Biol Blood Marrow Transplant 22 (2016) 487–492

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

ASBMT American Society for Blood and Marrow Transplantation

Clinical Research: Alternative Donors

Impact of Allele-Level HLA Mismatch on Outcomes in Recipients of Double Umbilical Cord Blood Transplantation

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Article history:
Received 4 June 2015
Accepted 23 September 2015

Key Words:
Alternative donor transplant
Umbilical cord blood
Histocompatibility

A B S T R A C T

The impact of allele-level HLA mismatch is uncertain in recipients of double umbilical cord blood (UCB) transplantation. We report a single-center retrospective study of the clinical effect of using allele-level HLA mismatch HLA-A, -B, -C, -DRB1, and -DQB1 of the 2 UCB units. We studied 342 patients with hematologic malignancy. Donor–recipient pairs were grouped according to the number of matched HLA alleles, with 32 matched at 9-10/10, 202 at 6-8/10, and 108 at 2-5/10 alleles. The incidence of hematopoietic recovery, acute and chronic graft-versus-host disease, and nonrelapse mortality and treatment failure was similar between groups. In an exploratory analysis of 174 patients with acute leukemia, after adjusting for length of first remission and cytogenetic risk group, a 2-5/10 HLA match was associated with lower risk of relapse and treatment failure. These data indicate that a high degree of allele-level HLA mismatch does not adversely affect transplant outcomes and may be associated with reduced relapse risk in patients with acute leukemia.

INTRODUCTION

HLA matching is a critical determinant of transplant outcome in that disparities between the donor and recipient can result in an immune response associated with graft failure, graft-versus-host disease (GVHD), delayed immune reconstitution, and therefore mortality. In contrast to outcomes after the transplantation of hematopoietic stem cells from HLA-mismatched unrelated adult donors (URD) [1,2], HLA mismatch may be more tolerable after umbilical cord blood transplantation (UCBT), but reports also demonstrate the importance of HLA matching in recipients of single UCB unit grafts [3-6].

In 2000, the introduction of double UCBT (dUCBT) extended the application of UCB as an allogeneic hematopoietic stem cell source to nearly all patients, particularly adults, who lacked an adequately dosed single UCB unit [7-10]. More recent reports on the effectiveness of dUCBT suggest that survival is similar to that reported in recipients of adequately dosed single UCB units and allele-level HLA-matched URD allografts [8-12]. Guidelines from the National Marrow Donor Program and Center for International Blood and Marrow Transplant Research state that "current practice is to maximize matching of the 2 units at antigen level for HLA-A and -B and at the allele level for -DRB1 with a minimum of 4 of 6 match" [13, p 260]. However, this practice recommendation was based on single UCBT data [3-6]. Because a substantial proportion of adults are routinely transplanted with 2 partially HLA-matched UCB units, we evaluated the effect of allele-level HLA mismatch in patients with hematological malignancy receiving a dUCBT.

METHODS

Patients

All recipients of a dUCBT for the treatment of a hematologic malignancy with allele-level HLA typing for both the patient and UCB units (excluding those with prior allogeneic hematopoietic stem cell transplant) were eligible. Treatment protocols were approved by the University of Minnesota Institutional Review Board. All patients were transplanted between May 2002 and September 2010 with a median follow-up of 48.3 months (range, .2 to 103.3).

UCB Unit Selection

Patients underwent dUCBT if an adequate single UCB unit could not be identified and 2 units were available that were ≥4/6 HLA matched with the

Financial disclosure: See Acknowledgments on page 492.
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http://dx.doi.org/10.1016/j.bbmt.2015.09.025
1083-8791/

patient and each other, typing HLA-A and -B at antigen level and HLA-DRB1 at allele level without consideration of HLA-C and -DQ. Graft selection criteria was previously reported [7]. However, before October 2010, the 2 UCB units with the highest cell doses matched at the 4-6/6 HLA loci meeting the interunit match criteria were selected. Testing for antidonor HLA antibodies was not routinely performed during this time period.

HLA Typing

Donor and recipient HLA typing at HLA-A, -B, -C, -DRB1- and -DQB1 was based on molecular testing. Class I alleles were typed by sequence-specific oligonucleotide probe methods before March 2002 [14] and by automated sequence-based typing thereafter [15]. Class II typing was performed using reverse sequence-specific oligonucleotide and sequence-specific PCR methods before June 2005 [16] and sequence-based typing [17] thereafter. HLA alleles were named according to World Health Organization's nomenclature for factors of the HLA system [18]. When residual genotype ambiguities occurred, they typically involved 1 common and well-documented HLA allele [19] with 1 or more alleles observed as rare or never previously reported to the National Marrow Donor Program Registry [20]. Residual genotypic ambiguities that involved alleles encoding distinct protein sequences in the antigen recognition site were resolved by sequence-specific PCR, hemizygous resequencing, or heterozygous ambiguity resolution sequencing. Donor–recipient HLA match assignment was based on final, actual high-resolution typing.

Treatment

Choice of conditioning was based on recipient age and presence of comorbidities. For patients aged <46 years and without comorbidities, myeloablative conditioning consisted of cyclophosphamide 120 mg/kg, fludarabine 75 mg/m^2, and total body irradiation 1320 cGy [8]. For patients aged 46 to 75 years or younger patients with comorbidities, reduced-intensity conditioning included cyclophosphamide 50 mg/kg, fludarabine 200 mg/m^2, and total body irradiation 200 cGy with antithymocyte globulin (ATG) [7] added for patients without chemotherapy within the prior 3 months.

The dUCB grafts were infused on day 0 in rapid succession and in random order. Thawing and infusion procedures and supportive care followed institutional guidelines. All patients received granulocyte colony-stimulating factor (filgrastim) 5 μg/kg/day beginning day +1 until the absolute neutrophil count was $\geq 2.5 \times 10^9$/L for 2 consecutive days. Immunoprophylaxis in 98% of patients consisted of cyclosporine A starting on day −3 with a slow taper starting at day +100 and mycophenolate mofetil starting on day −3 and discontinuation on day +30 in the absence of acute GVHD.

Data Collection and Statistical Considerations

Clinical data were prospectively collected in the University of Minnesota Blood and Marrow Transplant Program Database with retrospective review of GVHD grading and primary causes of death. HLA match assignment was based on the number of HLA matches at 10 alleles between the patient and worst matched UCB unit. Because there was no obvious break point when evaluating the effect of single-allele HLA matches (eg, 10/10 versus 9/10 versus 8/10) on either survival or engraftment, patients were grouped as allele matched at 9-10/10 alleles (n = 32), paralleling the match grade that is routinely accepted for recipients of URD allogeneic transplantation. The remaining match grades divided the population as HLA matched 6-8 alleles/10 (n = 202) and 2-5/10 (n = 108).

Event times were calculated from the date of transplant. Neutrophil recovery was defined as the first day of an absolute neutrophil count $\geq .5 \times 10^3$/μL for 3 or more consecutive days; platelet recovery was defined as the first day of a platelet count $\geq 20 \times 10^3$/μL without transfusion support for 7 consecutive days. Acute and chronic GVHD were defined and staged using established criteria [21,22]. Patients who died within 28 days of transplantation were considered as early deaths. Disease-free survival (DFS) was estimated by the Kaplan-Meier curve with 95% confidence intervals (CIs) derived from the standard errors. Cumulative incidence estimates were determined for neutrophil and platelet engraftment, acute and chronic GVHD, nonrelapse mortality (NRM), and relapse, treating nonevents as a competing risk. The effect of HLA match between the 2 UCB units was only considered for the analysis of the long-term predominating unit [23].

Cox regression was used to assess the independent effect of HLA disparity on DFS. Fine and Gray regression was used to assess the independent effect of HLA disparity on neutrophil and platelet recovery, GVHD, NRM, and relapse [24]. The competing risk for neutrophil and platelet recovery was nonengraftment death, for GVHD was non-GVHD death, and NRM and relapse were the competing risk for each other. Other factors considered in regression models included recipient age, disease risk group (standard versus high) based on the American Society of Blood and Marrow Transplantation guidelines [25], conditioning regimen intensity, use of ATG, Karnofsky performance score, cytomegalovirus serostatus (recipient negative versus positive), gender match (match versus mismatch), and cell doses/kg (infused CD34$^+$, CD3$^+$, and total nucleated cells).

RESULTS

We analyzed the allele-level HLA match of the worst matched UCB unit, as used in most prior reports of dUCBT. However, recognizing concerns about multiple statistical comparisons, we also provided the data on the best 10-locus HLA allele matched of the 2 UCB units and the predominant engrafting UCB unit in Supplementary Table 1. Results in these 2 alternative analytic models were similar to that presented in the worst HLA match.

Patients, Treatment and Graft Characteristics

The demographics of the study population and graft characteristics are summarized in Tables 1 and 2, respectively. All 3 groups were similar regarding patient and graft characteristics except for a higher proportion of nonwhite patients in the 2-5/10 allele-level HLA-matched group.

Hematopoietic Recovery

The incidence of neutrophil recovery by day +42 was 89% (95% CI, 83% to 95%), 89% (95% CI, 85% to 93%), and 93% (95% CI, 84% to 100%) in recipients of a 2-5/10, 6-8/10, and 9-10/10 matched unit ($P = .33$) (Figure 1A). The incidence of platelet recovery to 20,000/μL by day +180 was 64% (95% CI, 53% to 76%), 67% (95% CI, 59% to 76%), and 72% (95% CI, 51% to 93%), respectively ($P = .22$) (Figure 1B). In multivariate models, HLA-match group was not associated with hematopoietic recovery (Table 3). However, the odds of neutrophil recovery were higher in recipients of a nonmyeloablative conditioning without ATG and recipients of a total higher infused CD34$^+$ cell dose. The pace of neutrophil and platelet recoveries was similar between the 3 HLA-match groups. After adjusting for CD3$^+$ cell dose of the individual units, the odds ratio of the better HLA-matched unit predominating long term was 1.3 (95% CI, .7 to 2.6, $P = .36$).

Acute and Chronic GVHD

The incidence of grades II to IV acute GVHD was also similar between the 3 allele-level HLA-match groups, at 45% (95% CI, 34% to 59%), 49% (95% CI, 42% to 56%), and 44% (95% CI, 26% to 62%) with 2-5/10, 6-8/10, and 9-10/10 matched grafts ($P = .71$), respectively (Figure 1C). Similarly, the incidence of grades III to IV acute GVHD was 19% (95% CI, 11% to 26%), 20% (95% CI, 15% to 26%), and 13% (95% CI, 1% to 24%), respectively ($P = .67$). The incidence of any chronic GVHD was 27% (95% CI, 18% to 37%), 18% (95% CI, 12% to 23%), and 26% (95% CI, 10% to 42%), respectively ($P = .21$). In multivariate analysis, the HLA match was not associated with risk of either acute or chronic GVHD (Table 3). The use of ATG and reduced-intensity conditioning were independently associated with lower risks of acute GVHD. Younger age and lower combined graft CD34$^+$ cell dose were associated with lower risk of chronic GVHD. The combined CD3$^+$ cell dose was not associated with either acute or chronic GVHD.

NRM, Relapse, and Survival

In contrast to observations in recipients of URD bone marrow and peripheral blood hematopoietic cell transplantation (HCT) [1,2], NRM was not significantly influenced by increasing HLA mismatch. The incidence of NRM at 2 years was 36% (95% CI, 26% to 45%), 29% (95% CI, 23% to 36%), and