In this issue of Clinical Cancer Research, Nishida and colleagues elegantly document the kinetics and antigen specificity of tumor-reactive T cells developing in patients with chronic lymphocytic leukemia (CLL) following allogeneic hematopoietic stem cell transplantation (HSCT; ref. 1). These studies show that individual tumor-reactive T cells, arising in the first year after allogeneic HSCT, target three broad categories of cells: recipient cells of both hematopoietic and nonhematopoietic origin; recipient cells of hematopoietic lineage; and notably, only recipient CLL cells. Although the existence of tumor-specific immune responses have long been surmised, these responses have been difficult to separate from nontumor-specific immune responses arising as a result of alloimmunity (2). This study provides direct demonstration in patients that tumor-specific nonalloreactive T cells represent a sizable proportion of the postransplant immune response.

For many patients with hematologic malignancies, allogeneic HSCT remains the only curative therapy. Although the mechanisms by which patients can achieve durable remissions are not entirely understood, it is evident that donor immune cells play a critical role in the elimination of tumor cells after HSCT. The existence of this graft versus leukemia (GVL) effect was first noted in clinical studies demonstrating that patients who developed graft-versus-host disease (GVHD) had fewer relapses after transplant (3). Allo-transplant patients were also found to have a lower risk of relapse compared with patients undergoing autologous or syngeneic transplant, and depletion of donor T cells from the stem cell graft was associated with increased risk of relapse (4). The potency of GVL was most clearly shown through the results of donor lymphocyte infusion (DLI) in patients with relapsed leukemia after allogeneic HSCT (5). In this setting, single infusions of donor lymphocytes are capable of inducing remissions in the absence of further chemotherapy or radiation. Durable remissions are remarkably observed in 70% to 80% of patients with relapsed stable phase chronic myelocytic leukemia (CML). CLL and myeloma also respond to DLI, each demonstrating 30% to 50% response rates. The beneficial effects of GVL have led to major shifts in the landscape of allogeneic HSCT. Prior to the appreciation of GVL, preparative regimens were designed to be maximally intensive and myeloablative to provide effective antileukemia therapy and also to facilitate donor cell engraftment. Now, reduced-intensity preparative regimens are designed primarily to facilitate engraftment of donor stem cells. These regimens are well tolerated and have made it possible to offer allogeneic HSCT to older patients and those with comorbidities that preclude the administration of more intensive chemotherapy or radiotherapy (6, 7). Reduced-intensity preparative regimens alone do not eliminate recipient hematopoiesis nor provide durable leukemia responses. Thus, establishment of complete donor hematopoiesis as well as the maintenance of long-term remission results primarily from immunologic recognition and elimination of both normal recipient hematopoietic stem cells and leukemia cells.

Unfortunately, these desired immunologic effects come at a cost. GVL responses following reduced-intensity HSCT often arise in the setting of acute or chronic GVHD. Whereas the immunologic targeting of leukemia cells is beneficial, similar targeting of normal recipient tissues remains a major cause of morbidity and mortality following HSCT. Further studies to distinguish GVL from GVHD are needed to improve outcomes after allogeneic HSCT.

Clin one approach to distinguish GVL from GVHD is to determine whether the target specificities of the two responses differ. Because the vast majority of allogeneic transplants are carried out with recipients and donors that are HLA-matched, minor histocompatibility antigens (mHA) become the primary targets of allo-immunity. Unlike major histocompatibility antigens, which are encoded by a discrete set of genes on chromosome 6, mHA are derived from genetic polymorphisms that exist through the human genome (8). Genetic polymorphisms can give rise to allo-antigens through various mechanisms including amino acid substitutions that create antigenic peptides, creation of alternate transcripts, modification of proteosomal processing, posttranslational modifications, or gene deletions. Transplantation of mature T cells during allogeneic HSCT results in the transfer of
large numbers of cells capable of recognizing these mHA. The clinical significance of mHA is highly dependent on the tissues and cell types that express the target antigen (Fig. 1). Targeting allo-antigens that are broadly expressed in normal recipient tissues (hematopoietic and nonhematopoietic) results in GVHD. When these allo-antigens are also expressed on leukemia cells, targeting these antigens contributes to GVL. Consistent with this paradigm, male patients who receive stem cell transplants from female donors (wherein Y-encoded proteins represent widely expressed recipient allo-antigens absent in the donor) have more GVHD and less relapse than recipients with sex-matched donors (9). When mHA are only expressed in hematopoietic tissues, donor T cells targeting these antigens result in the elimination of recipient hematopoiesis and conversion to full donor hematopoiesis. When leukemia cells also express these mHA, targeting hematopoietic allo-antigens can result in GVL without concomitant GVHD (10).

Although mHA are known to be important targets after allogeneic HSCT, relatively little is known about donor immune responses directed against antigens solely expressed on leukemia cells. Many potentially important classes of antigens with leukemia-restricted expression are already known. These include leukemia-specific antigens (epitopes arising from chromosomal rearrangements such as BCR-ABL); virally encoded antigens (latent EBV epitopes); over-expressed self-antigens (proteinase-3, WT-1); cancer-testis antigens (NY-ESO-1); or mutated or modified self-antigens. In all instances, the immunogenicity of these targets is not dependent on genetic disparity between recipient and donor. Although recipients with leukemia may have become tolerant to these antigens, normal donors remain capable of developing effective immune responses after transplantation. In recent years, antibody responses to several GVL-associated antigens have been identified, many of which seem to represent tumor-associated rather than mHA, but the extent to which donor T cells respond to these antigens has not been established (11). Many of these antigens are highly expressed in malignant progenitor cells suggesting that curative GVL responses are directed against leukemia-initiating cells (12).

Nishida and colleagues (1) describe eight CLL patients who achieved remission or major antitumor response after HSCT and developed CD8+ and CD4+ T cells specific for antigens expressed by their own CLL cells. Conversely, CLL-directed T-cell responses were not detected in four individuals with persistent disease after transplant, despite the development of GVHD. Through detailed analysis of the CD8+ T-cell responses in responding patients, some T-cell clones were found to recognize both recipient CLL cells and nonmalignant B cells, but not recipient fibroblasts. These T-cell clones are presumed to recognize hematopoietic-restricted mHA. However, some T-cell clones recognized only CLL cells and not recipient nonmalignant B cells. The proportion of T-cell clones of this category varied from 30% to 79% of all T-cell clones isolated. Although the specific target antigens were not identified, these results suggest that tumor-specific T cells represent a significant component of the overall T-cell response to CLL after allogeneic HSCT.

These studies underscore the complex and polyclonal nature of responses required to generate clinically effective tumor immunity. An important therapeutic implication

**Fig. 1.** After allogeneic HSCT, donor T- and B-cell responses to leukemia cells can be directed against three categories of antigens. Targeting different sets of antigens can result in GVL, GVHD, or both.
of this study is that once antigen targets of the CLL-specific responses are identified, novel approaches, perhaps through vaccination or adoptive T-cell therapy, to amplify and maintain these tumor-specific responses can be developed. In the same way that we have learned much about mHA and how these epitopes are generated, we look forward to understanding the mechanisms that stimulate tumor-specific immunity.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

References

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