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T Cell Depletion of Donor Marrow for Prevention of Acute Graft-Versus-Host Disease*

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Allogeneic bone marrow transplantation can provide curative therapy for patients with acute leukemia or aplastic anemia. However, acute graft-versus-host disease (GVHD) occurs in a high proportion of patients, even when the donor is an HLA genotypically identical sibling. Observations that GVHD can be prevented in rodent models by removing mature T cells from the donor marrow have prompted similar investigations in human bone marrow transplantation. These investigations have been facilitated recently by the availability of monoclonal antibodies that recognize surface molecules expressed by T lymphocytes and not by hematopoietic precursors. In Seattle, 20 patients 31–50 years of age with hematologic malignancies received HLA identical allogeneic bone marrow grafts depleted of T lymphocytes with the use of monoclonal antibodies and rabbit serum complement. The patients were prepared for transplantation with cyclophosphamide (60 mg/kg, two doses) and fractionated total body irradiation. Cyclosporine was administered after transplantation for prophylaxis of GVHD.

Treatment of marrow resulted in 2–3 log depletion of T cells. Engraftment of granulocytes to > 1000/mm^3 was achieved at a median of 21 days, a time period comparable to that required for engraftment in historical controls who received unmodified marrow. Engraftment of lymphocytes, however, was delayed 3–4 days compared with historical controls. None of the patients who received T-depleted bone marrow developed grade III or IV acute GVHD and only three patients had grade II disease. These results represented a statistically significant decrease in acute GVHD compared with results in similar historical control patients who received unmodified donor marrow.

Despite the decreased incidence of GVHD, survival was not improved in our patients because of an increased incidence of graft failure which to date has been fatal in three patients. Graft failure represents a highly unusual outcome after HLA identical marrow transplantation in patients with hematologic malignancies. Also, the reduced incidence of GVHD in our study was not associated with a decrease in the mortality from CMV interstitial pneumonia. In previous studies, acute GVHD has been identified as a prognostic factor predictive of death from CMV interstitial pneumonia [1].

In the current study, five of the patients have had graft failure which was transient in one patient, but apparently irreversible in the others. It was noteworthy that all 5 patients who had difficulty with engraftment were in a group of 11 patients who were conditioned for transplantation with 12.0 Gy fractionated total body irradiation. In contrast, none of the nine patients who were conditioned with 15.75 Gy fractionated total body irradiation had difficulty with engraftment. The increased

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radiation administered to these patients may have been sufficient to overcome graft resistance caused either by disparity in minor histocompatibility antigens of the donor and recipient or by allosensitization associated with previous transfusions.

Our data suggest that lymphocytes may play a role in facilitating sustained engraftment after marrow transplantation. In recipients of conventional unmodified marrow, a graft-versus-host reaction may suppress or eliminate residual host hematopoietic and lymphoid cells, thereby preventing host cell-mediated effects such as graft rejection from occurring. In favor of this hypothesis are observations by Deeg et al. that thoracic duct lymphocytes can facilitate engraftment in dogs given marrow grafts from unrelated DLA nonidentical donors [2] and that cyclosporine can abrogate the graft enhancing effects of buffy coat cells in dogs given marrow grafts from unrelated DLA nonidentical donors [3]. It remains to be determined whether changes in the pre- or posttransplant regimens can decrease the graft failure associated with T cell depletion of donor marrow. Alternatively, it may be possible to distinguish between T cells that cause GVHD and those required to facilitate sustained engraftment.

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