Outcome of lung transplantation for adults with interstitial lung disease associated with genetic disorders of the surfactant system

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Shareable abstract (@ERSpublications)
Lung transplantation for adults with interstitial lung disease associated with genetic disorders of the surfactant system is a valid therapeutic option for end-stage patients. Bilateral transplantation is preferred because of the risk of lung cancer. https://bit.ly/47EEckL

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Abstract

Background Interstitial lung disease associated with genetic disorders of the surfactant system is a rare entity in adults that can lead to lung transplantation. Our objective was to describe the outcome of these patients after lung transplantation.

Methods We conducted a retrospective, multicentre study, on adults who underwent lung transplantation for such disease in the French lung transplant centres network, from 1997 to 2018.

Results 20 patients carrying mutations in *SFTPA1* (n=5), *SFTPA2* (n=7) or *SFTPC* (n=8) were included. Median interquartile range (IQR) age at diagnosis was 45 (40–48) years, and median (IQR) age at lung transplantation was 51 (45–54) years. Median overall survival after transplantation was 8.6 years. Two patients had a pre-transplant history of lung cancer, and two developed post-transplant lung cancer. Female gender and a body mass index <25 $kg \cdot m^{-2}$ were significantly associated with a better prognosis, whereas transplantation in high emergency was associated with a worst prognosis.

Conclusions Lung transplantation in adults with interstitial lung disease associated with genetic disorders of surfactant system may be a valid therapeutic option. Our data suggest that these patients may have a good prognosis. Immunosuppressive protocol was not changed for these patients, and close lung cancer screening is needed before and after transplantation.

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Introduction

Familial pulmonary fibrosis (FPF) represents a heterogeneous group of patients with interstitial lung disease (ILD) defined by the presence of at least two cases in the same family [1]. Approximately 60% of FPF cases have a noncontributory genetic investigation, and the two main categories of genes involved are those related to telomerase complexes (30% of cases) [2], and to surfactant proteins (<5% of cases). Genetic disorders of the surfactant system (GDS) may result in an alveolar epithelial dysfunction leading to extracellular matrix and fibroblast proliferation responsible for FPF [3]. They are associated with heterogeneous phenotype, from severe neonatal respiratory distress syndrome, to adult ILD leading to chronic respiratory insufficiency and also lung cancer [4–6].

There are no specific treatments for these patients, and lung transplantation (LTx) is the current standard treatment for end-stage lung disease. However, LTx for ILD is associated with a worst post-transplant prognosis with a median survival for these patients between 5.2 and 6.7 years after LTx, compared to almost 10 years for cystic fibrosis recipients [7]. Moreover, some retrospective studies suggest an impact of the genetic background in post-transplant outcome. Telomere-related gene (TRG) mutation carriers may have a poorer prognosis compared to ILD patients without any identified pathogenic mutation [8, 9]. Regarding to GDS, only one retrospective single-centre study in infants and children with ILD associated with *SFTPB*, *SFTPC*, *ABCA3* or *NKX2-1* mutation [10] who underwent bilateral LTx suggested that post-LTx morbidities and mortality remain substantial in these patients. To our knowledge, there are no available data on post-transplant outcome in adults in such genetic diseases. Hereby, we report post-transplant evolution of adult patients with ILD associated with GDS.

Methods

We conducted a retrospective, observational, French multicentre study, on adult patients (aged >18 years), who underwent LTx for ILD associated with a GDS between 1997 and 2018. Only patients with mutation in a gene encoding for surfactant protein classified as pathogenic, or likely pathogenic, according to the American College of Medical Genetics and Genomics and the Association for Molecular Pathology guidelines, were included [11]. Surfactant mutation testing was performed in patients with an age at onset of symptoms <50 years or with family history of diffuse interstitial lung disease [12]. However, surfactant mutation testing was not standardised during this period, but left to the discretion of the transplant team responsible for the patient.

Data were collected from patients' medical records. We assessed post-transplant survival and outcome, with a specific focus on primary graft dysfunction, cytomegalovirus (CMV) infection, acute cellular and antibody-mediated rejection [13, 14], chronic lung allograft dysfunction (CLAD) and cancer which are associated with post-transplant morbidity and mortality compared with the results published in patients with TRG mutation [15, 16]. CLAD was described as bronchiolitis obliterans syndrome (BOS) or restrictive allograft syndrome (RAS) based on the international guidelines [17].

Data were expressed as median (interquartile range (IQR)), and were compared using Fisher's exact test, Chi-squared test and t-test according to the distribution. A p-value <0.05 was considered as significant. We used Kaplan–Meier analyses to compare survival between the groups with a Cox proportional hazards model adjusted for baseline variables used as appropriate to calculate the hazard ratio (HR) and 95% confidence interval CI. Statistical analyses were performed using GraphPad Prism (San Diego, CA, USA).

The study was approved by the relevant ethics committees and written informed consent was obtained from all patients. Clinical information was collected in a legally authorised database (Commission Nationale Informatique et Liberté identifier 681248).

Results

Patient characteristics before lung transplantation

Patients' characteristics are summarised in table 1. Data from 32 adult patients with a history of GDS were gathered in French centres over this period. 12 patients have been excluded because they had mutations of uncertain significance according to international guidelines in *SFTPA1* (n=2), *SFTPA2* (n=3), *SFTPC* (n=2) and *ABCA3* (n=5) [11].

20 patients were included, including six (30%) women. Heterozygous mutations were identified in *SFTPA1* in five (25%) patients, *SFTPA2* in seven (35%) patients and *SFTPC* in eight (40%) patients. Among them, 11 (55%) had a pathogenic mutation, and nine (45%) a likely pathogenic mutation. There was a family history of ILD in 12 (60%) patients, and lung cancer in seven (35%) patients. Median (IQR) age at diagnosis of ILD was 45 (40–48) years.

TABLE 1 Patients' characteristics before lung transplantion (LTx)

	Total patients	*SFTPA1*	*SFTPA2*	*SFTPC*	p-value
Patients	20	5	7	8	
Female	6 (30)	4 (80)	1 (14)	1 (13)	0.019
Age at onset of respiratory symptoms (years)	42 (35–47)	44 (39–48)	43 (36–46)	39 (30–45)	0.6
Age at diagnosis of ILD (years)	45 (40–48)	49 (48–49)	44 (39–48)	43 (35–47)	0.17
Smoking history	6 (30)	1 (9)	3 (43)	2 (25)	0.68
Professional exposure	1 (5)	1 (9)	0 (0)	0 (0)	0.23
Lung histological pattern					
UIP	12 (60)	5 (100)	4 (57)	3 (38)	0.11
NSIP	2 (10)	0 (0)	1 (14)	1 (13)	0.67
Genetic mutation					
SFTPA1	5 (25)				
SFTPA2	7 (35)				
STPC	8 (40)				
Personal history of lung cancer	2 (10)	2 (40)	0 (0)	0 (0)	0.036
Respiratory family history	15 (75)	5 (100)	4 (57)	6 (75)	0.24
ILD	12 (60)	3 (60)	4 (57)	5 (63)	0.98
Lung cancer	7 (35)	3 (60)	1 (14)	4 (50)	0.21
BMI before LTx (kg·m^{-2})	23 (21–26)	21 (21–23)	23 (23–25)	25 (23–27)	0.38
Pulmonary function before LTx					
FVC (% pred)	39 (35–42)	42 (39–49)	35 (34–38)	39 (37–43)	0.06
D_{LCO} (% pred)	25 (17–29)	33 (29–36)	18 (10–22)	29 (25–30)	0.08
Pulmonary hypertension	7 (35)	2 (40)	3 (43)	2 (25)	0.74
Treatment before LTx					
Steroids	16 (80)	3 (60)	7 (100)	6 (75)	21
Immunosuppressive drug	10 (50)	3 (60)	4 (57)	4 (50)	0.93
Pirfenidone	6 (30)	2 (40)	2 (29)	2 (25)	0.84
Nintedanib	4 (20)	2 (40)	2 (29)	0 (0)	0.17

Data are presented as n, n (%) or median (interquartile range), unless otherwise stated. ILD: interstitial lung disease; UIP: usual interstitial pneumonia; NSIP: nonspecific interstitial pneumonia; BMI: body mass index; FVC: forced vital capacity; D_{LCO}: diffusing capacity of the lung for carbon monoxide.

Histological examination of the lung explants by pathologists identified a pattern of usual interstitial pneumonia (UIP) in 12 (60%) patients and nonspecific interstitial pneumonia (NSIP) in two (10%); the other patients had an association of UIP and NSIP (n=1), UIP and hypersensitivity pneumonitis (n=1), hypersensitivity pneumonitis (n=1), lymphocytic interstitial pneumonia (n=1) and unclassifiable fibrosis (n=1), and data were missing for one patient.

Lung transplantation and peri-operative conditions

The median (IQR) age at LTx was 51 (45–54) years, and median (IQR) delay between diagnosis of ILD and LTx was 4.6 (2.4–8.1) years. Six (30%) patients required a national high-emergency procedure. Four (20%) patients had a high-risk CMV mismatch (table 2).

Immunosuppressive regimens included induction therapy in nine (45%) patients, with basiliximab (n=7) and thymoglobulin (n=2), and maintenance therapy involved association of steroids, a calcineurin inhibitor, and a cell-cycle inhibitor. Five (25%) patients received a mammalian target of rapamycin inhibitor with rapamycin or everolimus due to mycophenolate mofetil intolerance.

Survival

At the end of the follow-up, median (IQR) survival was 8.6 (2.1–not applicable) years, and eight (40%) patients died (figure 1). Among them, three died within 3 months due to surgery complication; two deaths were related to lung cancer; one patient died because of CLAD; and one had massive haemoptysis secondary to bronchial prosthesis change. One patient was retransplanted 4 years after the first procedure and died a few days after surgery.

None of the five patients carrying *SFTPA1* mutation died. Conversely, three out of the seven patients with *SFTPA2* mutation and five out of eight patients with *SFTPC* mutation had died at the end of follow-up (figure 2).

TABLE 2 Patients' characteristics from lung transplantation (LTx) onwards

Patients	20 (100)
Age at LTx (years)	51 (45–54)
Delay between diagnosis of ILD and LTx (months)	4.6 (2.4–8.1)
Bilateral LTx	17 (85)
Unilateral LTx	
Left	1 (5)
Right	1 (5)
Heart and lung transplant	1 (5)
High-emergency procedure	6 (30)
Immunosuppressive induction	9 (45)
Basiliximab	7 (35)
Thymoglobulin	2 (10)
ECMO	
Before surgery	2 (10)
During surgery	15 (75)
After surgery	4 (20)
Mismatch	
CMV	4 (20)
EBV	1 (5)
Toxoplasmosis	1 (5)
Short-term revision surgery	2 (10)
Primary graft dysfunction	6 (30)
Lung rejection after LTx	
AMR	7 (35)
ACR	10 (50)
CLAD-BOS	4 (20)
CLAD-RAS	2 (10)

Data are presented as n (%) or median (interquartile range). ILD: interstitial lung disease; ECMO: extracorporeal membrane oxygenation; CMV: cytomegalovirus; EBV: Epstein–Barr virus; AMR: antibody-mediated rejection; ACR: acute cellular rejection; CLAD: chronic lung allograft dysfunction; BOS: bronchiolitis obliterans syndrome; RAS: restrictive allograft syndrome.

In univariate analysis, *SFTPA1* mutation (HR 0.22, 95% CI 0.05–0.99; p=0.049), female recipients (HR 0.19, 95% CI 0.04–0.83; p=0.03), recipients with body mass index <25 $kg \cdot m^{-2}$ (HR 0.17, 95% CI 0.03–0.85; p=0.03), and a non-high-emergency procedure (HR 6.46, 95% CI 1.1–38; p=0.04) were associated with better survival. Survival was not significantly associated with lung histological pattern, treatments received before LTx or CMV mismatch (table 3).

Neoplastic complications

Two unrelated patients with a *SFTPA1* mutation had a personal history of lung cancer before LTx. The first was a man with tobacco smoking history. He had a first surgery for a bronchioloalveolar carcinoma at the age of 50 years; he was operated for recurrence at 54 years; and was transplanted at the age of 57 years. The second was a nonsmoking woman who had surgery at 54 years for an adenocarcinoma and was transplanted at 56 years. They both were alive at the end of the study with a follow-up after LTx of 2.1 and 7.4 years, respectively.

Six (30%) patients developed cancer after LTx, including two lung cancers. A first patient with *SFTPA2* mutation had a smoking history before LTx, and lung explant histological analysis showed a previously undiagnosed lepidic adenocarcinoma. No specific oncological treatment was initiated post-transplant, since he had no extrathoracic metastatic disease. 6 months after LTx, the lung cancer relapsed and the patient died 22 months after LTx despite specific treatment. A second recipient carried a *SFTPC* mutation and developed metastatic bilateral lung adenocarcinoma 7 years after unilateral LTx and died 18 months after cancer diagnosis. Cancer origin from native or transplanted lung was impossible to establish. Neither of these two patients had a diagnosed cancer before LTx. Other patients developed skin (n=3), bladder (n=1) or uterus cancer (n=1). No patient developed myelodysplasia or malignant haematological complications.

Acute rejection and chronic allograft dysfunction

During the follow-up, 10 (50%) patients had at least one episode of acute cellular rejection and were treated with steroids, except for one asymptomatic patient. Seven (35%) patients experienced at least one

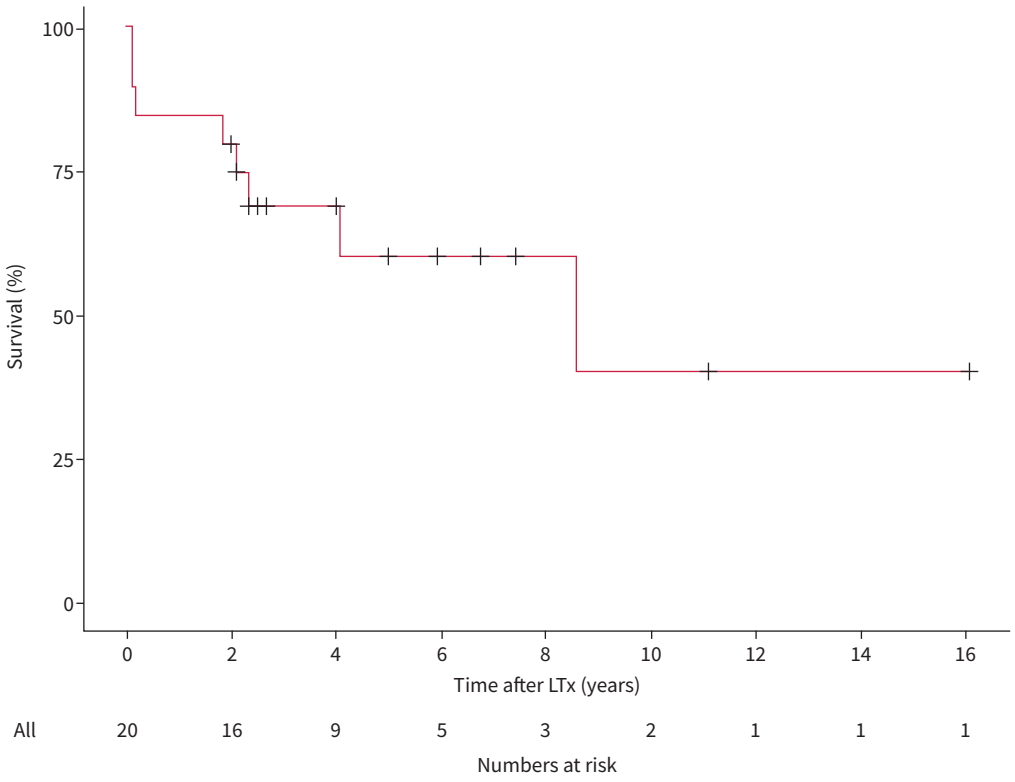

FIGURE 1 Overall survival after lung transplantation (LTx).

episode of antibody-mediated rejection. All of them were treated with rituximab, associated with immunoglobulins and plasmapheresis for four patients.

During the follow-up, six (30%) recipients developed CLAD, BOS (n=4) and RAS (n=2). Median (IQR) time between LTx and CLAD was 18.5 (11–29.8) months; among them, three developed CLAD during the first year post-transplant.

Other complications

Six (30%) patients were treated for a CMV viremia; among them one had a CMV mismatch (D^+/R^-). Two patients were treated for a mycobacterial infection (10%). Eight (40%) recipients experienced invasive fungal lung infection.

Five (25%) patients developed renal insufficiency due to calcineurin-inhibitor nephrotoxicity. Anaemia was found in five (25%) patients and was associated with renal insufficiency or iron deficiency for every patient.

Discussion

In this retrospective series, we studied the clinical outcome of adult patients who underwent LTx for ILD associated with GDS. With a median overall survival of 8.6 years, we demonstrate that LTx is a therapeutic valid option for these patients.

To our knowledge, this is the first assessment of lung transplanted adults in such context of rare genetic disorders including exclusively pathogenic or probably pathogenic mutations. However, this study meets limitations; indeed, its retrospective design and the few number of patients included makes necessary to interpret these results with caution.

This is an extremely rare situation given that only 20 adult recipients were identified over >4000 LTx in France from 1997 to 2018 (Agence de la Biomédecine, France). Regarding to LTx for TRG mutation, 38 LTx were performed in France in the period from 2008 to 2018 [15], highlighting how rare GDS are. However, it is likely that patients with such genetic disorders were underdiagnosed, at least in the first

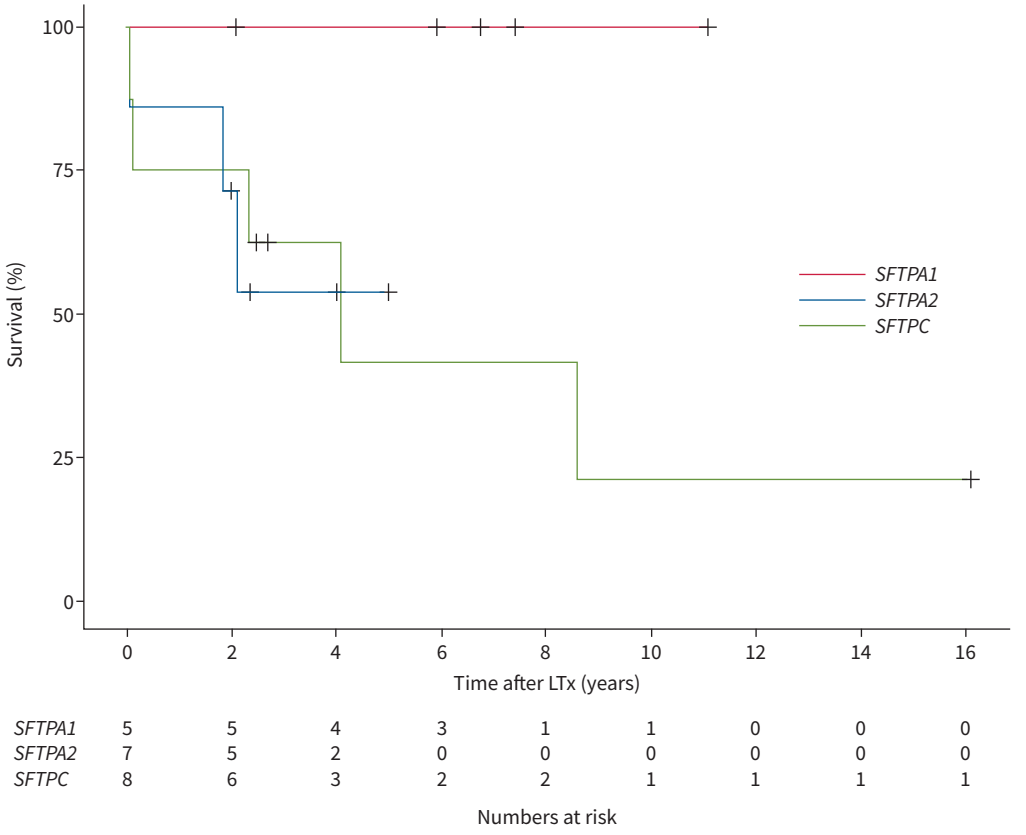

FIGURE 2 Overall survival after lung transplantation (LTx) according to surfactant mutations.

10 years of the study, when the systematic genetic testing for family forms of ILD was far from exhaustive. Indeed, for a long time, research for GDS in ILD has been carried out exclusively in infants and children and has been offered only recently to young adults with a history of ILD [18].

Very few data are available in lung transplanted patients with ILD associated with GDS; to date, it has only been reported in a selected paediatric population in the North America. Herein, mostly ILDs related to *SFTPA1* and *SFTPA2* were included, consistent with the fact that these surfactant disorders manifest mostly, but not exclusively, in adulthood. An increasing number of ILDs related to *SFTPC* [19] and more rarely *ABCA3* [20] mutations in adult patients are also being reported, either in patients diagnosed in childhood who reached adulthood, or in patients who developed symptoms in adulthood. In this study, eight patients had a *SFTPC* mutation, but interestingly, none had *ABCA3* mutation. These patients were excluded because they had mutation of uncertain significance, although they were treated as if they had a pathogenic/likely pathogenic variant. In addition, patient with non-null homozygous *ABCA3* mutations may show an improvement with immunosuppressive treatments, as recently reported [21, 22], and may eventually show better prognosis and less LTx. These two points highlight the role of expert genetic opinion and dedicated multidisciplinary discussion for their evaluation.

Median age at onset of respiratory symptoms was 42 years and 51 years at LTx, but one-third showed a sudden deterioration requiring an emergency LTx. These results suggest that despite their young age, patients should be referred to LTx centres at diagnosis to reduce the rate of high-emergency LTx and eventually improve the post-transplant survival. A young age at diagnosis and LTx has also been reported in patients with TRG mutations with symptoms beginning at ∼51 years and LTx ∼61 years [23]. Our data suggest that patients with ILD associated with GDS may develop symptoms even earlier than those with TRG mutations, and will need earlier LTx, highlighting the need to diagnose GDS in early forms of ILD before 50 years.

Median survival in our cohort was 8.6 years, which is better than that seen in patients transplanted for idiopathic and non-idiopathic ILD, for whom median survival was 5.2 years and 6.7 years, respectively, in

TABLE 3 Univariate analysis of predictive factors of death

	HR (95% CI)	p-value
Mutation		
SFTPA1	0.22 (0.048–0.99)	0.049*
SFTPA2	2.10 (0.39–11)	0.4
SFTPC	2.30 (0.55–9.7)	0.26
Patient characteristics		
Female sex	0.19 (0.04–0.83)	0.027*
Age at diagnosis of ILD ⩽45 years	0.98 (0.22–4.5)	0.98
Smoking history	4.90 (0.9–27.3)	0.067
BMI <25 kg·m^{-2}	0.17 (0.03–0.85)	0.03*
UIP histological pattern	2.70 (0.56–13.1)	0.21
Treatments before LTx		
Steroids	3.48 (0.47–24.8)	0.22
Immunosuppressive drug	0.80 (0.16–3.8)	0.78
Antifibrotic drug	1.12 (0.20–6.21)	0.9
LTx		
Before 2015	0.62 (0.13–2.94)	0.54
Age at LTx ⩽49 years	1.57 (0.34–7.22)	0.56
Emergency procedure	6.46 (1.1–37.75)	0.038*
ECMO during LTx	1.47 (0.23–9.5)	0.68
Events after LTx		
AMR	0.55 (0.13–2.30)	0.41
ACR	0.63 (0.14–2.8)	0.55
CLAD	1.19 (0.27–5.2)	0.82
CMV mismatch	0.26 (0.05–1.4)	0.16

HR: hazard ratio; ILD: interstitial lung disease; BMI: body mass index; LTx: lung transplant; ECMO: extracorporeal membrane oxygenation; AMR: antibody-mediated rejection; ACR: acute cellular rejection; CLAD: chronic lung allograft dysfunction; CMV: cytomegalovirus. *: p<0.05.

2019 [7]. This difference may be explained by some different demographic characteristics before LTx, with a younger age and fewer comorbidities. However, these data should be interpreted with caution given the small number of patients included. Even if our median survival was acceptable, three patients died within 3 months because of surgery complications. This data can be explained by the fact that 30% of patients were transplanted in high-emergency procedures, which are associated with a higher post-transplant mortality. Moreover, patients with ILD associated with TRG mutations will be at risk of developing other life-threatening disorders such as myelodysplasia, bone marrow failure and liver disease. These may not only develop before LTx, but also post-transplant, possibly triggered by immunosuppressive treatments or CMV infection, which will worsen prognosis [24]. In our study, few patients developed haematological complications (anaemia was secondary to renal insufficiency or iron deficiency) after LTx compared with patients with TRG mutations. None of them developed any myelodysplastic syndrome or malignant haemopathy, and CMV mismatch was not associated with a worst prognosis. These data would prompt the use of immunosuppressive and potentially haematotoxic drugs after LTx according to the usual protocol of each centre, unlike for TRG mutation carriers.

GDS, and especially *SFTPA1* and *SFTPA2* mutations, may be associated with lung cancer [25, 26] which is a classical contraindication to LTx within 5 years after cancer treatment [27]. However, in our series, two patients with an *SFTPA1* mutation had a history of localised lung cancer in the 5 years preceding LTx. They did not present a recurrence of lung cancer during follow-up and were still alive at the end of the study, with follow-up of 2.1 and 7.4 years. Although preliminary, these data could be a starting point to discuss lung cancer as a usual contraindication for LTx in candidates with GDS [28]. Conversely, two other patients developed lung cancer after LTx. One of them had an undiagnosed lung cancer at LTx, and the other one developed cancer a few years later after unilateral LTx. In a series of adult patients with ILD associated with GDS, a patient with a *SFTPA2* mutation, who underwent an initial single left LTx, had been retransplanted with bilateral LTx due to the occurrence of CLAD. This patient experienced a lung adenocarcinoma (diagnosed on the native right explanted lung) which led to death a few months following the retransplant [5]. These results emphasise the importance of detecting lung cancer in these young at-risk patients before LTx by close monitoring. Furthermore, in such patients, the potentially fast worsening of respiratory function, and the poor prognosis without LTx, could shorten the delay of 5 years classically

expected before LTx under cover of close cancer screening. Finally, a systematic bilateral LTx should be a better option to minimise the risk of cancer on the native lung in this at-risk population.

In post-transplant period, two of our 20 patients died of lung cancer. Even if our population is too small to make conclusions, this rate is higher than that found in recent published data showing an incidence of lung cancer in lung transplant recipients of 528 per 100 000 person-years [29]. In this way, these patients should be more closely screened for lung cancer especially patients with unilateral LTx with at least an annual computed tomography (CT) scan.

In our study, survival of lung transplant recipients with a *SFTPA1* mutation was found significantly better compared to patients with other genes involved, whereas the demographics were similar regarding age at diagnosis and ILD histological pattern. However, the *SFTPA1* mutation group consisted mainly of women, whereas there were mostly men in other groups of mutations; it is understood that registries of LTx such as the one kept by the International Society for Heart and Lung Transplantation shows that transplanted women had better prognoses than men [7]. Another hypothesis may be that pathogenicity of surfactant mutation is related to their structural and immune-modulatory function, which is essential for tissue homeostasis and to avoid chronic inflammation that promotes fibrosis. Given that the function of these proteins are different, it can explain that these mutations may have a different impact on the prognosis after lung transplant. However functional assessment of these mutations is currently limited and insufficient to find out a real mechanism explaining this difference [4]. These hypotheses will have to be confirmed in a larger group of patients allowing a multivariate analysis.

Conclusion

Our study shows that LTx in adult patients with ILD associated with *SFTPA1*, *SFTPA2* and *SFTPC* mutation is a valid therapeutic option. These patients, with fewer comorbidities and younger than other recipients at LTx, had a better post-transplant survival compared with currently available data from other recipients for ILD. Moreover, for these patients with an increased risk of lung cancer, LTx could be even discussed with a history of lung cancer within the past 5 years, subject to a close screening with at least annual CT scans, and should have bilateral transplantation to avoid occurrence on the native lung. Finally, patients did not develop severe haematological disorders nor sensitivity to CMV infection requiring any change in immunosuppressive protocol. With a larger access to high-throughput sequencing in familial forms of ILD, we expect a larger number of cases be diagnosed, and eventually larger cohorts that will allow better characterisation of these patients and their indications for LTx.

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