Lung Transplantation for Pulmonary Graft Versus Host Disease: Experience from a Referral Organ Transplantation Center

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Article

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Abstract

Introduction: Severe pulmonary GvHD after allo-HCT is a significant cause of morbidity and mortality with limited therapeutic options. Selected patients can be lung transplanted, however there are no consensus guidelines on whom to select nor on when to refer.

Method: Retrospective review of patients who underwent LT for lung GvHD after allo-HCT.

Results: Ten patients were identified between January 2002 and December 2020. The median age at LT was 31 years. Seven patients developed aGvHD after allo-HCT and all patients developed cGvHD. The median immunosuppressive lines used before lung transplant was four. The median time between allo-HCT and bronchiolitis obliterans syndrome was 20.5 months. The median time from allo-HCT to LT was 71 months. The median time from first lung transplant evaluation to actual LT was 61 months. The median time from listing for LT to actual LT was 4.8 months. The median FEV1 upon referral to LT clinic was 31% and the median FEV1 upon LT was 25%. All patients received cadaveric bilateral lung transplants. After a median follow up of 4.5 years post-LT, the estimated 5-years OS after LT was 85.7%. The cumulative incidence of CLAD was 50% with a median time from LT to CLAD of 47 months. The CLAD-free survival at 5 years was 50%. Two patients died after developing CLAD complications. No hematologic relapse nor secondary malignancies reported.

Conclusion: LT is an effective intervention for selected lung GvHD patients. Multidisciplinary management and consensus guidelines are needed to better serve these patients.

Introduction

More than 90 thousand allogeneic hematopoietic cell transplantation (allo-HCT) are carried out annually, and around 1.5 million post allo-HCT survivors exist worldwide [1]. Improved survival rates have been reported in recent decades with the use of less-toxic conditioning regimens, better donor selection and better supportive care [2, 3]. Chronic graft versus host disease (cGvHD) however is increasing with the increased use of alternate donors and peripheral blood as the main stem cell source [4, 5]. Late onset pulmonary complications in allo-HCT recipients are common, the majority are attributed to pulmonary cGvHD, which is a problematic complication with no proven successful therapies, and limited long-term survival rates [6-11]. In 1992, the first case of lung transplant (LT) for lung cGvHD was reported [12], and since then a significant number of cases underwent LT with various success rates [13-19]. The optimal timing for LT is controversial and needs to be made in a multidisciplinary setting. Many aspects have to be accounted for, including the risk of relapse of the underlying malignancy, the risk of other complications post LT, the availability of donors and the comorbidities of the recipient. We herein present 10 patients who underwent LT for lung GvHD post allo-HCT in our regional organ transplantation referral center.

Patients And Methods

Patients

We retrospectively reviewed our institutional allo-HCT database and identified patients who underwent LT after allo-HCT. Demographics were collected from the charts. Data on allo-HCT and LT including outcomes and transplant related variables were obtained from the institution's prospective transplantation (allo-HCT and LT) databases. LT recipients were selected after multidisciplinary assessment, as there are no international guidelines for selecting LT recipients for lung GvHD; however, the selection process was closely aligned with the international recipient selection guidelines [20]. Lung donors were selected according to standard protocols [21]. This study was approved by our Institutional Review Board.

Definitions

The primary endpoint for our study was the 5 years overall survival (OS) after LT. The secondary endpoints were the long-term complications (chronic lung allograft dysfunction (CLAD) incidence, CLAD-free survival, primary hematologic disease relapse, second cancers and Lung infection during first year post-LT). OS was calculated from the date of LT until death or last follow-up. CLAD, acute and chronic GvHD were defined according to the standard criteria [22-25].

Statistics

Patient characteristics were summarized using frequency with percentage for categorical variables and median with interquartile range (IQR) for continuous variables. Survival estimates were calculated according to the Kaplan-Meier method. Cumulative incidence was calculated using cumulative incidence function accounting for competing risks. Statistical analysis was carried out using RStudio 2022.07.2 Build 576© 2009-2022 RStudio, PBC.

Results

Patient, Donor, Transplantation, and Graft Characteristics

Ten patients who received LT after allo-HCT were identified between January 2002 and December 2020. The median age at LT was 31 years (IQR: 25.25 - 39.75). The indication for allo-HCT was acute lymphoblastic leukemia (ALL) in five cases, acute myeloid leukemia (AML) in two cases and severe aplastic anemia (SAA), classic Hodgkin lymphoma (cHL), chronic myeloid leukemia (CML) in lymphoid blast crisis one each. The stem cell donor was matched sibling donor (MSD) in all cases with peripheral blood stem cell source in all cases except the SAA case where the source was bone marrow. The conditioning was myeloablative in all cases except in the case of SAA and the case of cHL it was reduced intensity. Five patients received total body irradiation (TBI) based conditioning and the other five non-TBI based conditioning. Seven patients developed aGvHD after allo-HCT and all patients developed cGvHD. The median immunosuppressive (IS) lines used before lung transplant was four (range 3 - 6). At the time of referral for first evaluation for LT, one patient was on triple IS, four on double and five on single IS. At the time of LT, four patients were on single IS, three on double IS and three on no IS. The median time between allo-HCT and bronchiolitis obliterans syndrome (BOS) was 20.5 months (IQR: 12 - 24). The median time from allo-HCT to LT was 71 months (IQR: 50 - 137). The median time from first lung transplant evaluation to actual LT was 61 months (IQR: 14 - 114). The median time from listing for LT to actual LT was 4.8 months (IQR: 2 – 7.2). The median FEV1 upon referral to LT clinic was 31% (IQR: 23.75 - 32.6%) and the median FEV1 upon LT was 25% (IQR: 18.5 - 29.3%) with two patients being on mechanical ventilation, one on high flow oxygen and six dependent on home oxygen. The indication for LT was respiratory failure caused by fibrosis and BOS in all patients. All patients received cadaveric bilateral lung transplants. Five patients had donor specific antibodies against their lung donors. All LTs were ABO compatible except one and none was HLA matched. Lung retrieval and transplant surgery followed standard practice. **Table 1** summarizes the recipient's pre-LT characteristics.

Outcomes

After a median follow up of 4.5 years (95% CI: 3.9 – 5.1) post-LT, the estimated 5-years OS after LT was 85.7%. Three patients developed acute lung rejection, however two were grade A1 and did not require any intervention and the third was grade A2 and was managed successfully with pulse steroids. Six patients developed pulmonary infections in the first year post-LT (*Acinetobacter*, *Burkholderia* and *Staphylococcus*, *E. coli*, *Klebsiella* and *Staphylococcus*, *Klebsiella* and *Pseudomonas*, *Pseudomonas*). The cumulative incidence of CLAD was 50% with a median time from LT to CLAD of 47 months (IQR: 20 - 65). The CLAD-free survival at 5 years was 50%. Two patients died after developing CLAD complicated by frequent infections. Hematologic relapse did not occur in any of the patients nor post-transplant lymphoproliferative disorder. At the time of last follow up, none of the patients is on oxygen and no secondary malignancies have been reported. **Table 2** is a summary of the outcomes.

Discussion

Approximately 10% of patients with cGvHD develop pulmonary obstructive syndromes as part of their cGvHD manifestation, with variable rate and extent depending on the severity of cGvHD [6, 26-29]. The precise causes and risk factors remain unknown with many proclaimed factors (older age, pre allo-HCT lung diseases, autoimmune diseases, alternate donor, conditioning type and intensity, graft source, viral infections post allo-HCT, GvHD, etc.) [9, 26, 27, 30-32]. The prognosis of these patients is grim and their management is challenging and frustrating with limited survival in advanced cases [7-9, 11, 26, 30, 33, 34]. The management of these patients relies on immunosuppression and other supportive medications in addition to extracorporeal photopheresis (ECP) [9, 26, 30, 35-39]. Up to six lines of IS agents were tried in this cohort (with a median of four lines) before considering LT, an indication about the suboptimal efficacy of medical interventions for this deleterious condition. The median lines of IS before LT was not reported in the previously published reports to compare to the current report. Many groups reported good outcomes of LT for lung GvHD, however the number of cases reported in the literature still minuscule compared to the scale of the problem [13-19]. Additionally, it is unknown how many BOS patients need LT but are not eligible or die while on the LT waiting list.

The cases in this report are all young with a median age of 31 years. Although, this is a relatively young age, the majority of series reported a younger or similar median age reflecting the inherent selection bias favoring young patients [15-17, 40]. The majority received a myeloablative and radiation based conditioning along with peripheral blood stem cells as a graft source. All these factors predispose to GvHD and to the development of pulmonary obstructive syndromes [9, 26, 27, 30-32]. The median time between allo-HCT and BOS was 20.5 months with a median time from allo-HCT to LT of 71 months and a median time from first LT evaluation to actual LT of 61 months. The median time from listing for LT to actual LT was 4.8 months. In the largest published case series, the median time between allo-HCT and LT was 52.3 months and the other time intervals were not reported [16]. In another report, LT was performed at a median of 8.6 years after allo-HCT with a median interval of 16 months from the time of transplant review to actual LT [40]. Two case series of 9 patients each reported a median interval between HCT and LT of 10 years in one series[15] and a median interval from the diagnosis of BOS to LT of 17.1 months [17]. Another group reported 7 patients with a median time from HCT to BOS of 8.2 months and a median time between BOS and LT of 18.1 months [14]. These heterogeneous timelines reported and the variability reflects the need for a concise and consensus reporting methods in order to build guidelines and consensus

recommendations. The vast majority of literature reported oxygen dependency and lung function at the time of LT but did not report these upon the referral to consider LT evaluation [16, 17]. The median FEV1 upon referral in our report was 31% (down to 25% at the time of LT with two patients being on mechanical ventilation, one on high flow oxygen and six dependent on oxygen). Reporting these numbers is valuable to establish referral triggers and guidance on when to refer. In our cohort as well as the vast majority of reports, the patients received cadaveric bilateral lung transplants [13-17, 40-42]. However, living lobar LT is reported and can be an option for critically ill patients who cannot wait for cadaveric LT [16, 43, 44]. After a median follow up of 4.5 years post-LT, the estimated 5-years OS after LT in our cohort was 85.7%. This compares favorably with most reported literature about LT for cGvHD or other indications [13-17, 40-47]. The better survival of LT patients for BOS is probably related to the inherent selection bias as well as the management of these patients in highly specialized centers as compared to lung transplant patients transplanted for other indications. Three out of 10 patients developed acute lung rejection, a rate consistent with rejection rates after lung transplant in general [42]. The cumulative incidence of CLAD was 50% with a median time from LT to CLAD of 47 months, which is also consistent with rates after lung transplant in general [48]. These rates are also in line with the other publications regarding LT for BOS [13-17, 40-42]. Six patients developed lung infections in the first year post-LT and this does not appear higher than the general population of LT patients [46, 49]. None of our patients developed hematologic disease relapse. Relapse of the underlying disease has been consistently low as reported from different groups and has been linked to time from allo-HCT to LT with higher relapses in patients undergoing LT earlier post allo-HCT [16, 19, 41, 46, 50]. In general, patients with cGvHD are less likely to have disease relapse, as cGvHD is a surrogate marker for graft vs malignancy effect. The International Society of Heart and Lung Transplantation (ISHLT) does not recommend LT within the first 2 years after the treatment of malignancy and advices to have five years disease free interval prior to considering LT [20]. None of our patients developed secondary cancer during their follow up, a well know complication after solid organ transplants that increases with time from organ transplant [16, 46]. Two patients died after developing CLAD complicated by frequent infections and this is consistent with the causes of death after LT in general [13-17, 40, 46, 49, 50]. In the largest LT for BOS publication, the only variable associated with mortality was the LT recipient gender [16].

Our study suffers from the typical limitations of retrospective reviews and the small sample size impedes statistical validation of many variables and risk factors. Organ availability (with preferential selection of recipients without history of malignancy) and relapse of the underlying malignancy are major barriers. However, as shown in our cohort and from other publications, the results are comparable if not better than the results of LT in general and the risk of relapse is negligible. Acknowledging the need of appropriate utilization of the scarce resource of deceased donor lungs, young patients with at least two years relapse free post allo-HCT without other organ dysfunction or other severe manifestations of cGvHD are the best to benefit.

Conclusion

Many controversies remain surrounding LT for BOS patients. The literature suffers from being retrospective and of limited sample size. However, running prospective trials for such intervention is not practical. The lack of consistency in definitions between different reports and reporting bias are also major setbacks. Efforts should be undertaken, to unveil this option and to establish a consensus between hematologist and surgeons on triggers for referral, multidisciplinary management and patient selection. This report, added to the growing international literature, highlights the value of LT in patients with lung obstructive syndromes after allo-HCT.

Declarations

Author contributions: all authors contributed to the concept, design of this report, and contributed to data collection. R.E wrote the first draft. All authors reviewed and approved the final version.

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Tables

Table 1: summary of the recipient's pre-LT characteristics

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9	Case 10
Age	33	38	60	43	32	37	48	32	20	29
Sex	Male	Male	Male	Female	Male	Male	Male	Female	Female	Male
Allo-HCT indication	T-ALL	B-ALL	AML	B-ALL	SAA	AML	CML in lymphoid blast crisis	B-ALL	B-ALL	cHL
Conditioning	Cy/TBI	Cy/TBI	Bu/Cy	Cy/TBI	Flu/Cy	Bu/Cy	Cy/TBI	Cy/TBI	Thio/Bu/Flu	Bu/Flu
Acute GvHD	Grade II (upper GI)	Grade I (skin)	Grade I (skin)	Grade III (lower GI)	Grade II (lower GI)	No	No	No	Grade III (skin and liver)	Grade III (lower GI)
Organs affected by aGvHD	Upper GI	Skin	Skin	Gut	Gut	Na	Na	Na	Skin and liver	Gut
Chronic GvHD	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Organs affected by cGvHD	Oral, skin, liver, lung (BOS)	Oral, skin, eyes, lung (BOS)	Oral, skin, eyes, liver, lung (BOS)	Oral, skin, eyes, lung (BOS)	Skin, eye, liver, lung (BOS)	Oral, liver, lung (BOS)	Skin, eyes, liver, gut, lung (BOS)	Oral, skin, liver, gut, lung (BOS)	Oral, skin, liver, lung (BOS)	Oral, skin, lung (BOS)
Number of IS lines tried before LT	4	3	3	4	4	4	3	4	5	6
FEV1 before LT	N/A	On MV	28.6%	N/A	N/A	21%	30%	16%	On MV	25%
Sputum culture before LT	Clear	*Burkholderia*	Clear	Clear	*Candida*	Clear	Clear	Clear	*Pseudomonas*	N/A
Indication for LT	Fibrosis with BOS	Fibrosis with BOS	Fibrosis with BOS	Fibrosis with BOS	Fibrosis with BOS	Fibrosis with BOS	Fibrosis with BOS	Fibrosis with BOS	Fibrosis with BOS	Fibrosis with BOs

ALL (acute lymphoblastic leukemia), aGvHD (acute graft versus host disease), Allo-HCT (allogeneic hematopoietic cell transplant), AML (acute myeloid leukemia), BOS (bronchiolitis obliterans syndrome), Bu/Cy (busulfan/cyclophosphamide), Bu/Flu (busulfan/fludarabine), cGvHD (chronic graft versus host disease), cHL (classic Hodgkin lymphoma), CML (chronic myeloid leukemia), Cy/TBI (cyclophosphamide/total body irradiation), FEV1 (forced expiratory volume 1), GI (gastrointestinal), IS (immunosuppressive) , LT (lung transplant), MV (mechanical ventilation), N/A (not applicable or not available), SAA (severe aplastic anemia), Thio/Bu/Flu (thiotepa/busulfan/fludarabine)

Table 2: summary of the outcomes after LT

5 years OS after LT	85.7%
Median follow up post-LT	4.5 years
Acute lung rejection	30%
Grade	2 grade A1 and one grade A2
Lung infection during first year post-LT	60%
CLAD cumulative incidence	50%
CLAD-free survival at 5 years	50%
Median time from LT to CLAD	47 months
Oxygen use post-LT	0%
Hematologic disease relapse	0%
Second cancers	0%

CLAD (chronic lung allograft dysfunction), LT (lung transplantation), OS (overall survival)