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SURGEON'S VIEWPOINT ON LUNG TRANSPLANTATION IN CYSTIC FIBROSIS PATIENTS – PRELIMINARY REPORT

PUNKT WIDZENIA CHIRURGA NA PRZESZCZEPIANIE PŁUC U CHORYCH Z MUKOWISCYDOZĄ – DONIESIENIE WSTĘPNE

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Abstract

Introduction: *The surgeon's viewpoint on a patient with cystic fibrosis differs from that of a pediatrician or internist. The problems a cystic fibrosis specialist encounters are different from those faced by the surgeon who takes over the patient in a very advanced, often terminal stage of the disease. Hence, the main problem for the surgeon is the decision concerning the surgery (lung transplantation, pneumonectomy, lobectomy). It is, therefore, important to lay down fundamental and appropriate rules concerning the indications and contraindications for lung transplantation, especially in patients with cystic fibrosis.*

Aim: *The aim of this study was to analyze the methods of qualifying and preparing patients for surgery, as well as carrying out the procedure of transplantation and postoperative short and long-term care.*

Material and methods: *The investigation was carried out on 16 patients with cystic fibrosis. Three were operated on and 10 were on the waiting list for transplantation. Two patients on the waiting list died, one patient was disqualified from transplantation. During qualification for lung transplantation, strict indications, contraindications and other factors (such as blood type, patient's height, coexisting complications) were taken under consideration.*

Results: *All the 3 patients after lung transplantation are alive and under our constant surveillance. Ten patients await transplantation, though four of them are suspended due to hepatitis C infection. Two patients on the waiting list died: one from respiratory insufficiency and the other in the course of bridge-to-transplant veno-venous extracorporeal membrane oxygenation due to hepatic failure. One patient has been disqualified because of cachexia.*

Conclusions: *Since lung transplantation is the final treatment of the end-stage pulmonary insufficiency in cystic fibrosis patients, the number of such procedures in cystic fibrosis is still too low in Poland. The fast development of these procedures is highly needed. It is necessary to develop better cooperation between different disciplines and specialists, especially between pediatricians and surgeons. The correct choice of the suitable moment for lung transplantation is crucial for the success of the procedure.*

Key words: lung transplantation, qualification, cystic fibrosis, respiratory insufficiency

Streszczenie

Wstęp: Punkt widzenia chirurga odnośnie leczenia pacjenta z mukowiscydozą różni się od spojrzenia pediatry czy internisty. Duży jest bagaż zadań lekarza specjalisty w zakresie leczenia chorego z mukowiscydozą w różnych okresach choroby, a inny chirurga, który przejmuje go w bardzo zaawansowanym, a nierzadko w terminalnym stadium. Stąd dla chirurga głównym problemem jest podjęcie decyzji odnośnie leczenia operacyjnego (transplantacja płuc, pneumonektomia, lobektomia). Dlatego tak ważne jest sformułowanie podstawowych i właściwych zasad dotyczących wskazań i przeciwwskazań do transplantacji płuc zwłaszcza w odniesieniu do pacjentów z mukowiscydozą.

Cel: Celem pracy była analiza metod kwalifikacji i przygotowania, a także przeprowadzenia transplantacji oraz pooperacyjnej opieki krótko- i długoterminowej.

Materiał i metody: W niniejszej pracy przedstawiamy 3 przypadki pacjentów z mukowiscydozą po zabiegu transplantacji płuc oraz 10 kandydatów, którzy w chwili obecnej są potencjalnymi biorcami narządu i oczekują na jej przeprowadzenie. Dwoch pacjentów nie doczekano przeszczepienia, jedna pacjentka została zdyskwalifikowana z zabiegu. W toku kwalifikacji do transplantacji płuc omawiane są istniejące wskazania, przeciwwskazania i szereg innych czynników (takich jak grupa krwi, wysokość ciała pacjenta, istniejące powikłania choroby podstawowej, choroby współistniejące).

Wyniki: Wszyscy (troje) pacjenci po przeprowadzonej transplantacji żyją i są pod stałą kontrolą naszego ośrodka. Z dziesięciu kandydatów oczekujących na przeszczepienie, czterech jest zawieszonych na liście oczekujących z powodu infekcji (wirusowe zapalenie wątroby typu C). Dwoch pacjentów nie doczekano przeszczepienia: pierwszy zmarł z powodu niewydolności oddechowej, a drugi kwalifikowany do przeszczepienia płuci wątroby pozostający na pozaustrojowym natlenianiu membranowym żyłno-żylnym, zmarł wskutek niewydolności wątroby. Jedna pacjentka została zdyskwalifikowana z zabiegu z powodu skrajnego niedoboru masy ciała.

Wnioski: Biorąc pod uwagę, że transplantacja płuc jest ostatecznym leczeniem schyłkowej niewydolności oddechowej w mukowiscydozie. Liczba wykonywanych w Polsce przeszczepień płuc u chorych z mukowiscydozą jest ciągle za mała, o czym świadczy los oczekujących pacjentów. Konieczny jest więc szybki rozwój placówek zajmujących się przeszczepieniami płuc u tych chorych. Wybór odpowiedniego momentu przeprowadzenia transplantacji płuc, ma zasadnicze znaczenie dla powodzenia procedury.

Słowa kluczowe: przeszczepienie płuc, kwalifikacja, mukowiscydoza, niewydolność oddechowa

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INTRODUCTION

Cystic fibrosis (CF) is a genetically determined disease affecting many organs of exocrine secretion. The lungs are affected due to the gradual destruction of the bronchial and lung parenchyma due to the obstruction of dense exocrine secretions and infections (both bacterial and fungal), accompanied by recurrent pneumothorax and hemoptysis. At the beginning, the disease is suppressed by conservative treatment, but that also depends on the clinical expression of this genetic disorder. Lung transplantation is a therapeutic measure of last resort for end-stage diseased patients and brings improvement of survival and quality of life.

The first attempt at LuTx was made by Hardy in the early 1960s. Initially attempts were limited to patients with primary pulmonary hypertension or Eisenmenger's complex, and were gradually extended to patients with a variety of end-stage pulmonary disorders, including cystic fibrosis. However, these

patients did not survive the early post-operative period. The heart-lung transplantation (HLT) performed in Stanford in 1981 is considered the first successful attempt. The first lung transplantation with a good result took place in 1983 in Toronto, Canada, and was performed by Cooper and Patterson [1]. In Poland, the first unsuccessful attempt at HLT was made by Religa in 1986 in Zabrze. This one and other attempts at such treatment failed at that time. The first LuTx in Szczecin-Zdunowo was performed by Grodzki in 1996. It was a family transplantation of one lobe from the father to his son with lung fibrosis. The first successful HLT in Poland was performed by Zembala in Zabrze in 2001 and SLT in 2003. Since then, LuTx are routinely effected in that centre and since 2009 also in Szczecin-Zdunowo. Currently in Poland we perform almost 20 LuTx a year (SLT and BLT included) in two centres: Zabrze and our centre in Szczecin-Zdunowo.

The first LuTx in a patient with CF in Poland was performed in Zabrze in March 2011 and the first procedure

of this kind in a patient under 18 years of age (a 17-year-old boy) took place in the same centre in June 2012. As far as frequency is concerned, in the world's statistics CF is the third indication for LuTx in adults and the first one in children. Since 1995 until now the procedure was conducted in nearly 7000 adults and 1200 children with CF [2] around the world. The median survival for children after LuTx due to all indications is 4.9 years, whereas for adults suffering from cystic fibrosis the corresponding figure is 8 years. Therefore, it is of utmost importance to treat children conservatively for as long as possible and offer them LuTx when they are already grown up. On the other hand, 4.9 years of survival for children is better than death within 2 years, i.e. the time of referral for LuTx. The occurrence of the bronchiolitis obliterans syndrome (BOS) and other comorbidities in children is similar to that of adult recipients [3].

AIM

The aim of this study was to analyze the methods of qualifying and preparing patients for lung transplantation, as well as carrying out the procedure of transplantation and postoperative short and long term care.

MATERIAL AND METHODS

Qualifying for lung transplantation

Cystic fibrosis patients are usually in the group of the younger population of lung transplant candidates. However, in the overall group for transplantation the number of children and youth is evidently lower than that of adults. The inclusion criteria are: expected survival shorter than two years in children with CF and expected survival shorter than 5 years in adults with CF, forced expiratory volume in one second (FEV₁) below 30% of the predicted value and one of the following symptoms: recurrent hemoptysis requiring bronchial artery embolization, recurrent pneumothorax or frequent exacerbations demanding intensive care treatment (once a year) or more than three per year at the pulmonology department, respiratory failure with long term oxygen therapy (LOT), arterial blood carbon dioxide partial pressure pCO₂ > 50 mm of mercury (mmHg), pulmonary hypertension: right ventricle systolic pressure (RVSP) over 50 or mean pulmonary artery pressure (mPAP) over 25 mmHg. Absolute contraindications are as follows: recent malignancy, extrapulmonary organ failure (e.g. in our candidates: liver, pancreas, kidney insufficiency or intestine disorder leading to malnutrition), uncontrolled systemic infection (ex. *Burkholderia cenocepacia*), chest wall/spine deformity, non-adherence, lack of social support, psychiatric illness and drug abuse. Relative contraindications include: poor muscle status, high-resistant/virulent pathogens, significant comorbidities, age over 65, hospitalization in an Intensive Care Unit (ICU) (ventilator or ECMO) and body mass index (BMI) over 30 kg/m². Other frequent negative prognostic factors are: respiratory failure, insulin dependent diabetes mellitus, exacerbations, underweight and recurrent pneumothorax. Rare negative prognostic factors are: major hemoptysis,

rapid FEV₁ decline, severe exacerbations with ICU admission, mPAP over 25mmHg and the 6 minute walk test (6MWT) below 400 meters [4]. The ideal candidate should be fully adherent, self-manageable, with excellent health perception, low anxiety level, having firm social support, with no alcohol or drug abuse and able to communicate, memorize, calculate, write and read.

Lung transplantation treatment is a new procedure in Poland. Pulmonologists and transplantologists have to learn how to find proper pathways for selecting candidates. In Szczecin we have to deal with candidates with end-stage CF and hepatic failure, kidney failure or the malabsorption syndrome. It is hard to explain that LuTx is not the remedy for these additional failures. On the other hand, pulmonologists tend to either keep their patient long without presenting them to the transplantologist, i.e. presenting them too late or presenting them with an additional failure which we cannot manage. Better interdisciplinary cooperation is essential.

Another problem is viral hepatitis. Although latent type B hepatitis is not a contraindication, as we can treat the LuTx patient to prevent the recurrence of the illness, type C hepatitis really is an obstacle. The possible cure – sofosbuvir has not been registered in Poland and the monthly treatment costs ca. 80.000 Polish Zloty. It is not refundable by the Polish National Health Fund. Therefore, these patients have to be temporally excluded from the LuTx waiting list, until a post-operative treatment solution is found.

The blood type is important to assess the waiting time to find a compatible donor. The blood type distribution in Poland is as follows: "A" – 40%, "0" – 32%, "B" – 19% and "AB" – 9% [5]. As we are looking for an identical or compatible donor, the chances to find one is 32% for a 0 blood type recipient (only "0" type compatible), 51% for a "B" recipient ("0" and "B"), 72% for an "A" recipient ("0" and "A") and 100% for an "AB" blood type recipient. These conditions should be taken into consideration when listing the patient: the waiting time for a "0" blood type recipient is longer, therefore he or she should be listed earlier.

The height of the LuTx candidate is important. The average height of our LuTx candidates is lower than the population of lung donors. Therefore, candidates below 160cm of height require a longer time to find a suitable donor and should be listed earlier. As we can see, this is also a problem concerning children for LuTx – it is difficult to find a donor of a similar height.

RESULTS

From June 2012 we have been engaged in the medical care for CF patients. The investigation was carried out on 16 patients with cystic fibrosis. At present we take care of 3 patients with CF who remain after LuTx. The first of them underwent the procedure in Rigshospitalet in Copenhagen, Denmark. His transplantation was the effect of good cooperation between Polish and Danish Lung Transplant

Centres and now his follow-up is being conducted in our centre. The other 2 patients were operated on in our centre and one of them underwent LuTx with surgically reduced lung parenchyma. The mean age of those 3 transplant patients was 22.2 years (range 17.5-26.5). There were 2 males. The indication for the procedure in three cases was chronic respiratory failure due to CF. All the patients required home oxygen therapy and 2 of them were additionally treated with non-invasive ventilation. The average time of respiratory failure was 3.4 years (range 0.25-6) before LuTx. The mean FEV1 before the transplantation in this group was 19.9% of the predicted value (range 13.5-23.1), the mean BMI was 18.8 kg/m² (range 16.8-22.2) and the mean result of 6MWT was 243 m (range 211-297). As far as other CF manifestations are concerned, all of these patients suffer from pancreatic insufficiency and 2 of them are treated for cystic fibrosis related diabetes (CFRD). Every patient was diagnosed with a chronic *P. aeruginosa* infection before the transplantation and one of them also harbored *Achromobacter xylosoxidans* (*A. xylosoxidans*). None of them was infected with *Burkholderia spp.* All of the LuTx recipients are alive and under our constant surveillance.

We have 10 patients with CF who are either being observed or prepared for LuTx. The average age in this group is 33.5 years (range 17.5-42.0). There are 6 males. In every case the indication for the transplantation is chronic respiratory failure in the course of CF. The duration of this condition ranges from 1.0 to 19.0 years (average 8.2 years). There are 7 persons on home oxygen therapy and non-invasive ventilation is not necessary in this group. The mean FEV1 at present is 30.7% of the predicted value (range 13.6-39.8), the average BMI is 20.2 kg/m² (range 17.6-22.8) and the mean result of the 6 MWT is 345 m (range 184-600). Pancreatic insufficiency has been diagnosed in 7 patients and one of them is treated for CFRD. Seven patients have been diagnosed with chronic *P. aeruginosa* infection and one of them also harbors *A. xylosoxidans*. Like in the group after LuTx, there are no patients infected with *Burkholderia spp.* There are 3 individuals suspended on the waiting list due to hepatitis C infection. Four patients are still being observed, because they do not meet the criteria for the procedure yet.

Two patients on the waiting list with CF died before the operation: the first one due to respiratory insufficiency and the other in the course of bridge-to-transplant veno-venous extracorporeal membrane oxygenation (ECMO VV) due to hepatic failure. One female has been disqualified because of cachexia (BMI 14.3 kg/m²) not responding to nutritional treatment via percutaneous endoscopic gastrostomy (PEG). That patient has a history of *P. aeruginosa*, *A. xylosoxidans* and *Burkholderia spp.* infection.

The population of our CF LuTx candidates is illustrated in Table I.

DISCUSSION

The quality of health care is improving in our country and the number of adult CF patients is

increasing (currently there are approximately 700). As a result, adult pulmonologists have to take over patients from pediatric ones. This transmission of healthcare responsibility is not easy. Therefore, it is worth popularizing the lung transplantation method among these medical professionals to increase the awareness of the method and improve preparation for the surgery. The sooner the patient is accustomed to this treatment, the better results can be achieved. A patient in a critical condition, unable to walk or with uncontrolled second organ failure is not suitable for lung transplantation.

The correct choice of the suitable moment for lung transplantation (LuTx) qualification is crucial for the success of the procedure. It is a task for pediatricians and internists to choose the proper time to prepare the patient for the transplantation, to present him to the transplantologist and to submit him to the LuTx active list. The qualification cannot take place too late but it should not occur too early either. The patient's preparation for LuTx consists of several components. The first of them is intensive nutritional treatment. The patient should adhere to a strict amount of calories, protein, vitamins and minerals needed to maintain a positive nutritional status. The body mass index (BMI) should be between 17 and 27 kg/m². In those patients who are unable to eat enough to ensure proper caloric intake, the placement of feeding gastrostomy may be necessary. On the other hand, the patient should be in the best physical shape possible at the time of transplantation. Given the present respiratory failure and difficulty in performing any exercise, it is a big challenge for the patient and the team who are taking care of him. The individual exercise programme should include training for respiratory muscles and general conditioning. The preparation for LuTx also consists of: complementary vaccinations (mandatory and recommended), complete dental treatment, therapy of concomitant conditions if needed and finally psychological support, which plays a very important role.

Up to the year 2014 there were 1800 LuTx performed in children, most frequently at the age of over five years. CF and idiopathic pulmonary hypertension (IPH) were the most frequent indications. The median overall survival in these patients is 4.9 years. The occurrence of bronchiolitis obliterans (BO) and other comorbidities is similar to that in adult recipients [3]. The most common indications for LuTx are chronic obstructive pulmonary disease (COPD), idiopathic pulmonary fibrosis (IPF), CF, alpha-1-antitrypsin deficiency and idiopathic pulmonary arterial hypertension (IPAH).

CF associated liver disease is present in 30% of patients. It is the third cause of death after lung disease and Tx complications. Clinical symptoms are late, when the liver is already severely damaged. It often accompanies exocrine pancreatic insufficiency and meconium ileus. Conservative treatment is based on ursodeoxycholic acid, but the final treatment should be liver transplantation (LTx) (7). One of our patients was listed for lung and liver Tx, but did not make it to the operation. Psychological support is necessary to

Table I. Cystic fibrosis lung transplantation candidates considered by our centre as of 14 Sept., 2014.

Tabela I. Pacjenci z mukowiscydozą, będący kandydatami do przeszczepienia płuc lub po przeszczepieniu płuc w naszym ośrodku. Stan na 14.09.2014 r.

Number Numer	Initials Inicjały	Age (years) Wiek (lata)	Sex Płeć	Hight (cm) Wysokość ciała (cm)	Blood type Grupa krwi	Qualified Zakwalifikowany (-a)	Status Status	Survival (days) Przeżycie (dni)
1	PO	18	M/M	160	B	Yes/Tak	LuTx	840
2	MB	23	M/M	165	B	Yes/Tak	LuTx	402
3	AM	26	F/K	156	A	Yes/Tak	LuTx red	7
4	AI	27	M/M	179	O	Yes/Tak	Died waiting (ECMO VV) Nie doczekał przeszczepienia (ECMO VV)	NA
5	PF	19	M/M	163	O	Yes/Tak	Being prepared Przygotowywany	NA
6	SG	24	F/K	162	O	Yes/Tak	Died waiting Nie doczekała przeszczepienia	NA
7	KN	18	F/K	158	O	No: proteinuria, cachexia	Being observed Obserwacja	NA
8	JR-K	40	F/K	158	O	No: still fit Nie: nadal dobra wydolność	Being observed Obserwacja	NA
9	MCh	42	F/K	158	A	No: still fit Nie: nadal dobra wydolność	Being observed Obserwacja	NA
10	MSz	37	F/K	170	A	No: hepatitis C Nie: wirusowe zapalenie wątroby typu C	Being observed Obserwacja	NA
11	HK	31	M/M	167	B	No: hepatitis C Nie: wirusowe zapalenie wątroby typu C	Being observed/ Obserwacja	NA
12	PM	33	M/M	187	B	No: still fit Nie: nadal dobra wydolność	Being observed Obserwacja	NA
13	RS	37	M/M	173	B	No: hepatitis C Nie: wirusowe zapalenie wątroby typu C	Being observed Obserwacja	NA
14	PT	37	M/M	178	B	No: still fit Nie: nadal dobra wydolność	Being observed Obserwacja	NA
15	NN	17	F/K	156	O	No: cachexia, no weight gain despite PEG Nie: wyniszczenie, brak przyrostu masy ciała pomimo PEG	Disqualified Dyskwalifikacja	NA
16	RJ	42	M/M	185	A	Yes Tak	Being prepared Przygotowywany	NA

Abbreviations/Skróty: NA – not applicable/nie dotyczy, PEG – percutaneous endoscopic gastrostomy/przeznaczona endoskopowa gastrostomia, LuTx – lung transplantation/przeszczepienie płuc, Tx – transplantation/przeszczepienie, LuTx red – transplantation with surgically reduced lung parenchyma/przeszczepienie z redukcją miąższu płuc, ECMO VV – extracorporeal membrane oxygenation veno-venous/pozaustrojowe natlenianie membranowe żyłno-żyłne.

improve the adherence of the patient, to help in decision-making, and improve nutritional and psychosocial adjustment [8]. Body mass index (BMI) below 18.5 kg/m² did not influence the survival rate in LuTx patients independently of the indication, checked on 546 Pts [9]. On the other hand, we have a rule in our center not to enroll patients with a BMI below 18 kg/m². They should gain weight either with the help of a dietician or by having percutaneous endoscopic gastrostomy (PEG) instillation. CF patients after LuTx have an improved quality of life, though some social functioning and future concerns still exist [10]. Apparently they still need to be observed by diabetologists, hepatologists and gastroenterologists. Transplant function and survival in CF LuTx patients are better than in other indications. *Burkholderia cenocepacia* and *gladioli* are the most difficult pathogens to manage and they shorten survival [11]. In our center these two pathogens are exclusion criteria for LuTx. *Burkholderia cepacia complex* (BCC) invades the CF lung when it is already infected with *P.aeruginosa* and the bronchial lumen is anaerobic. BCC inhibits the *P.aeruginosa* biofilm-like growth and starts to invade the host macrophages [12]. In our patients *P. aeruginosa* and Bcc can be diagnosed, but to the best of my knowledge the exact description of the Bcc type is not possible in Poland. Therefore, the pulmonologist has to send the samples to a foreign laboratory in Vienna, Hannover, or elsewhere. LuTx in CF patients with *Mycoabacterium abscessus* infection is controversial.

ECMO is more often used for CF as the bridge to Tx [13]. In our experience we had one CF patient waiting for a bridge-to-transplant ECMO VV, but he died while waiting. Fifty seven percent of CF LuTx patients have secondary pulmonary hypertension, defined as mPAP>25 mmHg. Pulmonary hypertension (PH) has no influence on survival after LuTx in CF patients [14]. If we have a LuTx candidate with PH (primary or secondary), we are prepared to transplant him or her on ECMO VA (veno-arterial). Using cyclosporin A (CyA) or tacrolimus (Tac) in LuTx for all indications has no difference on survival and acute rejection frequency. Tac is associated with lower risk of developing BOS and arterial hypertension, but higher risk of diabetes mellitus [15].

The lung transplantation program is being developed in Poland. This treatment is difficult, multidisciplinary and laborious. Compared to patients with other diagnoses, it is CF LuTx patients who can benefit from Tx most, both in survival and the quality of life. There should be an improvement in the contacts between pulmonologists and lung transplantologists to identify the proper LuTx candidates. The timing and Tx listing of the patients is crucial and cannot be late. Special care concerning timing should be given to short patients with blood group 0, which is a parameter that is as important as FEV₁, pO₂ or DLCO. On the other hand, patients having second organ end-stage failure are bad candidates for LuTx. They should not be given a promise of LuTx, as the procedure will not cure them. There is the need to develop bacteriological

laboratories in Poland in order to detect types of Bcc in order to be able to exclude candidates whom we cannot help with Tx. A conservative treatment solution for hepatitis C LuTx candidates should be found to be able to cover their viremia after transplantation.

CONCLUSIONS

Since the lung transplantation is the final treatment of the end-stage pulmonary insufficiency in cystic fibrosis patients, the number of such procedures in cystic fibrosis is still too low in Poland. The fast development of these procedures is highly needed. A better cooperation between different disciplines and specialists, especially between pediatricians and surgeons is necessary. The correct choice of the suitable moment for lung transplantation is crucial for the success of the procedure.

At the end we would like to acknowledge and thank all the pulmonary centers in Poland for contributing and presenting LuTx candidates to us, as well as POLTRANPLANT and coordinators from all the Polish centers for identifying lung donors. We would also like to thank the Lung Transplant Team in Rigshospitalet in Copenhagen for the fruitful cooperation during the organization and procedure of LuTx of our mutual patient.

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Conflicts of interest/Konflikt interesu

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