and the hematopoietic hierarchy are maintained in the bone marrow (BM) microenvironment, we traced the repopulating dynamics of individual human HSC clones using viral integration site analysis. Our study presents several lines of evidence regarding the in vivo dynamics of human hematopoiesis. First, human LTRCs existed in a rare population of $CD34^+CD38^-$ cells that localized to the stem cell niches and maintained their stem cell activities while being in a quiescent state. Second, clonally distinct LTRCs controlled hematopoietic homeostasis and created a stem cell pool hierarchy by asymmetric self-renewal division that produced lineage-restricted short-term repopulating cells and long-lasting LTRCs. Third, we demonstrated that quiescent LTRC clones expanded remarkably to reconstitute the hematopoiesis of the secondary recipient. Finally, we further demonstrated that human mesenchymal stem cells differentiated into key components of the niche and maintained LTRC activity by closely interacting with quiescent human LTRCs, resulting in more LTRCs. Taken together, this study provides a novel insight into repopulation dynamics, turnover, hierarchical structure, and the cell cycle status of human HSCs in the recipient BM microenvironment. STEM CELLS *2008;26:3228–3236*

Disclosure of potential conflicts of interest is found at the end of this article.

INTRODUCTION

One of the essential features of hematopoietic stem cells (HSCs) is their ability to remain in a quiescent state to maintain long-term repopulating activity [1]. Regulatory mechanisms that govern this quiescent state are crucial for organizing the hierarchical structure of hematopoiesis and are also of critical biological importance in preventing premature HSC exhaustion under conditions of hematopoietic stress. Several murine studies have demonstrated that interactions between HSCs and stem cell niches, specialized bone marrow (BM) microenvironments created by supporting cells, via receptor-ligand interactions and cell-adhesion molecules expressed in both cell types play central roles in regulating stem cell properties [2]. At present, at least two distinct niches have been identified in the endosteal areas of BM: the osteoblastic niche and the vascular niche [3–5]. However, it remains unclear whether these principles of the niche-HSC regulatory system, extrapolated from murine studies, could apply to human situations.

The severe combined immunodeficient (SCID) mouse-repopulating cell (SRC) assay is considered to be the most reliable research tool for in vivo analysis of the biological processes of human hematopoiesis [6]. In this assay system, SRCs, defined by their ability to reconstitute human hematopoiesis in immunodeficient mice, can be classified into several subtypes on the basis of the lineage restriction of their progenies and the timing of their appearance after transplantation. Although long-term repopulating cell (LTRC) activities with lymphomyeloid potential are mostly restricted to the $CD34^+CD38^{neg}$ population, the $CD34^+CD38^+$ population exhibits only short-term repopulating cell (STRC) activities [7–9]. STRCs are further subdivided into myeloid-restricted STRCs (STRC-Ms) and lymphomyeloid STRCs (STRC-MLs) [10]. The hierarchical relationships of each SRC pop-

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Disease-specific analyses of unrelated cord blood transplantation compared with unrelated bone marrow transplantation in adult patients with acute leukemia

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We made a disease-specific comparison of unrelated cord blood (CB) recipients and human leukocyte antigen allele–matched unrelated bone marrow (BM) recipients among 484 patients with acute myeloid leukemia (AML; 173 CB and 311 BM) and 336 patients with acute lymphoblastic leukemia (ALL; 114 CB and 222 BM) who received myeloablative transplantations. In multivariate analyses, among AML cases, lower overall survival (hazard ratio [HR] = 1.5; 95% confidence interval [CI], 1.0-2.0, $P = .028$) and leukemia-free survival (HR = 1.5; 95% CI, 1.1-2.0, $P = .012$) were observed in CB recipients. The relapse rate did not differ between the 2 groups of AML (HR = 1.2; 95% CI, 0.8-1.9, $P = .38$); however, the treatment-related mortality rate showed higher trend in CB recipients (HR = 1.5; 95% CI, 1.0-2.3, $P = .085$). In ALL, there was no significant difference between the groups for relapse (HR = 1.4, 95% CI, 0.8-2.4, $P = .19$) and treatment-related mortality (HR = 1.0; 95% CI, 0.6-1.7, $P = .98$), which contributed to similar overall survival (HR = 1.1; 95% CI, 0.7-1.6, $P = .78$) and leukemia-free survival (HR = 1.2; 95% CI, 0.9-1.8, $P = .28$). Matched or mismatched single-unit CB is a favorable alternative stem cell source for patients without a human leukocyte antigen–matched related or unrelated donor. For patients with AML, decreasing mortality, especially in the early phase of transplantation, is required to improve the outcome for CB recipients. (Blood. 2009;113:1631-1638)

Introduction

Allogeneic hematopoietic stem cell transplantation (HSCT) with bone marrow (BM) or peripheral blood, the curative treatment of choice for acute leukemia, is limited by the inadequate supply of human leukocyte antigen (HLA)–identical related donors. Bone marrow from HLA-matched unrelated donors has been a major alternative graft source.[1-3] Umbilical cord blood (CB), an alternative stem cell source to BM or peripheral blood stem cells, has been used primarily in children,[4-10] but its use in adults is increasing.[11,12]

Clinical comparison studies of cord blood transplantation (CBT) and bone marrow transplantation (BMT) for leukemia from unrelated donors in adult recipients showed comparable outcomes.[11-13] Recipients of CBT showed delayed neutrophil recovery and lower incidence of acute graft-versus-host disease (GVHD).[11-13] Overall treatment-related mortality (TRM) was reported to be similar[12] or higher[11] compared with HLA-matched BM. Acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL) are different disease entities that require different chemotherapy regimens for treatment. However, previous comparison studies have included both diseases because of limitation in the number of CBTs given to adults.

In addition, the study periods of previous studies encompass the pioneering period of CBT, when the general practice was to use these grafts in patients in whom there were no other curative options and when the relevance of cell dose and HLA matching had not yet been recognized.[6,7,14]

Accumulation of a larger number of CBT results enabled us to make a controlled comparison with unrelated BMTs. To avoid the inclusion of the pioneering period of CBT, the subjects were limited to those who received transplantations in and after 2000.

Methods

Collection of data and data source

The recipients' clinical data were provided by the Japan Cord Blood Bank Network (JCBBN) and the Japan Marrow Donor Program (JMDP).[15]

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ASBMT
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Incidence and Risk Factors of Early Bacterial Infections after Unrelated Cord Blood Transplantation

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Incidence and characteristics of early bacterial infection within 100 days after unrelated cord blood transplantation (UCBT) were assessed for 664 pediatric and 1208 adult recipients in Japan. Cumulative incidence of early bacterial infection at day 100 post-UCBT was 11% (95% confidence interval [CI], 8%-13%) for children and 21% (CI, 19%-24%) for adults ($P < .0001$). Early bacterial infection in adults had a significant impact on mortality (hazard ratio [HR] = 2.1, CI, 1.7-2.6; $P < .0001$), although no significant risk factors were identified. Multivariate analysis identified older age group (6-10, and 11-15 years versus 0-5 years of age) at transplant (HR = 2.0 and 2.7, CI, 1.1-3.5 and 1.4-4.9; $P = .020$ and .002, respectively) as an independent risk factor of early bacterial infection for children. Early bacterial infection in children did not have a significant impact on mortality when adjusted. Of 315 bacteremia, 74% were caused by Gram-positive microorganisms. Pneumonia occurred in 39 patients including 13 cases of *Stenotrophomonas maltophilia* pneumonia. Early bacterial infection had a negative effect on survival for adults and the median day of development was 10 days after transplant, suggesting that the prevention of bacterial infection in the very early post-UCBT phase is important.

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KEY WORDS: Early bacterial infection, Cord blood transplantation, The Japan Cord Blood Bank Network, Risk factor for infection, Urelated donor

INTRODUCTION

Infection is 1 of the major causes of morbidity and mortality for patients undergoing bone marrow transplantation (BMT) and peripheral blood stem cell transplantation (PBSCT) [1,2]. Recently, use of cord blood transplantation (CBT) from unrelated donors has increased for patients who do not have suitable donors for BMT or PBSCT, yielding promising results [3-7]. However, neutrophil recovery has been significantly delayed in unrelated CBT patients compared to unrelated BMT patients. Bacterial infection remains 1 of the most common problems after unrelated cord blood transplantation (UCBT) [5,8-10].

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ORIGINAL ARTICLE

Survival after cord blood transplantation from unrelated donor as a second hematopoietic stem cell transplantation for recurrent pediatric acute myeloid leukemia

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Abstract The Japan Cord Blood Bank Network (JCBBN) reports the treatment of 22 children with acute myeloid leukemia (AML) who received umbilical cord blood transplantation from unrelated donors (CBT) as their second hematopoietic stem cell transplantation (HSCT). Provided by the JCBBN, between February 1997 and September 2006, 22 patients had CBT as a second HSCT. In the initial HSCT, eight received autologous, seven received CBT, and the remaining had allogenic BMT. At the time of CBT as a second HSCT, seven were in the second complete remission (CR2), two in the third CR (CR3), the remaining were not in remission. Reduced intensity conditioning (RIC) conducted for 10 cases and myeloablative conditioning (MAC) for 12 cases. The overall survival rate was 31.3%, 5 years after CBT. Second complete remission at second transplantation was favorable prognosis (58.3 ± 18.6%, compared with 17.1 ± 10.8% for the non-CR group. Mortality after CBT as a second HSCT accounted for 15 cases, 8 from treatment-related mortality. In conclusion, CBT combined with RIC as second HSCT may be useful against a recurrence of AML in children after the initial HSCT.

Keywords Cord blood transplantation · Hematopoietic stem cell transplantation · Second transplantation · Acute myeloid leukemia · Reduced intensity conditioning

1 Introduction

Hematopoietic stem cell transplantation (HSCT) remains the one of curative therapy for patients with high-risk leukemia. However, relapse remains a significant problem and is the major cause of post-transplantation mortality. Patients with relapsed leukemia after HSCT have a very poor prognosis and the optimal salvage therapy remains an open question. Second transplantation is often considered to be the standard of care for a patient with relapsed acute leukemia after allogeneic transplantation: it can provide a durable remission for a small number of patients who are

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ORIGINAL ARTICLE

Long-term outcome of cord blood transplantation from unrelated donors as an initial transplantation procedure for children with AML in Japan

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To assess the outcome of unrelated umbilical cord blood transplantation (UCBT), 141 children with AML who underwent UCBT (39 in first CR (CR1), 33 in CR2, 4 in CR3 and 65 at more advanced stages (not in CR)) were analyzed in a retrospective multicenter study in Japan. Short-term MTX was used for prophylaxis of acute GVHD in 80 cases (57%). The cumulative incidences of neutrophil recovery, platelet recovery and acute GVHD (grades 2–4) were 78.7, 62.4 and 40.1%, respectively, and the 100-day transplantation-related mortality (TRM) was 10.8%. Multivariate analysis showed that an infused CD34$^+$ cell dose of 1.35×10^5 cells per kg or more was associated with favorable neutrophil and platelet recovery, and that short-term MTX was associated with a lower 100-day TRM. The 6-year relapse rate was 38.8% and was associated with disease status. Six-year overall survival was 45.8% (70.4 ± 8.3% in CR1, 59.3 ± 11.3% in CR2, 75.5 ± 21% in CR3 and 20.6 ± 6.2% for children with non-CR). We conclude that the results of UCBT are particularly promising for children with a karyotype suggesting a poor prognosis, and for those who receive transplants in CR2 and CR3 after an early relapse.
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Keywords: cord blood transplantation; AML; children

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Introduction

With currently available treatment, 80–90% of children with AML achieve CR, but 30–40% of these patients subsequently suffer recurrence, reducing the long-term survival rate to only about 50%.[1–4] After recurrence, the likelihood of survival is poor, being 21–33% according to recent reports.[5–8] BMT from an HLA-matched sibling or unrelated donor has a major role in the treatment of children with high-risk or relapsed AML.[9–11] However, although there are currently more than 250 000 donors registered in the Japan Marrow Donor Registries Program, a substantial proportion of children who lack a sibling donor will never undergo BMT from an HLA-matched unrelated donor either because such a donor cannot be found or because the time required to identify a donor is too long. Moreover, for children who undergo unrelated BMT, the increased HLA disparity adversely affects survival because of the high risk of GVHD and opportunistic infections.

Hematopoietic stem cells from an unrelated cord blood (UCB) transplant can restore hematopoiesis and immune function after a myeloablative conditioning regimen, even if the graft is not perfectly HLA identical to the recipient.[12–15] This important medical advance led to the establishment of large cord blood (CB) banks that made possible the use of UCB to provide transplants for patients lacking a conventional related or unrelated BM (UBM) donor. In addition, when compared with the availability of UBM grafts, UCB offers the advantage of significantly faster availability of banked cryopreserved UCB units. A previous comparative study of children receiving UCB or UBM transplants for acute leukemia revealed that the relapse rate did not increase after umbilical cord blood transplantation (UCBT).[16] However, it was not possible to report specific

The impact of anti-HLA antibodies on unrelated cord blood transplantations

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The majority of cord blood transplantations (CBTs) have human leukocyte antigen (HLA) disparities. We investigated the impact that patients' pretransplantation anti-HLA antibodies have on the outcome of CBTs. Testing for anti-HLA antibody and its specificity was performed retrospectively at the Japanese Red Cross Tokyo Blood Center with sensitive solid-phase antibody detection assays. Among 386 CBTs, which were first myeloablative stem cell transplantations for malignancies and used a single unit of cord blood, 89 tested positive. Among the antibody-positive group, the cord blood did not have the corresponding HLA type for the antibody in 69 cases (ab-positive), while 20 cases had specificity against the cord blood HLA (positive-vs-CB). Cumulative incidence of neutrophil recovery 60 days after transplantation was 83% (95% confidence interval [CI], 79%-87%) for the antibody-negative group (ab-negative), 73% (95% CI, 61%-82%) for ab-positive, but only 32% (95% CI, 13%-53%) for the positive-vs-CB ($P < .0001$, Gray test). With multivariate analysis, the ab-positive showed significantly lower neutrophil recovery than the ab-negative (relative risk [RR] = 0.69, 95% CI, 0.49-0.96, p = .027). The positive-vs-CB had significantly lower neutrophil recovery (RR = 0.23, 95% CI, 0.09-0.56, $P = .001$) and platelet recovery (RR = 0.31, 95% CI, 0.12-0.81, $P = .017$) than the ab-negative. Patients' pretransplantation anti-HLA antibodies should be tested and considered in the selection of cord blood. (*Blood.* 2010;116(15): 2839-2846)

Introduction

The number of unrelated cord blood transplantations (CBTs) has increased, mainly because cord blood (CB) is more readily available than bone marrow. CB can be collected without burden or risk to the donors, and successful outcomes have been reported with less stringent requirements for human leukocyte antigen (HLA) compatibility.[1-3] Comparable outcomes have been reported with analyses of unrelated bone marrow transplantations (BMTs) and CBTs, although there were lower neutrophil and platelet recoveries in CBTs.[4-7] Graft failure, with a high mortality rate, has been noted as a problem.[8,9]

The role of anti-HLA antibodies in graft rejection of organ transplantations has been analyzed extensively.[10,11] However, only a few studies have analyzed the significance of anti-HLA antibodies in stem cell transplantations,[12-14] in which the recipient's immune system is taken over by the donor's cells and for which a great effort is made to match the recipient and donor HLA types at the allele level.

We investigated the impact that patients' pretransplantation anti-HLA antibodies have on the outcome of CBTs, for which the majority have HLA mismatches. We previously reported that anti-HLA antibodies, when the specificity corresponded to a mismatched antigen, had a negative effect on engraftment of CBTs.[15] However, this finding was from a single cord blood bank study with limited samples. In this study, the number of cases is increased retrospectively, in cooperation with 7 of the public banks in Japan, with the intention of clarifying the significance of anti-HLA antibodies.

Methods

Patients

This study included patients with hematologic malignancies who received their first hematopoietic stem cell transplantation with a myeloablative conditioning regimen, using a single unit of CB from 1 of the 7 CB banks. All patients underwent CBT between 2001 and 2007. To be eligible for this study, patients' plasma/sera had to be available for analysis. Patients were excluded if they had not received conditioning, received reduced intensity conditioning or had not received graft-versus-host disease (GVHD) prophylaxis. The criteria were met by 386 patients, including the 153 cases analyzed in our previous report.[15] As a standard procedure, the CB banks confirmed the HLA types of the patients and CB units before shipping, with samples being stored frozen, having obtained written consent from the patients in accordance with the Declaration of Helsinki. The procedures of our CB bank were approved by the institutional review board of the Japanese Red Cross Blood Service. HLA matching of CB and patient was performed using the antigen levels for HLA-A, -B and -DR. Each CB bank collected recipients' clinical information at 100 days after transplantation. Patient information on survival, disease status and long-term complications was updated annually with follow-up questionnaires.

Antibody testing

Patients' plasma/sera samples stored in each CB bank were sent to the Japanese Red Cross Tokyo Blood Center, where the plasma samples were treated with thrombin. All samples were tested with FlowPRA (One Lambda) for class I (ie, HLA-A/B/C) and class II (ie, HLA-DR/DP/DQ) anti-HLA antibodies. Samples of 20 μL were incubated with HLA class I–coated and HLA class II–coated microspheres, respectively, for

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Prediction of Reactivity to Noninherited Maternal Antigen in MHC-Mismatched, Minor Histocompatibility Antigen-Matched Stem Cell Transplantation in a Mouse Model

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The immunologic effects of developmental exposure to noninherited maternal Ags (NIMAs) are quite variable. Both tolerizing influence and inducing alloreaction have been observed on clinical transplantation. The role of minor histocompatibility Ags (MiHAs) in NIMA effects is unknown. MiHA is either matched or mismatched in NIMA-mismatched transplantation because a donor of the transplantation is usually limited to a family member. To exclude the participation of MiHA in a NIMA effect for MHC (H-2) is clinically relevant because mismatched MiHA may induce severe alloreaction. The aim of this study is to understand the mechanism of NIMA effects in MHC-mismatched, MiHA-matched hematopoietic stem cell transplantation. Although all offsprings are exposed to the maternal Ags, the NIMA effect for the H-2 Ag was not evident. However, they exhibit two distinct reactivities, low and high responder, to NIMA in utero and during nursing depending on the degree of maternal microchimerism. Low responders survived longer with less graft-versus-host disease. These reactivities were correlated with Foxp3 expression of peripheral blood $CD4^+CD25^+$ cells after graft-versus-host disease induction and the number of IFN-γ–producing cells stimulated with NIMA pretransplantation. These observations are clinically relevant and suggest that it is possible to predict the immunological tolerance to NIMA. ***The Journal of Immunology*****, 2010, 185: 7739–7745.**

Allogeneic hematopoietic stem cell transplantation (HSCT) is a curative treatment for various hematologic malignancies. Despite the presence of an increasing pool of unrelated volunteer donor registries, many patients who need allogeneic HSCT are not able to find a histocompatible donor in proportion to the patients who have a rare HLA haplotype, but transplants from HLA-mismatched donors are limited by a number of historical barriers such as intractable graft-versus-host disease (GVHD) or graft failure (1).

There have been several previously reported investigations of noninherited maternal Ags (NIMAs) (2, 3). A reciprocal process, trafficking of maternal cells across the placenta, has also been documented (4, 5) and can result in life-long microchimerism in the offspring (6). In addition, maternal cells and HLA proteins are ingested by the baby during nursing, possibly stimulating oral tolerance (7, 8). However, the mechanisms by which NIMAs actually drive the immune system toward tolerance or rejection of allograft are still unclear. The clinical benefits of developmentally acquired tolerance to NIMAs were first noted by Owen et al. (9) >50 y ago. Since then, tolerogenic effects of NIMAs have been documented at both T and B cell levels in a variety of clinical settings (3, 10, 11).

In allogeneic stem cell transplantation, Van Rood et al. and others (12, 13) showed that the patients who received non-T cell-depleted (TCD) bone marrow transplantation (BMT) from a NIMA-mismatched donor had a significantly lower incidence of GVHD than noninherited paternal Ags . However, in non-TCD BMT from a NIMA-mismatched donor, 10% of patients still experienced severe acute GVHD (13). Furthermore, graft rejection and hyperacute GVHD in HSCT from NIMA-mismatched siblings were observed despite detecting of maternal microchimerism (MMc) (14). In contrast, Kanda et al. (15) described that a substantial proportion of long-term survivors after NIMA-mismatched HSCT could discontinue administration of immunosuppressive agents despite the frequent occurrence of moderate to severe chronic GVHD. Thus, the immunologic effects of developmental exposure to NIMAs are heterogeneous (8, 16, 17).

Although mismatch at minor histocompatibility Ags (MiHAs) can provoke severe immune responses against host cells upon transplantation (18), the role of MiHAs in NIMA effects has not been described. Recently, naturally acquired tolerance and sensitization to MiHAs have been reported (19). They showed the presence of MiHA-specific regulatory T cells in healthy adult women and men. In addition, it remains to be studied whether particular microchimeric cell types are associated with either a sensitized or a tolerized MiHA immunization status.

We generated H-2–mismatched and MiHA-matched NIMA-exposed model mice. Surprisingly, a tolerogenic NIMA effect was not uniformly observed in this system. However, when re-examining the database on lymphoproliferation assay, we demonstrated that two distinct reactivities to NIMA were present depending on

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Abbreviations used in this paper: BMT, bone marrow transplantation; CTLp, CTL precursor; GVHD, graft-versus-host disease; HR, high responder; HSCT, hematopoietic stem cell transplantation; HTLp, Th lymphocyte precursor; LR, low responder; MiHA, minor histocompatibility Ag; MMc, maternal microchimerism; NIMA, noninherited maternal Ag; TCD, T cell-depleted.

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