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Early View

Research letter

Effect of Antifibrotics on Short-Term Outcome after Bilateral Lung Transplantation A Multi-Centre Analysis

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Effect of Antifibrotics on Short-Term Outcome after Bilateral Lung Transplantation
A Multi-Centre Analysis

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To the Editor:

Interstitial lung diseases (ILD) 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 two to three years [2-4]. Pirfenidone (Esbriet®) and nintedanib (Ofev®) were approved as IPF treatment showing a stabilisation of the disease [5, 6] and are the recommended treatments by international guidelines [1]. Nintedanib was shown to increase the risk for bleeding events in IPF patients during therapy [7], and the *European Medicines Agency* (EMA) recommended discontinuation of nintedanib before major surgery 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 interstitial lung diseases (disease category D in Eurotransplant) was performed in two large European lung transplant centres. Patients with a primary LAS diagnosis in category D of interstitial lung disease, including IPF, hypersensitivity pneumonitis, and pulmonary fibrosis, were included. Other lung diseases from LAS diagnosis category D, such as lymphoid interstitial pneumonia (LIP), diffuse alveolar damage (DAD), and acute interstitial pneumonitis (AIP), were excluded. The study population comprised all patients who were treated with BLTx between 01/2014 and 02/2017. Patients receiving unilateral lung transplantation for ILD were not included (n=7 within the study period). IPF was diagnosed based on the ATS guidelines [1]. Patients under medical treatment (steroids, nintedanib or pirfenidone) within four weeks before transplant surgery were compared to those without medical treatment. A combinational 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 four weeks after surgery or until hospital discharge were recorded. The study was approved by the *Ethics Committee of the Medical University of Vienna*, Austria (EK 1055/2017).

A total of 767 patient records for BLTx patients were screened (Vienna n=357 / Hannover n=410) and identified 132 patients with interstitial lung disease. Hundred patients (76%) 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 four weeks before transplantation at the recommended doses. 24 patients had no treatment with steroids, nintedanib or pirfenidone, or therapy was discontinued at least four weeks prior to transplantation. Nine (39%) patients with pirfenidone and four (31%) patients with nintedanib therapy received additional steroids.

Outcome parameters are summarized in the table. The mean surgical intervention time for the BLTx procedure was equally distributed for the specific groups. Despite a mean decrease in haemoglobin from 14.2 ± 1.8 g/dl to 11.2 ± 1.3 g/dl at day one after surgery, no differences in the use of supplemental erythrocyte concentrates during surgery were observed. Use of extracorporeal membrane oxygenation (ECMO) was similarly distributed for all antifibrotic treatment groups, with a larger proportion in the control group.

Postoperative complications were equally distributed as well. Hemothorax leading to surgical revision occurred in eleven out of 132 patients with no difference between groups. Wound infections with need for vacuum-assisted closure (VAC) were recorded in twelve (9%) patients with the highest incidence for 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 gastro-intestinal bleeding (p=0.52) and renal failure (in 10%; n=13). Patient characteristics and peri-/ postoperative variables are depicted in the table.

One patient in the steroids group died intraoperatively in hospital and was counted as event-free in the above analysis regarding this endpoint. Another patient, also in the steroid group, died at day 16 post surgery after having experienced surgical revision due to hemothorax. All further patients survived hospitalisation (maximum 64 days) after surgery with no difference between groups. Median follow up was 21 months (IQR 13-29), 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 for the one-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 patients (7%) died after BLTx, of which four patients died during the first three months after transplantation (intraoperatively n=1 and severe sepsis n=3). Four consecutive patients died thereafter within the first year after transplantation (severe sepsis n=2; NSCLC 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 for a better 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 four weeks before surgery. Compared to two previously published studies which 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 116 anastomoses reported by Leuschner et al. [14]. More importantly, the one-year survival for patients under pirfenidone therapy was reportedly 77% (compared to 96% in our study), for nintedanib 100% (vs. 100%) and 91% for the control group (vs. 100%). Two-year survival was 77% for pirfenidone (vs. 89% in our study) and 82% (vs. 100%) in the control group, while nintedanib was excluded from the two-year analysis [14]. In the study of Delanote, a case series of 9 patients under antifibrotic treatment, the one-year survival was 100%, and 80% after two years [15]. These results might be in part explained by the small number of bilateral lung transplantations performed in both studies (n=34 bilateral LuTx [14]; no BLTx in [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 bilateral lung transplantation 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 postoperative 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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Table. Patient demographics and peri-/ postoperative patient variables

none: no antifibrotic therapy prior to transplantation; IPF: idiopathic pulmonary fibrosis; NSIP: non-specific interstitial pneumonia; CPFE: combined pulmonary fibrosis and emphysema; BMI: body mass index; FVC: forced vital capacity; TLC: total lung capacity; LAS: Lung Allocation Score; 6 MW Test: 6 minute walking test; ECMO: extracorporeal membrane oxygenation; packed red blood cell units: total number of erythrocyte concentrates received intraoperatively; intubation duration: total time to first extubation; Hb pre-LuTx: haemoglobin level prior to transplant; Hb D1: haemoglobin on first postoperative day; variables depicted for the first 4 weeks after BLTx or discharge from hospital, whatever comes first: hemothorax surgery: surgical revision of hemothorax within two weeks after transplantation; wound infection VAC: wound infections with vacuum-assisted closure (VAC); GI bleed: gastrointestinal bleeding.

		Treatment groups				
Variable	all (n=132)	none (n=24)	steroids (n=72)	pirfenidone (n=23)	nintedanib (n=13)	p-values
Underlying disease						
IPF; n (%)	78 (59%)	14 (58%)	31 (43%)	23 (100%)	10 (77%)	0.001
Unspecified fibrosis; n (%)	22 (17%)	6 (25%)	15 (21%)	0 (0%)	1 (8%)	0.059
Fibroelastosis; n (%)	1 (1%)	1 (4%)	0 (0%)	0 (0%)	0 (0%)	0.209
NSIP; n (%)	8 (6%)	0 (0%)	7 (10%)	0 (0%)	1 (8%)	0.188
organising pneumonia; n (%)	1 (1%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)	0.840
hypersensitivity pneumonitis; n (%)	12 (9%)	0 (0%)	12 (17%)	0 (0%)	0 (0%)	0.012
CPFE; n (%)	6 (5%)	3 (13%)	2 (3%)	0 (0%)	1 (8%)	0.344
Silicosis; n (%)	1 (1%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)	0.840
Systemic sclerosis; n (%)	3 (2%)	0 (0%)	3 (4%)	0 (0%)	0 (0%)	0.465
Baseline characteristics						
Age; median [IQR]	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
Male sex; n (%)	93 (70%)	19 (79%)	41 (57%)	22 (96%)	11 (85%)	0.001
BMI kg/m²; mean ± SD	24.5 ± 3.3	23.1 ± 3.2	24.7 ± 3.3	25.8 ± 3.2	24.7 ± 2.7	0.251
FVC %; median [IQR]	42 [31-53]	46 [32.-60]	41 [30-51]	45 [37-52]	40 [27-53]	0.675
TLC %; mean ± SD	58 ± 13	63 ± 16	56 ± 12	55 ± 11	59 ± 13	0.507
LAS; median [IQR]	38 [33-43]	37 [33-40]	39 [34-45]	38 [26-50]	37 [33-40]	0.630
6 MW Test m; mean ± SD	266 ± 133	280 ± 149	241 ± 129	330 ± 121	310 ± 122	0.086

Peri- and postoperative specifics

Surgery duration min; mean ± SD	300 ± 68	286 ± 83	300 ± 65	306 ± 58	318 ± 70	0.661
ECMO support; n (%)	74 (56%)	18 (75%)	39 (54%)	11 (48%)	6 (46%)	0.191
Packed red blood cell units; median [IQR]	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; median [IQR]	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; mean ± SD	14.2 ± 2	14.3 ± 2	14.0 ± 2	14.1 ± 2	15.0 ± 2	0.391
Hb D1 g/dl; mean ± SD	11.2 ± 1	11.2 ± 1	11.2 ± 1	11.0 ± 2	11.7 ± 1	0.643
Hemothorax surgery; n (%)	11 (8%)	1 (4%)	7 (10%)	3 (13%)	0 (0%)	0.595
Wound infection with VAC therapy; n (%)	12 (9%)	2 (8%)	7 (10%)	3 (13%)	0 (0%)	0.763
GI bleed; n (%)	3 (2%)	1 (4%)	1 (1%)	1 (4%)	0 (0%)	0.520
Renal failure; n (%)	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