Comment on Nakasone et al, page 3193

HY antibodies as biomarkers for chronic GVHD

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In this issue of Blood, Nakasone et al report on an early biomarker for chronic graft–versus-host disease (cGVHD). In a prospective study, they demonstrated the detection of multiple HY antibodies (HY-Abs) 3 months after female-to-male allogeneic hematopoietic cell transplant (allo-HCT) can predict cGVHD development, severity, and nonrelapse mortality (NRM).1

The therapeutic effect of allo-HCT is often complicated by GVHD due to a strong donor alloimmune response against patients' healthy tissues. Although acute GVHD can be life threatening in the first months after HCT, cGVHD remains the major cause of long-term morbidity and NRM. Traditional cGVHD therapy with corticosteroids is not always effective, and alternative strategies based on more powerful immunosuppressive agents or on targeting B cells are not free of side effects. Hence, the discovery and validation of biomarkers that can predict the development, prognosis, and therapy response of patients with cGVHD are considered important tasks toward effective management of cGVHD.2

The study of Nakasone et al is perhaps one of the most successful attempts toward this goal, because numerous studies investigating the predictive value of various immune cell subsets or immune-related cytokines have not yet revealed an unambiguous biomarker for cGVHD. Consistent with the emerging data supporting the involvement of B cells in cGVHD, an increased ratio between the B-cell activating factor (BAFF) and circulating B cells has recently been shown to predict cGVHD,3 but this promising biomarker awaits further validation.

Like several other investigators, Nakasone et al studied the predictive value of alloimmune responses against minor histocompatibility (H) antigens, because these polymorphic antigens are the major targets of donor alloimmunity after HLA-identical HCT.4 Several minor H antigens are encoded by autosomal genes. The specific antigens studied by Nakasone et al, however, are encoded by genes on the Y chromosome and are designated “H-Y antigens.” Because there is a considerable level of amino acid sequence difference between H-Y antigens and their homologous counterparts encoded by the X chromosome, H-Y antigens are highly immunogenic and contribute importantly to the development of alloimmunity in female-to-male transplants. Whereas all minor H antigens can induce T-cell responses, H-Y antigens have been shown to induce antibody responses as well.6

In the current study, Nakasone et al specifically focused on HY-Abs, because in a previous study, they had demonstrated evidence for increased titers of HY-Abs in patients with cGVHD.5 Since then, they set out to determine the predictive value of HY-Abs for cGVHD and have established a comprehensive repository containing longitudinally collected samples from allo-HCT patients and prospectively analyzed samples of 136 female-to-male transplant patients. Testing them against a microarray containing 6 recombinant H-Y proteins revealed persistent antibody responses to multiple H-Y antigens starting at 3 months after allo-HCT. In multivariate analyses, antibodies against individual H-Y antigens detected at 3 months displayed significant association with cGVHD and NRM. The development of antibodies against more H-Y antigens seemed to increase the risk of cGVHD; therefore, Nakasone et al developed the “HY score” (the sum of the detected HY-Abs). They were able to demonstrate that patients with a 3-month HY score of 4 to 6 had a fivefold and 20-fold increased risk of developing cGVHD and NRM, respectively, thereby validating the detection of antibody responses against H-Y antigens as an early biomarker for cGVHD.

This discovery may have important clinical implications. As also suggested by Nakasone et al, a high HY score could be instrumental in selecting patients for experimental cGVHD-prevention trials through targeting B cells either with antibodies or with the Bruton tyrosine kinase inhibitor ibrutinib, which effectively ameliorates cGVHD in murine models.7 This study may also stimulate research toward identification of antibody-based biomarkers for patients who do not receive a sex-mismatched HCT. One option is to start searching for antibodies against autosomal minor H antigens. These efforts may require the intensification of the promising research toward identification of novel minor H antigens,8 because many of the currently known autosomal minor H antigens contain only a few amino acid polymorphisms and may not induce robust antibody responses. It may therefore be relevant to identify more minor H antigens as a result of gene deletions or frame shifts, because in those cases, the whole protein can be a target of alloantibodies. Alternatively, the early development of autoantibodies could be investigated as a predictive biomarker for cGVHD. Lastly, it would be interesting to study whether combining such a predictive score with those of other promising biomarkers, such as elevated BAFF/B-cell ratios, could increase the predictive value of alloantibody-based biomarkers.

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