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Repair of Impaired Pulmonary Function Is Possible in Very-Long-Term Allogeneic Stem Cell Transplantation Survivors

Natasha A. Jain [1], Priyanka A. Pophali [1], Jeffrey K. Klotz [1], Sawa Ito [1], Eleftheria Koklanaris [1], Kamna Chawla [1], Christopher S. Hourigan [1], Nicole Gormley [1], Bipin N. Savani [2], Austin John Barrett [1], Minoo Battiwalla [1,*]

[1] *Hematology Branch, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland*
[2] *Vanderbilt University Medical Center, Nashville, Tennessee*

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A B S T R A C T

Both early- and late-onset noninfectious pulmonary injury are important contributors to the nonrelapse mortality seen after allogeneic stem cell transplantation (allo-SCT), particularly in subjects conditioned with high-dose total body irradiation (TBI). To characterize the kinetics of recovery from pulmonary injury in long-term survivors, we collected data on 138 subjects who survived > 3 years (median survival, 10.2 years) after predominantly TBI-based allo-SCT from their HLA-matched siblings. Baseline pulmonary function tests served as the reference for subsequent measurements at 3, 5, 10, and 15 years for each survivor. The only parameter showing a clinically and statistically significant decline post-transplant was adjusted diffusion capacity of lung for carbon monoxide (DLCO), which reached a nadir at 5 years but surprisingly normalized at the 10-year mark. Multivariable modeling identified chronic graft-versus-host disease ($P < .02$) and abnormal baseline-adjusted DLCO ($P < .03$) as the only significant factors associated with the decline in adjusted DLCO at 5 years but excluded smoking, conditioning intensity, baseline C-reactive protein level, TBI dose to the lungs, disease, and demographic variables. In conclusion, pulmonary injury as monitored by the adjusted DLCO continues to deteriorate in the first 5 years after allo-SCT but recovers at 10 years.

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INTRODUCTION

Pulmonary injury is a frequent complication after allogeneic stem cell transplantation (allo-SCT) and is a leading contributor to nonrelapse mortality [1-10]. Previous studies have reported that pulmonary function abnormalities are largely associated with risk factors like smoking, total body irradiation (TBI), and impaired pretransplant pulmonary function [6,11-17]. Serial pulmonary function testing is very important in the detection and management of pulmonary injury.

We previously reported early- and intermediate-term pulmonary complications in a cohort of subjects undergoing predominantly myeloablative, full-dose, TBI-based conditioning followed by T cell–depleted HLA-identical sibling grafts. In the first year after allo-SCT, noninfectious pulmonary injury was seen in >10% of subjects, with pulmonary nonrelapse mortality occurring at a median of 90 days (range, 23 to 238 days). Pretransplant diffusion capacity of lungs for carbon monoxide (DLCO), smoking history, CD34+ dose, and lung shielding were independent risk factors [14,16]. With continued follow-up beyond the first year (median follow-up was 44 months), the median time to pulmonary function test (PFT) decline was 37 months. Pretransplant DLCO or forced expiratory volume in 1 second (FEV_1) < 80% and chronic graft-versus-host disease (GVHD) were independently associated with a decline in PFTs [15]. Interestingly, the adverse impact of TBI on PFTs was restricted to the first 2 years after SCT [16]. Much less data are available on pulmonary late effects in long-term allo-SCT survivors beyond 3 years. This led us to conduct a landmark analysis of subjects who were alive for more than 3 years after allo-SCT. The objectives were to identify patterns of PFT abnormality, study the kinetics of PFT decline, and identify underlying factors contributing to late PFT decline.

METHODS

Patients and Study Design

We studied the PFTs of 138 survivors beyond a 3-year post-transplant landmark who underwent allo-SCT from HLA-identical siblings at the Hematology Branch of the National Heart, Lung, and Blood Institute at the National Institutes of Health between September 1993 and September 2008. All subjects gave written informed consent for long-term evaluation and follow-up on a natural history protocol (NHLBI 05-H-0130; ClinicalTrials.gov Identifier NCT00106925). We conducted cross-sectional analyses at 3, 5, 10, and 15 years post-transplant to characterize the kinetics of pulmonary injury. Ninety-one patients were previously included in a study of early pulmonary mortality [14], and 69 patients were previously reported in a study of post-transplant PFT abnormalities with shorter follow-up [13].

Statistical Analysis

Summary statistics such as sample proportions, medians, standard deviations, and 95% confidence intervals were used to describe patient characteristics. Smoking, TBI dose delivered to the lungs, conditioning intensity, baseline C-reactive protein level, chronic GVHD, all PFTs, and demographic variables were entered into the multivariate model (forward-stepwise multiple regression). Paired *t*-tests were used to compare 3-year, 5-year, 10-year, and 15-year post-transplant observations to the pretransplant baseline PFTs. Sensitivity analyses were conducted to examine the impact of the loss of subjects in the cohort because of delayed mortality beyond 3 years and the influence of late survivors at 15 years. Statistical significance was considered when $P < .05$. All statistical analyses were performed using IBM SPSS v20 (SPSS Inc., Chicago, IL). Graphs were created using Prism 5.03 (GraphPad Software, Inc., La Jolla, CA).

Pulmonary Function Tests

Patients with baseline PFTs < 80% of their population reference were considered abnormal at baseline. Because of variability in the population

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* Correspondence and reprint requests: Minoo Battiwalla, MD, MS, Rm 5-3581, 10 CRC, 10 Center Drive, Bethesda, MD 20892.
E-mail address: minoo.battiwalla@nih.gov (M. Battiwalla).

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reference ranges at our institute during the course of the study and the inherent inaccuracy and assumptions related to such comparisons [18], we followed the method of Gore et al. [19] in using each subject's baseline PFT as the reference for all subsequent measurements at 3, 5, 10, and 15 years.

Baseline PFTs were obtained in all patients 5 to 21 days before allo-SCT. Ventilation capacity was measured by forced vital capacity (FVC), FEV_1, the FEV_1/FVC ratio, and peak expiratory flow. Lung volume measurements (by helium dilution) included vital capacity (VC), total lung capacity (TLC), residual volume, and the residual volume/TLC ratio. Gas exchange was determined by DLCO by using a carbon monoxide single-breath technique with correction for hemoglobin and alveolar ventilation (DLCO_Adj). Because alveolar ventilation is decreased in restrictive lung disorders, the findings for DLCO_Adj were confirmed by comparison with DLCO without this correction.

Pulmonary symptoms were not recorded prospectively for this study, and we defined a clinically significant change as a >10% further decline from their baseline PFT. PFTs were not performed in patients with recent infections because of the risk of adversely confounding PFT results.

RESULTS

Patient Characteristics

Patient and transplant characteristics are summarized in Table 1. The median age at transplant was 35 years. Most subjects received high-dose TBI–based conditioning with T cell–depleted grafts from their HLA-matched siblings. In subsequent years, patients older than 55 years were restricted to 400 cGy of TBI and younger patients had their dose of TBI reduced from 1360 cGy to 1200 cGy (with lung shielding to 900 or 600 cGy). In addition to TBI, patients also received cytoxan +/− fludarabine for conditioning.

Table 1
Patient and Transplant Characteristics at Allo-SCT

Characteristic	Percent
Gender	
Female	56
Male	44
Ethnicity	
Non-Hispanic	49
Hispanic	48
Not stated	2
Transplant indications	
CML	46
AML	23
MDS	14
ALL	9
NHL/CLL	4
SAA	1.4
CMML	1.4
Mastocytosis	.7
Graft source	
PBSC (ex vivo T cell depleted)	81.9
Bone marrow	11.6
PBSC (unmanipulated)	6.5
Intensity of conditioning	
Myeloablative	94.9
Nonmyeloablative	5.1
TBI (cGy)	
0	6.5
400	2.2
1200-1360	91
TBI dose to lungs	
0	6.5
400-600	35.5
900	15.2
1360	42.8
Busulfan exposure	
Yes (all pretransplant)	4.0
No	96.0
Smoking history	
Pretransplant	19.5
Post-transplant	12.2

ALL indicates acute lymphoid leukemia; AML, acute myelogenous leukemia; CLL, chronic lymphoid leukemia; CMML, chronic myelomnocytic leukemia; MDS, myelodysplastic syndrome; NHL, non-Hodgkin lymphoma; SAA, severe aplastic anemia.

Survivor Outcomes

At the time of analysis, 138 survivors were informative at the baseline/pretransplant time point, and 123 at 3 years, 113 at 5 years, 63 at 10 years, and 8 at 15 years post-SCT. The median survival was 10.2 years. Of the 16 patients who died after 3 years, 4 (2.8%) died of pulmonary causes, including 2 who died of lung cancer (Table 2).

Our previous analyses of late effects in T cell–depleted transplantation have shown an impact when chronic GVHD required the utilization of immunosuppressive therapy at 3 or more years post-transplant [13]. In this cohort, chronic GVHD was generally mild, only 30% of subjects required systemic immunosuppression at 3 years post-transplant, and all patients were free of chronic GVHD at 5 and 10 years post-transplant. Pulmonary forms of GVHD, either cryptogenic organizing pneumonia or bronchiolitis obliterans syndrome were observed in only 3.6%. Post-transplant smoking was confirmed in 10.4% of the informative subjects, but smoking data were only available for 35% of post-transplant survivors.

Baseline PFT Abnormalities

Baseline abnormalities (<80% predicted) in PFTs were found in 17.4% of subjects in the following declining frequencies: FVC%, VC, TLC, FEV_1, DLCO_Adj (adjusted for hemoglobin and alveolar ventilation) hemoglobin/alveolar ventilation, and FEV_1/FVC. Abnormalities in a single parameter were found in 5.8%, and abnormalities in multiple parameters were found in 11.6% of subjects. Baseline PFT are shown in Figure 1.

Changes in PFTs Post-SCT

The lung volumes as measured by FEV_1 (Figure 2A) and lung capacity as measured by the VC (Figure 2B) and TLC (Figure 2C) remained unchanged. The FEV_1/FVC ratio showed a statistically significant decline that was not clinically significant (Figure 2D). The only parameter that showed both a clinically and statistically significant decline post-transplant was DLCO_Adj which reached a nadir at 5 years, with subsequent normalization at the 10-year mark (paired *t*-test). Abnormal (<80% predicted) DLCO_Adj was found in 19.6%, 21.0%, .7%, and 0% of survivors at 3, 5, 10, and 15 years post-transplant, respectively. The mean DLCO_Adj (Figure 3) at 3, 5, 10, and 15 years were 91% ($P = .003$), 88% ($P = .001$), 98% (P = NS), and 100% (P = NS), respectively, when compared with baseline. A similar kinetic for decline and recovery was observed in DLCO without correction for alveolar ventilation (Supplementary Figure 1). Taken together with unchanged lung capacity measurements, this suggests the subsequent improvement in diffusion capacity

Table 2
Causes of Death in Long-Term Survivors Beyond 3 Years

Cause	Number
Relapse	6 (4.3%)
Lung cancer	2 (1.4%)
Respiratory failure, pneumonia	2 (1.4%)
Other malignancy	2 (1.4%)
Nonpulmonary infections	2 (1.4%)
Brain hemorrhage	1 (.7%)
Chronic GVHD, multiorgan failure	1 (.7%)

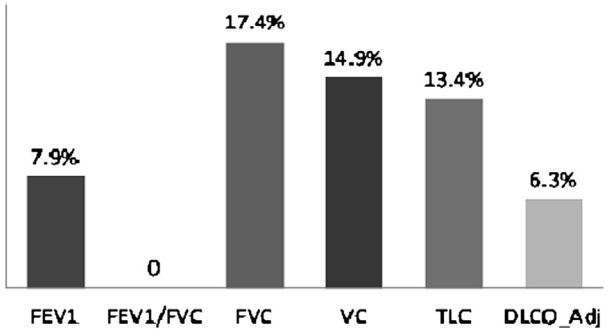

Figure 1. Proportions of patients with abnormal (<80% of the predicted) pretransplant PFTs. Proportions shown are not mutually exclusive.

was not falsely related to the late development of a restrictive process (lung fibrosis).

To exclude the possibility that the apparent improvement in DLCO_Adj beyond 10 years was a survivorship bias due to enrichment of survivors with better lung function, the analysis was repeated on the subgroup of 8 patients with data available at all time points (Figure 4A); a similar pattern of DLCO_Adj kinetics confirmed that inclusion of these subjects did not skew the results. Another sensitivity analysis, conducted in the 16 subjects who died beyond 3 years (Figure 4B), showed little decline in diffusion capacity, suggesting that loss of these subjects did not influence the results.

Risk Factors for Decline in DLCO_Adj at 5 Years Post-Transplant

We evaluated pre- and post-transplant smoking history, conditioning intensity, radiation doses delivered to the lung and the body, busulfan exposure, C-reactive protein levels, disease, chronic GVHD, abnormal (<80% reference) baseline DLC_Adj, and demographic variables in univariate and multivariable models for their impact on DLCO. Busulfan was not used in our transplant conditioning regimens, but 4% of subjects had prior busulfan exposure, which was not found to influence the DLCO_Adj; pre- or post-transplant smoking was also not found to influence the DLCO_Adj. In multivariable linear regression for the decline at DLCO_Adj at 5 years, any chronic GVHD at 3 years post-transplant ($P = .017$) and abnormal DLCO_Adj at baseline ($P = .023$) were the only significant factors associated with the decline in the DLCO_Adj at 5 years. The model excluded smoking, lung TBI dose, conditioning intensity, baseline C-reactive protein, disease, and demographic variables (ethnicity, sex, and age).

DISCUSSION

Pulmonary complications can represent one of the more delayed complications of allo-SCT. Chronic GVHD is considered a major risk factor responsible for late pulmonary complications and death. However, no extended studies have tracked pulmonary functions beyond the first decade after SCT. We found that DLCO_Adj was the only PFT that showed a clinically significant decline post-transplant, with a nadir at 5 years and, surprisingly, subsequent normalization at the

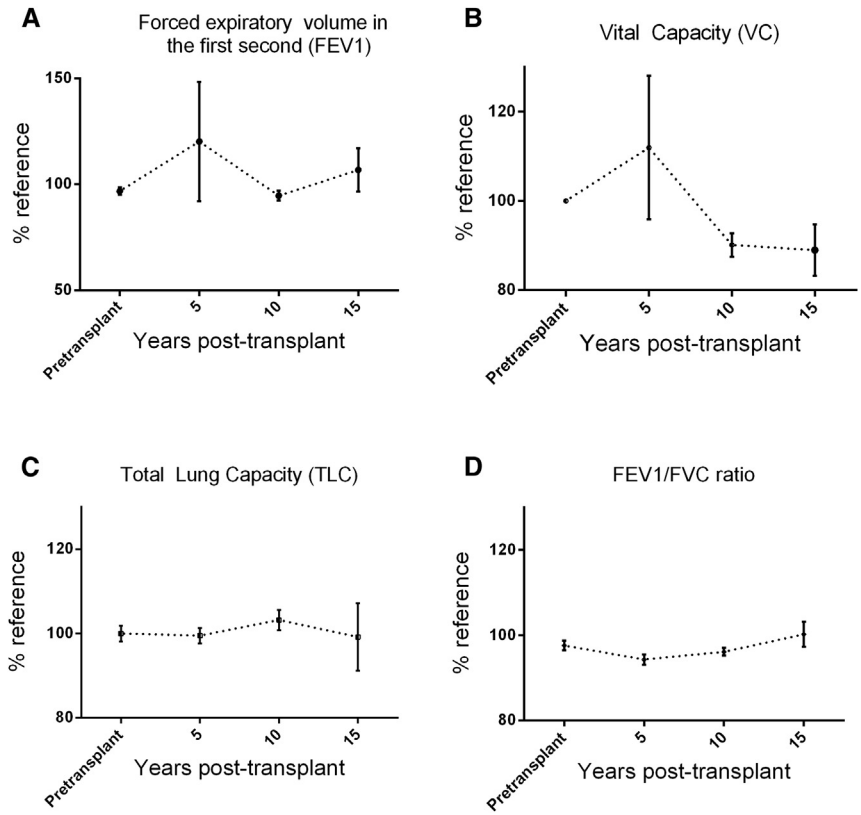

Figure 2. Lung volumes at baseline and at 5, 10, and 15 years post-transplant. A, trend of forced expiratory volume in the first second (FEV1) at baseline, 5, 10 and 15 years post transplant. B, trend of vital capacity (VC) at baseline, 5, 10 and 15 years post transplant. C, trend of total lung capacity (TLC) at baseline, 5, 10 and 15 years post transplant. D, trend of FEV1/FVC ratio at baseline, 5, 10 and 15 years post transplant.

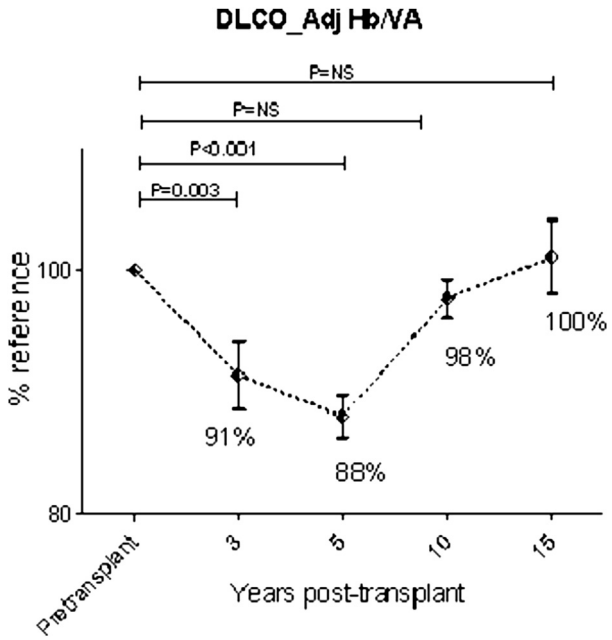

Figure 3. Mean DLCO adjusted for hemoglobin and alveolar ventilation at baseline and at 3, 5, 10, and 15 years.

10-year mark. There were no apparent biases from survivorship or attrition.

Decreased pulmonary function after SCT is considered a poor prognostic marker of incipient pulmonary failure after SCT. In this study of 138 patients, only 1 died of GVHD with pulmonary involvement. In fact, although we saw continued deterioration of pulmonary function up to 5 years, we observed a surprising improvement at 10 years even in patients with chronic GVHD. These findings point to pulmonary repair capacity of diffusion capacity, but notably there was no change in lung volumes or dynamic function as measured by TLC, FEV_1, and VC. The different finding of improved DLCO suggests repair that mainly involves the alveolar membrane. Without recourse to lung biopsy, we can only speculate on the mechanisms of repair at the alveolar vascular interface.

Other studies have demonstrated a significant association between poor pretransplant pulmonary function and the risk for development of early respiratory failure and mortality [11,13,19-23]. Chronic GVHD has also been associated with declines in PFTs [13]. Our study extends the importance of chronic GVHD at 3 years (despite rare lung involvement) and baseline PFTs in the late post-transplant period.

The rate of chronic GVHD in our cohort in this landmark analysis was remarkably low, and pulmonary forms of GVHD, either cryptogenic organizing pneumonia or bronchiolitis obliterans syndrome, were observed in only 3.6%. However, this should not imply that pulmonary mortality did not occur in our transplanted patients. We previously reported that of the 21 transplant-related deaths in a cohort of 146 new transplants, 14 were from pulmonary causes (10 from idiopathic pulmonary syndromes and 4 from infection) occurring at a median of 90 days (range, 23 to 238 days) after transplantation [14]. This implies that most patients with severe forms of pulmonary injury die early in the post-transplant period, but those with sublethal injury may recover their pulmonary function.

In our study, we used baseline PFTs of each patient as an internal control for subsequent time points. Gore et al. [19] also used pretransplant values as a basis for comparison with post-transplant measurements. They found that FEV_1, FVC, and TLC were lower at 6 months and 1 year post-transplant with subsequent recovery. DLCO adjusted for hemoglobin was significantly lower at all intervals and showed an incomplete trend toward recovery [19].

We had earlier shown that TBI, with or without lung dose reduction, has a small but statistically significant effect on PFTs at 1 year post–transplant but not at 2 years post-transplant [16]. This study confirms that TBI exerts no influence on the decline in DLCO at 5 years.

In a pediatric study by Quigg et al. [24], low pretransplant DLCO adjusted for both hemoglobin and alveolar volume was found to be predictive of death. They showed that PFTs were significantly lower at 1 year post-transplant but recovered at 2 years [24]. It is possible that the kinetics of PFT abnormality are influenced by age, and ours was a predominantly adult cohort.

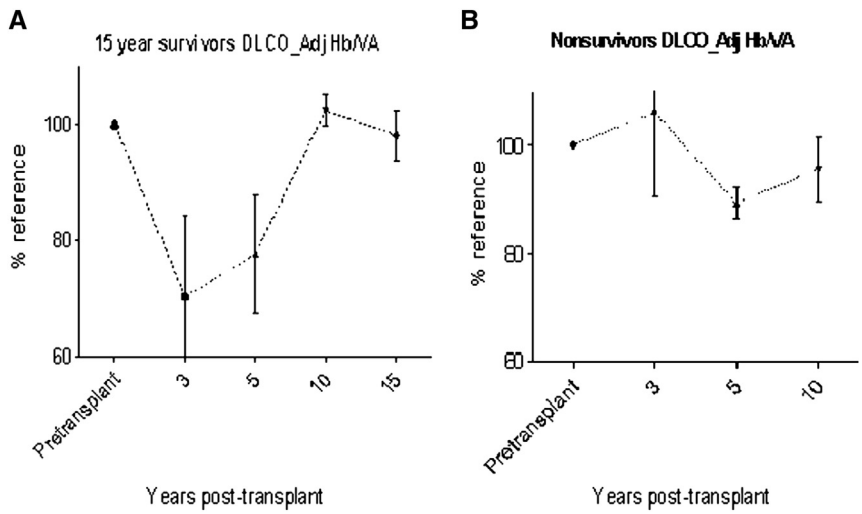

Figure 4. (A) Kinetics of recovery of DLCO adjusted for hemoglobin and alveolar ventilation in the subjects who survived for 15 years post-transplant. (B) Kinetics of recovery of DLCO adjusted for hemoglobin and alveolar ventilation in the subjects who died beyond 3 years post-transplant.

The strength of this study lies in the long follow-up of a mostly homogeneous group of subjects receiving high-dose TBI-based ablative conditioning and T cell–depleted grafts. Significant limitations to generalizability are related to our cohort of patients. Most of our subjects (>80%) had received an ex vivo T lymphocyte–depleted graft. It is likely that this might have reduced the prevalence and severity of chronic GVHD and mitigated pulmonary injury. This limits extrapolation to other transplant settings, specifically the more common T cell–replete grafts, mismatched transplants, and unrelated donor transplantation, which are more likely to have significant chronic GVHD at later time points. The relatively lower median age (35 years) and the preponderance of chronic myelogenous leukemia as the transplant indication are also very different from current transplantation practice. Other limitations are the attrition of subjects and incomplete smoking history.

In conclusion, our findings are important in revealing the capacity of the tissues damaged by radiation or GVHD to heal over time. The opportunity for lung repair post-SCT should be taken into consideration when reviewing patients with deteriorating pulmonary functions in the first 5 years after SCT.

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SUPPLEMENTARY DATA

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.bbmt.2013.10.025.

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