demonstrate that activated CD4+CD25+ T cells produce and release granzyme B similarly to CD8 T cells, an activity not found in CD4+CD25− T cells.

The authors further demonstrate that B-cell apoptosis mediated by CD4+CD25+ T cells can be antigen dependent. CD4+CD25+ T cells from mice bearing a transgenic TCR that recognizes an ovalbumin peptide were used for these experiments. Proliferating B cells were divided into 2 separate groups, one pulsed with ovalbumin and one unpulsed.

Ovalbumin-specific CD4+CD25+ T cells were dramatically more efficient at killing antigen-pulsed B cells, demonstrating that this Treg activity is indeed antigen dependent.

Thus, an entirely new mechanism of Treg activity has been discovered. B-cell proliferation is controlled in a completely different manner from T-cell proliferation. This mechanism involves direct, antigen-selective induction of B-cell apoptosis. These findings are an important advance in our knowledge of Treg function.

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**Comment on Mounier et al, page 3832**

**Simplified prognostic indicators for AIDS-related lymphoma**

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The final results of one of the largest clinical trials ever conducted for AIDS-related non-Hodgkin lymphoma with simplified prognostic indicators are reported by Mounier and colleagues in this issue of Blood. Between 1993 and 1999, 485 patients in 55 centers in the Groupe d’Etude des Lymphomes de l’Adultes (GELA) and the Gruppo Italiano Coooperativo AIDS e Tumori (GICAT) were enrolled in 3 randomized clinical trials according to a stratification to a model for AIDS status using 3 adverse risk factors: Eastern Cooperative Oncology Group performance status 2 to 4, prior AIDS diagnosis, and a CD4 cell count less than 0.10 × 10^9/L (100/mm^3). Patients with no risk factors were randomized to 4 cycles of standard cyclophosphamide, vincristine, doxorubicin, and prednisolone (CHOP) or 3 cycles of a more intensive regimen, doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisolone (ACVBP). Patients with 1 risk factor were randomized to 4 cycles of standard CHOP or 4 cycles of low-dose CHOP, and those with 2 or 3 risk factors to 4 cycles of low-dose CHOP or 12 treatments with vincristine and prednisolone. There was no difference in 5-year overall survival between the patients in each arm of all 3 stratifications.

Results were analyzed according to lymphoma status (International Prognostic Index [IPI]), entry into the trial before and after 1996 when highly active antiretroviral therapy (HAART) was introduced, and an older prognostic model. The strongest predictors of survival were AIDS status, lymphoma status (IPI), and use of HAART. The number of patients with 2 to 3 AIDS factors was significantly reduced by HAART. This subset analysis of a prospective study confirms the observation noted in retrospective analyses¹ that the survival of patients with AIDS-related lymphomas has improved with HAART and is now approaching that of patients with similar lymphomas in patients without HIV infection (see figure). It also confirms the utility of the IPI.

Deaths due to AIDS are less common in patients with AIDS-related lymphomas with preserved immune and associated bone marrow functions who receive HAART. As a result, older prognostic models that used both AIDS and lymphoma factors are now less useful. Although the results with 4 cycles of CHOP in patients with no AIDS risk factors were good, superior overall results have been reported with more prolonged infusion chemotherapy.² However, unlike most B-cell lymphomas where the addition of rituximab to chemotherapy has improved the outcome, improvements in tumor response in AIDS-related lymphomas have been tempered by infectious deaths, particularly in patients with poor immune function.³ Patients with AIDS-related Burkitt lymphomas often have well-preserved immune function with or without HAART, and they can now be expected to have an outcome similar to that of patients without HIV infection with intensive treatment.⁴,⁵ Clearly, we have entered a new era with HAART in which treatment can now be directed to the aggressive lymphomas seen with HIV infection without as much concern for the complications of AIDS.

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**REFERENCES**

2. Little RF, Pittaluga S, Grant N, et al. Highly effective
Comment on Kaeda et al, page 4171

Transplantation for CML: lifelong PCR monitoring?

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Chronic myelogenous leukemia (CML) management continues to evolve rapidly. Allogeneic transplantation had been considered the optimum management for the newly diagnosed CML patient for whom transplantation was feasible, as determined by age, donor availability, and lack of comorbid conditions. Imatinib has now relegated transplantation to second-line therapy, although some consider transplantation as third- or even fourth-line therapy. However, a recurring cautionary note is echoed that imatinib does not offer a known curative option and that we are delaying proven curative therapy to later in the disease course, possibly negatively influencing the excellent transplantation outcomes.

Recognizing that polymerase chain reaction (PCR) sensitivity has increased over the past decade, the findings are rather eye opening, especially in light of our desire to attribute “cured” status to allograft recipients. Specifically, of the patients studied by Kaeda and colleagues, 53% relapsed as determined by molecular criteria alone or by progression to abnormal cytogenetic or hematologic states. In addition, in the remaining 47%, the majority had multiple episodes when low positive BCR-ABL PCR results were observed after transplantation, from which the probability of future relapse could be defined (see figure). Thus, in the entire cohort, only approximately 15% were classified as persistently negative, defined as always PCR negative (6.6%; 16 patients) for BCR-ABL or with a single, detectable low-level positive result (8.2%; 20 patients). Patients were found with relapse or with BCR-ABL PCR signals whether or not T-cell depletion was used, thus raising the question, to these authors, whether some or potentially even all patients after allogeneic transplantation continue to harbor small quantities of residual leukemic cells.

Concomitant with this publication, at the IBMT/ASBMT 2006 meetings, one of the authors, Dr John Goldman, presented long-term follow-up of 8738 CML patients who had undergone transplantation between 1978 and 1998 and were evaluated for long-term survival.1 Nearly 3000 patients were identified as living 5 years or longer, and of those long-term survivors, approximately 10% experienced late relapse of their CML, even as late as 15 years after the transplantation. These data in combination with the data presented by Kaeda et al clearly indicate a critical need for ongoing serial monitoring of all CML patients who have undergone and will undergo allogeneic transplantation. The importance of this monitoring is highlighted by the desire to identify CML patients early, prior to hematologic relapse, so that they can be assessed for treatment options, such as donor leukocyte infusions, imatinib, or perhaps other second-generation kinase inhibitors.2 Thus, we laud these authors for their detailed analysis and await validation of these remarkable long-term data from other centers or other cooperative groups, and with recognition that at least one group has reported lower PCR BCR-ABL positivity and subsequent relapse rates in similar CML cohorts, although with less lengthy follow-up and in the absence of T-cell depletion.3

REFERENCES
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David J. Straus