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Does matching for SNPs in the MHC gamma block in 10/10 HLA-matched unrelated donor-recipient pairs undergoing allogeneic stem cell transplant improve outcomes?

Ann M. Moyer[a], Shahrukh K. Hashmi[b], Cynthia Kroning[a], Steven R. De Goey[a], Mrinal Patnaik[b], Mark Litzow[b], Dennis A. Gastineau[a,b], William J. Hogan[b], Eapen K. Jacob[a], Justin D. Kreuter[a], Laurie L. Wakefield[a], Manish J. Gandhi[a,*]

[a] Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN 55905, USA
[b] Division of Hematology, Mayo Clinic, Rochester, MN 55905, USA

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ABSTRACT

Background: Matching at the HLA-A, HLA-B, HLA-C, HLA-DRB1, and HLA-DQB1 loci is important in donor selection for patients undergoing unrelated allogeneic hematopoietic stem cell transplantation (ASCT). Additional matching across the MHC gamma region may further improve outcomes.

Methods: The MHC gamma region was retrospectively genotyped in 66 adult recipients of ASCT and their 10/10 matched unrelated donors. A chart review was performed to determine whether MHC gamma matching impacted survival, relapse, or graft-versus-host disease.

Results: Of 66 donor-recipient pairs, 26(39.4%) were gamma-type matches, 34(51.5%) were mismatches, and 6(9.1%) were "indeterminate." Matching status was not associated with overall survival ($p = 0.43$), relapse ($p = 0.21$), acute GVHD ($p = 0.43$), severe aGVHD ($p = 0.31$), or chronic GVHD ($p = 0.23$) in univariate analyses, nor in multivariate analyses ($p = 0.28$, 0.13, 0.29, 0.16, and 0.67, respectively), with or without adjusting for HLA-DPB1 matching status.

Conclusions: In our single institution study, gamma-type matching status was not associated with outcomes of adult ASCT recipients.

1. Introduction

Matching for human leukocyte antigens (HLA) between donors and recipients of allogeneic hematopoietic stem cell transplants (ASCT) is essential to minimize the risks of mortality, rejection, and graft-vs-host disease (GVHD). While the major histocompatibility locus (MHC) is inherited together as a block, infrequent recombination events do occur, which results in four major genomic blocks—alpha (containing HLA-A), beta (containing HLA-B and HLA-C), delta (containing HLA-DR, and HLA-DQ), and gamma (containing approximately 60 genes) [1,2]. The MHC gamma region, also known as the Class III region, contains genes that are involved in immune function as well as other genes that are not involved in the immune system [3,4]. Among the genes involved in immune function are genes that encode several components of the complement system (i.e. C2, C4a, C4b, Bf), genes that encode inflammatory cytokines (i.e. tumor necrosis factor family members), and several heat shock proteins. Certain combinations of genetic markers across genes within the MHC occur together and are considered "conserved extended haplotypes" (CEH) or "ancestral haplotypes" (AH) [2,5].

Despite the extensive matching protocols used today, a subset of patients continues to experience sub-optimal outcomes. Genes within the gamma block are typically not typed nor used for clinical matching of unrelated donors and recipients in ASCT. Previous studies have demonstrated that although HLA-identical sibling pairs also appear to be class III identical, this is not the case among unrelated donor-recipient pairs [6]. Therefore, mismatches within the MHC region that are not currently included in current matching algorithms, including regions within the gamma block, may in part be responsible when patients have undesirable outcomes [6–8]. While several abstracts have been presented at recent meetings suggesting that MHC gamma matching may impact the risk for GVHD and/or survival rates after ASCT, the data are

Abbreviations: HLA, human leukocyte antigens; ASCT, allogeneic hematopoietic stem cell transplants; GVHD, graft-versus-host disease; MHC, major histocompatibility locus; SNPs, single nucleotide polymorphisms

* Corresponding author at: 200 First Street SW, Rochester, MN 55905, USA.
E-mail address: Gandhi.Manish@Mayo.edu (M.J. Gandhi).

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currently quite limited [7,8]. Therefore, to better understand the potential importance of matching across the MHC gamma region in our local patient population, we performed a retrospective chart review study evaluating outcomes in 66 unrelated donor-recipient pairs who were genotyped for SNPs across the gamma region.

2. Materials and methods

2.1. Participants

This retrospective chart review study included 66 consecutive adult patients who underwent ASCT from unrelated donors for hematologic malignancies at Mayo Clinic, Rochester, MN between 1/26/2008 and 12/21/2010. Donor-recipient pairs were 10/10 matched (HLA-A, -B, -C, -DRB1, -DQB1) using standard clinical practices. Specifically, HLA genotyping was performed by sequence-specific oligonucleotide (SSO) typing using the One Lambda LABType SSO Class I and Class II typing kits (Thermo Fischer Scientific, Canoga Park, CA) and commercial sequence specific primer (SSP) amplification typing kits (Olerup Inc., West Chester, PA). Patients were followed for a median of 964.5 days from the date of transplant (mean 1004.9 days, range 11 to 2427 days). Clinical data was obtained from the Mayo Clinic electronic medical record system. This study was approved by the Mayo Clinic Institutional Review Board.

2.2. Genotyping

Genotyping of 25 single nucleotide polymorphisms (SNPs) within the gamma block was performed using a commercial kit as per the manufacturer's instructions (Gamma-Type, Connexio, Wangara, Australia). Each SNP was evaluated as the presence or absence of a target amplicon, which was then scored as present, absent, or indeterminate. If two samples matched for presence or absence of amplicon for all 25 reactions, the samples were considered a match. If they did not match at one or more of the 25 reactions, they were considered a mismatch. If there was an indeterminate call at one or more positions, the sample was repeated or resulted as "indeterminate" for a Gamma-Type match, unless there was a mismatch at a different position in which case the samples were classified as a mismatch. In addition, each recipient-donor pair underwent HLA-DPB1 typing as part of a prior study [9]. An online tool, the DPB1 T-Cell Epitope Matching Algorithm v2.0, available through the ImMunoGeneTics/HLA (IMGT/HLA) website (http://www.ebi.ac.uk/ipd/imgt/hla/dpb.html) was utilized to predict the immunogenicity and classify donor-recipient pairs into permissive (including HLA-DPB1 matches) or non-permissive status [10].

2.3. Statistical analysis

Statistical analyses were performed using JMP (v.10.0.0) software (SAS Institute Inc., Cary, NC, USA) with the association between Gamma-Type matching status and clinical outcomes assessed using Kaplan-Meier methods and Cox proportional hazards models with $p \leq 0.05$ considered statistically significant. In multivariate analyses, outcomes were adjusted for covariates associated with outcome as determined by a stepwise backward elimination approach. Covariates under consideration included diagnosis (lymphoid vs. myeloid malignancy), conditioning regimen (myeloablative vs. non-myeloablative/reduced intensity), T-cell depletion (by administration of antithymocyte globulin or alemtuzumab), ABO incompatibility, age at transplant, sex match vs. mismatch, graft type (peripheral blood stem cells vs. bone marrow), disease status at transplant (remission vs. not in remission), and GVHD prophylaxis.

Table 1
Patient and Donor Characteristics. Matched, mismatched, and indeterminate refer to matching status of the MHC-gamma block as determined by the Gamma-type kit from Connexio. P-values are given for the association between matching status and each parameter. Data in table refers to number of patients, aside from recipient age which is given as mean (range) for the group.

	Matched	Mismatched	Indeterminate	p
n	26	34	6	
Recipient Age at Transplant (years) [mean (range)]	46.8 (25.0–65.0)	49.9 (25.0–68.0)	49.0 (18.0–58.0)	0.60
Diagnosis				0.34
Myeloid	17	19	2	
Lymphoid	9	15	4	
Disease Status at Transplant				0.29
Remission	13	21	4	
Not in Remission	12	12	2	
Unknown	1	0	1	
Recipient-Donor Sex				0.22
Male-male	14	13	3	
Male-female	1	2	0	
Female-male	6	7	0	
Female-female	13	4	3	
ABO Incompatibility				0.53
None	13	17	3	
Minor	5	8	0	
Major	8	8	3	
Both	0	1	0	
Source of Cells				0.29
Bone Marrow	5	4	0	
Peripheral Blood Stem Cells	21	30	6	
Conditioning				0.13
Myeloablative	18	16	2	
Non-myeloablative/ Reduced Intensity	8	18	4	
T-cell Depletion				0.016
Yes	1	0	2	
No	25	34	4	
GVHD Prophylaxis				0.24
Tacrolimus/ Methotrexate	24	29	3	
Tacrolimus/ Mycophenolate	1	3	2	
Other	1	2	1	

3. Results

Recipient and donor characteristics are given in Table 1. The specific IBMTR diagnoses for patients with lymphoid malignancy included 13 patients with acute lymphoblastic leukemia, 7 with plasma cell disorders, and 8 with other leukemias; among the patients with myeloid malignancy the diagnoses included 17 patients with acute myelogenous leukemia, 2 with chronic myelogenous leukemia, and 19 with myelodysplastic/myeloproliferative disorders. Of the 66 recipients, 38 (57.6%) died, 21 (31.8%) experienced disease relapse, 46 (69.7%) developed aGVHD (any grade), 20 (30.3%) developed severe (grade III-IV) aGVHD, and 32 (48.5%) developed cGVHD during the follow-up period.

Of the 66 donor-recipient pairs, 26 (39.4%) were gamma-type matches, 34 (51.5%) were mismatches, and 6 (9.1%) were "indeterminate". The 6 indeterminate samples were matches for 19–21 (of