Characteristics and therapy of patients with severe interstitial lung disease

Ph.D. theses

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1. INTRODUCTION

Interstitial lung disease (ILD) includes more than 150 diseases which are characterized by diffuse, acute or chronic inflammation of the interstitium of the lungs followed by fibrotic transformation in a significant proportion of patients. Nearly two-thirds of ILDs are idiopathic, while one-third are caused by exogenous or endogenous factors. Among the ILDs of unknown origin, the most common form of idiopathic interstitial pneumonia is idiopathic pulmonary fibrosis (IPF).

The median survival of IPF patients is approximately 3-5 years. Functional impairment may be responsible for the primary cause of death. As a targeted therapeutic option, two antifibrotic drugs (nintedanib, pirfenidone) are approved that have shown potential to slow the progression of the disease through stabilization of FVC (forced vital capacity). The efficacy of the drugs has been demonstrated in previous large clinical trials, however, inclusion criteria excluded patients with functionally severe conditions (FVC<50%). In clinical practice, it is important to know the therapeutic possibilities for the most severe group of patients with FVC below 50%.

In Hungary, lung cancer (LC) is the leading cause of death among all type of cancers. LC is occurring in 4.4-9.8% of IPF patients at the same time as a result of shared risk factors and pathomechanisms. The expected course and the treatment to be chosen are determined by the histological type and the stage of the tumour, however, depending on the severity of the underlying disease, the therapeutic options may be limited. This rare group of patients has very special characteristics and little is known about survival data and disease outcome.

2. AIMS

Our research focused on the following questions:

1. What is the effect of nintedanib therapy in the most severe IPF patients?

2. What are the side effects of nintedanib treatment in the most severe IPF group?

3. What are clinical characteristics for LC with ILDs?

4. What is the survival and outcome of severe IPF and ILD-LC patients?

5. Which therapies are used in clinical practice for ILD-LC compared to the standard treatment in Hungary?

3. METHODS

3.1 Patient characteristics

Severe IPF population:

Between May 2015 and June 2017 103 IPF patients were diagnosed at the Department of Pulmonology, Semmelweis University. The analysis included only IPF patients with the most severe lung function impairment. Patients were selected according to the results of lung function tests (FVC<60%) at diagnosis and always before the start of the antifibrotic therapy. The inclusion criteria were met by 22 patients. In 8 cases FVC was less than 50% called Group A and 10 patients were classified into Group B (FVC%=50-60%).

ILD-LC population:

Between November 2012 and November 2018, we diagnosed 160 patients with ILD. Twenty-three cases had ILD with concomitant lung cancer (ILD-LC).

3.2 Examinations

At each consultation physical examination was performed and detailed medical history was recorded focusing on symptoms, comorbidities and drug side effects. Spirometry, body plethysmography with diffusion measurement were performed at the first and control examinations. The tests were performed uniformly with the PDD-301/s Piston according to the current ATS/ERS (American Thoracic Society/European Respiratory Society) guidelines. The forced manoeuvres were performed by technical staff.

Six-minute walk test (6MWT) was performed by a qualified physiotherapist. Pulse, oxygen saturation (SpO_2), and distance in meters were measured before and immediately after the start of the study. The extent of dyspnoea was given using the Borg scale.

Arterialized capillary or arterial blood was used for blood gas analysis and resting values (pO_2, pCO_2, pH, saturation) were recorded with Stat Profile® pHOx Plus® (Nova Biomedical Corporation, Waltham MA, USA).

High resolution computed tomography (HRCT) images were taken in prone position, with maximum inspiration and exhalation (Philips Brilliance 16 slice).

The EQ-5D (European Quality of Life 5-dimensional test) questionnaire was used to assess quality of life. The questionnaire data were recorded in coded form in our electronic database, the final number value was calculated with the program of the EMPIRE register (European Multipartner IPF Registry). We also signed the statement of consent approved by the Ethics Committee (TUKEB 69/2015). To examine mortality, GAP (Gender-age-physiology index) stages and days of survival were calculated.

In LC patients, in addition to the above comprehensive examination, the histological type of the tumor, TNM (tumor, node, metastasis) stage and ECOG PS (Eastern Cooperative Oncology Group performance status), were determined. For adenocarcinoma, EGFR (epidermal growth factor receptor), K-RAS mutation analysis, and PD-L1 (programmed death-ligand 1) expression analysis were also performed on a sample of appropriate size and quality. Tumour types were given according to the WHO (World Health Organization) guidelines and the current TNM 7th and 8th classifications were used. In all cases, therapy was initiated at the discretion

of the onco-team, and ILD patients were also discussed at the ILD-team.

3.3 Statistical analysis

GraphPad Prism 6 (GraphPad Software, Inc., La Jolla, CA, USA) was used for statistical analysis. Parametric values are given as mean ± standard deviation. Pearson's correlation was used for the non-normally distributed groups. Normality was examined by Kolmogorov–Smirnov test. Two-sample t-test, Mann-Whitney or $\chi 2$ test was used to compare groups. Survival was plotted with Kaplan-Meier curves. The difference was considered significant if $p < 0.05$.

4. RESULTS

4.1 Results I.: Long-Term effects and adverse events of nintedanib therapy in idiopathic pulmonary fibrosis patients with functionally advanced disease

In our first study, we investigated the long-term effects and adverse events of nintedanib and their effects on survival in the functionally most severe (Group A; FVC<50%) and moderate (Group B; FVC=50-60%) IPF groups. There was no significant difference between the two groups in terms of age, smoking history, body mass index values, and symptoms. The main complaints were dyspnoea and cough. Due to the higher number of female participants in Group B, significantly more patients were classified into the lowest mortality (GAP I) stage ($p = 0.027$).

All patients had at least 2 other comorbidities. Arterial hypertension was significantly more common in group A ($p=0.03$), but there was no other difference between the groups in comorbidities. Severe pulmonary fibrosis associated pulmonary hypertension was present in 9 cases.

Blood gas and 6MWT parameters in group A indicate disease progression, however, there was no significant difference between groups (O_2 saturation decline: Group A: $12.10 \pm 6.91\%$, Group B: $9.11 \pm 5.53\%$, p=ns),

Both groups rated their overall quality of life as worse than the Hungarian population of the same age group (0.80 ± 0.24; $p=0.012$ vs. Group A and $p <0.0001$ vs. Group B).

We followed the development of the therapy until the end of 12-month observation period or until the death of the patients. Nintedanib therapy was used except for 4 patients, however, in 2 cases we switched to pirfenidone due to side effects. Median survival did not differ between groups (Group

A: 444 days, Group B: 447 days). Nintedanib treatment stabilized FVC in 42% of Group A patients and 50% of Group B patients for at least 6 months.

No adverse events were reported in 50% of Group A and 30% of Group B, and 38% of patients tolerated the therapy well. In both groups, gastrointestinal adverse events and elevation in liver enzymes occurred predominantly but were transient in most cases. Dose reduction was required in 3 cases (17%) and discontinuation in 2 cases (11%). In one patient, we had to discontinue therapy due to high liver enzyme levels, in the other case due to severe persistent vomiting. One patient received reduced-dose nintedanib therapy due to disease-independent, common gastrointestinal complaints.

14 patients died during the study period. The most common deaths were progression of IPF or cardiopulmonary failure, and acute exacerbations occurring in 2 cases.

4.2 Results II: Impact of interstitial lung disease and simultaneous lung cancer on therapeutic possibilities and survival

Of our 160 ILD patients, 14% were diagnosed with concomitant lung cancer. The majority of the cases were older, with men being significantly older than women ($p=0.02$). Based on the GAP mortality score system, 32% belonged to GAP II and 27% to the highest mortality risk group (GAP III). Examining the two sexes, significantly more women were in GAP stage I than men ($p=0.02$).

Based on the ECOG performance status the majority of the patients (61%) were classified as stage 2. ECOG 2 refers to patients who are able to move and be self-sufficient but are

unable to work and are active and alert more than 50% of the time.

The most common symptoms were dyspnoea (74%), cough, sputum (16%) and chest pain (17%). More than 50% of the cases also had 2 or 3 comorbidities, most commonly with hypertension and type 2 diabetes. Most of the patients (78%) were diagnosed with IPF by the ILD team. Pulmonary function showed moderate restrictive ventilation disorder without gender differences (FVC: 80.80 ± 24.00 reference%). We found higher pCO_2 levels in women (40.6 ± 4.16 vs. 34.78 ± 3.35, p=0.01) without a difference in pO_2 compared to men.

The most common LC was histologically confirmed adenocarcinoma in 13 cases (56%) followed by squamous cell carcinoma in 6 cases (26%). Small cell lung cancer (SCLC) and undifferentiated non-small cell lung cancer (NSCLC) were diagnosed in 2-2 patients. At the time of LC diagnosis, 14 patients (61%) had locally advanced/metastatic tumour status (TNM IIIB, IV). Early stage (TNM I, II, IIIA) was found in 39% of cases. Adenocarcinoma mutation analysis was performed in 13 patients, EGFR mutation was detected in 1 case, K-RAS mutation in 4 cases, while PD-L1 expression was confirmed in 3 cases.

Lobectomy was recommended in only 1 case due to the poor condition of the patients. In terms of tumour, patients in the best condition (ECOG 0-1; 30%) were only suitable for combination oncotherapy. Chemotherapy was the most commonly used type of treatment (n=16), while 6 patients were only eligible for supportive therapy. Four IPF patients received concomitant antifibrotic nintedanib therapy.

The overall median survival was 321 days in all patients. There was no significant difference between sexes (p=0.643), with 340 days of survival from diagnosis of LC in men and 288 days in women.

5. CONCLUSIONS

The questions identified in our objectives focused on treatment options for the most severe IPF and lung cancer associated ILDs, mapping side effects and related survival.

1. What is the effect of nintedanib therapy in the most severe IPF patients?

Our results suggest that nintedanib therapy can be used in patients with advanced IPF with significant functional impairment and results seems to be similar than in clinical trials. Based on our real-life data, nintedanib therapy resulted in functional stability of at least 6 months in both FVC<50% and FVC=50-60% patients.

2. What are the side effects of nintedanib treatment in the most severe IPF group?

Nintedanib therapy had no serious adverse events and was well tolerated. In both groups, gastrointestinal adverse events and liver enzyme elevations of milder grade were observed, consistent with previous clinical trial findings. No new adverse events were detected. Undesirable complaints were mostly temporary, but dose reduction was required in 3 cases (17%) and adverse reactions led to discontinuation of therapy in 2 cases (11%).

3. What kind of clinical appearance can be demonstrated for LC with ILDs?

In contrast to the literature, in our study adenocarcinoma was the most common type of LC histology confirmed in ILD patients. In the majority of patients (61%), locally advanced / metastatic (TNM IIIB, IV) tumours were found at the time of first admission. Activating EGFR mutation was detected in 1

case, 62% of adenocarcinoma patients showed EGFR/K-RAS wild type, while PD-L1≥1% expression was detected in only 3 cases. The worse general condition of ILD-LC patients (ECOG PS>2; n=16) made it more difficult in certain cases to obtain appropriate and/or detailed diagnosis (e.g. performing a biopsy).

4. **What is the survival and outcome of severe IPF and ILD-LC patients?**

Median survival was determined first in this special group of patients: 476 days in the 50-60% FVC group and 444 days in the 50% FVC group. The co-occurrence of ILD and LC significantly worsens survival (321 days). Survival of ILD-LC patients is worse than that of the most severe IPF patients.

5. **Which therapies are used in clinical practice for ILD-LC compared to the standard treatment in Hungary?**

Therapeutic options are limited for ILD-LC: surgery was only possible in one patient in early-stage, and 26% of patients were not eligible for chemotherapy due to their general condition, pre-existing lung disease, or other comorbidities. The choice of individualized therapy is considered important, as the response to therapy may vary from patient to patient depending on the severity of the underlying disease.

6. LIST OF PUBLICATIONS

List of publications related to the Ph.D. theses

1/ Barczi, Eniko*; Starobinski, Livia*; Kolonics-Farkas, Abigel; Eszes, Noemi; Bohacs, Aniko; Vasakova, Martina; Hejduk, Karel; Müller, Veronika (2019) Long-Term Effects and Adverse Events of Nintedanib Therapy in Idiopathic Pulmonary Fibrosis Patients with Functionally Advanced Disease. Advances in Therapy 36: 1221-1232

*contributed equally to the work

Impact factor: 3.871

Quartile: Q1

2/ Barczi Eniko, Nagy Tamas, Starobinski Livia, Kolonics-Farkas Abigel, Eszes Noemi, Bohacs Aniko, Tarnoki Adam Domonkos, Tarnoki David Laszlo, Müller Veronika (2020) Impact of interstitial lung disease and simultaneous lung cancer on therapeutic possibilities and survival. Thoracic Cancer 11:1911-1917

Impact factor: 2.610

Quartile: Q2

List of publications not directly linked to the Ph.D. theses

1/ Bárczi Enikő, Dr. Bohács Anikó, Dr. Eszes Noémi, Dr. Vincze Krisztina, Dr. Tárnoki Ádám Domonkos, Dr. Tárnoki Dávid László, Dr. Karlinger Kinga, Dr. Fejér Bence, Dr. Farkas Abigél, Dr. Müller Veronika. (2017) Rekeszmozgás és életminőség kapcsolata idiopathias pulmonalis fibrosisban (IPF) szenvedő betegeknél. Medicina Thoracalis 7: 210-218.

2/ Bárczi Enikő, Dr. Bohács Anikó, Dr. Farkas Abigél, Dr. Vincze Krisztina, Dr. Balázs György, Dr. Müller Veronika: Orvosi esettanulmányok – Onkopulmonológia: Tüdő

adenokarcinóma mutációjának fontossága műtétet követően, Kiadó: SpringMed Kiadó Kft., ISBN: 978-615-5166-66-2, Megjelenés: 2017. december 08.

3/ dr. Bárczi Enikő*, dr. Mészáros Martina*, dr. Büdi Lilla, dr. Csoma Balázs, dr. Kristóf Katalin, Ballainé Hegedűs Judit, dr. Müller Veronika. (2020) Tapasztalatok a COVID-19 dolgozói szűrésről a Semmelweis Egyetem Pulmonológiai Klinikáján. Medicina Thoracalis 73: 196-199.
* contributed equally to the work

4/ dr. Csoma Balázs, dr. Bárczi Enikő, dr. Mészáros Martina, dr. Müller Veronika. Tapasztalatok a COVID-19 betegek kezelésével a Semmelweis Egyetem Pulmonológiai Klinikán. Medicina Thoracalis 73: 192-195.

5/ Bárczi Enikő, Müller Veronika. (2020) COVID-19 pulmonalis manifesztációi. Orvosképzés XCV. évfolyam, 3:432-584.

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