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Outcomes of Lung Transplantation after Allogeneic Hematopoietic Stem Cell Transplantation

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A B S T R A C T

Other than lung transplantation (LT), no specific therapies exist for end-stage lung disease resulting from hematopoietic stem cell transplantation (HCT)-related complications, such as bronchiolitis obliterans syndrome (BOS). We report the indications and outcomes in patients who underwent LT after HCT for hematologic disease from a retrospective case series at our institution and a review of the medical literature. We identified a total of 70 cases of LT after HCT, including 9 allogeneic HCT recipients from our institution who underwent LT between 1990 and 2010. In our cohort, the median age was 16 years (range, 10 to 35 years) at the time of HCT and 34 years (range, 17 to 44 years) at the time of LT, with a median interval between HCT and LT of 10 years (range, 2.9 to 27 years). Indications for LT-included pulmonary fibrosis (n = 4), BOS (n = 3), interstitial pneumonitis related to graft-versus-host disease (GVHD) (n = 1), and primary pulmonary hypertension (n = 1). Median survival was 49 months (range, 2 weeks to 87 months), and 1 patient remains alive at more than 3 years after LT. Survival at 1 year and 5 years after LT was 89% and 37%, respectively. In the medical literature between 1992 and July 2013, we identified 20 articles describing 61 cases of LT after HCT from various centers in the United States, Europe, and Asia. Twenty-six of the 61 cases (43%) involved patients age <18 years at the time of LT. BOS and GVHD of the lung were cited as the indication for LT in the majority of cases (80%; n = 49), followed by pulmonary fibrosis and interstitial lung disease (20%; n = 12). In publications reporting 3 or more cases with a follow-up interval ranging from the immediate postoperative period to 16 years, the survival rate was 71% (39 of 55). Most deaths were attributed to long-term complications of the lung allograft, including infections and BOS. Two deaths were related to recurrent or relapsed hematologic malignancy. LT can prolong survival in some patients who suffer from end-stage pulmonary complications after HCT. Patient factors that likely improve the chances of a good long-term outcome include young age, at least 2 years post-HCT free of relapse from the original hematologic malignancy, and lack of other end-organ dysfunction or manifestations of chronic GVHD that require treatment with immunosuppressive agents.

INTRODUCTION

Survival after allogeneic hematopoietic stem cell transplantation (HCT) has improved over the course of several decades, owing to the development of less-toxic pretransplantation conditioning regimens, more effective prophylaxis of acute graft-versus-host disease (GVHD), improved infection control, and advances in supportive care in the posttransplantation period [1]. Accordingly, more individuals are living longer after HCT.

Long-term survival still comes at a cost, however. Up to 26% of allogeneic transplant recipients develop late-onset noninfectious pulmonary complications, including bronchiolitis obliterans syndrome (BOS). BOS, considered part of the spectrum of chronic GVHD (cGVHD) manifestations [2], affects 5.5% of allogeneic transplant recipients and 14% of those who develop cGVHD [3]. In addition to BOS, allogeneic HCT recipients may suffer from other manifestations of pulmonary GVHD, such as cryptogenic organizing pneumonia, or from pulmonary fibrosis resulting from treatment for the underlying malignancy or the pretransplantation regimen. These noninfectious pulmonary complications of allogeneic HCT significantly compromise quality of life and contribute to nonrelapse mortality after cure of the patient's original hematologic disease.

Lung transplantation (LT) is now a well-established therapy for many pulmonary conditions—chronic obstructive pulmonary disease, cystic fibrosis, idiopathic pulmonary fibrosis—when all other forms of medical and surgical therapy have failed. Through June 2012, 45,000 LTs have been reported worldwide [4]. Similar to some of these pulmonary conditions, no specific disease-modifying therapies exist for BOS related to cGVHD or toxicity-related interstitial lung disease. Thus, it seems reasonable to consider LT as an option for BOS or other pulmonary complications when end-organ damage has resulted in severe compromise of activities of daily living and appears to be inexorably leading to the patient's early demise.

The first case of LT after bone marrow transplantation was reported in 1992 [5], and since then, sporadic case reports and case series have been published documenting the use of

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this procedure to treat life-threatening pulmonary complications of HCT. Even so, LT after HCT is rare, and the outcomes of LT in this population have not been well described.

In this report, we present our institutional experience with outcomes of LT after HCT and review the experience reported in the literature. We also review the current considerations of LT and propose recommendations for the selection of appropriate candidates for LT from this population of patients.

METHODS

Case Series

We performed a retrospective chart review of cases of LT performed after HCT at Fred Hutchinson Cancer Research Center (FHCRC). Cases of LT after HCT were identified by physicians of the Long-Term Follow-Up (LTFU) program and pulmonary consultative services. The data used in this study rely on documentation in the medical record generated by the LTFU, which provides lifelong telemedicine to all patients undergoing transplantation at FHCRC and to their physicians in addition to onsite consultation, as described previously [6]. All patients who underwent allogeneic HCT at FHCRC between January 1971 and December 2011 with proven documentation of LT from the LTFU database are included in this report. This time frame for the cohort was selected to ensure adequate follow-up time. Follow-up for identified LT cases was date of recorded death or December 31, 2013, whichever came first. Clinical information was extracted by chart and database review. Written consent for the use of medical records for research was obtained from patients before transplantation. This study was approved by the FHCRC Institutional Review Board.

Literature Review

We performed a computerized search of the MEDLINE and Scopus databases using the key terms "lung transplantation," "after," "bone marrow transplantation," "hematopoietic cell transplantation," and "bronchiolitis obliterans" between January 1991 and July 31, 2013. We also reviewed reference lists of included studies for additional publications. All English language publications describing a case of LT after HCT were included. Publications were reviewed individually, and specific parameters and outcomes were collated.

Statistical Analysis

Survival analysis was performed with the Kaplan-Meier method.

RESULTS

Patient Characteristics and Outcomes after LT

We identified 9 individuals out of 10,548 recipients of allogeneic HCT performed in Seattle between 1971 and 2011 who subsequently underwent LT between 1990 and 2010 (Table 1). The median age at HCT was 16 years (range, 10 to 35 years). Indications for HCT included acute leukemia (n = 7), chronic myelogenous leukemia (n = 1), and aplastic anemia (n = 1). Six patients underwent HCT from an HLA-matched related donor, and the other 3 did so from an HLA-matched unrelated donor. The median age at LT was 34 years (range, 17 to 44 years), with a median interval of 10 years (range, 2.9 to 27 years) from HCT to LT. Indications for LT included interstitial lung disease (ie, interstitial fibrosis, pulmonary fibrosis, interstitial pneumonitis) in 5 patients, BOS in 3 patients, and primary pulmonary arterial hypertension in 1 patient. Four patients underwent single LT, and 5 underwent bilateral LT; all transplanted lungs were from cadaver donors. Owing to a wide geographic distribution as well as variability in LT selection criteria, the patients underwent LT at several institutions. Data regarding pulmonary function tests, immunosuppressive medications, and the presence of active cGVHD were limited.

Of the 9 patients who underwent LT over a period of >20 years, 1 patient remains alive more than 3 years after his bilateral LT and 7 years after his HCT. Median survival after LT was 49 months in the remaining patients (Figure 1). One-year survival of this cohort was 89%, and 5-year survival was 37%. Most of the deaths were related to lung allograft rejection or infectious complications (Table 1). One patient died at 2 weeks after LT; the cause was not reported.

Literature Review

Excluding our present cohort, a total of 61 cases of LT after HCT were reported in 20 published manuscripts in the English language medical literature between 1992 and 2013

Table 1
Characteristics of the Case Series Cohort, FHCRC

Case	Sex	Year of LT	Age at HCT, yr	Age at LT, yr	Indication for HCT	HCT Source	Time from HCT to LT, mo	Indication for LT	Type of LT	Survival after LT	Cause of Death
1	Female	1990	19/23	25	ALL	BM (2), related	35	Pulmonary fibrosis due to chemotherapy	Single	6 yr, 2 mo	Chronic rejection/CMV pneumonitis
2	Female	1991	11	17	AML	BM, related	66	Interstitial fibrosis due to radiation therapy, versus interstitial pneumonitis due to GVHD	Single	4 yr, 6 mo	Respiratory failure/ progressive pneumonia due to stenotic complication of LT
3	Male	1995	16	40	Aplastic anemia	BM, related	292	BOS	Bilateral	3 yr, 8 mo	Chronic graft rejection (bronchiolitis obliterans), bilateral bronchial stenosis, pseudomonas infection
4	Female	1997	10	24	ALL	BM, related	174	BOS	Bilateral	2 yr, 7 mo	Brain damage due to cardiac/respiratory arrest
5	Male	2000	35	44	AML	BM, related	123*	Interstitial pneumonitis/ interstitial fibrosis	Single	2 wk	Immediate post-LT; immediate cause unknown
6	Female	2002	32	41	CML	BM, unrelated	113	Primary pulmonary hypertension not related to malignancy or HCT	Single	7 yr, 3 mo	Respiratory failure/viral pneumonia in transplanted lung; recurrence of CML
7	Female	2004	10	37	AML	BM, related	326	Pulmonary fibrosis due to chemotherapy and radiation therapy	Bilateral	6 yr, 1 mo	Septic shock, pulmonary fungal infection
8	Male	2009	16	34	ALL	PBSC, unrelated	204	Pulmonary fibrosis due to chemotherapy and radiation therapy	Bilateral	2 yr, 6 mo	Chronic graft rejection/ primary graft dysfunction
9	Male	2010	28	32	ALL	PBSC, unrelated	45	BOS	Bilateral	>3 yr	NA

LT, lung transplantation; HCT, hematopoietic stem cell transplantation; BM, bone marrow; PBSC, peripheral blood stem cells; ALL, acute lymphoblastic leukemia; AML, acute myelogenous leukemia; CML, chronic myelogenous leukemia; GVHD, graft-versus-host disease; BOS, bronchiolitis obliterans syndrome; CMV, cytomegalovirus; NA, not applicable.