To the editor:

Donor CTLA-4 +49 A/G*GG genotype is associated with chronic GVHD after HLA-identical haematopoietic stem-cell transplantations

The CTLA-4 gene encodes a molecule providing a negative signal for T-cell activation. CTLA-4 +49 A/G and CT60 polymorphisms have been associated with auto-immune diseases (AID). A recent study suggested that donor genotype AA of CT60 was associated with better survival, increased rate of acute graft-versus-host disease (GVHD) and lower relapse incidence. We evaluated the impact of +49 A/G and CT60 polymorphisms in 225 patients who received, after a myeloablative conditioning regimen, a non-T-depleted hematopoietic stem-cell transplant (HSCT) from a human leukocyte antigen (HLA)-identical sibling donor for malignant diseases. The donors were genotyped for +49 A/G and CT60 using polymerase chain reaction–restriction fragment length polymorphism (PCR-RFLP) techniques. The patient, donor, and transplant characteristics were not statistically different with respect to +49 A/G and CT60 polymorphisms. The end points were acute GVHD, chronic GVHD (cGVHD), relapse, survival, and bacterial, fungal, and cytomegalovirus (CMV) infections.

We did not find any association of donor +49 A/G or CT60 polymorphisms nor of +49 A/G CT60 genotypes with acute GVHD, relapse, survival, or infections. However, patients who received a graft from a donor with a GG genotype for +49 A/G had a stronger risk of developing cGVHD compared with those having a donor with either AG or AA genotype (73% vs 55% or 48%, respectively, \( P = .04 \)). CT60 polymorphism did not have any impact on the risk of cGVHD, relapse, survival, or infections. Therefore, the +49 A/G and CT60 polymorphisms did not have a significant impact on acute or chronic GVHD.

We also evaluated the impact of +49 A/G and CT60 genotypes with acute GVHD, relapse, survival, or infections. We found that patients with +49 A/G and CT60 genotypes had a higher risk of developing cGVHD compared with those having a donor with either AG or AA genotype (73% vs 55% or 48%, respectively, \( P = .04 \)). However, the same tendency without statistical significance was observed for CT60*GG genotype (62% vs 54% or 40%, respectively, \( P = .06 \)). In fact, CT60*GG and +49 A/G*AA or AG had the same risk of cGVHD as CT60*AA and +49 A/G*AA or AG genotypes (56% and 50%, respectively) and a statistically significant lower risk than the CT60*GG and +49 A/G*GG genotype (73%, \( P = .04 \)). CT60 polymorphism did not have any impact on the risk of cGVHD, relapse, survival, or infections. Therefore, the +49 A/G and CT60 polymorphisms did not have a significant impact on acute or chronic GVHD.


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appear to be an independent risk factor of cGVHD. This is due to the linkage disequilibrium between +49A/G*G and CT60*G polymorphisms. In Cox multivariate analysis (backward stepwise, logistic regression), when studying +49A/G polymorphisms, age of the patients, ABO incompatibilities, stage of disease, source of stem cells, and sex matching, as potent pregraft risk factors for cGVHD, 3 factors appeared to be independent risk factors of cGVHD: +49A/G (P = .03, hazard ratio [HR] = 1.76, 95% confidence interval [CI] 1.01-2.95), age of the patient (P = .01, HR = 2.28, 95% CI 1.21-4.27), and ABO incompatibility (P = .03, HR = 1.55, 95% CI 1.04-2.31).

While this study did not confirm the association of donor CT60 polymorphism with acute GVHD, relapse, and survival as suggested by Perez-Garcia,3 it showed a significant association of donor +49A/G*GG genotype with cGVHD. In vitro studies have shown that the +49A/G* GG genotype correlated with an increased T-cell proliferation after stimulation4 and decreased expression of CTLA-4.5 This effect was seen in CD4+ and not in CD8+ T lymphocytes.6 In vitro studies as well as the association with autoimmune disease (AID) support the fact that the +49A/G*GG genotype is associated with an increased CD4+ cell response to stimulation. As CD4+T cells play an important role in the occurrence of cGVHD, their increased activation in association with +49A/G*GG genotype could explain the observed association of +49A/G*GG genotype with cGVHD. These results illustrate the increasing role of non–HLA genetics in developing an HSCT risk index for use in the clinic.7

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