Effect of antifibrotics on short-term outcome after bilateral lung transplantation: a multicentre analysis

To the Editor:

Interstitial lung diseases (ILDs) are a heterogeneous entity of diffuse parenchymal lung diseases characterised by damage of the parenchyma as a result of varying patterns of inflammation and fibrosis [1]. Idiopathic pulmonary fibrosis (IPF) is a specific subgroup of ILDs and has a devastating prognosis [2] with a median survival time of 2–3 years [2–4]. Pirfenidone (Esbriet) and nintedanib (Ofev) were approved for IPF treatment, showing a stabilisation of the disease [5, 6], and are the treatments recommended by international guidelines [1]. Nintedanib was shown to increase the risk of bleeding events in IPF patients during therapy [7] and the European Medicines Agency recommended discontinuation of nintedanib before major surgery but without a definite time frame for discontinuation [8]. Corticosteroids have been the conventional strategy used as treatment in different ILD subtypes despite limited evidence regarding their efficacy [9, 10]. After failure of medical therapy in severe ILD, lung transplantation (LuTx) represents an established therapeutic option in order to improve quality of life and survival [11].

A retrospective analysis after bilateral lung transplantation (BLTx) of patients with ILDs (disease category D in Eurotransplant) was performed in two large European lung transplant centres. Patients with a primary Lung Allocation System (LAS) diagnosis in category D (ILD), including IPF, hypersensitivity pneumonitis, and pulmonary fibrosis, were included. Other lung diseases from LAS diagnosis category D, such as lymphoid interstitial pneumonia, diffuse alveolar damage and acute interstitial pneumonitis, were excluded. The study population comprised all patients who were treated with BLTx between January 2014 and February 2017. Patients receiving unilateral LuTx for ILD were not included (n=7 within the study period). IPF was diagnosed based on the American Thoracic Society (ATS) guidelines [1]. Patients under medical treatment (steroids, nintedanib or pirfenidone) within 4 weeks before transplant surgery were compared to those without medical treatment. Combination therapy of steroids with another antifibrotic agent was sorted into either the pirfenidone or the nintedanib group, respectively. Duration of mechanical ventilation was measured in days until decannulation, extubation or death, whichever occurred first. All complications within the first 4 weeks after surgery or until hospital discharge were recorded. The study was approved by the Ethics Committee of the Medical University of Vienna, Vienna, Austria (EK 1055/2017).

A total of 767 patient records for BLTx patients were screened (Vienna, n=357; Hannover (Germany), n=410) and 132 patients with ILD were identified. 100 (76%) patients were diagnosed as IPF according to the ATS guidelines [2]. Further patient demographics are listed in table 1.

Of these 132 patients, 108 received a medical regimen containing glucocorticoids (n=72; n=46 patients with IPF), pirfenidone (n=23) or nintedanib (n=13) within 4 weeks before transplantation at the recommended doses. 24 patients had no treatment with steroids, nintedanib or pirfenidone, or therapy was discontinued ⩾4 weeks prior to transplantation. Nine (39%) patients with pirfenidone and four (31%) patients with nintedanib therapy received additional steroids.

Outcome parameters are summarised in table 1. The mean surgical intervention time for the BLTx procedure was equally distributed for the specific groups. Despite an overall decrease in mean±SD haemoglobin from 14.2±1.8 to 11.2±1.3 g·dL^{-1} at day 1 after surgery, no differences in the use of

TABLE 1 Patient demographics and peri/post-operative patient variables

Variable	All	Treatment groups				p-value
		None	Steroids	Pirfenidone	Nintedanib	
Patients	132	24	72	23	13	
Underlying disease						
IPF	78 (59%)	14 (58%)	31 (43%)	23 (100%)	10 (77%)	0.001
Unspecified fibrosis	22 (17%)	6 (25%)	15 (21%)	0 (0%)	1 (8%)	0.059
Fibroelastosis	1 (1%)	1 (4%)	0 (0%)	0 (0%)	0 (0%)	0.209
NSIP	8 (6%)	0 (0%)	7 (10%)	0 (0%)	1 (8%)	0.188
Organising pneumonia	1 (1%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)	0.840
Hypersensitivity pneumonitis	12 (9%)	0 (0%)	12 (17%)	0 (0%)	0 (0%)	0.012
CPFE	6 (5%)	3 (13%)	2 (3%)	0 (0%)	1 (8%)	0.344
Silicosis	1 (1%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)	0.840
Systemic sclerosis	3 (2%)	0 (0%)	3 (4%)	0 (0%)	0 (0%)	0.465
Baseline characteristics						
Age years	57.0 (51.5–62.5)	58.5 (54–63)	56.0 (49–63)	59.0 (55.5–62.5)	58.0 (53.5–62.5)	0.097
Males	93 (70%)	19 (79%)	41 (57%)	22 (96%)	11 (85%)	0.001
BMI kg·m^{-2}	24.5±3.3	23.1±3.2	24.7±3.3	25.8±3.2	24.7±2.7	0.251
FVC % pred	42 (31–53)	46 (32–60)	41 (30–51)	45 (37–52)	40 (27–53)	0.675
TLC % pred	58±13	63±16	56±12	55±11	59±13	0.507
LAS score	38 (33–43)	37 (33–40)	39 (34–45)	38 (26–50)	37 (33–40)	0.630
6-min walking distance m	266±133	280±149	241±129	330±121	310±122	0.086
Peri- and post-operative specifics						
Surgery duration min	300±68	286±83	300±65	306±58	318±70	0.661
ECMO support	74 (56%)	18 (75%)	39 (54%)	11 (48%)	6 (46%)	0.191
Packed red blood cell units	2.0 (0–4.0)	2.0 (0–4.0)	2.0 (0–4.0)	2.0 (0–5.0)	1.5 (0–3.0)	0.828
Intubation duration days	1.0 (0.5–1.5)	2.0 (1.5–2.5)	1.0 (0.5–1.5)	1.0 (0.5–1.5)	1.0 (0.5–1.5)	0.629
Hb pre-LuTx g·dL^{-1}	14.2±2	14.3±2	14.0±2	14.1±2	15.0±2	0.391
Hb D1 g·dL^{-1}	11.2±1	11.2±1	11.2±1	11.0±2	11.7±1	0.643
Haemothorax surgery[#]	11 (8%)	1 (4%)	7 (10%)	3 (13%)	0 (0%)	0.595
Wound infection with VAC therapy	12 (9%)	2 (8%)	7 (10%)	3 (13%)	0 (0%)	0.763
GI bleeding	3 (2%)	1 (4%)	1 (1%)	1 (4%)	0 (0%)	0.520
Renal failure	13 (10%)	1 (4%)	9 (13%)	2 (9%)	1 (8%)	0.815
Anastomosis problems (total anastomoses)	1 (264)	0 (48)	1 (144)	0 (46)	0 (26)	0.841

Data are presented as median (interquartile range) or mean±SD, unless otherwise stated. None: no antifibrotic therapy prior to transplantation; IPF: idiopathic pulmonary fibrosis; NSIP: nonspecific interstitial pneumonia; CPFE: combined pulmonary fibrosis and emphysema; BMI: body mass index; FVC: forced vital capacity; TLC: total lung capacity; LAS: Lung Allocation System; ECMO: extracorporeal membrane oxygenation; packed red blood cell units: total number of erythrocyte concentrates received intraoperatively; intubation duration: total time to first extubation; Hb: haemoglobin; LuTx: lung transplantation; D1: first post-operative day; VAC: vaccum-assisted closure; GI: gastrointestinal. [#]: surgical revision of haemothorax within 2 weeks after transplantation.

supplemental erythrocyte concentrates during surgery were observed among the groups. Use of extracorporeal membrane oxygenation was similarly distributed for all antifibrotic treatment groups, with a larger proportion in the control group.

Post-operative complications were equally distributed as well. Haemothorax leading to surgical revision occurred in 11 out of 132 patients, with no difference between groups. Wound infections with a need for vacuum-assisted closure were recorded in 12 (9%) patients, with the highest incidence for those on steroid therapy (58%, n=7) and pirfenidone treatment (13%, n=3). The nintedanib group showed no occurrence of severe wound infections at all (n=0). No difference was observed for gastrointestinal bleeding (p=0.52) or renal failure (p=0.815). Patient characteristics and peri/post-operative variables are presented in table 1.

One patient in the steroid group died intraoperatively in hospital and was counted as event-free in the above analysis regarding this end-point. Another patient, also in the steroid group, died at day 16 post-surgery after having experienced surgical revision due to haemothorax. All further patients survived hospitalisation (maximum 64 days) after surgery with no difference between the groups. Median follow up was 21 months (interquartile range 13–29 months), with a maximum of 44 months observation time.

The overall survival between the four groups showed no significant differences (log-rank test p=0.32). The Kaplan–Meier estimate of the 1-year survival probability was 96% (95% CI 80–99.8%) under pirfenidone,

100% (95% CI 65–100%) under nintedanib, 90% (95% CI 81–96%) under steroids and 100% (95% CI 86–100%) without IPF treatment. A total of nine (7%) patients died after BLTx, of whom four patients died during the first 3 months after transplantation (intraoperatively, n=1; severe sepsis, n=3). Four consecutive patients died thereafter within the first year after transplantation (severe sepsis, n=2; non-small cell lung cancer in the donor lung, n=1; bronchial stenosis, n=1) and a single patient in the pirfenidone group died in a car accident after the first year post-BLTx.

IPF is the leading indication for lung transplantation but has an increased mortality on the waiting list compared to other BLTx indications. BLTx has been proven to have improved outcome [12, 13] and is the preferred technique for ILD patients in both study centres. In this large multicentre study, the use of nintedanib and pirfenidone alone or in addition to corticosteroids in BLTx patients was safe, even when administered within the last 4 weeks before surgery. Compared to two previously published studies that confirmed this safety profile in a small sample size [14, 15], our study included a total of 264 anastomoses in the analysis in contrast to a total of 96 anastomoses reported by LEUSCHNER et al. [14]. More importantly, the 1-year survival for patients under pirfenidone therapy was 77% (compared to 96% in our study), 100% for nintedanib (versus 100%) and 91% for the control group (versus 100%). 2-year survival was 77% for pirfenidone (versus 89% in our study) and 82% (versus 100%) in the control group, while nintedanib was excluded from the 2-year analysis [14]. In the study by DELANOTE et al. [15], a case series of nine patients under antifibrotic treatment, the 1-year survival was 100%, and 80% after 2 years. These results might, in part, be explained by the small number of BLTx performed in both studies (n=34 [14] and n=0 [15]), underlining that these studies are not comparable to our large multicentre study with a total of 132 bilateral lung transplantations.

In conclusion, our study represents the largest cohort of patients with antifibrotic therapy undergoing BLTx for ILD. The data show that BLTx is safe and a valuable therapeutic strategy in end-stage ILD. Our data analysis did not find any impairment of the post-operative course after BLTx associated with pre-transplantation treatment with pirfenidone or nintedanib. Antifibrotic drugs and steroids did not increase the risk for bleeding complications, disturb wound healing or impair the survival.

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