Lung Transplantation for Graft-Versus-Host Disease after Allogeneic Hematopoietic Stem Cell Transplantation: A Single-center Experience

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ABSTRACT **Background:** Late-onset pulmonary complications can occur following hematological stem cell transplantation (HSCT). In allogeneic HSCT these complications are often associated with chronic graft-versus-host disease (GVHD). Lung transplantation (LTx) often remains the only viable therapeutic option in these patients.

Objectives: To describe our experience with LTx due to GVHD after HSCT and to compare the long-term survival of this group of patients to the overall survival of our cohort of LTx recipients for other indications.

Methods: We retrospectively retrieved all data on patients who had undergone LTx for end-stage lung disease as a sequela of allogeneic HSCT, between 1997 and 2021, at Rabin Medical Center in Israel.

Results: A total of 15 of 850 patients (1.7%) from our cohort of LTx recipients fulfilled the criteria of LTx as a sequela of late pulmonary complication after allogeneic HSCT. The median age at the time of HSCT was 33 years (median 15–53, range 3–60). The median time between HSCT and first signs of chronic pulmonary GVHD was 24 months (interquartile range [IQR] 12–80). The median time from HSCT to LTx was 96 months (IQR 63–120). Multivariate analysis showed that patients transplanted due to GVHD had similar survival compared to patients who were transplanted for other indications.

Conclusions: LTx for GVHD after allogeneic HSCT constitutes an important treatment strategy. The overall survival appears to be comparable to patients after LTx for other indications.

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KEY WORDS: bronchiolitis obliterans syndrome (BOS), graft-versus-host disease (GVHD), hematological stem cell transplantation (HSCT), lung transplantation

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Allogeneic hematological stem cell transplantation (HSCT) is a well-established treatment for a variety of hematologic, malignant, immunologic, and genetic conditions with consistently improving overall survival in HSCT recipients [1]. However, chronic graft-versus-host disease (GVHD) occurs in 30–70% of allogeneic HSCT recipients, leading to reduced quality of life and increased risks of long-term morbidity and mortality [1]. GVHD is commonly manifested by bronchiolitis obliterans syndrome (BOS), with a prevalence of up to 14% in patients with chronic GVHD [2]. Despite progress in understanding the pathobiology of chronic GVHD, there have been relatively few advances in clinical management; thus, corticosteroids and meticulous organ-specific care remain the mainstay of therapies [3]. Currently, the recommended initial treatment for BOS is a combination of fluticasone, azithromycin, and montelukast, the so-called FAM regimen, in combination with systemic steroids. There is no standard second-line treatment, but the most widely used are calcineurin inhibitors, extracorporeal photopheresis, and mycophenolate mofetil [4]. Severe pulmonary chronic GVHD is a concerning adverse event and the prognosis is poor. The 5-year overall survival rate is only 13% when there is no response to first-line therapy [5].

Lung transplantation (LTx) has evolved as a potential therapeutic option for both adult and pediatric HSCT patients who develop life-threatening respiratory complications. Although data is still limited, LTx has been reported as a feasible treatment option in select cases [6-23]. HSCT patients who develop end-stage pulmonary fibrosis due to chemotherapy, chest wall irradiation, immunosuppression, and blood product transfusions may also be candidates for LTx. A high rate of serious pulmonary complications may develop in HSCT patients; nonetheless, the number of patients who proceed to LTx remains exceptionally small [14].

The aim of this study was to add our experience with lung transplantation for GVHD after allogeneic HSCT to the care of these patients and to compare the long-term survival of these patients to the overall survival of our cohort of LTx recipients for other indications.

PATIENTS AND METHODS

DATA COLLECTION

We retrospectively retrieved all data on patients who had undergone LTx for end-stage lung disease as a sequela of HSCT, between May 1997 and July 2021, at Rabin Medical Center. Clinical information was extracted by chart and database review. The control group was collected from the LTx database and included patients who had undergone LTx due to chronic obstructive pulmonary disease (COPD), idiopathic pulmonary fibrosis (IPF), cystic fibrosis (CF), bronchiectasis, and pulmonary hypertension (PHTN). The primary outcome was overall survival. Secondary outcomes were time from the HSCT to LTx, acute rejection, and recurrence of hematologic disease. The study was approved by the institutional review board (RMC 0590-20).

GVHD DEFINITION

Patients who underwent allogeneic HSCT were referred to our institute due to late pulmonary complications of chronic GVHD, which was defined by BOS. Patients were classified as having BOS when they had a new onset of obstructive impairment with a persistent decline in forced expiratory volume in 1 second (FEV1), a percent predicted FEV1 value of less than 75%, FEV1/ forced vital capacity (FVC) ratio of less than 0.7, and signs of air trapping or bronchial dilation on high resolution computed tomography with no evidence of infection despite thorough investigation.

STATISTICAL ANALYSIS

Clinical and baseline characteristics are reported as means and standard deviations (SD) or median and interquartile range (IQR). Clinical outcomes between different indications for LTx were compared with Student's *t*-test and chi-square test, as appropriate. Survival rates were analyzed with Kaplan-Meier curves and Cox regression. *P*-values < 0.05 were considered significant. Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 25 (SPSS, IBM Corp, Armonk, NY, USA).

RESULTS

In total, 15 of 850 patients (1.7%) from our cohort of lung transplantation recipients fulfilled the criteria of LTx for GVHD after allogeneic HSCT. Patient baseline characteristics are shown in Table 1. In all but two patients, the donor of the stem cells was an HLA-identical sibling. The median age at the time of HSCT was 33 years (median 15–53, range 3–60). All the patients, except one, developed extrapulmonary GVHD, mainly ocular. The median time between HSCT and the first signs of chronic pulmonary GVHD was 24 months (IQR 12–80). Table 1 summarizes the LTx data. The median time from HSCT to LTx was 96 months (IQR 63–120). All patients, but two, exhibited advanced obstructive lung disease with median percent predicted FEV1 of 23% (IQR 17–31) before transplant. The indication for LTx was BOS in most patients. The most common procedure was double LTx (10 patients), four patients had a single LTx, and one had a living donor transplantation with one lobe from each sibling. Acute rejection was seen in one patient. Seven patients died during the follow-up period (at 2, 6, 13, 15, and 122 months from LTx). The causes of death were sepsis in five and respiratory failure due to cytomegalovirus pneumonitis in one. The last patient died while waiting for a retransplant. There was no relapse of the hematolog-

Figure 1: Survival by indication

CF = cystic fibrosis, COPD = chronic obstructive pulmonary disease, GVHD = graft-versus-host disease, PHTN = pulmonary hypertension

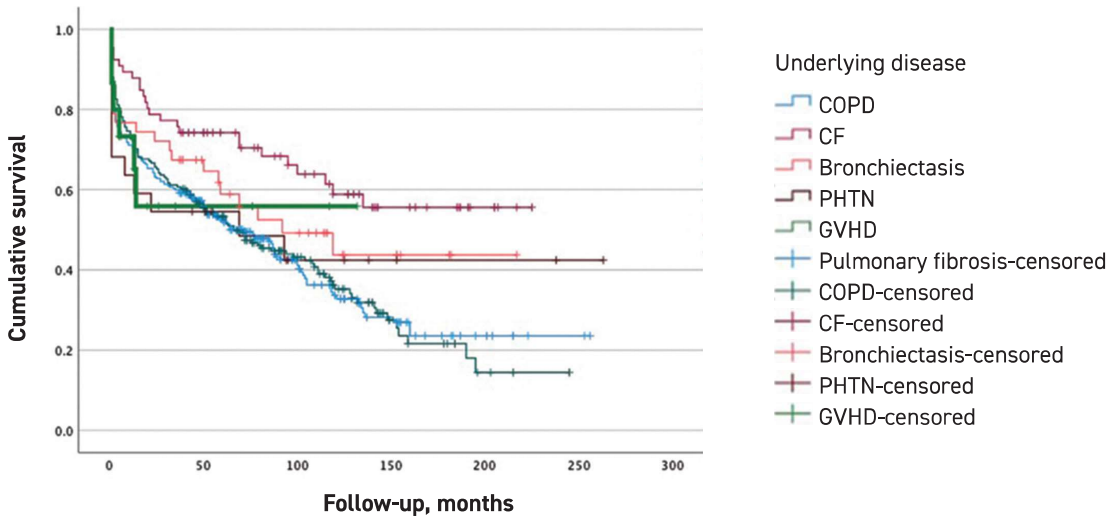

Table 1: Patients post-HSCT baseline characteristics and lung transplantation data

Episode of acute rejection	Hospital stay after LT (D)	Survival post LT (M)	Indication for LT	FEV1/DLco pre LT	Time from HSCT to LT (M)	Age in years at LT	Type of LT	Time from HSCT to pulmonary GVHD (M)	GVHD prophylaxis	GVHD extra pulmonary	Time from HSCT to LT (M)	Stem cell source	Type of HSCT	Hematologic disease	Age in years at HSCT	Sex	Patient number
No	17	6	BOS + Emphysema	41/29	96	61	Right	80	Prednisone	Ocular	96	Sibling	Allogeneic	AML	53	Male	1
Yes	19	136 (alive)	BOS	26/33	36	14	Double	12	MMF, cyclosporine, prednisone	Liver	36	Sibling	Allogeneic	MDS	11	Female	2
No	21	11 (alive)	PPFE	28/42	108	44	Left	18	Prednisone	Ocular, Skin	108	Sibling	Allogeneic	ALL	35	Male	3
No	15	15	BOS	37/52	48	42	Right	12	Cyclosporine, prednisone	Oral	48	Matched unrelated	Allogeneic	NHL	38	Female	4
No	200	13	BOS	15/NA	84	10	Double	24	Cyclosporine	Ocular	84	Sibling	Allogeneic	AML	3	Male	5
No	13	25 (alive)	BOS	17/20	120	60	Double	84	Cyclosporine, prednisone	Oral, Ocular, Liver, Skin	120	Sibling	Allogeneic	MDS	50	Male	6
No	9	40 (alive)	PPFE	22/33	108	42	Double	12	Cyclosporine, prednisone	Ocular, oral, Skin	108	Sibling	Allogeneic	AML	33	Male	7
No	9	122	BOS	17/46	72	38	Double	48	Prograf, imuran, prednisone	Ocular	72	Sibling	Allogeneic	AML	32	Female	8
No	62	2	BOS	21/NA	100	66	Double	14	Prednisone, cyclosporine	Oral, Ocular, Liver, Skin	100	Matched unrelated	Allogeneic	MDS	58	Female	9
No	16	80 (alive)	BOS	17/43	78	61	Double	60	Cyclosporine, crednisone	Ocular	78	Sibling	Allogeneic	NHL	55	Female	10
No	12	30 (alive)	BOS	40/10	180	30	Double	168	Cyclosporine	–	180	Sibling	Allogeneic	CVID	15	Male	11

Episode of acute rejection	Hospital stay after LT (D)	Survival post LT (M)	Indication for LT	FEV1/DLco pre LT	Time from HSCT to LT (M)	Age in years at LT	Type of LT	Time from HSCT to pulmonary GVHD (M)	GVHD prophylaxis	GVHD extra pulmonary	Time from HSCT to LT (M)	Stem cell source	Type of HSCT	Hematologic disease	Age in years at HSCT	Sex	Patient number
No	58	2	BOS	20/14	180	36	Living Donor	60	Prednisone	Ocular	180	Sibling	Allogeneic	ALL	21	Male	12
No	90	9 (alive)	BOS + Emphysema	24/35	63	60	Double	12	Cyclosporine, MMF, MTX, dexamethasone	Ocular, skin, oral, esophagus, liver, genitalia	63	Sibling	Allogeneic	AML	60	Female	13
No	68	18 (alive)	BOS	NA	156	18	Double	96	NA	–	156	Sibling	Allogeneic	AML	4	Male	14
No	32	2	BOS	30/ NA	42	36	Right	24	Cyclosporine, prednisone, MMF	Skin, GI	42	Sibling	Allogeneic	ALL	33	Male	15

ALL =acute lymphocytic leukemia, AML = acute myeloid leukemia, BOS = bronchiolitis obliterans syndrome, CVID = common variable immune deficiency, DLco = diffuse lung capacity, ECP = extracorporeal photopheresis, FEV1 = forced expiratory volume in one second, GI = gastrointestinal, GVHD = graft-versus-host disease, HSCT = hematopoietic stem cell transplantation, LTx =lung transplantation, MDS = myelodysplastic syndrome, MMF = mycophenolate mofetil, MTX = methotrexate, NA = not applicable, NHL = non-Hodgkin lymphoma, PPFE = pleuroparenchymal fibroelastosis

ic disease in any of these patients.

Compared to patients who were transplanted due to other indications, sex distribution was similar. Patients with GVHD were younger than patients who were transplanted due to IPF and COPD and at a similar age to those transplanted for CF, bronchiectasis, and PHTN. Ten of 15 patients underwent double LTx, which was higher than the rates of double LTx in IPF and COPD patients and lower than the rates in CF, bronchiectasis, and PHTN patients. Mean survival was higher than IPF and COPD transplanted patients, similar to bronchiectasis, and lower than CF and PHTN LTx patients. However, none of the differences were statistically significant [Figure 1]. Multivariate analysis for survival showed that age and double LTx have a significant effect on survival and that patients transplanted due to GVHD had a similar survival in comparison to patients who were transplanted for other indications [Table 2].

DISCUSSION

Late-onset pulmonary complications as a sequela of HSCT are a matter of concern. Recipients of allogeneic HSCT are at risk of developing chronic GVHD and approximately 20% will present with BOS with the risk of deteriorating to end-stage pulmonary disease. In the last decade there have been more publications of case series and studies that share their positive experience of LTx in patients with chronic pulmonary GVHD post-HSCT. Of the 850 LTx performed at our center over 23 years, 15 were due to chronic pulmonary GVHD post-HSCT. The majority of transplantations were performed between 2010 and 2020 reflecting a similar trend reported by other centers in the world of an increased number of LTx due to chronic pulmonary GVHD post-HSCT.

The mean survival after LTx of our 15 patients with chronic pulmonary GVHD following allogeneic HSCT was 34 months with a wide standard deviation (not shown). The cohort did not reach the median survival since eight patients are still alive and among those, two underwent LTx in the last year. The literature reveals similar results with one-year survival between 78–100% [6,7,10,12-14,16-20] and 5-year survival of 60–80%, [9,13-14,19-20,22,23] [Table 3]. We also reported similar survival rates in patients who underwent LTx due to chronic pulmonary GVHD post-HSCT and those transplanted for other indications. Multivariate analysis showed that age and double LTx were the only variables with a significant effect on survival, which con-

Table 2: Multivariate analysis for survival

	Hazard ratio	95% confidence interval	*P*-value
Age in years	1.01	1.0–1.02	0.05
Double lung transplantation	0.56	0.42–0.73	< 0.001
Sex	1.03	0.82–0.28	0.79
Graft-versus-host disease	1.47	0.65–0.35	0.35

curs with the results that have been published in the International Society for Heart and Lung Transplantation (ISHLT) registry.

The encouraging survival data demonstrates the feasibility of LTx in patients with chronic pulmonary GVHD post-HSCT, yet this treatment strategy is underutilized. Greer et al. [20], in their review of the pan-European experience of 105 patients, calculated that 350 patients die annually in Europe alone due to outcomes of late-onset noninfectious pulmonary complications of HSCT. At the Rabin Medical Center, 455 allogeneic HSCTs have been performed since 2007. Five other centers in Israel practice a similar amount of HSCT. Yet only 15 LTx post-HSCT have been performed at our center since 1997. This number of LTx recipients post-HSCT is similar to the rates reported in some other large centers for this indication [10,13,22,23] and further emphasizes the importance of raising awareness among hematologists and pulmonologists about this treatment option. Lack of organ availability might also hinder the implementation of LTx in chronic pulmonary GVHD. However, in HSCT patients living donor lobar transplantation is a viable possibility. The advantages of this procedure include a shortened time interval to transplantation since there is no need to wait for cadaveric donation. In our cohort, one patient had undergone a living donor lobar LTx. Unfortunately, the patient died 2 months after the transplantation due to respiratory failure while still in the intensive care. Most of the living donor lobar LTx are still performed in Japan. The study by Chen-Yoshikawa et al. [19] included six LTx centers in Japan. Amon 62 patients who underwent LTx after HSCT, 45 underwent living donor lobar LTx. The survival following living donor lobar LTx after HSCT from a different donor was almost identical to the survival of patients who underwent cadaveric LTx and inferior to that of patients who underwent living donor lobar LTx with at least one donor who served for both procedures [19]. In an era of continuous improvement in medical treatments, as seen for HSCT patients, the growing need for LTx is disproportionate to the available organ donations. It seems that in critically ill patients who cannot wait for cadaveric LTx, living donor lobar LTx could be a reasonable solution.

One of the main concerns in LTx after HSCT is the relapse of the underlying malignancy. According to the ISHLT consensus document for the selection of lung candidates from 2014, LTx should not be offered to adults with a recent history of malignan-

Table 3. Published cases of lung transplantation for graft-versus-host disease*,⁑

First author [reference number]	Year	Number of patients*	Origin of data	1-year survival %	5-year survival %	Additional information
Heath [6]	2001	4	Single center USA	100	NA	
Pechet [7]	2003	6	Single center USA	83	NA	
Yamane [8]	2008	7	Single center Japan	NA	NA	
Koenecke [9]	2010	13	Multicenter Pan European	NA	63	
Redel-Montero [10]	2010	3	Single center Spain	66	NA	
Beitinjaneh [11]	2010	3	Single center USA	NA	NA	
Whiston BA [12]	2012	4	Single center USA	100	NA	
Holm [13]	2012	13	Multicenter Europe/ Nordic countries	90	75	
Yousef [14]	2012	11	Multicenter USA/ Australia	80	60	
Vogl [15]	2013	7	Single center Austria	NA	NA	
Soubani [16]	2014	2	Single center USA	88	NA	Systematic review
Jung [18]	2016	9	Single center Korea	78	NA	
Chen-Yoshikawa [19]	2018	62	Multicenter Japan	85	64.2	
Greer [20]	2018	105	Multicenter Pan European	85	67	
Brockman [21]	2018	3	Single center Saudi Arabia	NA	NA	Systematic review
Kilman [22]	2019	18	Multicenter Australia	NA	80	
Lunardi [23]	2020	5	Single center Italy	NA	60	
Current report	2021	15	Single center Israel	80	NA	

*European and Japanese multicenter studies may have included patients from earlier reports
Single case reports were not included

cy [25]. A 2-year disease-free interval combined with a low predicted risk of recurrence after LTx may be reasonable. However, a 5-year disease-free interval is prudent in most cases. There was no evidence of recurrence of malignancy in our cohort. Moreover, an episode of acute rejection was rare among the LTx recipients in this cohort. In our institute, two bronchoscopies with lung biopsies are performed at weeks 2 and 4 after LTx to reveal a silent episode of acute rejection. Only one patient, who had a biopsy compatible with acute rejection, was treated with methylprednisolone. Long-term immunosuppression prior to LTx may have a protective role in this group of patients after HSCT. Thus, this group of patients may not be immunocompetent before LTx, as are other groups of patients who are candidates for LTx.

The major limitations of this study include its retrospective design, small cohort size, and short observation follow-up period in recent LTx cases. However, since LTx due to chronic GVHD post-HSCT is an emerging treatment option, it is of value to present this data to increase both awareness and confidence in this procedure.

CONCLUSIONS

LTx after HSCT constitutes an important treatment strategy. The overall survival appears to be comparable to patients after LTx for other indications. Future prospective studies are warranted to identify indications for LTx in this population and determine the precise immunosuppression and infection prophylaxis needed.

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Life is an adventure in forgiveness.
Norman Cousins (1915–1990), author, editor, journalist, and professor