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SEVERE PULMONARY TOXICITY AFTER MYELOABLATIVE CONDITIONING USING TOTAL BODY IRRADIATION: AN ASSESSMENT OF RISK FACTORS

Chris R. Kelsey, M.D.,* Mitchell E. Horwitz, M.D.,† Junzo P. Chino, M.D.,* Oana Craciunescu, Ph.D.,* Beverly Steffey, M.S.,* Rodney J. Folz, M.D. Ph.D.,‡ Nelson J. Chao, M.D.,† David A. Rizzieri, M.D.,† and Lawrence B. Marks, M.D.§

*Department of Radiation Oncology, Duke University Medical Center, Durham, NC; †Department of Medicine, Division of Cellular Therapy, Duke University Medical Center, Durham, NC; ‡Department of Medicine, Division of Pulmonary, Critical Care, and Sleep Disorders Medicine, University of Louisville Health Sciences Center, Louisville, KY; and §Department of Radiation Oncology, University of North Carolina, Chapel Hill, NC

Purpose: To assess factors associated with severe pulmonary toxicity after myeloablative conditioning using total body irradiation (TBI) followed by allogeneic stem cell transplantation.
Methods and Materials: A total of 101 adult patients who underwent TBI-based myeloablative conditioning for hematologic malignancies at Duke University between 1998 and 2008 were reviewed. TBI was combined with high-dose cyclophosphamide, melphalan, fludarabine, or etoposide, depending on the underlying disease. Acute pulmonary toxicity, occurring within 90 days of transplantation, was scored using Common Terminology Criteria for Adverse Events version 3.0. Actuarial overall survival and the cumulative incidence of acute pulmonary toxicity were calculated via the Kaplan–Meier method and compared using a log-rank test. A binary logistic regression analysis was performed to assess factors independently associated with acute severe pulmonary toxicity.
Results: The 90-day actuarial risk of developing severe (Grade 3–5) pulmonary toxicity was 33%. Actuarial survival at 90 days was 49% in patients with severe pulmonary toxicity vs. 94% in patients without ($p < 0.001$). On multivariate analysis, the number of prior chemotherapy regimens was the only factor independently associated with development of severe pulmonary toxicity (odds ratio, 2.7 per regimen).
Conclusions: Severe acute pulmonary toxicity is prevalent after TBI-based myeloablative conditioning regimens, occurring in approximately 33% of patients. The number of prior chemotherapy regimens appears to be an important risk factor.

Pulmonary toxicity, Pneumonitis, Stem cell transplant, Allogeneic, Total body irradiation.

INTRODUCTION

Myeloablative conditioning followed by allogeneic stem cell transplantation is often performed for high-risk or relapsed hematologic malignancies. This procedure is associated with significant morbidity and a 25% to 50% risk of nonrelapse mortality (1–4). In particular, the risk of severe pulmonary toxicity is high, including interstitial pneumonitis, infectious pneumonia, diffuse alveolar hemorrhage, and respiratory failure requiring ventilatory support. Pulmonary toxicity is prevalent with preparative regimens using only chemotherapy as well as regimens that include total body irradiation (TBI) (5–8).

Numerous factors have been associated with the development of pulmonary toxicity after allogeneic stem cell transplantation, including patient-specific factors (age, performance status, interval between diagnosis and transplant, pretransplantation pulmonary function), total body irradiation technique (total dose, fractionation, dose-rate), and posttransplantation events (graft-versus-host disease, cytomegalovirus reactivation). However, findings among studies have been conflicting, which is not surprising, given the multifactorial nature of pulmonary toxicity and differences in transplant techniques between and within institutions. This is particularly an issue in studies that use TBI as part of the preparative regiment since subtle changes in TBI technique may influence the risk.

Here we assess the impact of various clinical factors on the incidence of severe pulmonary toxicity in a series of adult patients treated with a relatively uniform TBI-based myeloablative regimen before allogeneic stem cell transplantation.

Reprint requests to: Chris R. Kelsey, M.D., Department of Radiation Oncology, DUMC 3085, Durham, NC 27710. Tel: (919) 668-5213; Fax: (919) 668-7345; E-mail: kelse003@mc.duke.edu

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METHODS AND MATERIALS

This Institutional Review Board-approved retrospective analysis identified 139 adult patients (≥18 years old) with hematologic malignancies who received TBI as part of the conditioning regimen before allogeneic stem cell transplantation between 1998 and 2008 at Duke University Medical Center. Patients who underwent a nonmyeloablative conditioning regimen (n = 38) were excluded, leaving 101 patients eligible for this analysis. Patients who underwent stem cell transplantation without TBI were not analyzed. The choice of conditioning regimen was made at the discretion of the treating physicians.

All patients were treated with a uniform TBI technique. Patients were treated supine with lateral fields using 4- to 6-MV photon energies. The total dose was 13.5 Gy in 1.5-Gy b.i.d. fractions delivered using a dose-rate of 15 to 20 cGy/minute. The dose to the lungs were attenuated in all patients using the arms and was supplemented with brass compensators. The lungs were attenuated to a median dose of 10 Gy (range, 7–10 Gy). The degree of lung attenuation was determined individually for each patient by that patient's treating physician, based on clinical factors such as baseline pulmonary function and the presence or absence of previous mediastinal irradiation.

Lung heterogeneity corrections were not performed during the early years of the study period but have since become standard at our institution and were performed on the last 40 patients. Among these, 29 patients had lung dose measurements using OneDose (Sicel Technologies, Morrisville, NC) during their first fraction. The median percentage increase in lung dose compared with the prescribed dose was 21% (range, 6–43%). Additional attenuation was necessary in 24 of 29 patients during their last eight fractions. The remaining 11 patients were corrected *a priori* using film measurements from a posterior–anterior chest x-ray and confirmed using OneDose during their first fraction.

After completing TBI, patients received high-dose cyclophosphamide (60 mg/kg × 2 doses on days −3 and −2), fludarabine (40 mg/m^2 × 4 on Days −5 to −2), etoposide (60 mg/kg on Day −3), or melphalan (45 mg/m^2 × 3 days). Patients received antithymocyte globulin with melphalan conditioning. Stem cells were derived from peripheral blood, bone marrow, or cord blood. Posttransplantation graft-versus-host disease prophylaxis was administered to all patients except 1 patient receiving a syngeneic transplant. This consisted of various combinations of methotrexate, cyclosporine, tacrolimus (FK506), mycophenolate mofetil, and sirolimus, depending on the underlying disease or treatment protocol. Low-dose heparin (100 units/kg per day) was administered as veno-occlusive disease prophylaxis beginning on Day −8 of the transplantation and continued until hematopoietic recovery.

Patients remained in the inpatient Bone Marrow Transplant Unit until absolute neutrophil count reached 500/μl. After discharge from the inpatient facility, patients were monitored closely in the outpatient Bone Marrow Transplant center until approximately 90 days after transplantation.

Acute graft-versus-host disease was recorded prospectively and graded using the Glucksberg grading system (9, 10). Acute pulmonary toxicity, occurring within 90 days of transplantation, was scored retrospectively using the Common Terminology Criteria for Adverse Events version 3.0.

Statistical analyses

Actuarial overall survival and the cumulative incidence of severe pulmonary toxicity was calculated using the Kaplan–Meier method (11) and compared using a log-rank test. A univariate and multivariate analysis was performed to assess risk factors for acute severe pulmonary toxicity. For these analyses, patients with severe pulmonary toxicity secondary to anaphylactic reactions (n = 4) were excluded, as all patients completely recovered within a few hours and the conditioning regimen was not believed to contribute to these events. The multivariate model was constructed via binary logistic regression. Therefore, patients who died before Day 90 without developing pulmonary toxicity were excluded (n = 5). Identical results were obtained when a Cox regression analysis was performed with the endpoint of interest "time to development of acute pulmonary toxicity" without these 5 patients excluded.

Rates of severe pulmonary toxicity were calculated in patient subgroups defined by clinical variables such as age, comorbidities, TBI dose, and number of chemotherapy regimens. A chemotherapy regimen was defined as an entire treatment course (*e.g.,* induction and consolidation chemotherapy for acute myelogenous leukemia would be considered one chemotherapy regimen). Fisher's exact test was used to test for significant associations between categorical patient variables and severe (Grade 3–5) pulmonary toxicity. Univariate logistic regression was used to test continuous variables. Factors with a value of $p < 0.10$ on univariate analysis were included in the multivariate model. All p values were calculated for two-tailed tests.

RESULTS

A total of 101 patients were identified. Median patient age was 38 years (range, 18–63 years). Patient characteristics and treatment details are listed in Table 1. Most patients were treated for either acute myelogeneous or acute lymphocytic leukemia (79%). Complete remission at the time of transplantation (without histologic, cytogenetic, molecular, or radiographic evidence of disease) was achieved in 58% of patients.

Pretransplantation pulmonary comorbidities were present in 10 patients before initiation of the preparative regimen. This included asthma requiring medication (n = 3), chronic, grade 3 cough (n = 1), recent bacterial pneumonia during previous chemotherapy regimens (n = 4), and previous intubation secondary to acute respiratory distress syndrome (n = 2).

All patients completed the conditioning regimen as planned. Stem cells were derived from a related (42%, including one syngeneic transplant) or unrelated (58%) donor. This included mobilized peripheral blood stem cells in 58%, stem cells derived from bone marrow in 6%, and cord blood in 37%. Post-transplant graft-versus-host prophylaxis included the use of methotrexate in 58% of patients. CMV reactivation occurred in 49%.

The 90-day actuarial risk of developing severe (Grade 3–5) pulmonary toxicity was 33% (Fig. 1). Among all 101 patients, intubation was necessary in 26%, and death from pulmonary toxicity occurred in 16% (Table 2). Actuarial overall survival at 90 days was 49% in patients with severe pulmonary toxicity vs. 94% without ($p < 0.001$) (Fig. 2). Survival at 1 year was 28% in patients who developed severe pulmonary toxicity compared with 81% in patients who did not develop severe pulmonary toxicity.

Factors associated with pulmonary toxicity on univariate analysis are listed in Table 3. On multivariate analysis, the