Long-term outcome of lung transplantation for cystic fibrosis — Danish results

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Abstract

Objective: Over the last decades improvements in medical therapies have delayed the progression of lung disease in cystic fibrosis (CF). However, lung disease is still the most common cause of premature death, and lung transplantation today is the only treatment for end-stage lung disease in patients with CF. We present a retrospective review of the outcome of CF patients transplanted in Denmark since start of the national lung transplantation programme in 1992.

Methods: In a 10-year period, 47 patients with CF were listed for lung transplantation; 29 patients underwent transplantation and 18 patients died while waiting for donor organs. Eleven patients received en block double lung transplantation with direct bronchial artery revascularization and 18 patients received bilateral sequential lung transplantation. Median age at transplantation was 29 years (range 11–50).

Results: The perioperative mortality (≤ 30 days) was 3.5% (1/29 patients). Actuarial survival of transplanted patients at 1, 3, 5 and 8 years was 89, 80, 80 and 70%, respectively. Actuarial survival of non-transplanted patients on the waiting list at 1 and 2 years was 28 and 11% (P < 0.0001). Causes of death of transplanted patients were: respiratory failure on day 7 (n = 1), bronchiolitis obliterans syndrome (n = 2), infection (Cytomegalovirus, Aspergillus fumigatus) (n = 2), bronchial anastomosis dehiscence (n = 1). Pulmonary function (FEV₁% predicted) improved from median 20% (range 13–31) pre-transplant to 71% (range 19–118) after 5 years (P < 0.0001). Renal function (51Cr-EDTA clearance) decreased from median 97 ml/min (range 45–190) pre-transplant to 32 ml/min (range 8–84) 6 months after transplantation (P < 0.001). Three patients (11%) received dialysis post-transplant of whom two underwent kidney transplantation. Immunosuppressive induction therapy with rabbit-antithymocyte-globulin compared to daclizumab resulted in fewer treatments for acute rejection within the first 3 months post-transplant (P = 0.05 at 5–8 weeks).

Burkholderia multivorans was present in three patients pre-transplant with satisfying long-term outcome in one patient.

Conclusions: Lung transplantation is a well-established life-extending treatment for patients with CF and end-stage lung disease. The operative mortality is low and CF patients have a significant early survival benefit after lung transplantation. Satisfying long-term results can be achieved in this young and severely ill group of patients.

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1. Introduction

Cystic fibrosis (CF) is the most common life-threatening inherited disease among Caucasians. The majority of pre-term deaths are caused by respiratory insufficiency due to many years of chronic infection with gram-negative, often multiresistant organisms [1]. However, life expectancy has been considerably improved, with a median survival of more than 30 years [2]. Lung transplantation is currently the only treatment for end-stage respiratory insufficiency and today CF is the second largest group of lung transplanted recipients in Europe (22.4%), globally the third largest (17.5%) exceeded only by emphysema/chronic obstructive pulmonary disease (COPD) (35.3%) and idiopathic pulmonary fibrosis (17.8%) (www.ishlt.org).

We present the Danish experience with en block double lung transplantation (DLTx) including direct bronchial artery revascularization (BAR) and bilateral sequential lung
transplantation (BLTx) over a 10-year period at our national center. The aims of this retrospective study are to evaluate survival, pulmonary and renal function, incidence of acute rejection and experience with different immuno-suppressive induction therapies, development of the bronchiolitis obliterans syndrome (BOS) and infection.

2. Materials and methods

2.1. Selection criteria

CF patients with a history of declining exercise tolerance, increasing requirements for hospitalisation, forced expiratory volume in the first second (FEV\textsubscript{1})<20\% of the predicted normal FEV\textsubscript{1} and increasing need for supplemental oxygen and difficulty in maintaining weight were evaluated for transplantation. Donor criteria were PaO\textsubscript{2} > 13 kPa at FiO\textsubscript{2}<40\% and PEEP<5 cm H\textsubscript{2}O (standard criteria in Scandinavian countries) and without signs of invasive lung infection or malignant lung disease. Recipient and donor were matched according to the ABO-system, measured and calculated total lung capacity (TLC) and height.

2.2. Patients’ clinical characteristics

Between January 1993 and 2003, 47 patients were accepted for transplantation. Twenty-nine patients, 14 females and 15 males, median age 29 years (range 11–50) achieved lung transplantation while 18 patients, median age 27 years (range 16–35) died awaiting donor organs. Median time on the waiting list among recipients was 267 days (range 14–902). Most candidates were in poor nutritional status with median body-mass index of 17.7 (range 14–21). Forty-five percent of the recipients were diagnosed with IDDM at time of transplantation. Pre-transplant FEV\textsubscript{1} was median 20\% predicted (range 13–31). All patients were in need of additional oxygen supply and 79\% required bilevel positive airway pressure (BiPAP). Three recipients (10%) and two patients awaiting donor organs (11%) were colonized with *Burkholderia multivorans* before transplantation.

2.3. Surgical procedure

Initially, our lung transplantation programme included DLTx with direct BAR, performed in the first 11 CF patients (38\%). The procedure was changed in 1998 and the last 18 patients (62\%) received BLTx. The surgical technique in DLTx with concomitant BAR using the recipients’ left internal mammarian artery grafted to donor intercostobronchial arteries has been described previously [3]. The tracheal anastomosis was made one tracheal ring above the carina with Prolene\textsuperscript{®} 4–0 as a running suture in the membranous part and interrupted sutures in the cartilaginous part, without telescoping or omental wrapping. BAR was applied to reduce the risk of necrosis of this anastomosis and of the carinal area. Access was made through a median sternotomy and cardiopulmonary bypass (CPB) and cardiac fibrillation was used in all of these patients. In BLTx the least functioning native lung was explanted first through a posterolateral thoracotomy. With respect to the bronchial anastomoses the same technique as in DLTx was applied, but on level of the distal main bronchi. After implantation of the first lung, the same procedure was applied to the opposite side. CPB was used only in two patients: an 11-year-old child and a recipient with a rigid right lung. Flexible bronchoscopy was performed in all patients at the end of operation in order to check the airway anastomoses and clear the lungs for secretion.

Until 1998, anaesthesia for all lung transplantations were planned with delayed extubation within 24 h in the intensive care unit (ICU). Conversion to BLTx and change of anaesthesia technique enables early extubation in the operating theatre, and was preferred hereafter [4].

2.4. Lung preservation

Pulmoplegia with modified Euro-Collins\textsuperscript{®} solution containing prostaglandin E\textsubscript{1} was used as anterograde single-flush perfusion to the pulmonary artery. A standard volume of 4000 ml solution was given to all donors. Before division of trachea both lungs were inflated with 40\% oxygen until 2/3 of full inflation. Donor lungs were kept in cold Ringer-lactate medium during transportation.

2.5. Immunosuppression

We used an immunosuppressive treatment including cyclosporine and azathioprine, adjusted according to renal function, leucocytes and platelets. Methylprednisolone 1 g was administered perioperatively and followed by tapered prednisolone to a daily dose of 0.1 mg/kg. All recipients received induction therapy consisting of either rabbit-antithymocyte-globulin (ATG, Imtix-Sangstat, initial 13 patients) 2.5 mg/kg for 3 days or daclizumab (Zenapax\textsuperscript{®}, Roche, 16 patients) 1 mg/kg every second week for 1.5 month. The ISHLT grading system for acute pulmonary rejection was used and episodes of acute rejection (A2–4) were treated with methylprednisolone 1 g daily for 3 days followed by tapered prednisolone.

2.6. Antibiotics

Patients were treated according to the resistance pattern of the microorganisms colonizing the patient before transplantation, as earlier reported [5]. All patients were treated for *Pseudomonas aeruginosa* infection prior to transplantation. Permanent prophylaxis after transplantation included sulfamethoxazole–trimethoprim and inhaled...
nebulized colistin. Initially donor and recipient were matched according to CMV status. This procedure was abandoned with introduction of CMV prophylaxis, and in 1998–1999 oral aciclovir was given for 3 months. At present, we use ganciclovir 5 mg/kg i.v. for 10 days followed by oral treatment for 3 months. CMV was diagnosed by sero-conversion or PCR in BAL. Aspergillus infection was treated with itraconazole, but without prophylaxis. Antibiotic treatment was adjusted according to donor tracheal culture after transplantation, and thereafter according to microbial findings in broncho-alveolar lavage (BAL) fluid.

2.7. Late follow-up

After discharge patients were followed in the outpatient clinic. Flexible bronchoscopy with BAL and transbronchial biopsy (TBB) were performed after 2, 4, 6, and 12 weeks, and then every 6 months for the first 2 years, or when clinically indicated.

2.8. Statistics

Actuarial survival was determined by the Kaplan–Meier method. The Mantel–Haenszel log rank test was used to compare survival curves. The Mann–Whitney non-parametric test was used to evaluate any difference between variables at different time intervals. A probability value of \( P < 0.05 \) was considered significant. Data are expressed as median and observed range unless other is noticed.

3. Results

3.1. Perioperative period

The perioperative mortality (\( \leq 30 \) days) was 3.5%; one patient died after 7 days of respiratory failure and ventricular tachycardia. Duration of stay in ICU was 2 days (2–30 days) (Fig. 1). Ischemia-reperfusion injury documented by chest X-ray and increasing oxygen requirement was recorded in two patients, both after BLTx. Two patients developed seizures, being successfully treated. Myocardial infarction (NSTEMI) was seen in the perioperative period in two patients after BLTx. Time to discharge from hospital was 34 days (17–73 days).

3.2. Survival

Actuarial survival (Kaplan–Meier) of transplanted patients at 1, 3, 5 and 8 years was 89, 80, 80 and 70%, respectively (Fig. 2, continuous line). The number of patients at risk at 1, 3, 5 and 8 years was 20, 12, 10 and 1 patient, respectively. Median follow-up time of recipients was 707 days (7–2920 days). From time of entrance on the waiting list, actuarial survival of listed patients not undergoing transplantation was significantly inferior to transplanted patients (\( P < 0.0001 \)) (Fig. 2). Median survival time of listed patients not undergoing transplantation was 189 days (2–1699 days). Late causes of death in transplanted patients were: BOS (n=2), infection (CMV, Aspergillus fumigatus) (n=2), dehiscence of a bronchial anastomosis (n=1).

3.3. Pulmonary function

Pulmonary function, expressed as FEV\(_1\)% of the predicted normal FEV\(_1\), improved from median 20% (13–31%) pre-transplant to 78% (59–111%) after 6 months. Among survivors 5 years post-transplant FEV\(_1\) remained significantly improved, 71% (19–118%) (\( P < 0.0001 \)) (Fig. 3).

3.4. Rejection

Episodes of acute rejection (A2–4) were mainly observed in the first 3 months after transplantation with a decreasing incidence and were infrequent after 1 year affecting only

![Fig. 1. Duration of stay in intensive care unit (ICU) after lung transplantation in CF patients.](image1)

![Fig. 2. Actuarial survival (Kaplan–Meier) of CF patients following lung transplantation (LTx) (continuous line). Dotted lines illustrate actuarial survival after LTx and of listed CF patients awaiting organs, where year zero indicate entrance on the waiting list for both groups (log rank \( P < 0.0001 \)). Patients at risk in parenthesis.](image2)
four patients (20%). Induction therapy with ATG compared to daclizumab resulted in fewer treatments for acute rejection within the first 3 months post-transplant (P<0.05 at 5–8 weeks) (Fig. 4).

3.5. Bronchiolitis obliterans syndrome

BOS is associated with an irreversible loss of FEV₁ to ≤80% of post-operative baseline FEV₁ [6]. Actuarial freedom from BOS for patients surviving more than 3 months and with a minimum of 15 months observation time at 1, 3 and 5 years post-transplant was 90, 77 and 60%, respectively (Fig. 5). Onset of BOS was median 2 years (1–5 years). The incidence of BOS was equal in the two groups of surgical procedures (n=3 in each group). Re-transplantation was not performed in any patient in this study.

3.6. Infection

Lower respiratory tract infection (bacterial, viral or fungal) diagnosed by TBB and BAL was treated 0.69 time per 100 patient days in the first 3 months post-transplant (Table 1). The incidence decreased to 0.50 time and 0.06 time in the following 4–6 months and 7–12 months, respectively. Bacterial infection (Staphylococcus aureus, P. aeruginosa, Enterococcus, Streptococcus, Acromobacter (Alcaligenes) xylosoxidans) dominated in the first 3 months and was generally well treated. Initially donor and recipient were matched according to CMV status. Later CMV prophylaxis for 3 months was introduced. Six patients (21%) were treated for CMV infection, with median onset at 3.3 months (1–6 months). In two patients (33%) CMV infection was diagnosed in combination with Aspergillus with a fatal outcome. Fungal infection (A. fumigatus, Candida albicans, Candida glabrata) was mainly treated in the first 3 months post-transplant. Six patients (21%) developed pulmonary Aspergillus infection with a fatal outcome in three patients (50%). Five of these six patients (83%) were colonized during early hospitalisation with median onset at 1.7 months (0.5–4 months). Owing to Aspergillus infection, one patient died within 6 months and one patient with an early 25-day stay in ICU is in terminal respiratory failure today. Three patients (10%) were colonized with B. multivorans (genomovar II) prior to transplantation without any de-novo infection occurring post-transplant. One of these patients is well being today after 22 months of follow-up with optimal pulmonary function despite a pre-transplant pan resistant colony.

<table>
<thead>
<tr>
<th>Infection type</th>
<th>Months post-transplant</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0–3</td>
</tr>
<tr>
<td>Bacterial</td>
<td>0.43</td>
</tr>
<tr>
<td>Viral (CMV)</td>
<td>0.04</td>
</tr>
<tr>
<td>Fungal</td>
<td>0.22</td>
</tr>
<tr>
<td>All events</td>
<td>0.69</td>
</tr>
</tbody>
</table>

Data presented as treatment per 100 patient days.
We found no difference in the incidence or spectrum of infections with regard to surgical procedure or immunosuppressive induction therapy.

### 3.7 Renal function

The majority of patients developed impaired renal function mainly due to cyclosporine treatment. Pre-transplant $^{51}$Cr-EDTA clearance was 97 ml/min (45–190 ml/min) and decreased to 32 ml/min (8–84 ml/min) 6 months after transplantation and 27.5 ml/min (13–42 ml/min) 6 years after ($P<0.001$) (Fig. 6). Three patients (11%) received dialysis post-transplant. Two of these patients underwent kidney transplantation without complications. One patient was listed for kidney transplantation.

### 4. Discussion

Lung transplantation for patients with CF was initially performed as a heart–lung transplantation and the first CF patient was transplanted in North America in October 1983 [7]. Since then, several surgical techniques for lung transplantation have been applied to this group of patients. Importance of the bronchial artery circulation as nutritive arterial blood supply to the transplanted lung(s) was suggested as early as in 1950 [8]. This could serve as a reinforced alveolar barrier after transplantation potentially leading to a decreased rate of infection and rejection. For this reason, our institution initially applied DLTx with concomitant BAR to the transplant programme [3]. The technique for BLTx with a transverse bilateral thoracosternotomy (clamshell) developed in parallel and the procedure could be done safely without CPB [9]. BLTx with bilateral posterolateral thoracotomy has gained acceptance in many centres and is the procedure of choice in our institution today. Comparison of the two procedures DLTx vs. BLTx as a prospective randomised study has never been undertaken.

In European and American multicentre studies CF patients were found to have a clear survival benefit from lung transplantation [10,11]. Timing of referring CF patients for transplantation has been widely debated because of an unpredictable course of this disease [12]. In our programme, we used the international guidelines for selection criteria throughout the time period of this study [13].

The overall cumulative survival presented here: 89, 80, 80 and 70% at 1, 3, 5 and 8 years is acceptable. We found a median survival of 189 days for patients on the waiting list with 1 and 2 years survival rate of 28 and 11%, respectively. The precipitous slope of this survival curve is rather reflecting ‘too late referral’ than ‘too late transplantation’ of candidates. Our data confirms the clear survival benefit in CF patients after lung transplantation found in previous studies.

Pulmonary function expressed as FEV$_1$% predicted increased to a plateau within 6 months after transplantation, as reported by others [14,15]. Renal function followed a reciprocal course mainly due to the nephrotoxity of cyclosporine. Three patients (11%) underwent dialysis of whom two patients underwent kidney transplantation without complications.

ISHLT is reporting a diminishing use of induction therapy to less than 50% of recipients and a shift away from polyclonal antilymphocyte/antithymocyte-globulin preparations to interleukin-2 receptor antagonists (daclizumab) [16]. Brock et al. have conducted the only prospective not randomised clinical trial comparing OKT3, ATG (equine) and daclizumab in lung transplant recipients using BLTx and CPB [17]. They found no significant difference in freedom from acute rejection or freedom from BOS between the groups and more patients on daclizumab remained free of infection in the first year. In contrast and with respect to the small number of patients in our study, we found that induction therapy with ATG compared to daclizumab resulted in fewer treatments for acute rejection within the first 3 months post-transplant ($P=0.05$ at 5–8 weeks) and no impact on incidence or spectrum of infections. At present we have reintroduced ATG, but a prospective randomised study between the different induction therapies is warranted.

Neither is maintenance immunosuppressive treatment standardised globally for lung transplant recipients. Substitution between cyclosporine and tacrolimus as well as azathioprine and mycophenolate mofetil is an alternative. Between transplantation centres these four combinations are distributed equally according to ISHLT [16]. In our programme we have consistently used the initial combination of cyclosporine and azathioprine (and steroids). In this study we have found an equal incidence of treated episodes of acute rejection within the first year compared to results from Washington, St Louis with the same maintenance immunosuppressive treatment, but without induction
therapy [15]. Chronic rejection (BOS) has a major impact on long-term survival and we found 33% BOS-related deaths. Freedom from BOS was found in 90, 77 and 60% of patients at 1, 3 and 5 years after transplantation. This result is equal or superior to other groups using the same immunosuppressive treatment [14,15].

CF patients have been considered high-risk candidates for lung transplantation due to the underlying suppurrative lung disease and persistent tracheal and sinus reservoirs after transplantation. Most centres report frequent early infectious complications and infection as the most common cause of early mortality [15,18]. In our experience, infection was a challenge generally within the first 6 months post-transplant. We found three cases of death (50%) related to infection in this study. A. fumigatus was present in all of these either as invasive Aspergillosis with bronchial dehiscence (n = 1) or together with CMV infection (n = 2).

Our infection rate (21%) and mortality rate (50%) of Aspergillus were equal to other centres: 20–60% incidence and 21–100% mortality rate [19]. Aspergillus is reported to occur predominantly as an opportunistic infection in lung-transplanted patients after several months post-transplant and rarely in the immediate post-operative period [19,20]. Without prophylactic therapy against Aspergillus we found early in-hospital infection in five of six infected patients (83%). This demonstrates the necessity of Aspergillus prophylaxis. Aspergillus infection appeared solely during the last 3 years of this study indicating an environmental cause, and a relationship to daclizumab in this period is improbable.

Burkholderia cepacia has been related to a poor outcome after lung transplantation and some centres consider this an absolute contraindication to lung transplantation [21,22]. Some taxonomonic diversity has existed and early studies are unclear with regard to sub-typing. At present B. cepacia is described as a complex consisting of nine species or genomovars with different virulence [23]. Especially B. cenocepacia (genomovar-III), the most frequent harboured, has been related to a poor outcome after lung transplantation. We have previously reported a low prevalence of chronic B. cepacia infection in our CF population, probably due to cohort isolation introduced in 1981 [24]. B. cenocepacia (genomovar-III) has not been isolated in our general population of CF patients. Three patients with chronic B. multivorans (genomovar-II) infection underwent lung transplantation in this study and we found no de-novo infection with this bacteria post-transplant. A satisfying long-term outcome was found in one of these three patients (despite a pan resistant colony). However, we still believe that successful lung transplantation is obtainable in recipients hosting B. multivorans.

We found no significant difference in 1 and 3 years survival rate between CF patients undergoing en block double lung transplantation with BAR or bilateral sequential lung transplantation. We have only seen two deaths (one long-term) among the initial eleven patients undergoing the DLTx procedure and four deaths after BLTx. We found no difference in incidence of BOS or infection rate between the two surgical procedures. Data from this retrospective small sample size study can hardly contribute to whether BAR can reduce BOS and infection, as earlier proposed. We still cannot exclude that the nutritive arterial blood supply to the lung allograft could be of importance.

In conclusion, lung transplantation is a well-established life-extending treatment for patients with CF and end-stage lung disease. The operative mortality is low and CF patients have a significant early survival benefit after lung transplantation. Satisfying long-term results can be achieved in this young and severely ill group of patients. Because of the very high early mortality on the waiting list a re-evaluation of the criteria for lung transplantation in CF patients is suggested.

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References


