Comment on Diaconescu et al, page 1550

Do "minitransplantations" have "minitoxicity"?

Brian L. Abbott UNIVERSITY OF MISSOURI AT KANSAS CITY

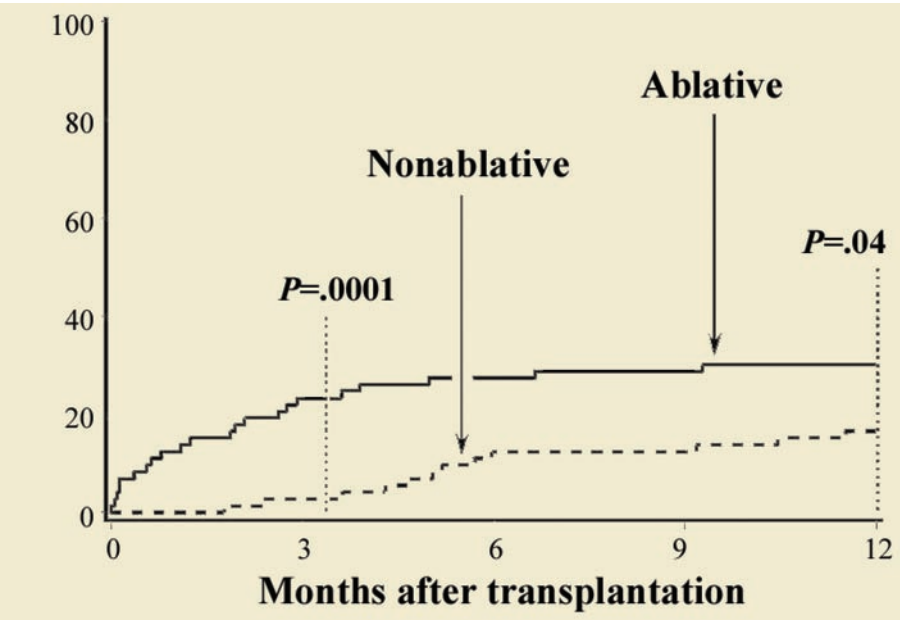
Reduced intensity, or nonablative, conditioning regimens have made allogeneic hematopoietic transplantation available to patients ineligible for conventional ablative regimens.

The rationale behind the nonablative approach rests on the theory that the curative aspect of allogeneic transplantation is mediated by a graft-versus-tumor effect rather than a high-dose cytotoxic effect. Since high-dose therapy is avoided, this approach was predicted to be safer for patients who were ineligible for conventional myeloablative regimens because of age or comorbidities. Investigators hypothesized that the early toxicity of high-dose regimens is caused by a combination of direct organ damage from the conditioning regimen as well as graft-versus-host disease (GVHD) provoked by a "cytokine storm" released from these damaged tissues. Although initial reports showed that successful donor engraftment is safely achievable with nonablative regimens, longer-term results of toxicities have thus far been lacking.[1-3]

In this issue of *Blood,* Diaconescu and colleagues present a comparison of results using nonablative conditioning regimens with historic controls receiving conventional myeloablative transplants. Nonablative conditioning regimens consisted of either low-dose total body irradiation (TBI) only or the combination of fludarabine and TBI. Comorbidities were retrospectively measured by the Charlson comorbidity index, which was developed and validated as a measurement of mortality risk in breast cancer patients.[4] This appears to be the first use of this scale to quantitate risk factors in recipients of hematopoietic cell transplants. Because of the incorporation of organ-specific functional assessments, this tool may provide additional power beyond nonspecific performance status assessments, such as the Eastern Cooperative Oncology Group score and Karnofsky scores. The authors present a systematic analysis of toxicities and the nonablative cohort experienced similar or lower toxicity rates for all parameters, with the exception of graft rejection. The authors conclude that despite the presence of higher levels of medical comorbidities, patients treated with nonablative allogeneic transplantation had significantly lower treatment-related mortality at 100 days and at 1 year after transplantation.

A few cautionary notes are warranted. First, over half of the nonablative patients received TBI-only conditioning, a regimen not widely used in other centers. Second, data regarding longer-term follow-up are needed to determine if rates of disease control are similar with ablative and nonablative conditioning regimens; results of disease-related response, morbidity, and mortality are not included. It is possible that certain malignancies are more responsive to the allogeneic antitumor effect than others. Finally, although the onset of acute GVHD was delayed in the nonablative cohort, overall rates of severe acute GVHD were not lower, contrary to reports from other clinical investigators.[5] The authors suggest this may have been due, in part, to a shorter course of cyclosporine GVHD prophylaxis in the nonablative cohort.

Nonablative conditioning regimens will clearly retain a place among the available treatment options in allogeneic hematopoietic transplantation. Further work is needed to directly compare the results of nonablative and conventional conditioning regimens and to define the diseases for which the allogeneic graft-versus-malignancy effect is adequate for disease cure. As nonablative allogeneic transplantation becomes more common, formal systems of risk assessment such as the Charlson index might become an important tool for treatment decisions and patient selection, if these results are confirmed in prospective studies. ■



Cumulative incidences of 1-year nonrelapse mortality among HC transplant recipients given nonablative versus ablative conditioning. See the complete figure in the article beginning on page 1550.

REFERENCES

1. McSweeney PA, Niederwieser D, Shizuru JA, et al. Hematopoietic cell transplantation in older patients with hematologic malignancies: replacing high-dose cytotoxic therapy with graft-versus-tumor effects. Blood. 2001;97:3390-3400.

2. Slavin S, Nagler A, Naparstek E, et al. Nonmyeloablative stem cell transplantation and cell therapy as an alternative to conventional bone marrow transplantation with lethal cytoreduction for the treatment of malignant and nonmalignant hematologic diseases. Blood. 1998;91:756-763.

3. Khouri IF, Keating M, Korbling M, et al. Transplant-lite: induction of graft-versus-malignancy using fludarabine-based nonablative chemotherapy and allogeneic blood progenitor-cell transplantation as treatment for lymphoid malignancies. J Clin Oncol. 1998;16:2817-2824.

4. Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40:373-383.

5. Couriel DR, Saliba RM, Giralt S. Acute and chronic graft-versus-host disease after ablative and nonmyeloablative conditioning for allogeneic hematopoietic transplantation. Biol Blood Marrow Transplant. 2004;10:178-185.

TRANSPLANTATION

Comment on Lee et al, page 1559

GVHD therapy: the best-laid schemes. . .

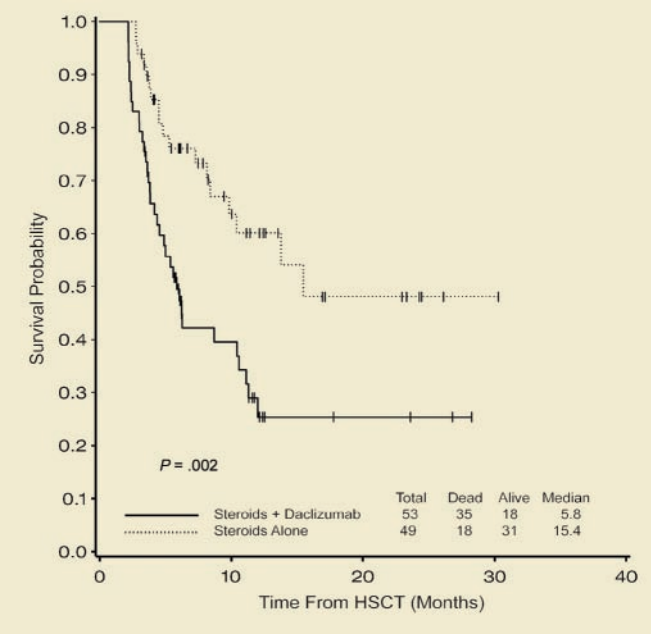
Krishna V. Komanduri and Richard E. Champlin UNIVERSITY OF TEXAS-M.D. ANDERSON CANCER CENTER

Approaches to eliminate interleukin-2 receptor alpha ($CD25^+$) cells have been widely pursued to selectively eliminate alloreactive cells that cause GVHD after allogeneic stem cell transplantation. In this issue, Lee and colleagues report paradoxical findings involving treatment with daclizumab, an anti-CD25 monoclonal antibody, possibly due to effects on $CD4^+CD25^+$ immunoregulatory cells.

The narrator in Robert Burns' 1785 poem "To a Mouse" laments to the murine protagonist: But, Mousie, thou art no thy lane, / In proving foresight may be vain; / The best-laid schemes o' mice an' men / Gang aft agley [often go astray] / An' lea'e us nought but grief an' pain.[1]

The ability to humanize a monoclonal antibody (MAb) produced by a mouse has proved to be one of the best schemes developed by scientists in human cancer therapy, as evidenced by the successes of rituximab and trastuzumab. Diseases of immune dysregulation are logical targets for MAb therapies, as resting and activated lymphocytes are amongst the best-characterized cells with respect to MAb binding.

Acute graft-versus-host disease (GVHD) is largely mediated by alloreactive T lymphocytes. Interleukin-2 receptor alpha chain (IL-2Rα, CD25) is upregulated on activated human T cells in vitro and in human disease states. The anti-CD25 monoclonal antibody, daclizumab, has been successfully used for treatment of steroid-resistant acute GVHD.[2] In this issue of *Blood*, Lee and colleagues hypothesize that the addition of the CD25-specific MAb daclizumab would increase the efficacy of standard therapy for acute GVHD. Their double-blinded and randomized multi-institutional trial was well designed to determine whether the addition of daclizumab to initial corticosteroid therapy for acute GVHD would improve clinical outcomes. Unfortunately, a planned interim analysis demonstrated that subjects receiving daclizumab experienced significantly worsened 100-day survival (77% vs 94%; $P = .02$) and 1-year overall survival (29% vs 60%; $P = .002$). These findings appropriately led to premature termination of the trial and the authors' conclusion that daclizumab should not be added to corticosteroids for the initial treatment of acute GVHD.



Probability of overall survival is better in the corticosteroids alone arm at 100 days and 1 year. See the complete figure in the article beginning on page 1559.

Some results were surprising, including the fact that while the response rate in the combined arm was similar to that in the steroid-only arm (53% vs 51% at day +42; P = not significant), GVHD-related and disease-related deaths occurred more frequently in the daclizumab arm. Given the established association between GVHD incidence and severity with decreases in relapse, the fact that relapses also occurred more frequently in the daclizumab group is counter-intuitive. Furthermore, the cumulative incidence of chronic GVHD in the daclizumab group was not higher than in the steroid-alone arm, even when death was considered as a competing risk.

The immunologic mechanisms responsible for the effects observed are not immediately clear, as the authors acknowledge. CD25 is also expressed on $CD4^+CD25^+$ immunoregulatory cells, which have been shown to inhibit GVHD in animal models.[3] It is tempting to lay the blame at the feet of these regulatory T cells that might have been depleted by daclizumab, thereby aggravating GVHD. Indeed, approaches to expand regulatory T cells hold significant clinical promise.[4] However, 2 studies recently published in *Blood* found that increased frequencies of $CD4^+CD25^+$ T cells were present in the donor grafts of recipients who experienced acute GVHD[5] and in the peripheral blood of stem cell transplant (SCT) recipients with chronic GVHD.[6] In aggregate, these results highlight our need to identify unique surface markers that may differentiate activated and regulatory CD25-expressing T cells so we may better design MAb-based and adoptive cellular therapies for hematopoietic transplantation. With better foresight, and more studies in both mice and men, we might finally advance the therapy for acute GVHD beyond the corticosteroid era. ■