Champlin and colleagues have elegantly summarized the concept of nonmyeloablative stem cell transplantation (NST), stressing the importance of this newly emerging procedure for the treatment of patients with life-threatening malignant hematologic and nonhematologic diseases. This review does not include a description of the safety and efficacy of NST for the treatment of many life-threatening nonmalignant diseases for which no alternative therapy exists. This category encompasses a long list of genetic disorders, diseases caused by a deficiency of stem cell products, and syndromes associated with immune deficiency. However, discussion of these illnesses is beyond the scope of this review, which focuses on cancer.

Crucial Role of Donor Lymphocyte Infusion

The authors also did not discuss the most important observation that led to the development of NST: the capacity of donor lymphocyte infusion (DLI) to reverse relapse in patients with disease recurrence following maximally tolerated doses of chemoradiotherapy. Such findings provided unequivocal evidence that immunotherapy mediated by donor lymphocytes may not infrequently be more effective than lethal chemoradiotherapy.[1,2]

Documentation of the role of alloreactive lymphocytes rather than myeloablative conditioning in eliminating the underlying malignancy, also supported by preclinical animal models,[3] led to the working hypothesis that myeloablative bone marrow transplantation may be replaced by a better-tolerated and safer two-step procedure: (1) induction of host-vs-graft transplantation tolerance by engraftment of donor stem cells following a window of immunosuppressive conditioning, thus enabling (2) engraftment of alloreactive donor lymphocytes that mediate graft-vs-malignancy effects.[4]

Although these facts were not mentioned in this review on nonablative regimens, they provide the strongest rationale for continuing and improving the clinical application of NST as a natural replacement of conventional myeloablative bone marrow transplantation.

Reduced-Intensity Conditioning and Mixed Chimerism

The authors describe the benefits of NST as being mediated primarily by alloreactive donor lymphocytes rather than through cytoreductive conditioning. They devote much attention to distinguishing between truly nonmyeloablative and reduced-intensity conditioning, but little attention to the fact that even a truly nonmyeloablative regimen eventually results in complete myeloablation of the host hematopoietic system. Indeed, in treating diseases of hematopoietic origin, the final outcome—e even following minimally cytoreductive conditioning—is usually complete myeloablation. This is precisely why patients with otherwise chemotherapy-resistant hematologic malignancies can be cured by NST despite minimally ablative preparatory conditioning.

Along the same lines is the claim that nonablative conditioning will result in mixed chimerism due to the fact that host stem cells are only minimally damaged, in contrast to fully myeloablative conditioning. In fact, most studies suggest that replacement of host with donor hematopoietic cells is
complete in the large majority of cases, accomplished within the first few weeks following transplantation, again stressing the importance of alloreactive lymphocytes in ablation of the malignant process rather than the conditioning itself.[5-7]

Efficacy of NST

Although some studies have suggested improved disease-free survival as a function of the intensity of the conditioning, the log-dose kinetics of tumor cell growth implies that major changes in the intensity of cytoreductive agents, far from being well-tolerated, are needed to accomplish significant tumor debulking and meaningful change in cell growth kinetics. Unfortunately, none of the conditioning regimens were shown to be superior, whereas following application of DLI, occasionally even the most resistant leukemia cells could be eradicated.[1,2]

Furthermore, in the context of NST being used as a second transplant following failure of a prior bone marrow transplant procedure, alloreactive donor lymphocytes expanding in response to alloantigens can be most effective against tumor cells that have escaped myeloablative chemoradiotherapy administered in preparation for the first transplant procedure.[8] In fact, the only modality that can indeed eliminate the "last" hematopoietic cell of host origin is the allogeneic lymphocyte.

In support of the above concept, transplantation of T-cell-depleted haploidentically mismatched stem cells most frequently results in rejection, despite the use of maximally tolerated doses of chemoradiotherapy. Nevertheless, engraftment cannot be achieved unless a megadose of donor stem cells are used, despite the use of supralethal doses of chemoradiotherapy. This suggests that no acceptable dose of chemotherapy, total body irradiation, or both combined can eliminate the last lymphocytes of host origin.

Therefore, in order to improve the outcome following NST, which is clearly safer and much more attractive for future application in all patients who need bone marrow transplantation, it would be much more important to focus on important biologic issues of cell regulation rather than on less relevant issues related to the components or the dose of the cytoreductive agents. However, considering the time factor, the authors are correct in stating that more intensive tumor debulking may be clinically more meaningful in patients with rapidly developing tumor cells or when tumor cells are not exquisitely amenable to immunotherapy mediated by donor lymphocytes. In such cases, although additional cytoreduction may not be sufficient to improve the outcome per se, it may provide more time for cell-mediated immunotherapy to control tumor expansion while allogeneic- or tumor-reactive T cells multiply.

Who Should Receive NST?

In full agreement with the authors, it seems reasonable that NST would be most justified initially for treating disease categories for which tumor cells have been shown to respond to DLI. As such, chronic myelogenous leukemia (CML) stands out as the best possible disease candidate for NST. Indeed, the combination of fludarabine (Fludara), busulfan (Busulfex, Myleran), and antithymocyte globulin (Thymoglobulin) resulted in particularly encouraging results in patients with CML. The combination produced a Kaplan- Meier actuarial probability of disease- free survival of 85% at 5 years in patients in first chronic phase with no relapse (Slavin et al, submitted for publication). NST may enable bone marrow transplantation in patients with poor performance status who would normally be excluded from transplant programs-mostly elderly individuals who would normally not be considered eligible candidates due to an anticipated high rate of fatal complications. In the younger age group, NST may prevent impairment of growth and development as well as sterility, and may allow faster immunologic reconstitution following transplantation.

Future NST Protocols

Other serious problems that remain unsolved are acute and mostly chronic graft-vs-host disease (GVHD). Therefore, the most important area in which progress is urgently needed (in addition to amplification of the antitumor capacity of effector cells) remains controlling or minimizing GVHD, which is easier to accomplish in patients with minimal residual disease.[2]

An elegant future approach not discussed by the authors involves the use of hematopoietic-specific minor histocompatibility antigens, as described by Goulmy and colleagues.[9,10] These investigators used immune donor lymphocytes specifically sensitized against hematopoietic- specific minor histocompatibility antigens (eg, HA-1 or HA-2 in patients with HLA-A2 expression), thus
maximizing the elimination of normal and malignant hematopoietic cells of host origin while sparing normal host somatic cells. Alternatively, supplemental immunotherapy may be administered using other nonalloreactive effector cells, such as NK or NKT cells, which may recognize tumor cells with low expression of major histocompatibility complex proteins while ignoring normal tissues.[11] The feasibility of effective and GVHD-free immunotherapy using specifically immune donor lymphocytes was recently documented in murine B-cell leukemia and metastatic breast cancer,[12] and more recently in humans.[2] Our own patient with CML relapsing after a myeloablative bone marrow transplant protocol, who failed to respond to DLI, shows no evidence of disease (negative bcr/abl for more than 10 years) following treatment with donor lymphocytes alloactivated against parental alloantigens. As indicated by Champlin and colleagues, further progress in this area may follow when tumor-specific antigens become available for more specific targeting of donor lymphocytes.

Other Potential Approaches

An alternative solution suggested by Champlin and colleagues was to use T-cell-depleted stem cells for induction of mixed chimerism and host-vs-graft unresponsiveness followed by administration of donor lymphocytes for induction of full chimerism and more effective elimination of tumor cells. Indeed, such an approach was pioneered at Hadassah in Jerusalem for patients conditioned with a myeloablative regimen, when donor bone marrow cells were T-cell-depleted with rat anti-human monoclonal anti-CD52 (alemtuzumab, Campath) with no posttransplant immunosuppression. This was followed by preemptive administration of graded increments of donor lymphocytes for induction of controlled graft-vs-leukemia (GVL) effects with satisfactory results. Nevertheless, GVHD—occasionally severe—and relapse cannot be consistently avoided.[13] Since donor T lymphocytes facilitate engraftment, T-cell depletion also necessitates much more intensive conditioning, thus losing some of the benefits of NST. Champlin and coauthors also mention the alternative approach of using donor T lymphocytes transduced with a suicide gene, with the option of using an aggressive DLI protocol to eliminate tumor cells and then to eliminate alloreactive T cells as soon as uncontrolled GVHD represents a threat. Whereas successful use of NST for patients with hematologic malignancies is already well established, it remains to be seen whether a similar approach can also be applied successfully for patients with metastatic solid tumors. Only a small fraction of these patients seem to respond favorably, even in the best studied group of those with renal cell cancer.[14]

Conclusions

As reviewed elegantly by Champlin and colleagues, NST based on the induction of host-vs-graft transplantation tolerance and adoptive allogeneic cell-mediated immunotherapy is minimizing procedure-related toxicity and mortality and opening new horizons for treatment in more patients who need stem cell transplantation, for a growing spectrum of hematologic malignancies and possibly certain metastatic solid tumors. Newer approaches for improved antitumor efficacy, while minimizing complications related to GVHD, are likely to provide new tools for effective control in patients with otherwise incurable cancer.

Financial Disclosure: The author has no significant financial interest or other relationship with the manufacturers of any products or providers of any service mentioned in this article.

5. 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
Commentary (Slavin): Nonmyeloablative Preparative Regimens for Allogeneic Hematopoietic Transplantation
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