HHS Public Access

Author manuscript

Biol Blood Marrow Transplant. Author manuscript; available in PMC 2017 August 01.

Published in final edited form as:

Biol Blood Marrow Transplant. 2016 August ; 22(8): 1531–1532. doi:10.1016/j.bbmt.2016.04.020.

A Validation Study Failed to Confirm Association Between Genetic Variants in the Base Excision Repair Pathway and TRM and Relapse post HCT

Mukta Arora[1], **Stephanie J Lee**[2], **Stephen R Spellman**[3], **Daniel J Weisdorf**[1], **Weihua Guan**[4], **Mike Haagenson**[3], **Tao Wang**[3], **Mary H Horowitz**[3], **Michael R Verneris**[5], **Katharina Fleischhauer**[6], **Katharine Hsu**[7], and **Bharat Thyagarajan**[8]

[1]Division of Hematology, Oncology and Transplant, University of Minnesota Medical School, Minneapolis, MN

[2]Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, WA

[3]Center for International Blood and Marrow Transplant Research, National Marrow Donor Program/Be The Match, Minneapolis, MN

[4]Division of Biostatistics, University of Minnesota

[5]Division of Pediatric Blood and Marrow Transplant, University of Minnesota

[6]University Hospital, Institute of Cellular Experimental Therapy, Essen, Germany

[7]Adult Blood and Marrow Transplant Service, Memorial Sloan Kettering Cancer Center, Weill Cornell Medical College, New York, New York; Sloan Kettering Institute, New York, New York.[5]Lab Medicine and Pathology, University of Minnesota

[8]Division of Lab Medicine and Pathology, University of Minnesota

Keywords

Hematopoietic cell transplant; BER Pathway; DNA repair pathway; transplant related mortality (TRM); disease relapse; single nucleotide polymorphism (SNP)

We previously reported associations between six recipient single nucleotide polymorphisms (SNPs) in four genes in base excision repair (BER) pathway with transplant related mortality (TRM) and disease relapse after hematopoietic cell transplant (HCT) in 470 recipients from a single institution[1]. To validate these results, we obtained an independent sample set from Center for International Blood and Marrow Transplant Research (CIBMTR). Our study population included 928 Caucasian adult patients (>18 years of age at HCT) with acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL) or chronic myeloid leukemia (CML) who received a myeloablative 10/10 matched unrelated donor (URD) T-cell

Corresponding Author: Mukta Arora, Division of Hematology, Oncology and Transplant, University of Minnesota, 420 Delaware Street SE, Minneapolis, MN 55455. arora005@umn.edu.

Conflict-of-interest disclosure

The authors declare no competing financial interests.

replete HCT from 1997–2007 facilitated by the National Marrow Donor Program (NMDP). Only patients with samples submitted to the Center for International Blood and Marrow Transplant Research (CIBMTR) Repository were included. The CIBMTR is a voluntary organization involving more than 500 transplantation centers that have collaborated to share patient data and conduct scientific studies[2].

Recipient DNA was extracted from samples using Flexigene DNA extraction method (Qiagen, Inc). SNPs were genotyped using the Taqman genotyping platform (ThermoFisher Scientific, USA). Minor allele frequencies (MAF) and Hardy Weinberg proportions for all six SNPs were estimated. Six SNPs in four genes in the BER pathway, previously identified to be associated with TRM and disease relapse[1], were evaluated (*OGGI*: rs159153, *LIG3*: rs3135974, *MUTYH*: rs3219463 and rs3219476, *TDG*: rs167715 and rs2374327). Competing risk methods were used to calculate the cumulative incidence of TRM and disease relapse[3]. Assuming an additive model for the SNPs, the association between each of the previously reported SNPs and TRM and disease relapse or progression at two years was evaluated in multivariate analysis using stepwise forward selection techniques after adjustment for covariates[4]. Covariates included recipient and donor age at transplant, Karnofsky performance status (KPS), disease, disease status at transplant, graft type, sex mismatch, donor-recipient CMV sero-status, conditioning regimen (total body irradiation (TBI) versus no TBI), GVHD prophylaxis and year of HCT.

Nine hundred and twenty eight recipients were included in this study. The median recipient age at HCT was 40.3 years. 45% of recipients underwent a HCT for AML, 23.5% for ALL and 31.5% for CML. Graft type was bone marrow in 48% and peripheral blood in 51%. TBI based conditioning was used in 60%. The median follow up was 48.8 months. The cumulative incidence of TRM was 24% (95% CI: 21.04–26.82) at 1 year and 28.3% (95% CI: 25.35–31.59) at 2 years, and the cumulative incidence of disease relapse was 20.34% (95% CI: 17.67–23.34) at 1 year and 25.73% (95% CI: 22.75–29.03) at 2 years. In multivariate analysis, none of the six SNPs were significantly associated with either TRM or disease relapse. Increasing recipient age at HCT (HR: 1.030, 95% CI: 1.018–1.042, $p< 0.0001$ and use of TBI in conditioning (HR: 1.3, 95% CI: 0.989–1.768, $p= 0.056$) were associated with higher risk for TRM and a KPS of 90–100 (HR: 0.69, 95% CI: 0.494–0.976, $p= 0.035$) and underlying disease (CML versus AML, HR: 0.54, 95% CI: 0.356–0.830, $p= 0.0047$) were associated with a lower risk of relapse.

We failed to validate our original results in the second cohort. One potential explanation is differences in the study populations. The original study included pediatric patients (28%), all hematologic malignancies, all donor types (HLA-identical siblings: 63%, URD: 16%, umbilical cord blood (UCB): 21%), 14% of non-Caucasian race and 20% with reduced intensity conditioning prior to HCT. For the validation cohort, we chose a more homogenous cohort of adult URD HCT recipients undergoing a myeloablative HCT as we anticipated a higher TRM, (hence greater power) in this cohort. Possibly, a similar analysis restricted to recipients of grafts from HLA identical siblings would help clarify the relevance of prior observation and subsequent donor selection process. Another potential reason why we failed to validate the original results is that they were possibly spurious. Since false positive associations are a major limitation of genetic association studies, confirmation of results in

large independent samples is needed. Studies need to be designed to test a hypothesis in a similar training and validation test to reduce the incidence of false positive associations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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