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The Impact of HLA Eplet Mismatching on GVHD, Relapse, and Survival Following Hematopoietic Stem Cell Transplantation: A Multidimensional Clinical and Statistical Evaluation

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Abstract

Objective: Graft-versus-host disease (GVHD) remains one of the leading causes of morbidity and mortality following allogeneic hematopoietic stem cell transplantation (allo-HSCT). Even when conventional HLA matching is achieved, epitope-level discrepancies may still trigger alloimmune responses. Eplet mismatching represents a novel and more sensitive parameter for evaluating such immune incompatibilities and has gained increasing importance in predicting transplant outcomes. In this study, the associations between donor- and recipient-directed Class I and Class II eplet mismatches and the development of acute/chronic GVHD, relapse, and overall survival (OS) were investigated.

Materials and Methods: A total of 56 allo-HSCT recipients followed at the Department of Hematology, Istanbul Faculty of Medicine, were included in this study. According to HLA matching, 18 patients received 5/10 matched, 7 received 6/10 matched, 1 received 7/10 matched, 2 received 8/10 matched, and 28 received 9/10 matched transplants. High-resolution HLA typing was performed using next-generation sequencing (NGS) for all patients. Donor–recipient eplet mismatches at HLA-A, -B, -C, -DRB1, and -DQB1 loci were calculated using the HLAMatchmaker algorithm. Clinical endpoints included GVHD, relapse, and overall survival. Statistical analyses were performed using multivariate Kruskal–Wallis and Dunn–Bonferroni post hoc tests, Cox proportional hazards regression, and logistic regression models.

Results: Donor-directed Class II eplet mismatching was significantly higher in patients who developed chronic GVHD ($p<0.05$), with the most prominent organ involvement observed in the gastrointestinal tract. Furthermore, Class II eplet mismatch showed an independent positive association with relapse development (OR>1, $p<0.05$). Kaplan–Meier survival analysis demonstrated that a high Class II eplet burden was significantly associated with reduced overall survival ($p<0.05$). In multivariate Cox regression analysis, chronic GVHD and Class II eplet mismatching were identified as independent predictors of mortality (HR>1, $p<0.05$). When relapse was added to the model, the risk of mortality increased markedly (HR≫1), while the effect of Class II eplet mismatching diminished, indicating that Class II mismatching affects mortality indirectly through relapse and/or chronic GVHD. In contrast, Class I eplet mismatching showed no significant effect on GVHD, relapse, or overall survival.

Conclusion: Our findings demonstrate that Class II eplet mismatching adversely affects survival indirectly by

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increasing the risk of chronic GVHD and relapse. In contrast, the impact of Class I eplet mismatching appears to be limited. These results are consistent with previous reports indicating that HLA-DR/DQ eplet disparities enhance alloreactive T-cell activation and increase the risk of chronic GVHD and relapse.

In conclusion, eplet-level matching provides a more sensitive and predictive approach for evaluating transplant outcomes compared with conventional antigen-based HLA matching. Incorporating eplet mismatch analysis into donor selection strategies may improve risk stratification and post-transplant prognosis.

Keywords: Eplet analysis, HLA, GVHD, HSCT