CMV Replication After Allogeneic Hematopoietic Cell Transplantation and Relapse Risk: Evidence for Early Protection Against Relapse in Acute Leukemia and Lymphoma

Margaret L. Green1, Roland B. Walter2, Hu Xie3, Wendy Leisenring4, Marco Mielcarek5, Brenda M. Sandmaier5, Stanley Riddell6, Michael J. Boeckh6, 1 Vaccines and Infectious Disease Division, Fred Hutchinson Cancer Research Center, Seattle, WA; 2 Clinical Research Division, Fred Hutchinson Cancer Research Center; 3 Fred Hutchinson Cancer Research Center; 4 Fred Hutchinson Cancer Research Center, Seattle, WA; 5 Division of Clinical Research, Fred Hutchinson Cancer Research Center, Seattle, WA; 6 Vaccine and Infectious Disease Division, Fred Hutchinson Cancer Research Center, Seattle, WA.

Recently an association between cytomegalovirus (CMV) replication after allogeneic hematopoietic cell transplantation (HCT) and decreased risk of relapse was described in a cohort of patients with acute myeloid leukemia (AML) [Blood. 2011;118(5):1402]. We evaluated this proposed protective effect of CMV replication in a larger cohort of consecutive patients with AML (n=761), as well as patients with acute lymphoblastic leukemia (ALL) (n=322), chronic myelogenous leukemia (CML) (n=646), and lymphoma (n=254) who received an allogeneic HCT at the FHCRC between 1995 and 2005. All patients underwent weekly surveillance for CMV replication with pp65-antigenemia through day 100 after HCT. Antiviral therapy with ganciclovir was initiated after any positive antigenemia. In multivariable models, CMV antigenemia at any level was associated with a decreased risk of morphologic relapse by day 100 among patients with AML (adjusted HR 0.56, 95% CI 0.34-0.91, P = .02), ALL (adjusted HR 0.21, 95% CI 0.05-1.00, P = .05) and lymphoma (adjusted HR 0.37, 95% CI 0.13-1.02, P = .05) but not CML (adjusted HR 0.72, 95% CI 0.2-2.3, P = .58). Higher levels of antigenemia (>10 positive cells, and >10 positive cells for two consecutive weeks) were not associated with incremental protection from relapse for any group. The effect appeared to be independent of acute GvHD (grade 3-4) or ganciclovir-related neutropenia (ANC 10 positive cells, and 10 positive cells for two consecutive weeks) were not associated with incremental protection from relapse for any group. The effect appeared to be independent of acute GvHD (grade 3-4) or ganciclovir-related neutropenia (ANC < 500). The association between early CMV reactivation and relapse protection in patients with acute leukemia and lymphoma persisted at 1 year after HCT (adjusted HR 0.69, 95% CI 0.5-0.9, P = .006) but was undetectable at 3 years. However, there was no difference in overall survival at either 100 days or 1 year after HCT among patients with any level of CMV antigenemia compared to patients with no CMV reactivation. In conclusion, these data demonstrate an association between CMV reactivation and decreased risk of early relapse among AML, ALL and lymphoma, but not CML, patients after allogeneic HCT. Further laboratory investigations are warranted to define the mechanisms of this protection.

Background: Idiopathic pneumonia syndrome (IPS) is a severe respiratory complication that can occur in 2-15% of allogeneic hematopoietic cell transplant (HCT) recipients. IPS is clinically characterized by widespread alveolar injury, not caused by infection, cardiac dysfunction, acute renal failure, or fluid overload. Although current understanding of IPS pathogenesis is limited, human and animal models of IPS and acute lung injury suggest that inflammatory and fibrotic pathways may be involved. We investigated whether single nucleotide polymorphisms (SNPs) in and near candidate genes previously found to be associated with acute lung injury may influence the risk for developing IPS.

Methods: We conducted a genetic association study using clinical data and DNA from 67 IPS and 783 control patients. IPS was defined by chart review according to American Thoracic Society Guidelines. All SNPs within the candidate gene and +/-50kb identified from the 1000 Genome Project were either genotyped using the Affymetrix GeneChip® Genome-Wide SNP 5.0 (n=470) or the Illumina 1M Quad (n=380), or imputed using previously published methods. All SNPs were analyzed in additive, dominant, and recessive multivariate genetic models and the Bonferroni method was used to adjust for multiple comparisons. Association between the AGT SNPs and plasma AGT levels was evaluated in an independent cohort of 378 allogeneic HCT patients.

Results: A total of 1277 SNPs (31 genotyped in both cohorts, 293 genotyped in one cohort and imputed in another, 953 imputed in both cohorts) in 8 candidate genes (ACE, AGT, SP-B, RANTES, DARC, MCP-1, TNFa and TNFR II) were evaluated. Six SNPs in AGT (rs3827749, rs3789666, rs3789667, rs2478345, rs2478544 and rs1078499, five out six are imputed) met the significance threshold and were associated with an increase in IPS risk in a recessive genetic model (hazard ratio range 3.58-4.71, P-value range .001-.0004). In an independent cohort of 6 SNPs were found to be significantly associated with lower plasma AGT levels in the recessive genetic model (mean AGT levels: homozygous recessive 17.8 - 22.4 ng/mL, heterozygous and homozygous wild type 27.3 ng/mL, P-value range .002-.0001).

Conclusions: These results suggest that renin-angiotensin system may be involved in the pathogenesis of IPS after allogeneic HCT.

Association Between AGT SNPs, Plasma AGT Levels, and Risk for IPS After Allogeneic HCT

Makoto Onizuka1, Yao Li2, WenHong Fan3, Cindy Zhang3, Hongwei Wang4, Lue Ping Zhao4, David K. Madtes5, Paul J. Martin6, Barry Storer7, John A. Hansen6, Jason Chien8.

1 Hematology and Oncology, Tokai University School of Medicine, Isehara, Japan; 2 PS Statistics, Fred Hutchinson Cancer Research Center, Seattle, WA; 3 Quantitative Genetic Epidemiology, Fred Hutchinson Cancer Research Center, Seattle, WA; 4 Applied Statistics, Fred Hutchinson Cancer Research Center, Seattle, WA; 5 Division of Pulmonary and Critical Care Medicine, University of Washington, Seattle, WA; 6 Fred Hutchinson Cancer Research Center, Seattle, WA; 7 Vaccine and Infectious Disease Division, Fred Hutchinson Cancer Research Center, Seattle, WA; 8 Pulmonary and Critical Care Medicine, Fred Hutchinson Cancer Research Center, Seattle, WA.

Background: Idiopathic pneumonia syndrome (IPS) is a severe respiratory complication that can occur in 2-15% of allogeneic hematopoietic cell transplant (HCT) recipients. IPS is clinically characterized by widespread alveolar injury, not caused by infection, cardiac dysfunction, acute renal failure, or fluid overload. Although current understanding of IPS pathogenesis is limited, human and animal models of IPS and acute lung injury suggest that inflammatory and fibrotic pathways may be involved. We investigated whether single nucleotide polymorphisms (SNPs) in and near candidate genes previously found to be associated with acute lung injury may influence the risk for developing IPS.

Methods: We conducted a genetic association study using clinical data and DNA from 67 IPS and 783 control patients. IPS was defined by chart review according to American Thoracic Society Guidelines. All SNPs within the candidate gene and +/-50kb identified from the 1000 Genome Project were either genotyped using the Affymetrix GeneChip® Genome-Wide SNP 5.0 (n=470) or the Illumina 1M Quad (n=380), or imputed using previously published methods. All SNPs were analyzed in additive, dominant, and recessive multivariate genetic models and the Bonferroni method was used to adjust for multiple comparisons. Association between the AGT SNPs and plasma AGT levels was evaluated in an independent cohort of 378 allogeneic HCT patients.

Results: A total of 1277 SNPs (31 genotyped in both cohorts, 293 genotyped in one cohort and imputed in another, 953 imputed in both cohorts) in 8 candidate genes (ACE, AGT, SP-B, RANTES, DARC, MCP-1, TNFa and TNFR II) were evaluated. Six SNPs in AGT (rs3827749, rs3789666, rs3789667, rs2478345, rs2478544 and rs1078499, five out six are imputed) met the significance threshold and were associated with an increase in IPS risk in a recessive genetic model (hazard ratio range 3.58-4.71, P-value range .001-.0004). In an independent cohort of 6 SNPs were found to be significantly associated with lower plasma AGT levels in the recessive genetic model (mean AGT levels: homozygous recessive 17.8 - 22.4 ng/mL, heterozygous and homozygous wild type 27.3 ng/mL, P-value range .002-.0001).

Conclusions: These results suggest that renin-angiotensin system may be involved in the pathogenesis of IPS after allogeneic HCT.