SPECIAL REPORT

Harnessing alloreactivity to achieve anti-leukemic responses

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One of the hallmarks of a successful cancer is the development of one or more mechanisms to circumvent immune responses. Mechanisms by which acute myeloid leukemia circumvent immune responses that have been identified include loss of human leukocyte antigens, expression of ligands for inhibitory receptors, induction of the accumulation of suppressor cells, producing IDO and elimination of leukemia reactive cells.¹ One possible approach to overcome these inhibitory hurdles is to harness alloreactive responses to achieve anti-leukemic responses. Explanations for the potent alloreactive responses have included the ability of the T-cell receptor (TCR) to crossreact with allogeneic major histocompatibility complex molecules presenting endogenous peptides or that alloreactive cells express two different TCR.^{2,3} Initial attempts to harness alloreactivity have used allogeneic stem cell transplantation. In this procedure the recipient immune system is knocked down as part of the conditioning regimes, resulting in primarily donor anti-recipient responses following the stem cell transplant. While the donor anti-recipient response can generate graft-versus-leukemia responses, there is a high incidence of graft-versus-host disease (GVHD).⁴ Donor lymphocyte infusions following the development of tolerance have been used to enhance donor anti-tumor responses.⁵ In contrast, the cellular immunotherapy protocol, in which large numbers of haploidentical cells ($1-2 \times 10^8$ CD3+ cells/kg) are infused in non-conditioned patients, results in both donor anti-recipient responses as well as recipient anti-donor responses.⁶ The recipient anti-donor responses are sufficient to eliminate the donor cells within several weeks, thereby preventing GVHD. Anti-leukemic responses were detected despite the elimination of the donor cells. This clinical trial has been reopened and ongoing studies are attempting to define the immune responses responsible for the anti-leukemic responses in this protocol.⁷ Possibilities to be tested include alloreactive cells crossreacting with leukemic cells, alloreactive responses reactivating memory T cells or the presence of activated CD3+ cells permitting anti-leukemic responses using non-TCR receptors. Preliminary results with the initial patients enrolled in the cellular immunotherapy trial have found increased expression of cytolytic effector molecules in recipient T cells, but little

cytolytic activity based on low levels of CD107a expression. Rapid upregulation of PD-1 ligands on leukemic cells after infusion of donor cells was detected in 2/3 patients and could provide one explanation for the lack of response. Analysis of additional clinical trial patients combined with development of *in vitro* assays will help define how the use of alloreactivity can be improved to generate more potent anti-leukemic responses.

CONFLICT OF INTEREST

The author declares no conflict of interest.

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