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Mismatched unrelated alternative donors for hematological malignancies

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ABSTRACT

For the majority of hematologic malignancies allogeneic hematopoietic cell transplantation (HCT) is the only curative treatment option. Sibling donors have been the standard for adult patients. Since there is not a suitable family donor for all patients, the need for alternative donors for HCT is great. Fortunately, the availability of unrelated volunteer donor registries has expanded over the years and the results of HCT with matched unrelated donors (MUD) are comparable to the results with matched related donors (MRD). Nevertheless, there are many patients lacking a well-matched donor. To increase the applicability of transplantation, alternative donors such as mismatched unrelated donors (MMURD), cord blood stem cell products and haploidentical related donors have been widely used. This review seeks to give insights into the use of MMUD donors for HCT and summarize the existing data.

1. Results in mismatched unrelated donor transplantations

According to the Center for International Blood and Marrow Transplant Research (CIBMTR), approximately 1,000,000 hematopoietic cell transplantation (HCT) procedures have been performed worldwide. In 2012, about 6,000 allogeneic transplants were performed in the United States, with nearly two thirds from unrelated donors. Approximately 75% of transplants used peripheral blood stem cells [1]. In 16,211 allogeneic HCTs performed by the European Group for Blood and Marrow Transplantation (EBMT) unrelated donor transplants account for 53% of the allogeneic transplants [2]. The human leukocyte antigen (HLA)-identical donor is the ideal donor in HCT because the risk of alloimmune complications is directly correlated to the number of HLA mismatches. The effects of the HLA mismatch are graft rejection and/or graft-versus-host disease (GVHD). Historically, HCTs from matched unrelated donor (MUD) matching at HLA-A, HLA-B, and HLA-DR loci were inferior to HCTs from matched related donors (MRD) due to the high rates of acute GVHD (aGVHD) and consecutive treatment-related mortality (TRM). Improved HLA typing techniques and deeper understanding of the importance of HLA matching at the six "classical" polymorphic HLA loci (HLA-A, -B, -C, -DR, -DQ, -DP) has led to significantly improved outcomes in HCT of MUD comparable to HCT from MRD. Due to numerous studies, a 10/10 matched donor (HLA-A, -B, -C, -DR, DQ) is considered as an ideal (= matched) unrelated donor (MUD). In many circumstances the use of a 9/10 match has been associated with an outcome equally as good as a 10/10 match. However, the allele where the donor is mismatched is likely to be important for HCT outcomes. The impact for HLA-DP and HLA-DQ seemed to be less distinct; therefore, high-resolution DNA matching for HLA-A, -B, -C, and -DRB1 (8/8 match) is claimed to be the minimum level of matching [3,4].

The effects of HLA mismatches on outcome of HCT have been investigated in numerous national and international studies. Petersdorf et al on behalf of the International Histocompatibility Working Group (IHWG) in Hematopoietic Cell Transplantation reported outcome analysis in 4,796 unrelated donor HCTs receiving myeloablative conditioning (MAC) regimens. Of those in the study, 61% were 10/10 matched and 39% were mismatched for a single allele or antigen. After adjusting for disease stage, age, and ethnicity, the hazard of mortality conferred by a single HLA mismatch, without regard to the mismatched locus, was 1.20 (95% confidence interval [CI]: 1.12–1.30, $P < .0001$). Of note, the effect of a single HLA mismatch on mortality is best seen in low-risk disease patients (hazard ratio [HR] 1.50, 95% CI: 1.28–1.76, $P < .0001$), less marked in intermediate-risk patients (HR 1.15, 95% CI: 1.0–1.29, $P = .02$), and statistically not significantly different in patients with high-risk disease (HR 1.06, 95% CI: 0.92–1.22, $P = .43$) [5]. The same group already showed this phenomenon in a study of 948 unrelated donor transplant pairs where a single HLA mismatch led to increased mortality only in low-risk disease patients (HR 2.27), whereas a single HLA mismatch had no significant different effect on mortality in intermediate-risk/high-risk disease (HR 1.09) [6]. Fürst et al reported on 2,646 patients

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from 28 German transplant centers. Of those all were high-resolution–typed for HLA-A, -B, -C, -DRB1, and -DQB1. The highest mortality in overall survival (OS) analysis was seen for HLA-A, -B, and -DRB1 mismatches. HLA-DQB1–mismatched cases showed a nonsignificant trend toward higher mortality, mostly due to HLA-DQB1 antigen disparities. HLA incompatibilities at >1 locus showed additive detrimental effects. HLA mismatching had no significant effect on relapse incidence and primary graft failure [7]. Support for the permissibility of a single HLA mismatch was reported by Shaw et al in a study from 144 patients receiving T-cell–depleted reduced-intensity conditioned (RIC) unrelated donor transplants. In this study there was no significant difference in OS between 10/10 and single HLA-mismatched grafts. However, in multiple mismatched grafts, OS was worse ($P = .005$). The only deleterious effect in the single HLA mismatch cohort was an increase in the rate of primary graft failure (6/47 [13%] v 1/93 [1%], $P = .006$) [8].

The same group reported a national multicenter Study from the United Kingdom with 423 unrelated donor HCT patients. MUD had a significant better OS at 3 years compared to mismatched unrelated donors (MMURD) (47% v 40%; $P = .04$); however, in patients with a single HLA mismatch the OS was 43% versus 30% in those with multiple HLA mismatches. The majority (86%) of patients received T-cell–depleting agents, mostly in vivo T-cell depletion by the CD52 antibody alemtuzumab (92%) [9]. This suggests that single HLA mismatches may be tolerated in the setting of T-cell depletion. A conclusion could also be drawn from a study reported by Tiercy et al on behalf of the EBMT in 114 chronic myeloid leukemia patients. All patients received MAC (one third of whom received anti-thymocyte globulin [ATG]). In MMURD patients, there was a significant 5-year OS detriment (HR 2.43, $P = .0019$) and increase in TRM (HR: 2.58, $P = .0027$). This influence of HLA mismatch was scarcely evident in those patients receiving ATG [10].

Obviously the "donor of choice" is highly HLA-matched. Unfortunately, the probability of finding an at least 8/8 MUD is only around 60%–70% for patients with European (Caucasian) ancestry. For patients with non-European (Caucasian) ancestry and/or rare HLA alleles, the probability is even worse. Taking into account the efficiency of the searches, at least one third of all patients lack a "suitable" donor [11]. Nevertheless, in certain circumstances (low probability of successful donor search, rare HLA alleles, and HLA associations, high urgency of HCT) mismatches may be tolerated. For these patients, the careful choice of the best "alternative donor" is a clinical challenge.

2. Graft failure, relapse rate, and GVHD in MMURD transplants

Lower OS rates in the MMURD cohort are mainly due to alloimmune complications leading to higher TRM caused by the existing HLA disparity. HLA mismatch in the graft-versus-host (GVH) or the host-versus-graft (HVG) direction is associated with a higher rate of aGVHD and graft failure, respectively. There is an approximately 10% graft failure rate in MMURD transplants, significantly higher than that observed in MRD and MUD transplants [12–15]. Similar to MUD transplants, the risk of graft failure is higher with bone marrow (BM) than with peripheral blood stem cells (PBSC) as a graft source in MMURD transplants (16% with BM v. 3% with PBSC) [16].

In MMURD, regardless of the indication for transplant and the conditioning regimen, patients generally have relapse rates comparable to those of MUD and MRD transplant recipients. Arora et al reported a retrospective CIBMTR analysis that compared 521 patients who received a ≥1-allele MMURD to 3,514 patients who received an MRD transplant. Relapse rates at 5 years were 14% in MRD, 12% in MUD, 11% in single class I mismatch, and 9% in single class II mismatched donors, and these were not significantly different in multivariate analysis [17].

In MMURD GVHD remains the main challenge in achieving successful outcome. GVHD incidence and severity depend primarily on donor and recipient matching for HLA and the regimen used for immune suppression. Woolfrey et al examined MMURD with PBSC as a graft source and found an increased risk of acute grade 3–4 GVHD with single-allele MMURD when compared with matched transplants (relative risk [RR], 1.59; 95% CI, 1.20–2.09) but no difference in chronic GVHD (cGVHD) [3]. Whereas some reports do show a higher risk of cGVHD with HLA class I–mismatched transplants [17–19]. A study by Lee et al in patients receiving a BM graft showed that single-allele MMURD transplants had more grade 3-4 aGVHD (RR, 1.48; 95% CI, 1.29–1.68) than MUD transplants [4]. The majority of patients in these studies received MAC, but in a more recent publication Verneris et al on behalf of the CIBMTR reported in 2588 patients receiving RIC a similar increase in aGVHD and not cGVHD, resulting in inferior outcome in 7/8 MMURD transplantations when compared with 8/8 MUD transplantations [20]. Therefore, transplant-related strategies such as improved GVHD prophylaxis should be investigated to determine the influence on allele- and antigen-mismatched transplantation from unrelated donors. GVHD prevention has been based largely on the use of pharmacological agents and, to a lesser degree, on the depletion of T cells from the stem cell graft [21,22]. A phase III, multicenter, controlled trial established tacrolimus plus methotrexate as the state-of the-art regimen for GVHD prophylaxis in the unrelated donor setting [23]. In contrast a more recent retrospective analysis of 456 consecutive patients showed no difference in aGVHD, cGVHD, PFS, and OS comparing tacrolimus and calcineurin inhibitors as immunosuppressive drugs [24]. Extensive studies have focused on the use of ATG for GVHD prophylaxis and therapy (noteworthy, there are several different types of ATG preparations available, differing in way of immunization with either human thymocytes in rabbits or horses [thymoglobulin, lymphoglobulin, ATGAM] or the use of the human T-cell acute lymphoblastic leukemia cell line Jurkat for immunization of rabbits [ATG-F] with differences in strength and target cell populations). In PBSC or BM MMURD transplants, calcineurin inhibitor–based GVHD prophylaxis without ATG results in aGVHD rates of 50%–80%. Adding ATG to calcineurin inhibitors for GVHD prophylaxis results in a significantly lower rate of grade 2–4 aGVHD of 30%–40% [13,25–27]. We could show that with respect to aGVHD grade III–IV, there is almost no difference between patients with a 10/10 matched and a mismatched donor when adding ATG-F to GVHD prophylaxis. Also the cGVHD rates are similar for patients with 10/10 matched and MMURDs, and no effect of HLA-mismatch on relapse, non-relapse mortality, disease-free survival (DFS), and OS was shown [28]. Kroeger et al even showed in a national single-center analysis of 268 patients that in pretransplant ATG-F–treated patients there was no significant difference in DFS, TRM, and incidence of aGVHD comparing transplantations completely matched for 10 alleles, with single allele-mismatch
(9/10), and with patients mismatched for 2–4 alleles (6–8/10) patients [29]. In conclusion, in vivo T-cell depletion by ATG-F seems to allow allogeneic HCT from unrelated donors with HLA disparities. The impact of in vivo T-cell depletion on outcome of MMURDs could also be confirmed using a different way for T-cell depletion. Mead et al reported on 157 consecutive patients receiving alemtuzumab-containing RIC. In patients with 10/10-matched donors compared to 6–9/10 MMUDs there was no difference in 3-year OS, graft failure rates, or incidences of aGVHD and extensive cGVHD, though rejection/relapse rate (recipient chimerism) was higher in MMUDs potentially due to the high