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REFERENCES

1. Kim EJ, Hess S, Richardson SK, et al. Immunopathogenesis and therapy of cutaneous T cell lymphoma. J Clin Invest. 2005;115:798-812.

2. Talpur R, Jones DM, Alencar AJ, et al. CD25 expression is correlated with histological grade and response to denileukin diftitox in cutaneous T-cell lymphoma. J Invest Dermatol. 2006;126:575-583.

3. Thursky KA, Worth LJ, Seymour JF, et al. Spectrum of infection, risk and recommendations for prophylaxis and screening among patients with lymphoproliferative disorders treated with alemtuzumab®. Br J Haematol. 2006;132:3-12.

4. Akdis CA, Akdis M, Bieber T, et al. Diagnosis and treatment of atopic dermatitis in children and adults: European Academy of Allergology and Clinical Immunology/American Academy of Allergy, Asthma and Immunology/PRACTALL Consensus Report. Allergy. 2006;61:969-987.

GENE THERAPY

Comment on Ciceri et al, page 4698, and comment on Traversari et al, page 4708

Altruistic donor T cells

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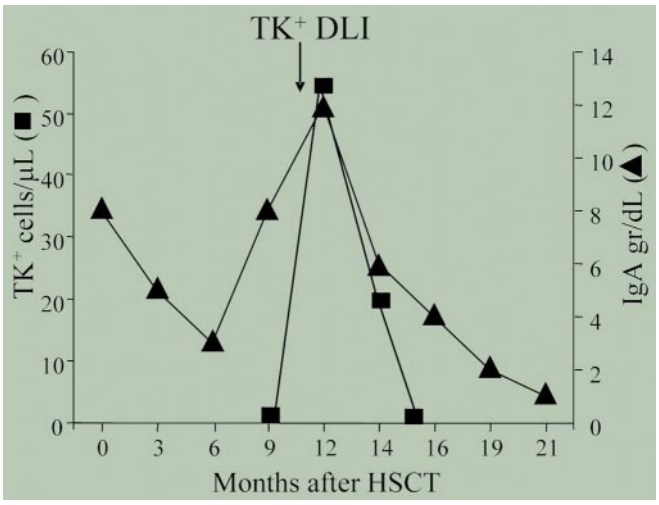
Use of suicidal donor T cells could ensure efficient modulation of alloreactivity after hematopoietic cell transplantation. How realistic is this approach? Ciceri and colleagues and Traversari and colleagues report from the clinic and the lab.

Donor T cells can wrongly recognize a host as dangerous, resulting in graft-versus-host disease (GvHD). On the other hand, these same cells play a major role in tumor eradication and, when infused with a hematopoietic graft, in engraftment and immune reconstitution as well. Adequate modulation of alloreactivity remains an elusive goal, and innovation in this field is needed.

Use of donor T cells expressing a suicide gene such as thymidine of herpes simplex virus (TK) could allow for selective in vivo depletion if GvHD were to occur. Beforehand, and possibly permanently in the absence of GvHD, the recipient could enjoy the full benefit of donor T cells. In addition, conditional selective depletion of alloreactive donor T cells could result in reduced toxicity compared to the broad immunosuppressive agents presently used for GvHD prophylaxis and treatment.

In a pioneering study, Bonini et al reported in 1997 effective ganciclovir (GCV)–mediated control of GvHD in patients receiving TK^+ donor lymphocyte infusion (DLI).[1] We subsequently reported, in patients receiving TK^+ T cells with a T-cell–depleted graft, similar GCV-sensitive GvHD.[2] However, occurrence of Epstein-Barr virus (EBV) lymphoproliferative diseases suggested that ex vivo manipulation of T cells might be impairing immune competence.[3] Additional difficulties emerging subsequently included the occurrence of immune responses against transgenes, with a consequent efficient clearance of gene-modified cells,[4] as well as, in a study involving gene transfer in hematopoietic stem cells, leukemia resulting from insertional mutagenesis.[5] Taken together, these findings highlight the potential pitfalls associated with this elegant but technologically complex approach.



Quantification of monoclonal IgA level (▲) and of TK^+ donor T cells (■) in a patient with IgA multiple myeloma following a single infusion of TK^+ DLI. See the complete figure in the article starting on page 4698.

Studies from Ciceri and colleagues and Traversari and colleagues in this issue of *Blood* report encouraging results with respect to these issues. Stemming from a cohort of 30 recipients with recurrence of malignancy after transplantation, long-term results in 23 patients having received TK^+ cells are presented. Clinical benefit was evidenced in 11 recipients (see figure). Interestingly, responses were associated with strong in vivo expansion of circulating TK^+ cells. Furthermore, responses potentially persisted despite subsequent occurrence of immune responses against gene-modified cells. This observation, suggesting a therapeutic benefit of such a transient alloreactivity, could open new venues in the field of adoptive immunotherapy. Immune responses were directed mainly against TK, less so against the selection markers, and appeared to be favored by an immunocompetent environment. Despite the infusion of large numbers of donor T cells, GvHD occurred in a minority of available patients, thus suggesting that, despite improvements in the technologies to prepare TK^+ cells, alloreactivity (and antitumor efficacy as well?) of such cells remains inferior to that of unmanipulated T cells. Ganciclovir treatment resulted in the elimination of TK^+ cells and successful treatment of acute GvHD. Lastly, no evidence for deleterious insertional mutagenesis was found.

Overall, the suicide gene approach to modulate alloreactivity is progressing. Continuous efforts to improve the involved technologies (including improved ex vivo gene transfer methods and use of alternative nonimmunogenic transgenes) and to perform careful clinical evaluations are required.

The author declares no competing financial interests.

REFERENCES

1. Bonini C, Ferrari G, Verzeletti S, et al. HSV-TK gene transfer into donor lymphocytes for control of allogeneic graft-versus-leukemia. Science. 1997;276:1719-1724.

2. Tiberghien P, Lioure B, Milpied N, et al. Administration of herpes simplex-thymidine kinase-expressing donor T cells with a T-cell-depleted allogeneic marrow graft. Blood. 2001;97:63-72.

3. Sauce D, Bodinier M, Garin M, et al. Retrovirus-mediated gene transfer in primary T lymphocytes impairs their anti-Epstein-Barr virus potential through both culture-dependent and selection process-dependent mechanisms. Blood. 2002;99:1165-1173.

4. Berger C, Flowers ME, Warren EH, Riddell SR. Analysis of transgene-specific immune responses that limit the in vivo persistence of adoptively transferred HSV-TK-modified donor T cells after allogeneic hematopoietic cell transplantation. Blood. 2006;107:2294-2302.

5. Hacein-Bey-Abina S, Von Kalle C, Schmidt M, et al. LMO2-associated clonal T cell proliferation in two patients after gene therapy for SCID-X1 [erratum in: Science. 2003; 302:568.]. Science. 2003;302:415-419.

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