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Hematopoietic Cell Transplantation from an HLA-Mismatched Familial Donor Is Feasible Without Ex Vivo-T Cell Depletion after Reduced-Intensity Conditioning with Busulfan, Fludarabine, and Antithymocyte Globulin

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To extend the use of allogeneic hematopoietic cell transplantation (HCT) to patients without an HLA-matched donor, we investigated HCT from a related donor with 1 fully mismatched HLA-haplotype after conditioning with busulfan in reduced-dose, fludarabine, and antithymocyte globulin. Hematopoietic cells were collected from the donors via leukapheresis after mobilization and infused without further manipulation. Cyclosporin and methotrexate were administered for graft-versus-host disease (GVHD) prophylaxis. Posttransplant engraftment, GVHD, and transplantation-related mortality (TRM) were recorded. Thirty-one patients (age range: 16-69 years) with high-risk acute leukemia/myelodysplastic syndrome (n = 25) or bone marrow failure (n = 6) were enrolled. The donors were either mothers (n = 14), offspring (n = 9), or siblings (n = 8) of these patients. Excluding 3 patients who died or relapsed with leukemia within 3 weeks after HCT, all the remaining 28 patients engrafted with neutrophils (>500/μL) at a median of 16.5 days. Twenty-two of 24 evaluated patients achieved complete donor chimerism (≥95%) 2 weeks after HCT and none experienced graft failure subsequently. The cumulative incidences of grade 2-4 acute GVHD (aGVHD) and moderate-severe chronic GVHD (cGVHD) were 19% (95% confidence interval [CI], 9%-40%) and 20% (95% CI, 10%-41%), respectively. After a median follow-up of 18.2 months (range: 6.3-52.1), 18 patients remained alive (53%). Four patients died without recurrence/progression of underlying diseases giving a TRM of 13% (95% CI, 5%-33%). HCT from an HLA-mismatched family member is feasible without ex vivo T cell depletion when reduced-intensity conditioning containing anti-hymocyte globulin is performed.

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INTRODUCTION

Allogeneic hematopoietic cell transplantation (HCT) is a well-established curative treatment for a significant proportion of patients with hematologic malignancies and bone marrow failure syndrome. Wider application of this procedure, however, is impeded by limited donor availability [1]. Less than one-third of patients who require allogeneic HCT have a human leukocyte antigen (HLA)-matched family member who can donate hematopoietic cells. HLA-matched unrelated donors can be found for patients who do not have an appropriate donor unless these patients carry rare or private HLA-haplotype; however, significant time delays (3-5 months) and additional costs are associated [2]. Unrelated umbilical cord blood transplantations may be considered for patients without an HLA-matched familial or unrelated donor available, but the smaller number of hematopoietic cells in these graft can result in delayed engraftment or eventual graft failure [3].

Nearly all patients who are in need of allogeneic HCT have at least 1 HLA-haploidentical family

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member who is willing to donate hematopoietic cells immediately, not only for the initial transplantation, but also for any additional donations that may be necessary [4]. Early attempts to transplant allogeneic hematopoietic cells across the HLA-haplotype barrier result in high frequencies of engraftment failure and severe graft-versus-host disease (GVHD) [5,6]. Depletion of donor T cells from the grafts prior to HCT decreases the frequency and severity of GVHD, but it results in increased graft failure, delayed immune reconstitution, and increased fatal infections [7,8]. Induction of specific donor T cell anergy against host tissue has been attempted in a small number of patients [9]. Recent efforts to improve the outcomes of HLA-mismatched family donor HCT have included transplantation of higher dose of purified $CD34^+$ cells [10], the use of polyclonal [11,12] or monoclonal [13,14] antibodies against T cells as a part of the conditioning regimen (in vivo T cell depletion), and incorporation of the concept of feto-maternal immune tolerance in selecting donors from among several available HLA-mismatched family members [15]. Despite these efforts, HCT from an HLA-mismatched family member remains a procedure that is associated with high regimen-related toxicity and high transplantation-related mortality (TRM) ranging from 20% to 40% [10,11,15].

In addition to the aforementioned approaches, reduced-intensity conditioning (RIC) may be effective in the setting of HLA-mismatched family donor HCT. Various RIC regimens, utilizing total-body irradiation (TBI) [16], busulfan [17,18], or melphalan, along with fludarabine, have been shown effective in achieving successful engraftment with a reduced frequency of TRM, particularly in elderly patients and in patients with organ dysfunctions, for HCT from both HLA-matched siblings and unrelated donors. These findings showed that, under conditions of adequate immunosuppression of the patient, but not necessarily myeloablation, donor hematopoietic cells can engraft and a complete donor hematopoietic chimerism can be achieved. The same principle may be extended to HLA-mismatched HCT settings. In fact, successful engraftment of allogeneic hematopoietic cells across HLA-haplotype differences after RIC has been observed in animal models [19-21], in infants with severe combined immunodeficiency syndrome [22,23], and in adult patients with hematologic malignancies using heterogeneous RIC regimens [24-29]. Furthermore, the beneficial effects of RIC in a HLA-haploidentical HCT setting may include decreased acute GVHD (aGVHD) and TRM, as has been shown in a swine leukocyte antigen (SLA)-haploidentical transplantation model [19]. Low frequencies of aGVHD (grade 2-4 of 16% to 20%) have been reported in adult patients with hematologic malignancies after HLA-mismatched HCT after RIC [28,29]. These findings indicate the need to further investigate the role of RIC in HLA-mismatched familial donor HCT. We therefore investigated the feasibility of HLA-mismatched familial donor HCT in patients with high-risk hematologic disorders after conditioning with busulfan in reduced-dose, fludarabine, and antithymocyte globulin (ATG), an RIC regimen based on the original regimen developed by Slavin et al [17]. Similar RIC regimens, including oral busulfan, fludarabine, and ATG, have been used in an HLA-mismatched HCT setting by Ogawa et al [28]. The hematopoietic cells were obtained from the donor via peripheral blood after mobilization with granulocyte colony-stimulating factor (G-CSF) and no ex vivo T cell depletion was performed from the graft.

METHODS

Patients and Hematopoietic Cell Donors

An allogeneic HCT protocol for patients with high-risk hematologic disorders, utilizing an HLA-mismatched family member as the donor, was initiated in April 2004. Thirty-one patients (20 males, 11 females; median age: 34 years [range: 16-69 years]; summarized in Table 1) were enrolled before April 2008. All patients were unable to find suitable HLA-matched hematopoietic cell donors in their families or from the donor registries. At study entry, 21 patients were deemed not suitable as candidates for myeloablative conditioning for HCT because of; age $\geq$50 years (n = 4), previous allogeneic HCT (n = 6), immediate prior exposure to salvage chemotherapy including intermediate/high-dose ara-C (n = 9), and the poor general condition (n = 2; UPNs 495 and 618). All patients in the study also met the following entry criteria: age of 15 to 75 years; diagnosis of high-risk acute leukemia (acute leukemia in the first complete remission [CR] but with high-risk chromosomal changes/after salvage or in over first CR); high-risk myelodysplastic syndrome (MDS) (ie, refractory anemia with excess blasts-1, -2, or chronic myelomonocytic leukemia), or bone marrow failure syndrome (severe aplastic anemia or low-risk myelodysplastic syndrome, that is, refractory anemia or refractory cytopenia with multilineage dysplasia) with failure to respond or recurrent cytopenia after treatment with ATG or hypomethylating agents; a Karnofsky performance scale $\geq$70; and adequate organ function (total bilirubin $<$2.0 mg/dL, aspartate aminotransferase [AST] $<$120 U/L, creatinine $<$2.0 mg/dL, and cardiac ejection fraction $>$45% by multigated blood pool scan). HLA-A, -B, -C, and -DR typing of the patients was performed using PCR sequencing-based methods, and of the family members was determined by serologic methods or by PCR. All patients had at least 1 family member, aged 70 years or less, who were