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Recipient *PTPN22* −1123 C/C Genotype Predicts Acute Graft-versus-Host Disease after HLA Fully Matched Unrelated Bone Marrow Transplantation for Hematologic Malignancies

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A B S T R A C T

PTPN22 is a critical negative regulator of T cell responses. Its promoter gene variant (rs2488457, −1123G>C) has been reported to be associated with autoimmune diseases. This study analyzed the impact of the *PTPN22* variant on transplantation outcomes in a cohort of 663 patients who underwent unrelated HLA-matched bone marrow transplantation (BMT) for hematologic malignancies through the Japan Marrow Donor Program. The recipient C/C genotype versus the recipient G/G genotype resulted in a lower incidence of grade II-IV acute graft-versus-host disease (hazard ratio [HR], 0.50; 95% confidence interval [CI], 0.29-0.85; $P = .01$), as well as a higher incidence of relapse (HR, 1.78; 95% CI, 1.10-2.90; $P = .02$), as demonstrated on multivariate analysis. In patients with high-risk disease, the recipient C/C genotype was associated with significantly worse overall survival rates than the recipient G/G genotype (HR, 1.60; 95% CI, 1.02-2.51; $P = .04$), whereas this effect was absent in patients with standard-risk disease. In addition, the donor G/C genotype was associated with a lower incidence of relapse (HR, 0.58; 95% CI, 0.40-0.85), which did not influence survival. Our findings suggest that *PTPN22* genotyping could be useful in predicting prognoses and creating therapeutic strategies for improving the final outcomes of allogeneic BMT.

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INTRODUCTION

The *PTPN22* gene encodes lymphoid specific phosphatase (Lyp), expressed in T and B lymphocytes, monocytes, dendritic cells (DCs), neutrophils, natural killer cells and thymocytes [1]. *PTPN22* is an important negative regulator of T cell activation involved in the dephosphorylation and inactivation of TCR-associated kinases. A single nucleotide variant of the *PTPN22* promoter gene, rs2488457 (−1123G>C), is associated with susceptibility to autoimmune diseases, including type 1 diabetes and rheumatoid arthritis, in Caucasian and Asian populations [2-6].

The role of *PTPN22* in the immune response, as well as the association of the *PTPN22* variant with autoimmunity, prompted us to investigate the impact of donor and recipient −1123G>C variation in the *PTPN22* gene on the clinical outcomes of patients undergoing allogeneic bone marrow transplantation (BMT) using an HLA allele-matched unrelated donor through the Japan Marrow Donor Program (JMDP). Our data show that the recipient C/C genotype is associated with a significantly lower incidence of grade II-IV acute graft-versus-host disease (aGVHD) and a higher incidence of relapse, which predict worse survival outcomes for patients with high-risk disease.

PATIENTS AND METHODS

Patients

PTPN22 genotyping was performed on 663 patients with hematologic malignancies and their unrelated donors who underwent BMT through the JMDP with T cell–replete marrow from HLA-A, -B, -C, -DRB1, -DQB1, and -DPB1 allele-matched donors between January 1993 and December 2007. This cohort represents 7% (663 of 9229) of all recipients of unrelated BMT in Japan during the study period. All available data and samples for eligible patients and their donors were analyzed. None of the patients had a history of previous transplantation. The study cohort included Asian patients only. The final clinical survey of these patients was completed by November 1, 2008. Diagnoses included acute myelogenous leukemia (AML) in 215 patients (32%), acute lymphoblastic leukemia (ALL) in 164 patients (25%), chronic myelogenous leukemia (CML) in 118 patients (18%), myelodysplastic syndrome (MDS) in 89 patients (13%), malignant lymphoma (ML) in 73 patients (11%), and multiple myeloma in 4 patients (1%) (Tables 1 and 2). The median follow-up duration in the survivors was 2103 days (range, 124-5136 days); 183 recipients (28%) relapsed or progressed, and 322 (49%) died, 16 (2%) before engraftment. Recipients with AML or ALL in first complete remission, CML in any chronic phase, ML in any complete remission, or MDS were classified as having standard-risk disease. All others were classified as

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Table 1
Donor and Recipient Characteristics

Variable	Value
Number of cases	663
Recipient age, years, median (range)	34 (1-67)
Donor age, years, median (range)	34 (20-57)
Year of BMT, median (range)	2001 (1993-2007)
Recipient *PTPN22* genotype, n (%)	
G/G	228 (34)
G/C	331 (50)
C/C	104 (16)
Donor *PTPN22* genotype, n (%)	
G/G	219 (33)
G/C	324 (49)
C/C	120 (18)
Recipient sex, n (%)	
Male	395 (60)
Female	268 (40)
Donor sex, n (%)	
Male	420 (63)
Female	243 (37)
Donor/recipient sex match, n (%)	
Sex-matched	426 (64)
Female/male	106 (16)
Male/female	131 (20)

having high-risk disease. Myeloid malignancies included AML, CML, and MDS, and lymphoid malignancies included ALL, ML, and multiple myeloma. All patients received cyclosporine- or tacrolimus-based therapy for GVHD prophylaxis; none received anti–T cell therapy, such as antithymocyte globulin or ex vivo T cell depletion. All patients and donors provided written informed consent to participate in molecular studies of this nature at the time of transplantation, in accordance with the Declaration of Helsinki. This project was approved by the Institutional Review Board of Kanazawa University Graduate School of Medicine and the JMDP.

PTPN22 Genotyping

Genotyping of *PTPN22* was performed using the TaqMan-Allelic discrimination method as described previously [7]. The genotyping assay was conducted in 96-well PCR plates using specific TaqMan probes for the *PTPN22* gene single nucleotide polymorphism rs2488457 (catalog C_16027865_10) in a StepOne Plus real-time PCR system (Applied Biosystems, Foster City, CA).

Table 2
Pretransplant Characteristics

Variable	Value
Disease, n (%)	
AML	215 (32)
ALL	164 (25)
MDS	89 (13)
ML	73 (11)
CML	118 (18)
Multiple myeloma	4 (1)
Disease stage, n (%)	
Standard risk	406 (61)
High risk	257 (39)
ABO matching, n (%)	
Major or/and minor mismatch	255 (38)
Major mismatch	145 (22)
Minor mismatch	129 (19)
Bidirectional	19 (3)
Missing	9 (1)
Conditioning regimen, n (%)	
Myeloablative	583 (88)
Reduced intensity	80 (12)
With total body irradiation	525 (79)
Pretransplantation CMV serostatus, n (%)	
CMV-positive recipient	420 (72)
Missing	80 (12)
GVHD prophylaxis, n (%)	
With cyclosporine	376 (57)
With tacrolimus	285 (43)
Missing	2 (0)
TNC, $\times 10^8$/kg, median (range)	5.0 (0.1-316.8)

Data Management and Statistical Analysis

Data were collected by the JMDP using a standardized report form. Follow-up reports were submitted at 100 days and 1 year post-transplantation, and annually thereafter. Pretransplantation cytomegalovirus (CMV) serostatus was routinely tested in recipients only, not in donors. Engraftment was confirmed by an absolute neutrophil count of $>0.5 \times 10^9$/L for at least 3 consecutive days. Outcome classification, including GVHD, did not change over time.

After data collection, aGVHD and chronic GVHD (cGVHD) were diagnosed and graded based on classically defined criteria [8,9]; namely, aGVHD was defined as GVHD developing within the first 100 days post-transplantation, and cGVHD was defined as GVHD occurring after day 100. Data using the updated criteria for assessment of GVHD [10,11] were not available for our cohort. The overall survival (OS) rate was defined as the number of days from transplantation to death from any cause. Disease relapse was defined as the number of days from transplantation to disease relapse. Transplantation-related mortality (TRM) was defined as death without relapse. Any patients alive at the last follow-up date were censored. Data on infectious organisms, postmortem changes in causes of death, and supportive care, including prophylaxis for infections and therapy for GVHD given on an institutional basis, were not available for this cohort.

All statistical analyses were performed with the EZR software package (Saitama Medical Center, Jichi Medical University), a graphical user interface for R version 2.13.0 (R Foundation for Statistical Computing, Vienna, Austria) [12], as described previously [13]. The probability of OS was calculated using the Kaplan-Meier method and compared using the log-rank test. The probabilities of TRM, disease relapse, aGVHD, cGVHD, and engraftment were compared using the Gray test [14] and analyzed using cumulative incidence analysis [15], considering relapse, death without disease relapse, death without aGVHD, death without cGVHD, and death without engraftment as respective competing risks. Variables included recipient age at the time of BMT, sex, pretransplantation CMV serostatus, disease characteristics (ie, disease type, disease lineage, and disease risk at transplantation), donor characteristics (ie, age, sex, sex compatibility, and ABO compatibility), transplant characteristics (ie, conventional or reduced-intensity conditioning [16], total body irradiation–containing regimens, tacrolimus versus cyclosporine, and total nucleated cell count harvested per recipient weight), and year of transplantation. The median was used as the cutoff point for continuous variables. The χ^2 test and Mann-Whitney *U* test were used to compare data between 2 groups. The Hardy-Weinberg equilibrium for the *PTPN22* gene variant was determined using the Haploview program [17].

Multivariate Cox models were used to evaluate the hazard ratio (HR) associated with the *PTPN22* variation. Covariates found to be significant in the univariate analyses ($P \leq .10$) were used to adjust the HR. For both the univariate and multivariate analyses, *P* values were 2-sided, and $P \leq .05$ was considered to indicate statistical significance.

RESULTS

Frequencies of PTPN22 Genotypes

The rs2488457 single nucleotide polymorphism in the *PTPN22* gene was genotyped in 663 unrelated BMT donor–recipient pairs (Table 1). The genotype frequencies of G/G, G/C, and C/C were 34%, 50%, and 16% in recipients and 33%, 49%, and 18% in donors, respectively. These results are in accordance with the Hardy-Weinberg equilibrium ($P = .49$) and similar to HapMap data reported in the Japanese population [5]. Donor and recipient *PTPN22* genotype did not significantly influence the cumulative incidence of engraftment (data not shown).

Effects of Recipient PTPN22 Genotype on Transplantation Outcomes

Transplantation outcomes according to *PTPN22* genotype are summarized in Table 3. Recipient C/C genotype was significantly associated with a lower incidence of grade II-IV aGVHD (18%) compared with recipient G/G (33%; $P = .009$) and G/C (35%; $P = .02$) genotypes (Figure 1A), suggesting the homozygous recessive effects of the C allele. We randomly split the study cohort into 2 subcohorts to test the validity of these associations. Subcohort 1 included 116 (35%) recipient C/C, 164 (49%) recipient G/C, and 52 (16%) recipient G/G genotypes, and subcohort 2 comprised 116 (35%) recipient G/G, 167 (50%) recipient G/C, and 52 (16%) recipient C/C

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