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Examination of Single Nucleotide Polymorphisms in the Major Histocompatibility Complex Gamma Block in Relation to Clinical Results of Hematopoietic Cell Transplantation

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Abstract

HLA haplotype mismatches have been linked to an increased risk of acute graft-versus-host disease (aGVHD) in patients receiving hematopoietic cell transplants from unrelated donors who are HLA-matched (HCT). Gamma block (GB) comprises many inflammatory and immunological regulating genes, such as Bf, C2, and C4 genes, and is situated in the middle MHC region between beta and delta blocks containing HLA-B and -C and HLA-DQ and -DR antigens, respectively. Mismatches in the c.2918+98G, c.3316C, and GB block SNPs were linked to a higher risk of grade III–IV aGVHD, according to a single-center analysis. We looked at how outcomes following 10/10 and 9/10 URD HCT were affected by GB SNP (GBS) mismatches (n = 714). The main consequence was acute GVHD. Overall survival, disease-free survival, death from transplants, recurrence, and chronic engraftment were examined as well. Using the Illumina NGS platform, 338 SNPs were located over 20 kb to GBS genotype DNA samples. The overall incidence of aGVHD grade II-IV and II-IV was 41% and 17%, respectively, during the course of 100 days. At all tested GBSs, the overall rate of matching was 23%, and at the C4 SNPs, it was 81%. Both having more GBS mismatches and having more matches across all GB SNPs evaluated had no effect on the success of transplantation. Except for an unanticipated significant relationship between having two C4 SNP mismatches and a higher hazard ratio (HR) for relapse association reported in only 15 patients (HR, 3.38, 95% confidence range, 1.75 to 6.53; P), there was no association between C4 SNP mismatches and outcomes.

Keywords: Gamma block; Major histocompatibility; Complex; Single nucleotide polymorphism; Transplantation

Introduction

Following hematopoietic cell transplantation from an unrelated donor, HLA mismatches have the biggest effect on clinical outcomes. Major histocompatibility complex (MHC) haplotype mismatches have also been linked to a higher risk of graft-versus-host disease (GVHD) and a lower risk of disease relapse in URD HCTs that are otherwise genotypic ally HLA-matched [1]. More than 269 loci make up the 3.8 Mb MHC regions, which is located on the short arm of chromosome 6 at position 6. 12 single nucleotide polymorphisms (SNPs) were found to be predictors of transplantation. The hazards linked to these SNPs were significantly correlated with either donor or recipient SNP genotype or donor- recipient SNP mismatch in a multivariate analysis that controlled for HLA mismatching and nongenetic factors. These SNPs could be in linkage disequilibrium (LD) with transplant factors that are not HLA-related [2]. Similar to this, a recent study using donor-recipient whole-exome sequencing data and a mix of integrative computational techniques and random forest analysis discovered 65 non-HLA variations linked to a risk of antibody-mediated rejection in kidney transplant recipients. These variations are associated with genes that are abundant in genes expressed in kidney and vascular endothelium and underpin the immunobiology, making them functionally relevant to the rejection process in the kidney [3].

Rejection of the graft. The current gold standard of care in clinical HCT, however, only takes into account matching at the HLA-A, -B, -C, -DRB1, -DQB1, and -DPB1 loci. The alpha, beta, gamma, and delta blocks are four large genomic blocks [4], designated as the alpha, beta, and gamma blocks. Family pedigree analysis of HLA typing has demonstrated that recombination occurs at specific sites within the MHC. The genes for HLA-A, HLA-C, and HLA-B are found in the alpha block. The complement proteins C2, C4, and factor B (Bf) are found in the gamma block (GB), and the HLA-DR and -DQ genes are found in the delta block [5]. The GB is situated between the beta and delta blocks in the central MHC area. Mismatches between GB donors and recipients still have therapeutic significance. Given its chromosomal placement between the MHC class I and class II loci and the numerous inflammatory and immunological regulatory genes it contains, such as complement component genes C2, C4, and Bf, examining the clinical implications of mismatches at GB in the clinical context of HCT is a crucial concern [6]. C4 mismatch was found to be a major risk factor for the emergence of acute GVHD in matched URD HCT in a multivariate analysis. Additionally, a single-center investigation revealed that grade III-IV aGVHD was linked to mismatches in SNPs , and in the GB block (C4A SNP). In this investigation, we investigated the theory that GB mismatch is related to GVHD risk rising following URD HCT [7].

Methods

Study Design and Population

714 URD HCT recipients who received an HLA-A, -B, -C, -DRB1 and -DQB1 mismatched (9/10) (n = 551) or 9/10 HLA-B mismatch alone graft made up the study population. When genomic DNA was made available at the CIBMTR research repository for GB SNP

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genotyping of recipients and their corresponding donors, we included adult and paediatric patients who had been reported to the Center for International Blood and Marrow Transplant Research (CIBMTR) between 1999 and 2011 [8]. Acute myelogenous leukaemia (AML), acute lymphoblastic leukaemia (ALL), and myelodysplastic syndrome patients only were eligible for the trial (MDS). In order to increase the incidence of GB SNP mismatches due to the chromosomal placement of GB between the HLA-B gene and class II HLA, the 9/10 mismatched HCTs were restricted to HLA-B mismatches. As previously mentioned, DNA-based techniques at high resolution were used to confirm all HLA typing [9].

Outcome Definitions

AGVHD and chronic GVHD were the study's main endpoints of interest. Limited and extensive were characterised in accordance with the Seattle criteria, whereas Grade II-IV and III-IV aGVHD were defined using the Glucksberg scale. Overall survival (OS), disease relapse, disease-free survival (DFS), treatment-related mortality (TRM), and neutrophil engraftment were among the secondary outcomes examined. The OS was calculated as the interval between the HCT and the death, regardless of the cause [10]. The CIBMTR criteria were used to define relapse and DFS. TRM was outlined as passing away while experiencing ongoing remission from the original cancer. The achievement of an absolute neutrophil count of 500/mL for three days in a row was referred to as engraftment.

Genotyping and Analysis

The next-generation sequencing platform and supplies from Illumina were used to determine the genotype of GBS. The National Marrow Donor Program Research Repository provided DNA samples. Using primers and a PCR mixture from Conexio Genomics, the GB region was amplified into 4 long-range fragments ranging in size from 1.5 to 5.5 kbp. Following the manufacturer's instructions, the resultant amplicons were purified using the Agencourt AMPure XP technique. Prior to miSeq sequencing, libraries were created using the Illumina Nextera XT DNA library preparation kit and methodology [11]. Data from the experiment was examined in Assign MPS Conexio Genomics. The minor allele frequencies (MAFs) and genomic locations of the SNPs examined are displayed in Supplementary. 10 of the 338 SNPs were left out of the LD analysis. Because there were more than two alleles found in the files. The ambiguity in this situation was caused by gene overlap at these specific common SNPs. Although the testing kit can easily distinguish between determine if the donor and recipient pairs were matched. It is not intended to identify people who are mismatched at these SNPs. replica numbers The four SNPs that were examined were 4-bp insertions. And deletions were treated as one variant. event. 325 SNPs altogether were included in the LD and MAF analyses [12]. The Plink pedigree was used to format input files for The LD was produced using a mat and the software Hap loview plots.

Statistical Analysis

Sequence mismatches were taken into account across all SNPs tested, totally matched versus mismatched at 1+ SNPs, and mismatches at previously reported C4A SNP as well as the number of GB SNP mismatches (considering GB mismatches as a continuous variable) were examined for various outcomes. Age at the time of HCT, sex, and Karnofsky Performance Status score were patient-related factors. The presence of a disease (ALL, AML, or MDS) and its stage were among the disease-related factors. Hematopoietic cell source (bone marrow versus peripheral blood stem cells), donor age, year of HCT, donor-recipient cytomegalovirus serostatus, conditioning regimen, and GVHD prophylaxis tacrolimus with or without others versus cyclosporine with or without others versus others were among the transplantation-related variables. In multivariate analysis, variables such as patient, disease, characteristics of transplantation, including recipient and donor age, racial/ethnic background, and other elements.

Discussion

HLA matching has been demonstrated to significantly affect the clinical outcomes of HCT in a number of trials. In comparison to HCT with matched URDs, HCT with HLA-matched sibling donors is linked to decreased incidences of life-threatening GVHD. The fact that URDs, despite being HLA-matched, may be haplotype-mismatched and consequently mismatched at additional genetic variants within the MHC, such as SNPs, indels, and copy number variations, differs from matched siblings, who share an HLA haplotype by descent. Mismatches at non-HLA MHC sequences are thought to play a role in the inflammatory processes seen in post-transplant problems. By physically separating the DNA from different haplotypes, Petersdorf proved that HLA-matched URDs might either be haplotype-matched or -mismatched. Haplotype compatibility meant that while being haplotype-mismatched meant that matched HLA alleles were linked to distinct alleles at the other loci, matching HLA alleles meant that the donor and patient's alleles at separate loci were physically linked on the same haplotype. Patients in this trial who were haplotype matched to their donors had a lower probability of developing severe aGVHD. If these results are repeatable, they might be useful in choosing donors. Alternative methods are required to assess the likelihood of haplotype matching because the methods used to separate haplotypes are not technically practical for routine HLA testing laboratories. Understanding the MHC structure is necessary for creating these methods. Mismatches in non-HLA loci, such as the MHC class I chain-related gene, that are situated between HLA class I and class II loci.

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