LETTER TO THE EDITOR

Re: High Rate of Graft Failure in 25 Patients with Chronic Myelogenous Leukemia Conditioned with a Reduced-Intensity Regimen of 550 cGy Total Body Irradiation and Cyclophosphamide for Unrelated Donor Transplantation

Historically, myeloablative conditioning regimens for patients with chronic myelogenous leukemia (CML) undergoing unrelated donor (URD) hematopoietic stem cell transplantation (HSCT) have incorporated high-dose (>1000 cGy) total body irradiation (TBI) and chemotherapy [1,2]. These regimens are associated with a high risk of transplant-related mortality (TRM). Recent clinical trials have explored reduced-intensity conditioning (RIC) regimens in an effort to reduce TRM.

Previously, we investigated an RIC regimen consisting of single-exposure, low-dose (550 cGy), high-dose-rate (30 cGy/min) TBI and cyclophosphamide for HLA-matched sibling peripheral blood stem cell (PBSC) transplantation as therapy for patients with CML in chronic phase (CP) [3]. Graft-versus-host disease prophylaxis consisted of cyclosporine alone. We observed no graft failure and relatively low rates of relapse (10%) and TRM (17%). At day +30, 93% of patients had 100% donor chimerism in unsorted marrow cells. The overall survival at 2 years was 83%. On the basis of these results, we hypothesized that this regimen would be effective for patients with CML undergoing URD HSCT. Between 1997 and 2003, 25 consecutive patients with CML undergoing URD HSCT were conditioned with this regimen. Disease status at transplantation was CP, accelerated phase, and blast phase in 10, 6, and 9 patients, respectively. Sources of stem cells included non–T cell–depleted bone marrow (n = 23) and PBSC (n = 2). Graft-versus-host disease prophylaxis consisted of cyclosporine, methotrexate, and corticosteroids. The median patient age was 39 years (range, 21-55 years). Time from diagnosis to transplantation was 24 months (range, 6-113 months). Donor/recipient pairs were HLA-A, -B, and -DRB1 matched in 22 and single-antigen mismatched in 3. Donor/recipient pairs were HLA-A, -B, -C, -DRB1, and -DQB1 matched in 17 (68%). The median administered cell numbers were 2.78 (range, 0.24-15.6) \times 10^8 \text{ total nucleated cells per kilogram} and 3.22 (range, 1.08-15.9) \times 10^6 \text{ CD34^+ cells per kilogram. Eighteen patients received \alpha-interferon before HSCT; this was discontinued 3 or more months before transplantation in 14. The median follow-up of the 4 surviving patients was 925 days (range, 366-1703 days).}

Graft failure, as previously defined [3], occurred in 5 (3 primary and 2 secondary) of 22 evaluable patients (23%). Graft failure occurred in 4 patients in CP and 1 in accelerated phase. Three patients were not evaluable for engraftment because of early TRM (n = 1) and persistent cytogenetic disease (n = 2). At day +30, the number of patients with 100%, 50% to 99%, and 0% to 49% donor chimerism in unseparated marrow nucleated cells by variable numbers of tandem repeat (VNTR) was 15 (68%), 4 (18%), and 3 (14%), respectively. The rate of graft failure in patients with CML (23%) was higher than the rate (3%) that we observed in patients with other diagnoses undergoing URD HSCT with the same RIC regimen (P = .004) [4]. Additionally, the incidence of 100% donor chimerism in unseparated marrow cells at day +30 for patients with CML was lower than that observed for patients with acute leukemia in remission (68% versus 96%, respectively; P = .015) [5].

After graft failure, therapy included withdrawal of immunosuppression (n = 5), institution of imatinib mesylate with or without additional chemotherapeutic agents (n = 4), or a second URD HSCT (n = 3). After therapy, 4 patients achieved a partial or complete hematologic response, and 1 patient also achieved a complete cytogenetic response. However, no patient demonstrated evidence of donor cell recovery (>1% donor cells by VNTR) at any subsequent follow-up.

High rates of graft failure have been reported for patients with CML undergoing URD HSCT after conditioning with other regimens. In 1423 patients with CML undergoing URD HSCT after conven-
tional TBI-based regimens, the graft failure rate was 15.5% [1]. With refinements in HLA typing methodology, the rate of graft failure has been lower in more recent reports [2]. The risk of graft failure in patients with CML has also been high after nonmyeloablative regimens for URD HSCT. A RIC regimen of 200 cGy of TBI and fludarabine was associated with a graft failure rate of 29% (4 of 14 patients) [6]. A non–TBI-based RIC regimen of fludarabine, busulfan, and antithymocyte globulin was associated with a graft failure rate of 44% (3 of 8 patients) [7]. Thus, the rate of graft failure in patients with CML undergoing URD HSCT remains disturbingly high, especially with current RIC regimens.

In patients with CML undergoing URD HSCT with RIC regimens, assessment of graft failure must be made cautiously, because early donor cell chimerism may be present but at undetectable levels with standard VNTR techniques. Subsequently, the percentage of donor cells may increase either spontaneously or in response to the addition of other therapies (imatinib mesylate, discontinuation of immunosuppression, and so on) [8]. However, we did not observe this phenomenon in the 5 patients in this study who experienced graft failure.

In an effort to reduce the risk of graft failure in patients with CML undergoing URD HSCT, we are examining 2 modifications to this single-exposure, low-dose (550 cGy) TBI-based regimen. Alemtuzumab has been added to further immunosuppress the recipient. Alemtuzumab is administered 3 weeks before transplantation such that the serum antibody concentration at the time of stem cell infusion is relatively low, thus minimizing posttransplantation drug interactions with donor T cells mediating graft-versus-leukemia effects [9]. Additionally, PBSCs are being used (instead of bone marrow) on the basis of observations from Maris et al. [6] that the use of PBSCs (versus bone marrow) was associated with a significantly lower risk for graft failure in patients conditioned with 200 cGy of TBI and fludarabine. Alternative means of recipient immunosuppression or donor leukocyte infusions could be used to reduce the risks of graft failure and mixed chimerism in these patients.

REFERENCES


C. Hallemeyer, MD
Bone Marrow Transplantation & Leukemia
Washington University School of Medicine
St. Louis, Missouri