Biol Blood Marrow Transplant 19 (2013) 1197–1203

# Significance of Ethnicity in the Risk of Acute Graft-versus-Host Disease and Leukemia Relapse after Unrelated Donor Hematopoietic Stem Cell Transplantation

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*Article history:*
Received 3 March 2013
Accepted 29 May 2013

*Key Words:*
Unrelated donor transplantation
Ethnicity
Acute Graft-versus-host disease
Leukemia relapse

A B S T R A C T

The significance of patient and donor ethnicity on risk of acute graft-versus-host disease (GVHD) and disease relapse after unrelated donor hematopoietic cell transplantation (HCT) is not known. A total of 4335 patient–donor pairs from the International Histocompatibility Working Group in HCT met the following 3 criteria: (1) HLA-A, -B, -C, -DRB1, and -DQB1 allele matched donor, (2) diagnosis of leukemia, and (3) non–T cell depleted GVHD prophylaxis. Posttransplantation risks of acute GVHD and leukemia relapse were defined in Asian/Pacific Islander, white, African American, Hispanic, and Native American patients that underwent transplantation from donors with the same self-described background. Asian patients had a significantly lower incidence of acute GVHD (Japanese patients: 40.0% grades II to IV and 15.3% grades III to IV; non-Japanese Asian patients: 42.1% grades II to IV and 15.7% grades III to IV) compared with white patients (56.5% grades II to IV and 22.6% grades III to IV) ($P < .001$). The hazard ratio of acute GVHD for white patients was significantly higher than for Japanese patients. Unexpectedly, the hazard ratio of leukemia relapse in white patients with early disease status was also significantly higher than that in Japanese patients. These results provide a platform for future investigation into the genetic factors for unrelated donor HCT and clinical implications of diverse ethnic background.



## INTRODUCTION

Patients who lack a matched sibling to serve as the transplantation donor benefit from hematopoietic cell transplantation (HCT) from an HLA matched unrelated donor [1-6]. In both settings, donor recognition of recipient polymorphisms may lead to acute graft-versus-host disease (GVHD), a potentially life-threatening complication that necessitates long-term immunosuppressive therapy. HLA identical siblings are identical by descent; hence, acute GVHD arises from donor recognition of non-HLA polymorphisms located outside the HLA region [7]. Criteria for unrelated donor selection is based on compatibility for alleles of HLA-A, -C, -B, -DRB1, and -DQB1 genes because matching is associated with lower risks of acute GVHD than HLA mismatching. Acute GVHD after HLA matched unrelated donor HCT may result from donor recognition of genome-wide polymorphisms, including undetected variation within the HLA region [8,9].

Clinical outcome after HCT depends on many factors contributed by the patient, the donor, and the specific transplantation procedures used. In HLA matched sibling transplantation, patient ethnicity has been reported to influence the incidence of GVHD where white Americans, African Americans, and Irish cohorts were at significantly higher risk for acute GVHD than were Japanese or Scandinavian cohorts [10]. The genetic basis that might explain these different outcomes has not been defined. The distribution of HLA alleles is reflected in the ethnicity of the population [11], and the probability of finding an HLA matched unrelated donor is highest when the donor and patient share the same ethnicity. The results of transplantation from selected populations have been extensively reported. In the US population of white patients receiving a transplantation from a white unrelated donor [4], the incidence of grades III to IV acute GVHD is 28% compared with 11.8% observed in the Japanese experience [5]. These data individually suggest that the risk of acute GVHD after unrelated donor HCT depends on the patient's and donor's ethnic backgrounds; however, a formal comparison of outcomes among patients with different ethnic backgrounds has never been undertaken. If the complications after

*Financial disclosure*: See Acknowledgments on page 1202.

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1083-8791/$ – see front matter © 2013 American Society for Blood and Marrow Transplantation.
http://dx.doi.org/10.1016/j.bbmt.2013.05.020

**Table 1**
Characteristics of Hematopoietic Cell Transplantation from Unrelated Donors by Ethnicity

| | Total Number of Pairs | Ethnicity of Patient–Donor Pair | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Japanese* | Asian Excluding Japanese | White | African American | Hispanic | Native American | Mismatched Ethnicity | Unknown Ethnicity |
| Number of pairs | 4335 | 1734 | 19 | 1794 | 34 | 27 | 1 | 171 | 555 |
| HLA-DPB1 matching status (GVH direction) | | | | | | | | | |
| Match | 1053 | 622 | 8 | 320 | 2 | 9 | 0 | 27 | 65 |
| One allele mismatch | 1530 | 798 | 3 | 553 | 12 | 3 | 0 | 45 | 116 |
| Two allele mismatch | 818 | 307 | 1 | 383 | 3 | 5 | 1 | 38 | 80 |
| Unknown | 934 | 7 | 7 | 538 | 17 | 10 | 0 | 61 | 294 |
| Patient age, mean | 33.8 | 30.4 | 33.9 | 36.5 | 34.1 | 30.4 | — | 35.3 | 35.4 |
| Donor age, mean | 34.7 | 34.3 | 35.4 | 35.1 | 38.9 | 34.0 | — | 35.1 | 34.6 |
| Disease | | | | | | | | | |
| ALL | 1232 | 620 | 11 | 424 | 8 | 9 | 0 | 41 | 119 |
| AML | 1758 | 709 | 4 | 703 | 11 | 8 | 0 | 83 | 240 |
| CML | 1345 | 405 | 4 | 667 | 15 | 10 | 1 | 47 | 196 |
| Disease risk† | | | | | | | | | |
| Low | 938 | 273 | 3 | 480 | 5 | 7 | 1 | 29 | 140 |
| Intermediate | 2441 | 1093 | 10 | 910 | 19 | 16 | 0 | 94 | 299 |
| High | 931 | 352 | 6 | 399 | 10 | 4 | 0 | 46 | 114 |
| Unknown | 25 | 16 | 0 | 5 | 0 | 0 | 0 | 2 | 2 |
| Patient–donor sex | | | | | | | | | |
| Female–male | 756 | 302 | 3 | 308 | 9 | 10 | 1 | 33 | 90 |
| Male–female | 944 | 341 | 6 | 435 | 5 | 4 | 0 | 45 | 108 |
| Female–female | 811 | 335 | 3 | 324 | 9 | 3 | 0 | 39 | 98 |
| Male–male | 1789 | 752 | 7 | 725 | 11 | 10 | 0 | 54 | 230 |
| Unknown | 35 | 4 | 0 | 2 | 0 | 0 | 0 | 0 | 29 |
| GVHD prophylaxis | | | | | | | | | |
| Cyclosporine based | 2593 | 964 | 9 | 1167 | 19 | 12 | 1 | 97 | 324 |
| Tacrolimus based | 1536 | 757 | 10 | 592 | 15 | 14 | 0 | 70 | 78 |
| Other | 78 | 8 | 0 | 23 | 0 | 1 | 0 | 4 | 42 |
| Unknown | 128 | 5 | 0 | 12 | 0 | 0 | 0 | 0 | 111 |
| Conditioning regimen | | | | | | | | | |
| Myeloablative | 3687 | 1631 | 18 | 1545 | 27 | 25 | 1 | 149 | 291 |
| Nonmyeloablative/ reduced intensity | 381 | 103 | 1 | 219 | 7 | 2 | 0 | 21 | 28 |
| Unknown | 267 | 0 | 0 | 30 | 0 | 0 | 0 | 1 | 236 |
| Total body irradiation | | | | | | | | | |
| No | 949 | 315 | 1 | 423 | 10 | 5 | 0 | 44 | 151 |
| Yes | 3371 | 1419 | 18 | 1360 | 23 | 22 | 1 | 125 | 403 |
| Unknown | 15 | 0 | 0 | 1 | 1 | 0 | 0 | 2 | 1 |
| Stem cell source | | | | | | | | | |
| Bone marrow | 3481 | 1734 | 9 | 1272 | 24 | 19 | 1 | 105 | 317 |
| Peripheral blood stem cells | 854 | 0 | 10 | 522 | 10 | 8 | 0 | 66 | 238 |
| Transplanted yr (median) | — | 1993-2005 (2000) | 1991-2005 (2000) | 1984-2007 (1999) | 1991-2005 (2000) | 1996-2006 (2001) | — | — | — |

* Japanese include only individuals from the Japan Marrow Donor Program.
† Disease status before transplantation is categorized as low (CP of CML); intermediate (the first or second CR of ALL, AML, or the second CP or accelerated phase of CML); high risk (more advanced stage than intermediate risk).

transplantation depend on donor–recipient ethnicity, then this information will facilitate future mapping of polymorphisms responsible for complications such as acute GVHD and provide insight into the genetic basis of acute GVHD. Furthermore, the information may have practical value in the search for suitable unrelated donors.

We undertook a large-scale international study to define risks after HLA matched unrelated donor HCT performed for patients with different ethnic backgrounds within the International Histocompatibility Working Group (IHWG) in HCT [12]. These data provide a unique opportunity to elucidate the clinical effects of ethnicity on risk of acute GVHD and leukemia relapse in HLA matched unrelated HCT.

## METHODS

### *Study Population*

A total of 4335 patients from the IHWG database met the following criteria and were included in the current analysis: (1) transplantation from an HLA-A, -B, -C, -DRB1, and -DQB1 allele compatible unrelated donor; (2) patient diagnosis of acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), or chronic myeloid leukemia (CML); and (3) non–T cell depleted stem cell source without the use of antithymocyte globulin for GVHD prophylaxis.

Patient characteristics by ethnicity are described in Table 1. Among these subjects, 1232 patients carried the diagnosis of ALL, 1758 AML, and 1345 CML. Low-risk disease was defined as a CML chronic phase (CP) at the time of transplantation. The definition of disease risk was comparable among clinical centers within IHWG. Intermediate risk was defined as transplantation in the first or second complete remission (CR) of ALL, AML, or the second CP or accelerated phase of CML. High risk was defined as transplantation in a more advanced stage than intermediate risk. Early status of disease included patients in first and second CR of ALL or AML at transplantation or first CP of CML at transplantation.

For GVHD prophylaxis, a tacrolimus-based regimen was used in 1536 patients, a cyclosporine-based regimen in 2593, and other regimens in 78. Patients were conditioned for transplantation using either a myeloablative (n = 3687) or a nonmyeloablative/reduced-intensity regimen (n = 381). A total of 3481 patients was transplanted with bone marrow and 854 with peripheral blood stem cells.

Informed consent was obtained from patients and donors in accordance with the Declaration of Helsinki in each registry or institution, and consent