Allogeneic Bone Marrow Transplantation With a Fixed Low Number of T-Cells in the Marrow Graft

To the Editor:

Verdonck et al. have extended their earlier results on the above topic. Their approach is reminiscent of other experiences, in which T lymphocytes are added back to a graft in which this population has first been removed using monoclonal antibodies. The pros and cons of this manipulation have recently been commented on in some detail as a result of cumulative studies from the Campath Users' Group. Although theoretically attractive, this method undoubtedly has limitations and it therefore may be of interest that a slightly different technique, in which we expose the graft to Campath 1G in vivo, abolishes acute and chronic graft-versus-host disease (GVHD). Updated figures are given below. Thus, in 42 consecutive patients, engraftment was uniform and swift. In 30 with hematologic malignancy, rejection has not occurred and relapse rates are low. In 10 with aplasia and 2 with Fanconi's anaemia, the pattern was similar, although grafts were lost in 3 requiring retransplantation (twice in 1 individual), but all are alive and completely well. Conditioning in this protocol includes 6 Gy total nodal irradiation, aimed at increasing immunosuppression. In the case of malignant disease, this modality might add an antitumor effect that, theoretically at least, might balance any graft-versus-leukaemia (GVL) effect that could, otherwise, have arisen in association with GVHD.

Interestingly, the Dutch group encountered the latter complication in 70% of their patients, although it was only grade I or II in 49%. In contrast, our experience is that even this is often unacceptable because it generates significant morbidity and, although generally underplayed in reports, may be sufficient to substantially impair performance status. Furthermore, the chronic variant is noted to occur in nearly one-third of those at risk, an additional, and far from significant, price that these individuals have to pay. Of note is a procedure-related mortality of 11%, which seems high when considering that none of the patients, in our present series, died as a result of the conditioning or transplant itself. It is possible that, in the high-risk category, these figures may be substantially worse.

Although quality of life is reported using a Karnofsky score at 1 year, this seems to refer only to standard-risk patients; again, presumably the remainder would have fared less well. Performance status is also notoriously underreported. Thus, even using well-established criteria, little real appreciation emerges for the social embarrassment created by the widespread skin lesions and the misery experienced by patients with what is euphemistically referred to as mild or limited. These points are labored to emphasize, based on our reported data, that any degree of GVHD is necessary to achieve a GVL effect. This is certainly an area worthy of more investigation.

Thus, although the reported results are of scientific interest, we believe that the clinical experience, particularly when the substantial in-house mortality is added to the acute and chronic GVHD, needs to be seen in the light of alternatives, one of which is the much simpler procedure that we have used in Cape Town that seems able to circumvent complex immunologic manipulations of the graft and, especially if the results can be confirmed, would offer a much more practical approach to allogeneic bone marrow transplantation.

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REFERENCES


RESPONSE

The goals of our approach of partial T-cell depletion of the marrow graft (through a T-cell addback to the maximal T-cell-depleted graft, performed with a physical technique) were of two kinds: (1) To prevent severe acute graft-versus-host disease (a-GVHD) but certainly not to abolish a-GVHD completely, rather to induce a mild a-GVHD and by that the graft-versus-leukemia (GVL) effect, and (2) to prevent the high incidence of graft failure occurring after maximal T-cell-depleted marrow grafting.1 Graft failure and loss of the GVL effect are the major drawbacks of maximal T-cell-depleted marrow grafting, occurring more often after T-cell depletion by monoclonal antibodies than by physical techniques.2 In our opinion, the high relapse rate occurring after maximal T-cell-depleted marrow grafting justifies the inconvenience to the patient of a mild GVHD, hopefully with maintenance of GVL. Indeed, our approach seems to have a relapse rate that is not different from that of non-T-cell-depleted marrow grafting, whereas severe GVHD has never been observed.

We do agree that the occurrence of grades I and II a-GVHD (only of the skin) in 70% of the cases and of chronic GVHD in 30% of the cases observed with our approach generates morbidity. However, the GVHD is always very responsive to corticosteroid therapy (if treatment is indicated), which is in contrast to the data of non-T-
cell-depleted marrow grafting, and all patients become free of GVHD and immunosuppressive therapy during follow-up.

The treatment-related mortality of 11% (which includes the occurrence of secondary malignancies; otherwise, it is 7%) observed in patients with standard-risk diseases is low and compares favorably to that observed in the summing-up of the Campath-1 users.

Furthermore, graft failure, which is encountered in 5% to 24% of the patients receiving transplants with maximal T-cell-depleted marrow grafts, has been observed in only 1 of 131 BMTs (including grafts from HLA-nonidentical sibs) performed to date with our approach.

Finally, the results of different techniques of T-cell depletion for BMT, in regard to the raised issues, are determined also by the intensity of the conditioning regimen used and comparisons can only be made by prospective randomized trials.

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REFERENCES


Allogeneic bone marrow transplantation with a fixed low number of T-cells in the marrow graft [letter; comment]

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