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Long-Term Pulmonary Function Trajectories After Allogeneic Bone Marrow Transplantation

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To the Editor:

Pulmonary complications are common after hematopoietic stem cell transplantation (HSCT) and a major threat to the survival of the HSCT recipient.[1] Pulmonary function tests (PFTs) are part of the evaluation before allogeneic HSCT. After transplantation, PFTs can help to diagnose pulmonary toxicities from chemotherapy or radiation therapy and in diagnosing specific syndromes after HSCT such as bronchiolitis obliterans syndrome (BOS). Given the frequency and negative prognostic implications of pulmonary complications of HSCT developing,[2] postoperative guidelines for HSCT recommend that patients undergo pulmonary function monitoring at least annually after HSCT.[3]

Although the trajectory of lung function has been relatively well characterized in adult patients with BOS,[4] a relative paucity of long-term pulmonary function data is available for those who do not experience BOS. In contrast, substantial data are available from the pediatric HSCT population showing that survivors typically have lasting impairments in pulmonary function, even in those patients who do not experience BOS.[1,5] Our objective with this study was to describe the long-term trajectory of pulmonary function measures after allogeneic HSCT.

Methods

This was a longitudinal cohort study conducted at the Mayo Clinic, Rochester, Minnesota, between January 1, 2005, and December 31, 2020. The requirement for written informed consent was waived by institutional review (Identifier: 13–002869). All PFTs were performed by a trained technician at a single PFT laboratory. European Respiratory Society and American Thoracic Society technical standards were followed in the performance and interpretation of testing.[6,7] Our detailed PFT protocol is outlined elsewhere.[8] Specific measurements routinely measured in patients included FVC, FEV_1, diffusing capacity of

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the lungs for carbon monoxide (D_{LCO}), FEV_1 to FVC ratio, forced midexpiratory flow, and peak expiratory flow (PEF). To mitigate the effects of age-related changes in lung function, comparison measures were performed with % predicted values, unless otherwise specified. For the reference value before transplantation, the spirometry and diffusing capacity measurement closest to transplantation was used. For each 6-month longitudinal time point, each patients could be included only once. If they underwent multiple tests, the best measurement within 90 days either side of that time point was used. BOS diagnosis was performed via manual chart review by two of the study investigators (H. Y. and M. H. T.) in line with the 2014 National Institutes of Health Consensus Statement for diagnosis of chronic graft vs host disease after allogeneic HSCT.[8,9] All four National Institutes of Health criteria were met in 90 of 118 patients with a diagnosis of BOS, with 28 of 118 patients having three of four criteria (typically not having FEV_1 to FVC ratio < 0.7). These 28 patients received a diagnosis of and were treated for BOS by their primary clinician.[8]

Statistical Analysis

Continuous variables were summarized as mean ± SD and were compared between patients with a paired *t* test and across case status using an unpaired *t* test. Longitudinal comparisons were performed using linear mixed-effects modeling (lme4 package within R software). JMP Pro software (SAS Institute) was used for data collection and handling. Data analysis was performed in R version 3.6.3 software (R Foundation for Statistical Computing) using the R Studio 2022.02 integrated development environment (PBC).

Results

Between January 1, 2005, and December 31, 2020, 1,249 patients underwent first-time allogeneic HSCT. Of these, 19 declined research participation and 83 did not undergo PFTs before transplant. Therefore, 1,145 patients were included, of whom 118 received a diagnosis of BOS at a median of 14 months after HSCT (10.3%). Median follow-up was 5.85 years for survivors, with a median of three PFTs per patient.

Pulmonary function declined after transplantation, regardless of BOS diagnosis (Fig 1, Table 1, 2). In those who never demonstrated BOS, FVC % predicted declined by 6.0% (95% CI, 5.1%–6.8%) within the first 6 months and by 8.7% (95% CI, 6.9%–10.5%) by 2 years post-transplantation ($P < .001$ for both). FEV_1 % predicted declined by 7.9% (95% CI, 7.0%–8.7%) within the first 6 months and by 12.6% (95% CI, 10.6%–14.6%) at 2 years ($P < .001$ for both). D_{LCO} % predicted declined by 7.6% (95% CI, 6.5%–8.6%) within the first 6 months and was 6.7% lower at 2 years (95% CI, 4.7%–8.6%; $P < .001$ for both). Forced midexpiratory flow % predicted declined by 4.4% (95% CI, 1.4%–7.3%) in the first 6 months and by 16.4% (95% CI, 9.7%–23.2%) at 2 years ($P = .004$ and $P < .001$, respectively). Finally, peak expiratory flow declined by 2.5% (95% CI, 1.4%–3.6%) at 6 months and 4.9% (95% CI, 2.8%–7.1%) at 2 years ($P < .001$ for both). For most parameters, the decline in pulmonary function was greater for those who ultimately received a diagnosis of BOS compared with those who did not, with FVC at most time points being the exception (Table 1, 2).

Discussion

This study provides an unique analysis of the trajectory of pulmonary function after allogeneic HSCT in a large, contemporary cohort of HSCT recipients. The key finding of our study is that multiple parameters of pulmonary function decline after HSCT, regardless of BOS diagnosis. These include both routinely reported measures such as FEV_1, FVC, and D_{LCO}, but also less commonly reported measures such as forced midexpiratory flow and PEF.

This study supports prior smaller series that reported potential declines in pulmonary function in adult patients who survived allogeneic HSCT.[10] In a cross-sectional survey of 103 patients who survived allogeneic HSCT, in those who did not demonstrate BOS, pulmonary function was lower than that of healthy control participants, although still in the normal range.[1] Our data suggest that adult recipients of allogeneic HSCT who do not demonstrate BOS show pulmonary function decline and that these declines are persistent. The declines are in the range of 5% to 10%, exceeding the expected threshold of minimal clinically important difference.[11] Although our modeling in the first 5 years after HSCT suggests a linear decline, it may be that lung function plateaus in the longer term. The cause of lung function decline may be multifactorial in those without lung graft vs host disease, including toxicity from conditioning chemotherapy or radiation therapy, sequalae of lung injury syndromes after HSCT (infectious and noninfectious), or chest wall limitation (eg, pleural effusion, weight gain). Conditioning toxicity has been noted in those patients with myeloablative conditioning, especially regimens that contain total body irradiation.[8]

Our study also describes the accelerated declines in expiratory flow in those patients who demonstrate BOS and in PEF, in addition to conventional PFT measures. PEF has the advantage of being reproducible and inexpensively measured with portable peak flow meters. Because PEF correlates closely with FEV_1, it may represent a mechanism for early detection of BOS in allogeneic HSCT recipients.

Our study has several strengths worth noting. It is a large, contemporary cohort of allogeneic HSCT patients with high rates of follow-up and protocolized PFT monitoring at regular intervals after HSCT. Our study also has several limitations. The single-center nature of the study limits generalizability. The retrospective nature of the study meant that we were reliant on clinician orders of PFTs. Although our institution protocolizes performance of PFTs at routine milestone visits, those patients with pulmonary symptoms or conditions may have undergone more frequent PFT monitoring and may be overrepresented in the cohort. A prospective study evaluating pulmonary function after allogeneic HSCT would address these issues and is supported by our findings.

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Take-home Point

Study Question:

What is the trajectory of pulmonary function measures after allogeneic hematopoietic stem cell transplantation (HSCT)?

Results:

FEV_1, FVC, and diffusing capacity all decline in the first 5 years after allogeneic HSCT, and this decline is more pronounced in those patients who demonstrate lung graft versus host disease.

Interpretation:

Survivors of allogeneic HSCT experience lasting declines in spirometry and diffusing capacity after HSCT, regardless of whether they demonstrate lung graft versus host disease.

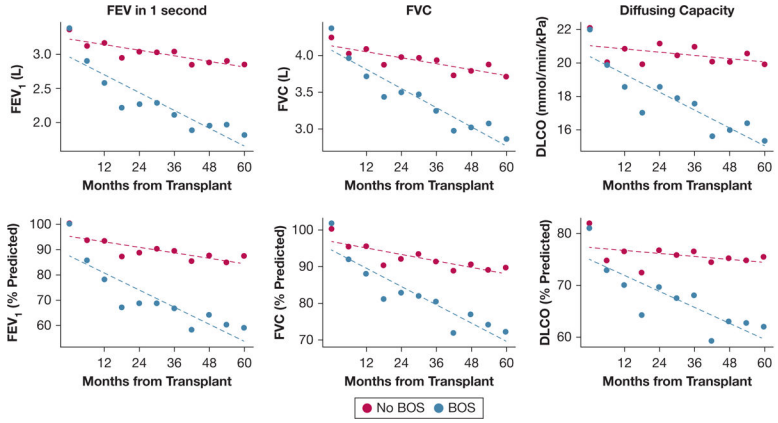

Figure 1 –.

Graphs showing change in FVC, FEV_1, and diffusing capacity in the first 5 years after allogeneic hematopoietic stem cell transplantation. BOS = bronchiolitis obliterans syndrome.

TABLE 1]

Change in Pulmonary Function Testing Parameters Over Time Compared With Baseline (Before Transplantation) Values

Variable	BOS (n = 118)	*P* Value[a]	No BOS (n = 1,027)	*P* Value	
				Paired *t* Test[a]	Unpaired *t* Test[b]
FVC, % predicted					
Baseline	101.8 ± 14.5%	…	100.1 ± 14.5%	…	.23
Change at 6 mo	9.6% (6.7%–12.6%)	< .001	6.0% (5.1%–6.8%)	< .001	.41
Change at 12 mo	13.6% (10.7%–16.5%)	< .001	5.9% (4.8%–7.0%)	< .001	.02
Change at 24 mo	21.3% (17.6%–24.9%)	< .001	8.7% (6.9%–10.5%)	< .001	.10
Change at 60 mo	29.9% (22.7–37.0%)	< .001	12.0% (7.9%–16.0%)	< .001	.003
FEV_1, % predicted					
Baseline	100.3 ± 14.1%	…	100.2 ± 15.3%	…	.96
Change at 6 mo	13.9% (10.1%–17.7%)	< .001	7.9% (7.0%–8.7%)	< .001	.003
Change at 12 mo	21.7% (17.5%–25.9%)	< .001	8.2% (7.1%–9.4%)	< .001	< .001
Change at 24 mo	33.3% (28.2%–38.4%)	< .001	12.6% (10.6%–14.6%)	< .001	< .001
Change at 60 mo	41.2% (34.3%–48.1%)	< .001	14.3% (10.2%–18.3%)	< .001	< .001
DLCO, % predicted					
Baseline	81.0 ± 13.9%	…	81.8 ± 14.1%	…	.55
Change at 6 mo	8.6% (5.6%–11.5%)	< .001	7.6% (6.5%–8.6%)	< .001	.17
Change at 12 mo	12.0% (8.7%–15.2%)	< .001	7.3% (5.9%–8.7%)	< .001	.002
Change at 24 mo	14.7% (11.6%–17.8%)	< .001	6.7% (4.7%–8.6%)	< .001	.02
Change at 60 mo	19.7% (12.6%–26.9%)	< .001	8.7% (4.8%–12.6%)	< .001	.003
Forced midexpiratory flow, % predicted					
Baseline	105.8 ± 33.5%	…	111.4 ± 36.9%	…	.38
Change at 6 mo	9.3% (1.1%–17.6%)	.02	4.4% (1.4%–7.3%)	.004	.06
Change at 12 mo	21.6% (10.5%–32.8%)	.003	8.8% (5.3%–12.4%)	< .001	.001
Change at 24 mo	36.9% (23.3%–50.6%)	< .001	16.4% (9.7%–23.2%)	< .001	.003
Change at 60 mo	56.2% (32.7%–79.7%)	< .001	3.6% (25.0%–32.3%)	.74	.02
FEV_1 to FVC ratio					
Baseline	0.79 ± 0.06	…	0.80 ± 0.07	…	.01
Change at 6 mo	0.054 (0.035–0.073)	< .001	0.022 (0.018–0.026)	< .001	< .001

Variable	BOS (n = 118)	*P* Value[a]	No BOS (n = 1,027)	*P* Value	
				Paired *t* Test[a]	Unpaired *t* Test[b]
Change at 12 mo	0.095 (0.070–0.121)	< .001	0.027 (0.022–0.033)	< .001	< .001
Change at 24 mo	0.137 (0.106–0.168)	< .001	0.046 (0.038–0.055)	< .001	< .001
Change at 60 mo	0.136 (0.087–0.184)	< .001	0.035 (0.017–0.053)	< .001	< .001
PEF, % predicted					
Baseline	118.4 ± 18.2%	…	118.8 ± 21.8%	…	.86
Change at 6 mo	3.7% (0.01%–7.3%)	.049	2.5% (1.4%–3.6%)	< .001	.13
Change at 12 mo	13.6% (9.1%–18.0%)	< .001	2.4% (1.0%–3.8%)	< .001	.009
Change at 24 mo	20.9% (14.9%–26.8%)	< .001	4.9% (2.8%–7.1%)	< .001	< .001
Change at 60 mo	33.9% (25.8%–42.1%)	< .001	9.0% (4.5%–13.6%)	< .001	.002

Data are presented as mean (95% CI) or mean ± SD, unless otherwise indicated. BOS = bronchiolitis obliterans syndrome; DLCO = diffusing capacity of the lungs for carbon monoxide; PEF = peak expiratory flow.

[a]Paired *t* test comparing pulmonary function parameter before transplantation with time point after transplantation.

[b]Comparing time point between those with BOS and those without BOS.

TABLE 2]

Mixed Linear Effects Modeling for Decline in Pulmonary Function Parameters per Year for the First 5 Years After HSCT

Variable	BOS (n = 118)	95% CI	No BOS (n = 1,027)	95% CI
FVC				
% predicted/y	6.52	5.89–7.14	2.08	1.78–2.36
mL/y	320.4	292.6–348.2	117.6	105.0–130.2
FEV_1				
% predicted/y	8.98	8.16–9.78	2.67	2.37–2.97
mL/y	333.3	304.9–361.6	117.4	106.8–128.0
DLCO				
% predicted/y	4.32	3.76–4.88	1.24	0.94–1.54
mL/min/mm Hg/y	1.380	1.227–1.533	0.497	0.410–0.582

BOS = bronchiolitis obliterans syndrome; D_{LCO} = diffusing capacity of the lungs for carbon monoxide;