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Chronic GVHD and Pretransplantation Abnormalities in Pulmonary Function Are the Main Determinants Predicting Worsening Pulmonary Function in Long-term Survivors after Stem Cell Transplantation

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ABSTRACT

Pulmonary function (PF) was studied in 69 consecutive patients with hematologic diseases, with a minimum 5-year (range, 5-13 years) follow-up after allogeneic stem cell transplantation from an HLA-matched sibling. Fifty-six patients (81%) received total body irradiation based myeloablative stem cell transplantation (MT) and 13 (19%) underwent nonmyeloablative stem cell transplantation (NST). Thirty-one patients (45%) developed a late decrease in PF from baseline, 25 with a restrictive and 6 with an obstructive pattern PF abnormality. Twelve patients (17%) were symptomatic, 8 with a severe restrictive PF defect, but none required supplemental oxygen. The incidence of developing a late PF abnormality was comparable in MT (24 of 56) and NST (5 of 13; $P = .51$). In multivariate analysis, chronic graft-versus-host disease (relative risk, 16) and pretransplantation diffusion capacity for carbon monoxide or forced expiratory volume in the first second <80% predicted were independently associated with a late decrease in PF from baseline (relative risk, 7). Our results indicate that late PF abnormality is common after MT and NST. Patients with a low pretransplantation diffusion capacity for carbon monoxide of or forced expiratory volume in the first second who developed chronic graft-versus-host disease were most severely affected. Longer follow-up is needed to determine whether PF will continue to decrease or reach a plateau and whether more patients with PF abnormality will eventually become symptomatic.
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KEY WORDS

Pulmonary complications • Myeloablative • Nonmyeloablative • Stem cell transplantation

INTRODUCTION

Despite the success in treating otherwise fatal disease, allogeneic stem cell transplantation (SCT) is associated with multiple and life-threatening complications from organ damage. Lung injury is a frequent complication after allogeneic SCT [1-7]. In our experience in adults with hematologic malignancies receiving SC transplants from HLA-identical siblings, noninfectious pulmonary deaths accounted for 66% of transplant-related mortality occurring mainly in the first 6 months after SCT [8]. Delayed pulmonary injury can also occur: the lifetime risk of chronic pulmonary dysfunction in long-term SCT survivors ranges from 30% to 60% [1,9-11], depending on donor source and elapsed time from SCT. Chronic pulmonary dysfunction in long-term SCT survivors can be of an obstructive or restrictive pattern [1,7,9,12-14]. In addition, an association of defective pretransplantation pulmonary function (PF) and the development of obstructive PF abnormality after transplantation have been recently reported [15]. Pulmonary dysfunction has been linked to chronic graft-versus-host disease (cGVHD) in children undergoing SCT [7] and in adults with unrelated SC transplants [16]. Reduced

intensity SCT has become increasingly popular based on the assumption that lower intensity conditioning regimens will cause less direct organ damage, resulting in an improvement in long-term outcomes. Better identification of pretransplantation factors associated with worsening PF are needed to define patients at greatest risk who might benefit from preventive strategies. We describe PF abnormalities in a cohort of patients surviving ≥5 years after myeloablative SCT (MT) and nonmyeloablative SCT (NST) and identify pre- and post-transplantation risk factors.

METHODS

Study Group

Sixty-nine consecutive patients who underwent transplantation between September 1993 and March 2001 (minimum 5-year follow-up after SCT) were included in this analysis. All received SCT from an HLA-identical sibling in 5 successive National, Heart, Lung and Blood Institute (NHLBI) institutional review board-approved protocols (93-H-0212, 97-H-0099, 97-H-0202, 99-H-0046, and 99-H-0050). All patients and donors gave written informed consent according to principles outlined in the Declaration of Helsinki.

Transplantation Regimens

Conditioning regimens. Two approaches were evaluated. For MT (n = 56), total body irradiation (TBI) at 1360 rad in 8 fractions in 4 days was followed by cyclophosphamide 60 mg/kg × 2 days and bone marrow transplantation (n = 18) or granulocyte colony-stimulating factor (G-CSF)-mobilized peripheral blood stem cell transplantation (PBSCT; n = 38). In debilitated or older patients, NST (n = 13) consisted of cyclophosphamide 120 mg/kg plus fludarabine 125 mg/m^2 and G-CSF-mobilized PBSCT (patients with aplastic anemia or at increased risk for graft rejection, ie, those with heavy transfusion burden or evidence of alloimmunization, also received antithymocyte globulin 40 mg/kg intravenously on days −5, −4, −3, and −2).

GVHD prophylaxis. Patients undergoing MT received cyclosporine alone days −4 to +120-180. All patients undergoing NST received cyclosporine with methotrexate 5 mg/m^2 on days +1, +3, and +6 or mycophenolate mofetil 1 g orally 2 times daily.

Transplantation. Patients undergoing NST received an unmanipulated T cell-replete PBSCT. T cell depletion was performed in all MTs. In the first protocol (93-H-0212), stem cells were collected after bone marrow harvesting and were depleted of T cells by elutriation [17]. In all subsequent protocols, the donor underwent G-CSF-mobilized peripheral blood apheresis followed by stem cell selection. In protocol 97-H-0099, T cells were depleted by CD34$^+$ selection on the "Ceprate SC" immunoabsorption column, followed by negative selection of T cells using anti-CD2 (CellPro, Bothell, Wash). More recent protocols used the Isolex 300i immunomagnetic cell separation system (version 2.5, Nexell Therapeutics, Irvine, Calif) for positive selection of CD34$^+$ cells, followed by negative selection of T cells using an antibody cocktail of anti-CD2, anti-CD6, and anti-CD7, as previously described [18].

Donor lymphocyte infusion. In MT in the absence of GVHD or complete molecular remission of chronic myeloid leukemia (CML), T cells were added back between days 30 and 100. Patients undergoing NST received donor lymphocyte infusion for disease progression or for persistent mixed T cell chimerism after cyclosporine tapering.

Supportive care. Standard prophylaxis against infection included fluconazole to day 100, Bactrim for 6 months after transplantation, and weekly surveillance for cytomegalovirus antigenemia, as described previously [18,19]. Acute GVHD (aGVHD) was managed with high-dose steroids. Steroid-refractory patients received treatment with daclizumab (anti-CD25 monoclonal antibody) alone or in combination with infliximab (anti-tumor necrosis factor), as described previously [20].

Pulmonary Function Tests

Baseline PF was obtained in all patients 5 to 21 days before SCT, after SCT at 3 months, 6 months, and 1 year, and thereafter annually when possible. In patients with a concurrent acute respiratory illness, PF tests were deferred until recovery from illness or return to baseline status. Ventilatory capacity was measured by forced vital capacity, forced expiratory volume in the first second (FEV_1), ratio of FEV_1 to forced vital capacity, and peak expiratory flow. Lung volume measurements included vital capacity, total lung capacity (TLC), residual volume, and ratio of residual volume to TLC. Diffusion capacity for carbon monoxide (DLCO) was determined by using a carbon monoxide single-breath technique with correction for hemoglobin concentration. PF was expressed as a percentage of the predicted value in healthy controls with corresponding age, sex, and smoking habits. Eligibility criteria for enrollment into protocols included a DLCO ≥60% of predicted.

Definitions

Stringent criteria for the definition of abnormal PF results were chosen because of inherent variability in the tests employed. Abnormal PF before transplantation was defined as DLCO and/or FEV_1 ≤80% predicted. PF abnormality after transplantation was defined as restrictive when there was significant de-

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