Abnormalities of Pulmonary Function Tests After Marrow Transplantation Predict Nonrelapse Mortality

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To determine whether pulmonary function test (PFT) results after marrow transplantation were predictive of nonrelapse mortality, a review was made of prospective, nonrandomized PFT results for association with nonrelapse mortality by log-rank test and Cox proportional hazards modeling. The setting was a tertiary referral center. The patients were all marrow recipients who performed PFT between Days 60 and 120 after marrow transplantation between July 1, 1983 and December 31, 1990 (n = 906). At 3 mo after transplantation, the mean values for total lung capacity (TLC) and diffusing capacity decreased, and restrictive ventilatory defects (TLC < 80% of predicted) were noted in 34% of the cohort. Airflow rates (FEV_1/FVC) were unchanged. A restrictive lung defect at 3 mo after transplant or a significant decline (≥ 15%) in TLC from baseline despite remaining within the normal range was associated with a twofold increased risk of nonrelapse mortality. Neither airflow obstruction nor impairment in diffusing capacity was associated with an increased risk. Abnormalities of the TLC at 3 mo after transplant were associated with death with respiratory failure, but not with an increased risk of chronic graft-versus-host disease (GVHD). There is an increase in the nonrelapse mortality rate associated with either the presence of a restrictive defect 3 mo after marrow transplantation or a significant decline in lung volume compared with baseline. This effect is most pronounced more than 1 yr after marrow transplant and appears to be a result of an increase in the rate of death with respiratory failure, not chronic GVHD. These results suggest that routine evaluation of lung function after marrow transplantation is warranted. **Crawford SW, Pepe M, Lin D, Benedetti F, Deeg HJ. Abnormalities of pulmonary function tests after marrow transplantation predict nonrelapse mortality.**

AM J RESPIR CRIT CARE MED 1995;152:690–5.

Numerous studies have shown both acute and long-term decrements in pulmonary function after intensive chemotherapy and irradiation as utilized in marrow transplantation (1–10). Pulmonary function test (PFT) abnormalities have been reported to include declines in lung volumes, gas diffusion, and airflow. Reductions in lung volumes and diffusing capacity are common "early" (that is, within months) after marrow transplant. The declines in lung volumes may be at least partially reversible within 2 yr after transplantation (3, 4), but the low diffusing capacity reportedly persists for several years. Development of airflow obstruction has been seen in approximately 10% of allogeneic marrow recipients in the presence of chronic graft-versus-host disease (GVHD) and most often is related to obliterative bronchiolitis (11–13).

(Received in original form September 5, 1994 and in revised form February 13, 1995)

Supported by Grant Nos. CA-18029, CA-18221, and CA-15704 from the National Cancer Institute and by Grant No. HL-36444 from the National Heart, Lung, and Blood Institute.

Dr. Benedetti was supported by a grant from the University of Verona, Italy. Dr. Deeg is supported by a grant from the National Marrow Donor Program/Baxter Health Care Division.

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There are several risk factors for the impairment of lung function after marrow transplant. These include chemoradiation damage, infection, cytokine effects, and cell-mediated immune reactions. The impact of a decline in pulmonary function on the lives of marrow transplant recipients is unclear. The onset of airflow obstruction after allogeneic marrow transplant has been associated with an increased risk of mortality (13). However, few reports have examined abnormalities in other lung functions for association with increased mortality. Badier and coworkers noted that both relapse of malignancy and overall mortality correlated with falls in lung volumes and diffusion 1 yr after marrow transplantation (10).

The purpose of this study was to investigate the clinical significance of declines in pulmonary function early after marrow transplantation. We sought to determine whether pulmonary function test results 3 mo after marrow transplantation were predictive of nonrelapse mortality. Because the initial analyses suggested that restrictive ventilatory defects were associated with an increased risk of nonrelapse mortality, we investigated further whether this effect was mediated by other recognized risk factors for nonrelapse mortality, specifically chronic GVHD.

Methods

Subjects and PFT Methods

All surviving marrow recipients who were capable performed PFT between Days 60 and 120 after marrow transplantation at the Fred Hutch-

inson Cancer Research Center between July 1, 1983 and December 31, 1990. Included in this study were all patients tested who had engrafted and were discharged from Seattle without relapse of disease (n = 906). Testing was done according to American Thoracic Society guidelines (14). A Gould 1000 IV pulmonary function analyzer (Gould, Inc., Dayton, OH) with nitrogen washout was used to determine lung volumes. The diffusing capacity for carbon monoxide (D_{LCO}) was measured by the single-breath technique and corrected for hemoglobin content (D_{LCO}sb). The total lung capacity and diffusion capacity results were compared with published normal values (15–17). Specifically, for each individual, we calculated the ratio of the observed value to that predicted on the basis of age, gender, and height. For airflow, the actual FEV_1/FVC ratio (not the percentage of predicted) was used as a measure because this value has been shown to be a sensitive and specific indication of airways obstruction (18). Arterial blood gases were not routinely obtained after marrow transplantation.

The PFT results were categorized as normal, mild impairment, and moderate to severe impairment as follows (19): FEV_1/FVC, normal ≥ 80%, mild obstruction < 80% and < 60%, and moderate/severe obstruction < 60%; total lung capacity (TLC), normal ≥ 80% of predicted, mild restriction < 80% and ≥ 60% of predicted, and moderate/severe restriction < 60% of predicted, and (D_{LCO}sb); normal ≥ 80% of predicted, mild deficit < 80% and ≥ 60% of predicted, and moderate/severe deficit < 60% of predicted.

PFT were routinely performed before marrow transplantation and repeated 80 to 100 d after transplant. These PFT results are referred to as "3 mo" studies in this report.

Marrow Transplantation

Marrow transplantation was performed according to published techniques. Patients received autologous, syngeneic or HLA-identical or HLA-nonidentical allogeneic marrow. Patients receiving HLA-nonidentical marrow shared one haplotype and differed from one to three antigens at HLA-*A*, B, or D loci on the nonshared haplotype (20–22). Conditioning regimens for transplantation have been described in detail (22–24). Most patients received a combination of radiation therapy and chemotherapy. Total-body irradiation (TBI) was usually delivered as 1,200–1,575 cGy midline dose from opposing cobalt 60 sources given at an exposure rate of 6 to 7 cGy/min in 6 to 12 fractions without lung shielding. A group of 16 marrow recipients were conditioned with a single fraction of 1,000 cGy. Methotrexate, cyclosporine, or a combination of both with or without the addition of methylprednisolone were given as graft-versus-host disease prophylaxis to allogeneic marrow recipients (25–27). The grading of acute GVHD and the details of supportive care are described elsewhere (22–24).

Patients were treated either in a conventional hospital room or in a laminar airflow isolation room (28). Patients not allergic to sulfamethoxazole and trimethoprim received these drugs prophylactically for 2 wk before transplant and from the time of primary discharge after transplant until normalization of peripheral white blood cell counts or for at least 6 mo (29). Since 1987, patients seronegative for cytomegalovirus (CMV) have received screened, seronegative blood products after transplant (30). Since 1985, acyclovir has been administered to herpes simplex virus seropositive recipients in doses of 250 mg/m² ever 12 h intravenously until 30 d after transplant, and, since 1988, to CMV-seropositive marrow recipients in doses of 500 mg/m² every 8 h (31).

Statistics

All data were retrieved at least 1 yr after transplant from clinical information prospectively collected at the time of transplantation and reviewed for the purposes of this study. Statistical analyses were performed to study the associations between death as a result of nonrelapse causes and the PFT measurements obtained 3 mo after marrow transplantation: (*1*) FEV_1/FVC (%), (*2*) TLC (as a percentage of predicted), and (*3*) D_{LCO}sb (as a percentage of predicted).

The probability of nonrelapse death was estimated by the cumulative incidence curve (32). The difference in the risk of nonrelapse mortality between different levels of a given PFT variable was determined by the log-rank test. The Cox proportional hazards model was used to adjust for other PFT variables, as well as non-PFT variables suspected to be predictive of nonrelapse mortality.

Identification of the risk factors for the development of PFT abnormalities was not the focus of this study. Therefore, indicator variables for potential risk factors, such as smoking history, CMV serology, and history of pneumonia, were not included in the analyses.

RESULTS

Patient Characteristics

A total of 906 marrow recipients underwent PFT 3 mo after transplantation. The characteristics of the patients included in the study are presented in Table 1. Of the cohort, 90% were transplanted as treatment for malignancy. Acute leukemia accounted for the largest proportion of diagnoses (43%). Patient ages ranged from 5.5 to 62.5 yr. The number of patients studied each year increased over the time of the study. The majority of marrows transplanted were allogeneic (86%), 9% being from unrelated donors and 13% from HLA-disparate family members. Most marrow recipients (82%) were conditioned for transplant with TBI, usually (80%) for a total dose of 1,200 cGy or more. Of the allogeneic marrow recipients, 46% developed acute GVHD of Grade II or higher.

Minimum follow-up period was 1 yr; 291 patients died during the study. The follow-up period for the survivors ranged from 349 to 3,220 d, with a median of 1,286 d. Supplemental oxygen was required by 22%, and respiratory failure requiring assisted mechanical ventilation occurred in 2% of the 906 patients be-

TABLE 1

PATIENT CHARACTERISTICS (*n = 906*)

Characteristic	Number	% Total
Disease status		
Chronic myelogenous leukemia, chronic phase	221	24
Chronic myelogenous leukemia, other	79	9
Acute leukemia, remission	223	25
Acute leukemia, relapse	162	18
Myelodysplastic syndrome	29	3
Solid tumor	20	2
Lymphoma, remission	48	5
Lymphoma, relapse	60	7
Aplastic anemia	64	7
Age, yr		
Mean ± SD	28.7 ± 12.6	
Range	5.5–62.5	
Sex		
Male	499	55
Female	407	45
Transplant year		
1983–1985	194	21
1986–1988	346	38
1989–1990	366	40
Transplant type		
Autologous/syngeneic	124	14
Allogeneic donor	782	86
Matched related	576	64
Mismatched related	121	13
Unrelated	85	9
Total-body irradiation, cGy		
None	168	19
≤ 1,000	16	2
1,200	333	37
≥ 1,200	389	43
Acute GVHD grade (allogeneic recipients only)		
0	316	41
I	104	13
II	245	31
III–IV	117	15
Discharge from Seattle (day after transplant)		
Median	99	
10th to 90th percentile	91–119	
Range	38–201	

TABLE 2

MEAN PULMONARY FUNCTION TEST VALUES BEFORE AND 3 MO AFTER BONE MARROW TRANSPLANTATION*

Pulmonary Function Test Variable	Before BMT (n = 753)	3 Mo After BMT (n = 906)
Total lung capacity, % of predicted	94 ± 17	87 ± 17
FEV_1/FVC, %	83 ± 7	84 ± 14
D_{LCO}sb, % of predicted	80 ± 18	67 ± 17

Definition of abbreviations: BMT = bone marrow transplantation; FEV_1/FVC = forced expiratory volume in the first second/forced vital capacity; D_{LCO}sb = single-breath diffusing capacity for carbon monoxide.

* Values are mean ± SD.

TABLE 3

PULMONARY FUNCTION IMPAIRMENT 3 MO AFTER BONE MARROW TRANSPLANTATION*

PFT Variable	Significant Decline from Pre-BMT	Impairment at 3 Mo† n (% total) None	Mild	Moderate to Severe	Totals
TLC	No	422 (58%)	124 (17%)	8 (1%)	554 (76%)
	Yes‡	69 (9%)	81 (11%)	23 (3%)	173 (24%)
FEV_1/FVC	No	505 (68%)	157 (21%)	1 (0.1%)	663 (90%)
	Yes§	38 (5%)	37 (5%)	2 (0.3%)	77 (10%)
D_{LCO}sb	No	106 (15%)	179 (25%)	61 (9%)	346 (48%)
	Yes‡	31 (4%)	174 (24%)	152 (23%)	337 (52%)

Definition of abbreviations: PFT = pulmonary function test; BMT = bone marrow transplantation; TLC = total lung capacity; FEV_1/FVC = forced expiratory volume in the first second/forced vital capacity; D_{LCO}sb = single-breath diffusing capacity for carbon monoxide

* Among marrow recipients with pulmonary function test results before bone marrow transplantation.

† Degree of impairment: TLC, none ≥ 80% predicted, mild restriction < 80% and ≥ 60% of predicted, moderate/severe restriction < 60% predicted; FEV_1/FVC, none ≥ 80%, mild obstruction < 80% and ≥ 60%, moderate/severe obstruction < 60%; and D_{LCO}sb, none ≥ 80% of predicted, mild deficit < 80% and ≥ 60% of predicted, moderate/severe deficit < 60% of predicted.

‡ Decline ≥ 15% compared with baseline.

§ Decline ≥ 5% compared to baseline.

for discharge from Seattle, which was usually 100 d after transplantation.

Pulmonary Function Test Results

PFT were performed before marrow transplantation by 753 (83%) patients in the cohort (Table 2). The mean TLC (mean ± standard deviation, SD, = 94 ± 17% of predicted) and FEV_1/FVC (83 ± 7%) were within the normal range. However, 18% had at least a mild restrictive defect and 32% had at least a mild obstructive airflow defect before marrow transplantation. The mean D_{LCO}sb (corrected for hemoglobin) was reduced slightly (80 ± 18% of predicted). Only 48% of the patients had D_{LCO}sb values within the normal range (≥ 80% of predicted) before marrow transplantation.

At 3 mo after transplantation, the mean TLC and D_{LCO}sb had decreased to 87 ± 17% and 67 ± 17% of predicted, respectively (Table 2). Restrictive ventilatory defects were noted in 32% of patients, and 24% had experienced a significant decrease (at least 15%) in TLC compared with pretransplant (Table 3). D_{LCO}sb was abnormally low in 81% of patients 3 mo after the transplant. D_{LCO}sb declined by more than 15% compared with baseline in 52% of patients and by more than 25% in over half of these (Table 3).

The mean FEV_1/FVC essentially was unchanged (84 ± 14%) 3 mo after transplant (Table 2). Airflow obstructive defects were

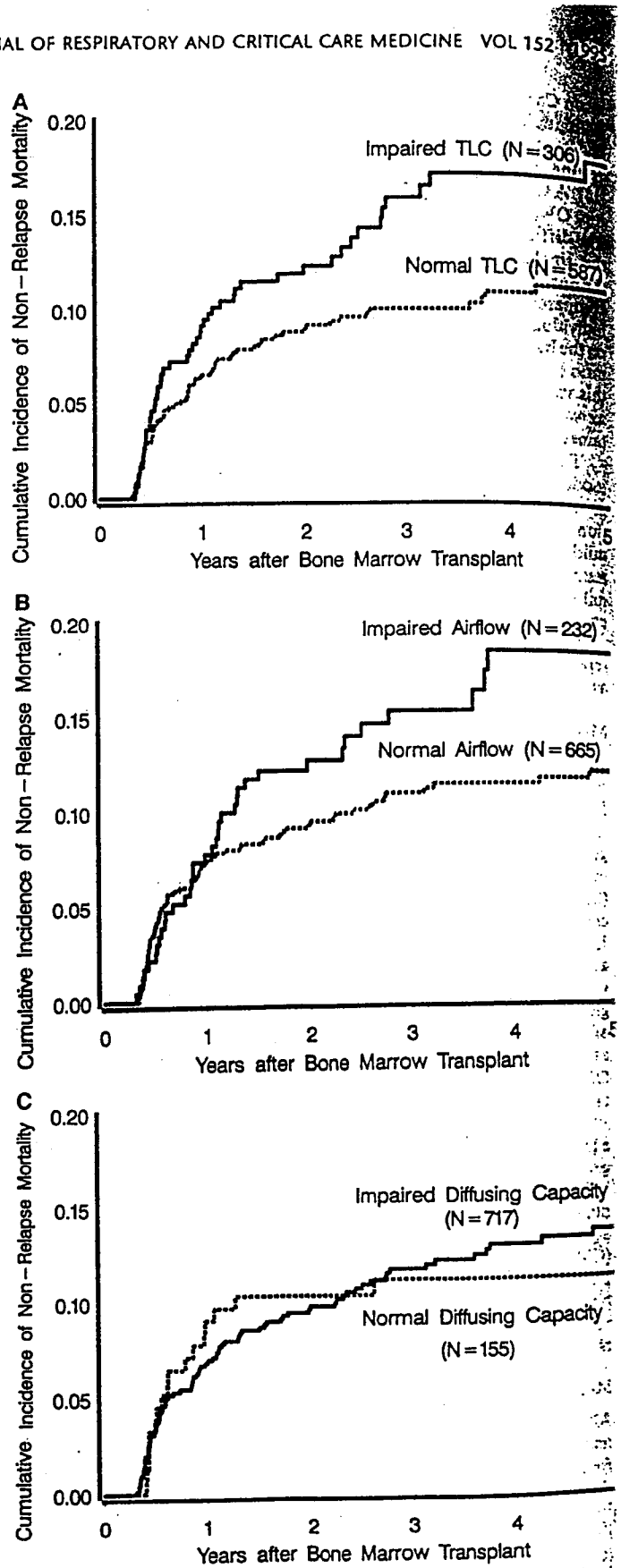

Figure 1. Estimates of the cumulative probabilities of nonrelapse death as functions of pulmonary function test results 3 mo after marrow transplantation: (*A*) total lung capacity (p = 0.004, log rank); (*B*) FEV_1/FVC (p = 0.08, log rank; and (*C*) diffusing capacity ($p > 0.05$ log rank). In each plot, the *solid curve* corresponds to marrow recipients with pulmonary function test result impairment and the *dashed curve* to those with normal pulmonary function test results.

TABLE 4

COX REGRESSION ANALYSIS OF THE ASSOCIATION BETWEEN PULMONARY TEST RESULTS 3 MO AFTER BONE MARROW TRANSPLANTATION AND NONRELAPSE MORTALITY

Variable	Relative Risk (95% CI)*	Relative Risk (95% CI) Adjusted for Other PFTs†
Total lung capacity		
Normal and no significant change	1.00	1.00
Any impairment	2.40 (1.49, 3.88)	2.11 (1.24, 3.59)
≥ 15% decline from pre-BMT‡	2.26 (1.20, 4.29)	1.96 (1.00, 3.82)
FEV_1/FVC		
Normal and no significant change	1.00	1.00
Any impairment	1.11 (0.68, 1.77)	1.22 (0.75, 1.99)
≥ 5% decline from pre-BMT‡	0.72 (0.22, 2.36)	0.90 (0.27, 3.01)
Diffusing capacity		
Normal and no significant change	1.00	1.00
Mild impairment	0.90 (0.49, 1.05)	0.87 (0.48, 1.60)
Moderate to severe impairment	1.48 (0.77, 2.85)	1.09 (0.54, 2.21)
≥ 15% decline from pre-BMT‡	0.22 (0.03, 1.71)	0.22 (0.03, 1.69)

Definition of abbreviations: BMT = bone marrow transplantation; PFT = pulmonary function testing.

* Controlling for diagnosis, donor-recipient HLA identity, and whether the transplant was autologous or allogeneic, whether the patient received total-body irradiation, whether the patient developed acute GVHD, gender, and age.

† Controlling for diagnosis, donor-recipient HLA identity, and whether the transplant was autologous or allogeneic, whether the patient received total-body irradiation, whether the patient developed acute GVHD, gender, age, *and* other pulmonary function test results.

‡ Analysis restricted to those with values within the normal range at 3 mo after marrow transplantation.

less frequent at 3 mo after transplant than pretransplant (26% compared with 32%). In 10% of patients a significant worsening in airflow (≥ 5% decline in FEV_1/FVC) compared with baseline (Table 3) was seen.

Analysis of Risk for Nonrelapse Death

The probabilities of nonrelapse mortality in relation to the results of PFT 3 mo after marrow transplantation are shown in Figure 1. Impairment of TLC was associated with an increase in the probability of nonrelapse mortality ($p = 0.004$, log rank). The impact of airflow obstruction was less profound ($p = 0.08$, log rank). Impairment of diffusing capacity was not associated with an increase in nonrelapse mortality.

The relative risk of nonrelapse mortality for each of the PFT variables evaluated at 3 mo is displayed in Table 4. In both columns relative risks were calculated, adjusting for other non-PFT variables suspected of being risk factors for nonrelapse mortality after marrow transplantation. The categoric variables considered were indicators for diagnosis and disease status at transplant (relapse versus remission), transplant type (autologous versus allogeneic), donor-recipient HLA identity among allogeneic marrow recipients, dose of total body irradiation in the conditioning regimen, grade of acute GVHD, gender, and age (by 20 yr increments). Among the PFT results, only TLC was associated with an increased risk of nonrelapse mortality. Not only the presence of impairment of TLC at 3 months after transplant was a risk for nonrelapse mortality but also a significant decline from baseline despite remaining within the normal range for TLC. Neither airflow obstruction nor impairment in diffusing capacity was associated with an increase in the risk of nonrelapse mortality (Table 4).

The effect of TLC on nonrelapse mortality was independent of the effect of other variables. Restrictive ventilatory defect, manifested either by impairment of TLC 3 mo after marrow transplant or by a significant reduction (≥ 15%) compared with baseline, was associated with a twofold increase in the risk of nonrelapse mortality relative to a normal and unchanging TLC after transplant.

Analysis of Risk for Chronic GVHD

Chronic GVHD is a major risk for nonrelapse mortality. Among patients with chronic GVHD, the relative risk of nonrelapse mortality was 2.10 (95% confidence interval, CI: 1.36, 3.24) ($p < 0.001$) after adjusting for other non-PFT-related risk factors. Therefore, we determined whether the association of restrictive ventilatory defects after transplant with an increased risk of nonrelapse death could be accounted for by an increase in incidence or severity of GVHD. However, a Cox proportional hazards regression analysis failed to provide any evidence that PFT defects, in particular impaired TLC, predicted the development of chronic GVHD (data not shown).

The impact of TLC and chronic GVHD on nonrelapse mortality is shown in Table 5. The incidence of nonrelapse mortality among patients with neither restrictive ventilatory defects nor chronic GVHD was 6%. The incidence increased to 13 to 15% among patients with either impairment in TLC or chronic GVHD and was 23% among patients with both abnormal TLC and chronic GVHD. In addition, the association between TLC and nonrelapse mortality was not higher among patients with chronic GVHD. Thus, chronic GVHD, by itself, does not fully explain the increased risk of nonrelapse mortality associated with TLC.

Cause of Death in Nonrelapse Mortality

Chart review revealed that 28 of the 104 nonrelapse deaths (27%) were associated with respiratory failure without evidence of pulmonary infection. The impact of restrictive ventilatory defects and chronic GVHD on the cause of death is shown in Table 6. The incidence of death with respiratory failure increased from 1.9% among patients with normal and unchanging TLC to 5.3% among those with new restrictive ventilatory defects. Chronic GVHD did not appear to increase the rate of death with respiratory failure. In contrast, the incidence of death without respiratory failure increased two to threefold among marrow recipients with chronic GVHD compared with those without. These deaths were largely associated with infection, multiorgan failure, and bleeding.

DISCUSSION

The purpose of this study was to determine whether changes in lung function occurring relatively early after marrow transplantation affected transplant outcome as measured by nonrelapse mortality. This was an objective end point that avoided the subjective nature of symptomatology and was not influenced by mortality as a result of relapse of the initial disease.

TABLE 5

INCIDENCE OF NONRELAPSE MORTALITY AS A FUNCTION OF TOTAL LUNG CAPACITY 3 MO AFTER MARROW TRANSPLANTATION AND PRESENCE OF CHRONIC GRAFT-VERSUS-HOST DISEASE

	Chronic GVHD n/n* (%)		
Total Lung Capacity at 3 Mo	No	Yes	Total
Normal and < 15% change from baseline	15/237 (6%)	28/185 (15%)	43/422 (10%)
Abnormal or ≥ 15% change from baseline†	31/246 (13%)	30/129 (23%)	61/375 (16%)
Total	46/483 (10%)	58/314 (18%)	104/797 (13%)

* Number of nonrelapse deaths/number of patients.
† Decline ≥ 15% among those with values within the normal range at 3 mo after marrow transplantation.

TABLE 6

INCIDENCE OF DEATH WITH AND WITHOUT RESPIRATORY FAILURE AS A FUNCTION OF TOTAL LUNG CAPACITY 3 MO AFTER MARROW TRANSPLANTATION AND PRESENCE OF CHRONIC GRAFT-VERSUS-HOST DISEASE

	Chronic GVHD n/n* (%)		
Total Lung Capacity at 3 Mo	No	Yes	Total
Incidence of death with respiratory failure			
Normal and < 15% change from baseline	5/237 (2.1%)	3/185 (1.6%)	8/422 (1.9%)
Abnormal or ≥ 15% change from baseline†	12/246 (4.9%)	8/129 (6.2%)	20/375 (5.3%)
Total	17/483 (3.5%)	11/314 (3.5%)	28/797 (3.5%)
Incidence of death without respiratory failure			
Normal and < 15% change from baseline	10/237 (4.2%)	25/185 (13.5%)	35/422 (8.3%)
Abnormal or ≥ 15% change from baseline†	19/246 (7.7%)	22/129 (17.0%)	41/375 (10.9%)
Total	29/483 (6.0%)	47/314 (15.0%)	76/797 (9.5%)

* Number of deaths/number of patients.
† Decline ≥ 15% among those with values within the normal range at 3 mo after marrow transplantation.

The mean decline in (the percentage of the predicted) TLC was 7% and significant reductions in TLC occurred in 24% of patients Declines in the single-breath diffusing capacity were even more pronounced, the mean value dropping by 13%. Over half of the patients experienced significant reductions in D_{LCOSB} and 82% had values less than 80% of predicted 3 mo after transplantation. Airflow obstruction was uncommon 3 mo after marrow transplantation, and the mean value did not change from baseline. Only 10% of marrow recipients experienced a > 5% reduction in airflow. These alterations in PFT results generally are in keeping with reports from other marrow transplant units (3–10).

An increase in the nonrelapse mortality rate was associated with either the presence of a restrictive defect 3 mo after marrow transplantation or a significant decline in lung volume compared with baseline, even if the absolute value remained within the normal range. The relative risk of nonrelapse mortality associated with a restrictive lung defect compared with normal lung volumes was 2.4 and did not change substantially when other potential confounding variables, such as age, diagnosis, total-body irradiation, transplant type, and acute GVHD, were included in the regression model. This suggests a strong influence of lung volume at 3 mo after marrow transplant on survival. The impact of the restrictive lung defects appears most pronounced more than 1 yr after marrow transplant.

Abnormal diffusing capacity before marrow transplantation has been shown to increase the risk of transplant-related mortality (19). Most deaths occurred in the first 3 mo after marrow transplant. Surprisingly, although reductions in diffusing capacity were both common and severe 3 mo after marrow transplant, there was no statistical association with nonrelapse mortality. This may reflect the high sensitivity of this test for pulmonary capillary endothelial injury associated with intensive chemoirradiation therapy employed in marrow transplantation. However, such injury does not appear to be associated with an increased risk of death after 3 mo. Restrictive lung defects appear to indicate more severe lung injuries that are clinically significant.

Previous reports by Clark and colleagues showed an increase in mortality among allogeneic marrow recipients with new onset airflow obstruction compared with a control group of patients with chronic GVHD (12). We expected decreases in airflow at 3 mo to be associated with increased mortality. Only 10% of the marrow recipients in this study had a decline in airflow compared with baseline. Most had mild defects at an earlier time point than many of the marrow recipients described by Clark and colleagues. Surprisingly, in this study there was no association between the minimal airflow abnormalities detected early after transplant and nonrelapse mortality. In log-rank analysis, the association between airflow obstruction and nonrelapse mortality approached but did not reach statistical significance, possibly because of the small number of affected patients. Further analysis demonstrated that any increased risk of nonrelapse mortality could be explained by associations with other risk factors (such as GVHD) for nonrelapse mortality. Although we could not confirm an association between airflow obstruction at 3 mo after marrow transplantation and an increase in nonrelapse mortality, severe airflow obstruction occurring later after transplant is a significant clinical problem.

It is commonly appreciated that the most common conditions associated with death occurring "late" after marrow transplantation are relapse of the primary disease and complications of chronic GVHD. In our patients, chronic GVHD increased the risk of nonrelapse mortality more than twofold. Our analyses did not suggest that restrictive defects were associated with an increased risk of chronic GVHD. Furthermore, examination of the effect of the interaction of TLC and chronic GVHD on the incidence of nonrelapse mortality suggested that the two factors are independent risks for death.

Over one-quarter of the nonrelapse mortality in this study was attributed to respiratory failure. Restrictive ventilatory defects and chronic GVHD appear to mediate nonrelapse mortality through different mechanisms. Declines in lung volumes 3 mo after marrow transplantation were associated with an increased risk of death with respiratory failure. This risk was independent of the presence of chronic GVHD. In contrast, chronic GVHD appeared primarily to increase the risk of nonrespiratory death.

Interestingly, PFT variables 3 mo after marrow transplantation that were associated with nonrelapse mortality differed from those previously identified pretransplant as associated with an increased risk of death (19). Both low diffusing capacity and widened $A_aP_{O_2}$ before marrow transplant were found to be independently associated with death after marrow grafting. In that study, restrictive lung defects were also associated with increased mortality, but this effect was not independent of alterations in diffusion or gas exchange. The differences between the predictive value of PFT obtained before and after marrow transplant in part may be explained by the likely modes of death. Survival plots show that most of the mortality associated with pretransplant diffu-

sion and gas exchange abnormalities occur within the first 3 mo after marrov infusion. That is, the deaths most likely are related to toxicities of the conditioning chemotherapy and irradiation or infection. Lung function parameters that serve as possible markers for preexisting endothelial cell injury may be markers for an increased risk of conditioning-related toxicities. Much of the nonrelapse mortality associated with restrictive lung defects "early" after marrow transplant tend to occur after the first year posttransplant. This indicates that the deaths are long-term sequelae, not acute toxicities of the transplant procedure. In addition, there is a selection bias for patients who were able to tolerate the transplant and survived to be tested at 3 mo. Based on these results, it is not surprising that the predictive value of PFT is different before and after marrow transplantation.

Restrictive lung defects are common 3 mo after marrow transplantation and are associated with a significant increase in the risk of nonrelapse mortality and an increased risk of death with respiratory failure. These findings provide a rationale for the routine measurement of lung function after marrow transplantation. It is unclear how frequently these tests should be performed to identify the largest possible proportion of patients at risk. Because previous studies have noted that lung volumes reach a nadir approximately 6 mo after marrow grafting, testing at least once between 3 and 6 mo seems appropriate for prognostic purposes. Further study of lung function changes after marrow transplantation and analysis of the clinical course of patients with restrictive impairment are necessary to identify mechanisms of lung injury and methods to prevent the associated mortality.

Acknowledgment: The authors appreciate the critical review by Joan G. Clark, M.D. and the computer skills of Gary Schoch.

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