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INTERSTITIAL LUNG DISEASE

Experience of Lung Transplantation in Patients with Lymphangioleiomyomatosis at a Brazilian Reference Centre

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Abstract

Introduction Lung transplantation (LT) is the standard of care for patients with advanced lung diseases, including lymphangioleiomyomatosis (LAM). LAM accounts for only 1% of all LTs performed in the international registry. As a result, the global experience, including the use of mechanistic target of rapamycin (mTOR) inhibitors before and after LT in LAM, is still limited.

Methods We conducted a retrospective review of all LAM patients who underwent LT at our centre between 2003 and 2016. Pre- and post-transplant data were assessed.

Results Eleven women with LAM underwent LT, representing 3.3% of all procedures. Ten (91%) patients underwent double-LT. The mean age at diagnosis was 39 ± 6 years and the mean FEV_1 before LT was $28 \pm 14\%$. Only one patient underwent pleurodesis for recurrent pneumothorax. Pulmonary hypertension was confirmed in 3 (27%) patients. Four (36%) patients received sirolimus preoperatively; three of them received it until the day of LT, and there was no occurrence of bronchial anastomotic dehiscence after the procedure. Four patients (36%) received mTOR inhibitors post-transplant. The median follow-up from LT was 44 months. There were 3 deaths (27%) during the study and survival probabilities at 1, 3, and 5 years after LT were, 90, 90, and 77%, respectively.

Conclusions This data reinforces the role of LT for LAM patients with end-stage disease. The use of sirolimus seems to be safe before LT and the occurrence of complications after LT, including those LAM-related, should be continuously monitored.

Keywords Complications · Immunosuppressive agents · Lung transplantation · Lymphangioleiomyomatosis · Mortality

Abbreviations

6MWT	Six-minute walk test
BD	Bronchodilator
BOS	Bronchiolitis obliterans syndrome
CLAD	Chronic lung allograft dysfunction
CMV	Cytomegalovirus
CNi	Calcineurin inhibitor
DL_{CO}	Carbon monoxide diffusion capacity
FEV_1	Forced expiratory volume in the first second
FVC	Forced vital capacity
LAM	Lymphangioleiomyomatosis
LT	Lung transplantation
mTOR	Mechanistic target of rapamycin
PFT	Pulmonary function test
PH	Pulmonary hypertension
RHC	Right heart catheterisation
RV	Residual volume
Sp_{O_2}	Oxygen saturation
TLC	Total lung capacity

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Introduction

Lymphangioleiomyomatosis (LAM) is a rare low-grade neoplasm that is characterized by proliferation of atypical muscle-cells (LAM cells) around airways and lymphatic and blood vessels, leading to diffuse pulmonary cyst formation [1, 2]. The main pulmonary manifestations of LAM include progressive dyspnea and recurrent pneumothorax, whereas extrapulmonary manifestations include renal angiomyolipoma and chylous effusions. LAM occurs sporadically or associated with tuberous sclerosis complex. It presents a variable course from indolent lung cysts to progressive respiratory insufficiency [1, 3]. Prognosis in LAM is therefore heterogeneous and recent data demonstrate the 5- or 10-year survival rates to be approximately 90% [3, 4].

Recently, a molecular-targeting therapy for LAM has been established. A multicenter clinical trial showed that sirolimus, an inhibitor of mechanistic target of rapamycin (mTOR), may stabilize or improve results of pulmonary function tests (PFTs) in LAM patients [5]. In addition, sirolimus is recommended for patients with extrapulmonary manifestations, such as renal angiomyolipoma and chylous effusions [2, 6].

Despite using mTOR inhibitors, some LAM patients may require lung transplantation (LT) due to progressive loss of pulmonary function; and LT significantly increases survival benefit and improvement in quality of life [7–14]. Although it is not completely defined when to refer LAM patients to a transplant program, LT should be considered for those who present with severe functional impairment (forced expiratory volume in the first second, FEV_1 below 30% of predicted), New York Heart Association functional class III or IV, and/or hypoxemia at rest [1].

Over the past few decades, mTOR inhibitors have increasingly been used as adjunctive immunosuppressive drugs in LT, mainly as an approach to minimize exposure to renal toxic effects of calcineurin inhibitors (CNis) [15]. However, there is still concern regarding its perioperative use because of the possibility of increase in the risk of bronchial dehiscence postoperatively due to impaired wound healing secondary to its antiproliferative effects. Therefore, it is controversial whether the use of this drug is safe until LT and it may be used postoperatively only after confirming complete bronchial anastomotic healing [16].

LAM is a rare indication for LT compared to other end-stage lung disease such as chronic obstructive pulmonary disease. It accounts for only 1% of all LT in the international registry [7], and the survival rate seems to be comparable among these diseases.

The aim of this study is to describe pre-transplant features of LAM patients that underwent LT in a Brazilian reference centre and postoperative outcomes, including early morbidity and mortality, disease-related complications and survival. Furthermore, we discuss the role of mTOR inhibitors in the pre and post LT period.

Methods

We conducted a retrospective study that included all LAM patients who underwent LT at a national reference centre in Sao Paulo, Brazil, from 2003 to 2016. The following data were analyzed in all patients: pre-transplant characteristics, such as demographic and clinical findings, diagnostic methods to confirm LAM diagnosis, PFTs, six-minute walk test (6MWT) results, prevalence of pulmonary hypertension (PH), use of mTOR inhibitors and supplemental oxygen therapy; post-transplant data, including immunosuppressant therapy, prevalence of complications of the underlying disease, and related to LT, causes of death and survival. The choice of side selection when single-LT was performed was based on the availability of the donor lung. Basiliximab was universally used in the LT induction protocol for all patients since 2014. Our standard protocol for immunosuppression after LT included a CNi (tacrolimus or cyclosporine), plus azathioprine or mycophenolate, plus prednisone. The goal serum levels for sirolimus and everolimus users post-transplant were 5–15 and 3–6 ng/mL, respectively, whereas for tacrolimus and cyclosporine users they were 8–12 and 150–200 ng/mL, respectively. Our standard prophylaxis after LT included cefepime, sulfamethoxazole–trimethoprim, ganciclovir, itraconazole, nystatin, and inhaled amphotericin B. The study was approved by the Local Research Ethics Committee.

PH was defined by the presence of mean pulmonary arterial pressure $\geq$25 mmHg obtained in the right heart catheterisation (RHC) and could be pre-capillary PH (when pulmonary artery occlusion pressure $\leq$15 mmHg) or post capillary PH (when pulmonary artery occlusion pressure >15 mmHg) [17].

All PFTs were obtained based on the American Thoracic Society/European Respiratory Society standards [18–20]. Spirometry was performed using a calibrated pneumotachograph (Medical Graphics Corporation, St. Paul, MN), and lung volumes and carbon monoxide diffusion capacity (DL_{CO}) values were obtained with a body plethysmograph (Elite Dx, Elite Series; Medical Graphics Corporation). The following variables were obtained: forced vital capacity (FVC), FEV_1, total lung capacity (TLC), residual volume (RV), and DL_{CO}. Predicted values were derived from the Brazilian population [21–23]. The prevalence of a positive response to bronchodilators (BDs) was defined by changes in FEV_1 and/or FVC of $\geq$12% and 200 mL over baseline [24].

Patients performed the 6MWT according to recommended standards [25]. Oxygen saturation (Sp_{O_2}) as

measured by pulse oximetry (Onyx, model 9500; Nonin, Plymouth, MN) was obtained at rest and at the end of exercise.

Statistical Analysis

Continuous variables are reported as mean ± SD for those with normal distribution, whereas categorical variables are presented as proportions. Survival was calculated by Kaplan–Meier analysis. Data were analyzed with SigmaStat version 3.5 (Systat Software, Inc., San Jose, California).

Results

From 2003 to 2016, 11 LAM patients underwent LT at our centre representing 3.3% of all LTs performed. Ten (91%) patients underwent double-LT, while 1 (9%) patient underwent single-LT. The main clinical characteristics before LT are described in Table 1. The mean age at diagnosis was 39 ± 6 years, whereas the mean interval between LAM diagnosis and transplant was 4 ± 3 years. Most patients had sporadic LAM (91%), and the main respiratory manifestations were dyspnea and pneumothorax. Only 1 patient underwent pleurodesis for recurrent pneumothorax, whereas 5 patients (45%) underwent lung biopsy to confirm the diagnosis of LAM. Six patients underwent RHC, with mean pulmonary arterial pressure of 26 ± 4 mmHg (range 20–35 mmHg). PH was confirmed in 3 patients (27%), all of them with pre-capillary PH. Four (36%) patients received sirolimus preoperatively, and three of them (27%) received it until the time of LT. The other patient stopped using sirolimus due to recurrent respiratory infections 6 months before LT. No patient had preoperative diabetes.

The last PFT and 6MWT results before LT are included in Table 1. The FEV_1 and DL_{CO} were 28 ± 14% of predicted and 30 ± 18% of predicted, respectively. All patients had an obstructive pattern, air trapping, and reduced DL_{CO}. Nine (82%) patients performed the 6MWT. The mean distance walked was 325 ± 109 m, and the minimum Sp_{O_2} at the end of the test was 84 ± 8%.

The ischemic time for the right LT was 354 ± 94 min and for the left lung, it was 388 ± 131 min. Specifically, for the three patients who received sirolimus until the time of LT, the ischemic time for the right and left lung was 352 ± 63 and 385 ± 123 min, respectively. There was no intraoperative complication, although 1 patient (9%) required cardiopulmonary bypass for persistent hypoxemia. Three patients (27%) received intraoperative basiliximab, and all patients received 500 mg of methylprednisolone induction during the procedure. All patients received postoperative norepinephrine. The duration of hospitalization after LT was 34 ± 17 days (range 19–71).

Postoperative details are described in Table 2. All patients received triple-drug maintenance immunosuppressive therapy following transplantation. Four patients (36%) received mTOR inhibitors after transplantation, two received sirolimus and two received everolimus, as CNi sparing strategy for renal dysfunction. mTOR inhibitors were started 32 ± 24 months after LT (range 8–60 months). There was no LAM recurrence, no patient developed malignant neoplasm after the procedure, and no patient underwent lung retransplantation. Seven patients (63%) experienced at least one episode of acute rejection; three patients graded a2bx and four graded a1bx. Three patients (27%) required pulse methylprednisolone for acute rejection and 1 patient (9%) required intravenous immunoglobulin and plasmapheresis for confirmed humoral rejection. No patient had primary graft dysfunction. Bronchiolitis obliterans syndrome (BOS) was diagnosed in 5 (45%) patients; 6 patients (55%) experienced at least one fungal pulmonary infection (five caused by *Aspergillus* spp. and one by *Rhizomucor* spp.). There was no difference in the prevalence or severity of postoperative early infections comparing patients who received sirolimus until the time of LT with those that did not use (data not shown). Only 1 patient (12.5%) is currently using supplemental oxygen therapy.

The median follow-up from LT to either death or closing date was 44 months (range 2–112). There were 3 deaths (27%) during the study, 1 from pulmonary embolism, 1 from systemic infection due to *Burkholderia cepacia* and 1 from BOS. Survival probabilities at 1, 3, and 5 years after LT were 90, 90, and 77%, respectively (Fig. 1).

Discussion

To our knowledge, this study has provided data on the largest sample of LAM patients from Latin America who underwent LT, including pre-transplant characteristics, intraoperative information, and post-transplant outcomes. LT is a reasonable treatment modality for LAM patients who have advanced pulmonary disease. Our results revealed that survival after LT for LAM was 90% at 1 year, 90% at 3 years, and 77% at 5 years. These survival rates are similar to those observed in recent studies from different countries and greater than those observed in older studies [8, 10, 12, 14]. Moreover, long-term survival after LT was greater for LAM patients than that found in patients with other diseases in several studies, which may

Table 1 Clinical characteristics, last pulmonary function tests, and 6-min walk test before lung transplantation ($n = 11$)

Clinical characteristics	
Women (*n*, %)	11 (100)
Age at LAM diagnosis (years)	39 ± 6
Age at transplantation (years)	43 ± 7
Time from LAM diagnosis to transplant (years)	4 ± 3
BMI (kg/m^2)	23.6 ± 2.2
TSC (*n*, %)	1 (9)
Pneumothorax (*n*, %)	4 (36)
Chylothorax (*n*, %)	0
Pleurodesis (*n*, %)	1 (9)
Dyspnea (*n*, %)	11 (100)
Grade of dyspnea (mMRC)	3 ± 1
Hemoptysis (*n*, %)	2 (18)
Chylous ascites (*n*, %)	1 (9)
Renal angiomyolipoma (*n*, %)	3 (27)
Ex-smokers (*n*, %)	2 (18)
Pulmonary hypertension (*n*, %)	3 (27)
Diagnosis of LAM	
Clinical plus tomographic findings (*n*, %)	6 (55)
Lung biopsy (*n*, %)	5 (45)
Supplemental oxygen therapy (*n*, %)	10 (91)
Use of sirolimus (*n*, %)	4 (36)
Use of sirolimus until lung transplantation (*n*, %)	3 (27)
Pulmonary function tests	
FEV_1 (L, %predicted)	0.77 ± 0.36, 28 ± 14
FVC (L, %predicted)	1.86 ± 0.48, 50 ± 10
FEV_1/FVC	0.45 ± 0.16
RV (L, %predicted)	3.08 ± 0.86, 203 ± 53
TLC (L, %predicted)	5.18 ± 0.87, 109 ± 16
RV/TLC	0.59 ± 0.13
DL_{CO} (mL/min/mmHg, %predicted)	6.85 ± 3.15, 30 ± 18
Positive response to BDs (*n*, %)	3 (27)
6-min walk test	
Distance (m)	325 ± 109
Minimum Sp_{O_2} (%)	84 ± 9
Change in Sp_{O_2} (%)	10 ± 6

Values are the mean ± SD or percentage (%)

BDs bronchodilators, *BMI* body mass index, DL_{CO} lung diffusing capacity for carbon monoxide, FEV_1 forced expiratory volume in the first second, *FVC*: forced vital capacity, *LAM* lymphangioleiomyomatosis, *mMRC* modified Medical Research Council, *TSC*: tuberous sclerosis complex, *RV* residual volume, Sp_{O_2} oxygen saturation, *TLC* total lung capacity

be attributable to the fact that it often involves younger patients without any extrapulmonary organ dysfunction [7, 13].

LAM accounts for 3.3% of all LTs that were performed in our centre between 2003 and 2016 compared with the international registry in which only approximately 1% of such procedure was secondary to LAM [7]. This difference may be explained by the fact that our hospital is the main reference centre for LAM in Brazil, and patients from different regions of the country are referred to us. In addition, LAM accounts for 4% of our current waiting list.

In several recent series and in the international registry, double-LT was performed with higher frequency than single-LT for LAM [7, 10, 14]. Global proportion of double-LT has surpassed single-LT and is actually the preferred procedure for the majority of lung diseases, with better long-term outcomes [7, 26]. For some interstitial lung diseases, mainly idiopathic pulmonary fibrosis, single-

Table 2 Post-lung transplantation data ($n = 11$)

Follow-up (months, range)	44 (2–112)
Immunosuppression	
Tacrolimus plus azathioprine plus prednisone (*n*, %)	2 (18)
Tacrolimus plus mycophenolate plus prednisone (*n*, %)	6 (55)
Cyclosporine plus mycophenolate plus prednisone (*n*, %)	3 (27)
mTOR inhibitor (*n*, %)	4 (36)
Complications	
Recurrence of LAM (n, %)	0
Chylothorax (*n*, %)	2 (18)
Pulmonary retransplantation (*n*, %)	0
Neoplasm or lymphoproliferative disease (*n*, %)	0
Bronchial stenosis (*n*, %)	1 (9)
Acute rejection (*n*, %)	7 (63)
Bronchiolitis constrictive syndrome (*n*, %)	5 (45)
Humoral rejection (*n*, %)	1 (9)
Pulmonary infections (*n*, %)	6 (55)
Aspergillus sp. (*n*, %)	5 (45)
Rhizomucor sp. (*n*, %)	1 (9)
Mycobacterium avium (*n*, %)	1 (9)
Influenza virus (*n*, %)	1 (9)
Respiratory syncytial virus (*n*, %)	1 (9)
Other treatment modalities	
Pulse methylprednisolone (*n*, %)	3 (27)
Intravenous immunoglobulin plus plasmapheresis (*n*, %)	1 (9)
Cause of death	
Acute pulmonary embolism (*n*, %)	1 (9)
Sepsis secondary to pulmonary infection (*n*, %)	1 (9)
Bronchiolitis constrictive syndrome (*n*, %)	1 (9)

Values are median (range) or percentage (%)

LAM lymphangioleiomyomatosis

LT may be the procedure of choice as it has a shorter duration and therefore is preferable for older patients and for those who would not tolerate long durations of anesthesia. Ninety-one percent of transplants in our study were double-LT, which is currently the procedure of choice due to institutional protocol, to reduce the rate of LAM-related complications in the native lung, such as pneumothorax, chylothorax, and the recurrence of LAM following LT, and to determine better PFTs. In addition, LAM patients are often younger and healthier than other recipients to tolerate double-LT. The only patient who underwent single-LT in our sample died from pulmonary embolism 6 months after the procedure.

The main pre-transplant symptoms in our sample were dyspnea and pneumothorax, discovered in 100 and 36% of patients, respectively, and 91% of patients used supplemental oxygen therapy. The age at transplantation of our patients was 43 ± 7 years, similar to that described in other studies [8–14]. In our sample, pre-transplant FEV_1 was $28 \pm 14\%$ of predicted and was similar to that found in the majority of previous reports, ranging from 19 ± 11 to $33 \pm 17\%$ [8–11, 13, 14].

Regarding PH and LAM, our findings reinforce the fact that it is predominantly pre-capillary and of mild severity, even in patients with advanced lung disease [27]. The prevalence of PH in LAM patients just before LT, including our study, ranged from 27 to 67%. However, those studies described the data based variably on either RHC or echocardiogram, which is subject to criticism in PH evaluation [8–10].

LAM is associated with recurrent pneumothorax and chylothorax, which may require surgical or chemical pleurodesis, and although not contraindications, those procedures may increase the risk of complications, such as bleeding and renal dysfunction [7]. This issue was not a challenge in our sample, because there was only one patient who underwent pleurodesis or pleurectomy before LT, and that patient did not have any intraoperative complication. In previous studies with LAM patients that underwent LT, the pre-transplant rate of pleurodesis and

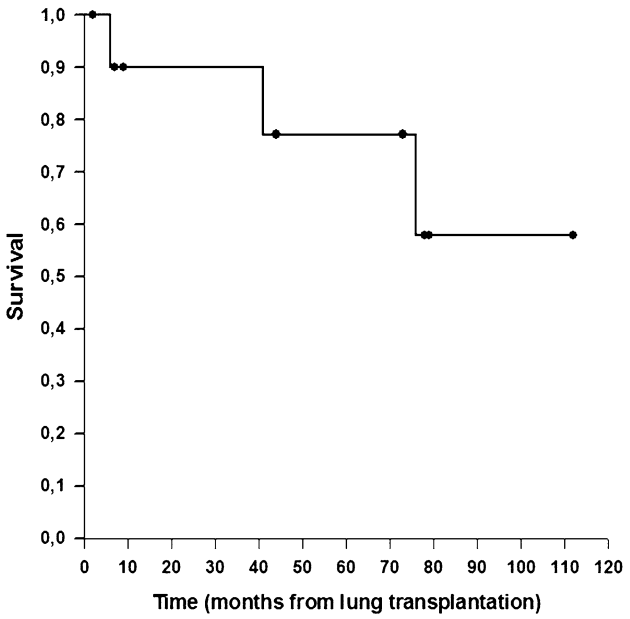

Fig. 1 Kaplan–Meier survival analysis of mortality of 11 LAM patients after lung transplantation

pleurectomy ranged from 18 to 100% and from 21 to 43%, respectively, whereas the rate of intraoperative complications varied from 25 to 71% [9–14].

The use of mTOR inhibitors is of special interest in this group of patients. Primarily, sirolimus proved to be useful in stabilizing lung function in LAM, and may also be useful for treating extrapulmonary manifestations, such as renal angiomyolipoma [5, 6]. Additionally, mTOR inhibitors seem to be safe and have comparable results to azathioprine or mycophenolate in LT outcomes when used in conjunction with CNi and prednisone [28, 29]. In addition, given that cytomegalovirus (CMV) infection is closely related to increased morbidity and chronic lung allograft dysfunction (CLAD) incidence in LT, mTOR inhibitors appear to be interesting as long-term drugs, due to the fact that they decrease the rate of CMV infection after cardiothoracic transplant. However, formal indication for this purpose is still under debate [30]. Finally, mTOR inhibitors use is suggested to prevent or treat LAM recurrence or chylothorax occurrence following LT [31].

There is a great concern about using mTOR inhibitors in patients waiting for LT and in the early period after the procedure. This is because mTOR inhibitors impair the inflammatory cell activity responsible for promotion of wound healing with corresponding suppression of fibroblast proliferation and angiogenesis, which results in an increased risk of bronchial anastomotic dehiscence [15, 32, 33]. However, 3 patients (27%) from our sample used sirolimus preoperatively until the day of LT and none of them developed bronchial anastomotic dehiscence after the procedure. Our findings suggest that the use of sirolimus may be safe until the day of LT. After LT, it is recommended to initiate mTOR inhibitors only after confirming complete bronchial anastomotic healing.

LAM-related complications may occur after LT. There is a risk of development of chylothorax after the procedure, which ranged from 0 to 28% in previous series, and was found in 18% of patients in our study [8, 9, 11–14]. Pneumothorax may also occur mainly in the native lung after single-LT and did not occur in our study, most likely because all except for one patient underwent double-LT. The rate of this complication ranged from 8 to 15% in previous studies [8, 12, 14]. The recurrence of LAM in the lung allograft is also a concern, especially in those who present with a decline in PFTs. It is noteworthy that frequently patients are asymptomatic and LAM may be identified incidentally at autopsy. This complication has not occurred in our series, but was described in previous studies, its frequency varying from 3 to 8% [8, 9, 12–14]. The main differential diagnosis of recurrence of LAM when there is a decline in PFTs is CLAD, mainly in the form of BOS.

In our sample, 63% of LAM patients presented with at least one episode of acute rejection after LT, in comparison with previous studies having an incidence ranging from 41 to 82%. The rate of BOS in our study was 45% and was comparatively higher than other studies that varied from 18 to 36% [9, 11, 13]. Infections are a major complication after LT in LAM. Among our patients, 55% of them presented with at least one episode of pulmonary infection and the most common etiology was *Aspergillus* sp. In previous studies, the frequency of respiratory infections ranged from 10 to 59%, and their etiology was heterogeneous, including viruses, such as CMV, *Aspergillus* sp., bacterial pathogens [9, 11, 13, 14]. Malignant neoplasms and lymphoproliferative disorders may be found after LT in LAM and immunosuppressant therapy is certainly a risk factor. Although none were identified in our study, the rate of malignant neoplasms and lymphoproliferative disorders has been reported from 10 to 21% [9, 11–13].

Our study has limitations that need to be addressed, such as the small sample size, the inclusion of patients from a single centre, and its retrospective characteristic.

In summary, these data reinforce the role of LT for LAM patients with end-stage disease, and determines favorable outcomes, such as improvement in survival and quality of life. Nevertheless, the occurrence of LAM-related and transplant-related complications, mainly chylothorax, acute rejection, infections and BOS, should be continuously monitored. The use of sirolimus may be safe preoperatively until the day of LT, whereas its use as immunosuppressive approaches after LT confers special interest in further studies in LAM.

Compliance with Ethical Standards

Conflict of interest None.

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