Degree of Predicted Minor Histocompatibility Antigen Mismatch Correlates with Poorer Clinical Outcomes of Nonmyeloablative Allogeneic Hematopoietic Cell Transplantation

In fully HLA-matched allogeneic hematopoietic cell transplantations (HCT), the main mechanism of the beneficial graft-versus-tumor (GVT) effect and of the detrimental graft-versus-host disease (GVHD) is believed to be caused by donor cytotoxic T cells directed against disparate recipient minor histocompatibility antigens (miHAs). The most common origin of disparate miHAs is non-synonymous single nucleotide polymorphism (nsSNP) differences between donors and patients. At this time, only some 30 miHAs have been identified and registered, but considering the numerous different HLA-types in the human population as well as all the possible nsSNP differences between any two individuals, it is likely that many miHAs have yet to be discovered. The objective of the current study was to predict novel HLA-A and HLA-B restricted miHAs in a cohort of patients treated with non-myeloablative conditioning allogeneic HCT (matched related donor, n=70; matched unrelated donor, n=56) for hematologic malignancies. Initially, the cohort was genotyped for 53 nsSNPs in 11 known miHA source proteins. Twenty-three nsSNPs within six miHA source proteins showed variation in the graft-versus-host (GVH) direction. No correlation between the number of disparate nsSNPs and clinical outcome could be observed.

Next, miHAs in the GVH direction were predicted for each patient-donor pair. Using the NetMHCpan predictor, we identified peptides encompassing a nsSNP variant uniquely expressed by the patient and with predicted binding to any of the HLA-A or -B molecules expressed by the patient and donor. Patients with more than the median of three predicted miHAs had a significantly lower five-year overall survival (42% vs 70%, P=0.0060, adjusted hazard ratio (HR) 2.6, P=0.0047) and significantly higher treatment related mortality (39% vs 10%, P=0.0094, adjusted HR 4.6, P=0.0038). No association between number of predicted miHAs and any other clinical outcome parameters was observed. Collectively, our data suggest that the clinical outcome of HCT is not affected by disparate nsSNPs per se, but rather by the HLA-restricted presentation and recognition of peptides encompassing these. Our data also suggest that 6 of the 11 proteins included in the current study could contain more miHAs yet to be identified, and that the presence of multiple miHAs confers a higher risk of mortality after non-myeloablative conditioning HCT. Furthermore, our data suggest a possible role for in silico based miHA predictions, in donor selection as well as in selecting candidate miHAs for further evaluation in in vitro and in vivo experiments. Copyright © 2010. Published by Elsevier Inc.
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