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HLA-Haploidentical Stem Cell Transplantation for Hematologic Malignancies

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Partially HLA-mismatched related, or HLA-haploidentical, donor stem cell transplantation (SCT) is a feasible therapeutic option for advanced hematologic malignancies patients who lack an HLA-matched related or unrelated donor. Advances in conditioning regimens, graft manipulation, and pharmacologic prophylaxis of graft-versus-host disease (GVHD) have reduced the risk of fatal graft failure and severe GVHD, two of the most serious complications of traversing the HLA barrier. Clinical observations reveal a potential role for natural killer (NK) cell alloreactivity in reducing the risk of relapse of acute myeloid leukemia after HLA-haploidentical SCT. NK cell infusions attempt to harness the graft-versus-leukemia effect without producing GVHD. The availability of multiple potential HLA-haploidentical related donors for most patients opens the possibility of optimizing transplantation outcome through intelligent donor selection.

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INTRODUCTION

Donor availability is one of the major obstacles to the success of allogeneic hematopoietic stem cell transplantation (HSCT) for the treatment of hematologic malignancies or nonmalignant hematologic disorders. Because of historically superior outcomes of human leukocyte antigen (HLA)-matched compared to partially HLA-mismatched HSCT [1,2], an HLA-matched sibling or unrelated donor (URD) is the preferred source of stem cells for transplantation. However, an HLA-matched donor can be identified for only 50% to 60% of patients referred for HSCT, lower still for patients in ethnic minorities. The ability to cross the HLA boundary safely would increase the availability of a stem cell donor to nearly 100% of patients referred for allogeneic HSCT.

There are two potential sources of grafts for patients lacking HLA-matched donors: (1) unrelated umbilical cord blood (UCB), and (2) partially HLA-mismatched, or HLA-haploidentical, related donors. Results of UCB transplantation in children are encouraging [3], and transplantation of 2 UCB units generates cell doses that are sufficient for engraftment in adults [4,5]. The initial studies of HLA-haploidentical HSCT employed lethal conditioning, infusion of T cell-replete marrow grafts, and graft-versus-host disease (GVHD) prophylaxis with methotrexate (MTX), with or without cyclosporine (CsA) [6]. These transplants were complicated by excessive bidirectional alloreactivity resulting in high rates of graft failure [7], severe GVHD, and nonrelapse mortality (NRM) [8]. Consequently, event-free survival (EFS) was poor, especially when donors and recipients were mismatched for 2 or more HLA antigens [1,8]. Results of HLA-haploidentical HSCT have improved significantly over the past decade owing to the development of highly immunosuppressive yet nonmyeloablative (NMA) conditioning, novel graft manipulation, and improved prophylaxis of GVHD. Further, HLA-haploidentical HSCT harnesses the potential of natural killer (NK) cell alloreactivity to kill tumor cells and reduce the risk of posttransplantation relapse. These recent developments are the subject of this review.

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HLA-Haploidentical HSCT after NMA Conditioning

Graft failure is a major complication of HLA-haploidentical HSCT [6,9] and is usually a fatal event after myeloablative (MA) conditioning. Truly NMA conditioning offers the safeguard of reconstitution of autologous hematopoiesis in the event of graft failure. Most NMA conditioning regimens incorporate the highly immunosuppressive drug fludabarine (Flu). Studies from Tuebingen, Germany, and from Duke University in the United States have combined Flu-based conditioning with in vivo T cell depletion (TCD) using OKT3 [10] or CAMPATH [11], respectively, to enable the engraftment of HLA-haploidentical stem cells. These regimens were associated with acceptable nonhematologic toxicities and sustained engraftment of donor cells in patients up to the age of 66 years. Overall survival (OS) at 1 year after transplantation ranged from 31% to 37% [11,12], establishing the feasibility of HLA-haploidentical HSCT after NMA conditioning.

The groups at Johns Hopkins in Baltimore and the Fred Hutchinson Cancer Research Center in Seattle have been pioneering the use of high-dose, posttransplantation cyclophosphamide (Cy) to achieve the selective depletion of alloreactive cells after NMA conditioning and HLA-haploidentical HSCT. In an early report, 68 patients with poor-risk hematologic malignancies were conditioned with Flu, Cy, and 2 Gy total body irradiation (TBI) prior to receiving T cell-replete bone marrow (BM) from HLA-haploidentical, first-degree relatives (Figure 1) [13]. Donors and recipients were mismatched at a median of 4 HLA alleles. GVHD prophylaxis comprised Cy 50 mg/kg i.v. on day 3 (n = 28) or on days 3 and 4 (n = 40) after transplantation, followed by tacrolimus and mycophenolate mofetil (MMF), each beginning on day 5. Graft failure occurred in 9 patients (13%) but was fatal in only 1. Grades II-IV and III-IV acute GVHD (aGVHD) occurred in 34% and 6% of patients, respectively, and chronic GVHD (cGVHD) developed in 15% of patients. The cumulative incidences of relapse and NRM at 1 year after transplantation were 15% and 51%, respectively, and OS and EFS at 2 years after transplantation were 36% and 26%. Only 6 patients died of infection (n = 4) or GVHD (n = 2). In this early report, patients with lymphoid diseases had a superior EFS compared to patients receiving HSCT for myelogenous diseases ($P = .02$).

A subsequent report retrospectively compared the outcomes of Hodgkin lymphoma (HL) patients treated with NMA conditioning and grafts from HLA-matched related (n = 38), URD (n = 24), or HLA-haploidentical related (n = 28) donors [14]. Recipients of HLA-haploidentical grafts were conditioned as in Figure 1. Patients had received a median

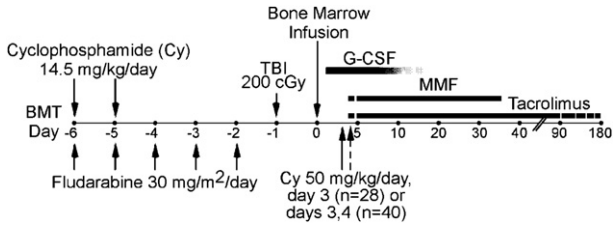

Figure 1. Treatment schema for nonmyeloablative conditioning and HLA-haploidentical bone marrow transplantation. From ref. 11.

of 5 prior regimens, including autologous HSCT in 92%. With a median follow-up of 25 months, 2-year OS, EFS, and incidences of relapsed/progressive disease were 53%, 23%, and 56% (HLA-matched related), 58%, 29%, and 63% (URD), and 58%, 51%, and 40% (HLA-haploidentical related), respectively. NRM was significantly lower for HLA-haploidentical related recipients compared to HLA-matched related recipients ($P = .02$). There were also significantly decreased risks of relapse for HLA-haploidentical related recipients compared to HLA-matched related ($P = .01$) and URD ($P = .03$) recipients. In a recent report from the Center for International Blood and Marrow Transplant Research (CIBMTR), HL patients receiving reduced intensity, unrelated donor HSCT had a 2-year OS and EFS of 37% and 20%, respectively [15]. HLA-haploidentical HSCT may therefore be uniquely effective for patients with relapsed or refractory HL.

We have recently analyzed, retrospectively, the effect of HLA mismatching on the outcome of 185 hematologic malignancies patients treated with NMA, HLA-haploidentical SCT and posttransplantation Cy [16]. The cumulative incidences of grade II-IV aGVHD and cGVHD were 31% and 15%, respectively. The cumulative incidences of NRM and relapse or progression at 1 year were 15% and 50%, respectively. Actuarial EFS at 1 year was 35%. Increasing degrees of HLA mismatch at either class I or class II loci had no significant effect on the cumulative incidence of aGVHD or cGVHD or NRM. In contrast, the presence of an HLA-DRB1 antigen mismatch in the GVH direction was associated with a significantly lower cumulative incidence of relapse (Figure 2A; $P = .04$) and improved EFS (Figure 2C; $P = .009$), whereas HLA-DQB1 antigen mismatch status had no effect. Additionally, the presence of 2 or more class I allele mismatches (composite of HLA-A, -B, and -Cw) in either direction was associated with a significantly lower cumulative incidence of relapse (Figure 2B; $P = .045$ for GVH direction, $P = .01$ for HVG direction) and improved EFS (Figure 2D; $P = .07$ for GVH direction, $P = .001$ for HVG direction). Although the analysis was limited by its retrospective nature and the small numbers of pairs with 2 or fewer HLA antigen mismatches (n = 26), the results