A New Treatment Strategy for Advanced Idiopathic Interstitial Pneumonia*

Living-Donor Lobar Lung Transplantation

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Background: Among patients awaiting cadaveric lung transplantation, patients with idiopathic interstitial pneumonia (IIP) have been demonstrated to have the highest mortality rate. Contraindications to cadaveric lung transplantation include current high-dose systemic corticosteroid therapy because it may increase airway complications and various types of infection. Study objectives: To analyze the effect of living-donor lobar lung transplantation (LDLLT) for patients with advanced IIP including those receiving high-dose systemic corticosteroids.

Design: Retrospective analysis.

Setting: Okayama University Hospital and Okayama Medical Center.

Patients: We report on the first nine patients (seven female and two male; age range, 13 to 55 years) with advanced IIP receiving LDLLT. All nine patients had a very limited life expectancy, and eight patients were dependent on systemic corticosteroid therapy as high as 50 mg/d of prednisone. LDLLT was performed under cardiopulmonary bypass using two lower lobes donated by two healthy relatives.

Results: There were no airway complications in the 18 bronchial anastomoses. There was one early death (11%) due to severe acute rejection. Eight patients (89%) are currently alive with a follow-up period of 10 to 48 months. Their vital capacity reached 2.03 ± 0.20 L (mean ± SEM), 71.4% of predicted at 1 year. All 18 donors have returned to their previous lifestyles. Excised lungs were pathologically diagnosed as usual interstitial pneumonia (UIP) in six cases and fibrotic nonspecific interstitial pneumonia (NSIP) in three cases.

Conclusions: These early follow-up data support the option of LDLLT in patients with advanced IIP, including UIP and fibrotic NSIP, who would die soon otherwise. Current high-dose systemic corticosteroid therapy is not a contraindication in LDLLT.

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Key words: idiopathic interstitial pneumonia; idiopathic pulmonary fibrosis; living-donor lobar lung transplantation; nonspecific interstitial pneumonia; usual interstitial pneumonia

Abbreviations: AZA = azathioprine; CMV = cytomegalovirus; CSA = cyclosporine; FK = tacrolimus; IIP = idiopathic interstitial pneumonia; IPF = idiopathic pulmonary fibrosis; LDLLT = living-donor lobar lung transplantation; MMF = mycophenolate mofetil; NSIP = nonspecific interstitial pneumonia; OKT3 = murine monoclonal anti-C3 antibody; UIP = usual interstitial pneumonia; USC = University of Southern California; VC = vital capacity

Idiopathic pulmonary fibrosis (IPF) is a major type of idiopathic interstitial pneumonias (IIPs), and usual interstitial pneumonia (UIP) is the histopathologic subset of IIPs found in IPF patients. UIP-pattern IPF is a fatal disease of unknown cause.1–3 No medical treatment has been clearly shown to prolong survival. Lung transplantation has emerged...
as a viable option for some patients with IPF. However, the short window of opportunity for lung transplantation is reflected in the high mortality rate in IPF patients awaiting lung transplantation. It is because of the limited transplant window and the difficulty predicting survival that IPF patients in the United States are given a 3-month waiting advantage.

Living-donor lobar lung transplantation (LDLLT) is a new and evolving option for patients with end-stage lung disease. It was clinically developed at the University of Southern California as an alternative to cadaveric lung transplantation. Because only two lobes are transplanted, this procedure seems to be best suited for children and small adults, and has been applied most exclusively to patients with cystic fibrosis. The aim of this study was to analyze the effect of LDLLT for patients with advanced IIP including those receiving high-dose systemic corticosteroids, which is known to be a contraindication in cadaveric lung transplantation.

Materials and Methods

Patient and Donor Selection

The policy of our program has been to limit LDLLT to critically ill patients who would either die or become unsuitable recipients before cadaveric lungs become available. Immediate family members, relatives within the second degree, or spouse have been the only donors used at our institution. Potential donors were informed about possible perioperative complications and the permanent loss of pulmonary function. The larger donor was selected for donation of the right lower lobe. We have previously proposed a formula to estimate the graft FVC based on the donor’s measured FVC and the number of pulmonary segments implanted. When the total FVC of the two grafts was >50% of the predicted FVC of the recipient (calculated from a knowledge of height, age, and sex), we accepted the size disparity. Following multidisciplinary assessment, each case was carefully reviewed by the Lung Transplant Evaluation Committee at Okayama University Hospital.

Operative Technique

Right and left lower lobes from two healthy donors were implanted in the recipient in place of whole right and left lungs, respectively. A detailed description of the technical aspects of the implanted lobes is per-donor lobectomy and bilateral lobar implantation has been respectively. A detailed description of the technical aspects of the implanted lobes was performed through a “clamshell” incision with the use of cardiopulmonary bypass. The first implanted graft was packed in iced saline solution and shush, while the second graft was implanted. The bronchial anastomosis was begun with a running 4–0 polydioxanone suture for membranous portion. The cartilaginous rings of the donor and recipient were jointed with simple interrupted 4–0 polydioxanone sutures. No attempt was made to intentionally intussuscept the donor lower bronchus to the recipient main bronchus. The bronchial wrapping with local fat tissue was employed for the patients receiving high-dose steroid therapy, and 15 g of γ-globulin was administered during the operation to prevent infection.

Postoperative Management of the Recipient

The patient was kept intubated for at least 3 days to maintain optimal expansion of the implanted lobes. We used pressure-limited ventilation and kept maximal ventilation pressure <25 cm H₂O. Fiberoptic bronchoscopy was performed every 12 h during intubation to assess donor airway viability and to suction any retained secretions. An intensive program of chest physiotherapy was performed every 4 h, and bedside postoperative pulmonary rehabilitation was initiated as soon as possible. Perioperative antibiotics consisted of cefotiam and imipenem. Postoperative immunosuppression consisted of triple drug therapy with cyclosporine (CSA), azathioprine (AZA), and corticosteroids. Patients receiving high-dose steroid therapy were administered 5 g of γ-globulin for the first 3 days. We judged acute rejection on the basis of radiographic and clinical findings without transbronchial lung biopsy because the risk of pneumothorax and bleeding after transbronchial lung biopsy might be greater after LDLLT. Because two lobes were donated by different donors, acute rejection was usually seen unilaterally. When acute rejection seemed to be the problem, the patient was treated with a bolus injection of methylprednisolone. When acute rejection was encountered more than three times, CSA plus AZA was switched to tacrolimus (FK) plus mycophenolate mofetil (MMF). When all these treatments failed, murine monoclonal anti-C3 antibody (OKT3) was used. Oral fluconazole therapy was begun 3 weeks after the transplantation. Cytomegalovirus (CMV) prophylaxis with ganciclovir was routinely administered for the first 3 months.

Long-term Follow-up of the Recipient

Three months after LDLLT, patients were allowed to return to their home town. They were asked to keep a diary that included daily pulmonary function, digital saturation, body temperature, body weight, BP, and heart rate. The diary was sent to a lung transplant coordinator every month. Routine full postoperative assessment was performed at 6 months, 12 months, and then annually.

Results

Baseline Clinical and Pulmonary Variables of Recipients

Between October 1998 and May 2004, we performed LDLLT in 31 patients with various lung diseases. Table 1 lists the preoperative data on the nine IIP patients (29%) who underwent LDLLT from February 2001 through May 2004. There were seven female and two male patients (age range, 13 to 55 years; average, 41.8 years); their height ranged from 149 to 165 cm (average, 157 cm), weight ranged from 24.0 to 61.0 kg (average, 49.2 kg), and body mass index ranged from 10.8 to 26.8 kg/m² (average, 19.9 kg/m²). Time of onset of symptoms prior to transplant ranged from 16 to 62 months (average, 37.6 months). Mean (± SEM) vital capacity (VC) was 0.90 ± 0.15 L, and mean VC percentage...
of predicted was 31.2 ± 4.5%. Three patients (cases 4, 5, and 8) were too sick to undergo pulmonary function testing prior to transplantation, so VC measured 9 months prior to transplant was used for preoperative data. Excluding these three patients, the mean VC was 0.67 ± 0.11 L (24.7 ± 4.1% of predicted). Systolic pulmonary artery pressure was 52 ± 6 mm Hg (range, 23 to 74 mm Hg). All nine patients were dependent on continuous oxygen inhalation, and seven patients (78%) were completely bed bound. The duration of oxygen therapy ranged from 1 to 31 months (average, 12.2 months). Two patients (cases 2 and 4) were about to be intubated and required a noninvasive positive pressure ventilator with 100% inspired oxygen. Mean Pa\textsubscript{co}\textsubscript{2} was 53.7 ± 4.0 mm Hg. Eight patients were dependent on systemic steroid therapy for 8 to 60 months (average, 24.0 months). The dose of prednisone ranged from 15 to 50 mg/d. One patient (case 2) was being treated with bolus injection of methylprednisolone, 1 g, due to rapid exacerbation. Five patients (cases 3, 4, 5, 6, 8) were receiving AZA and/or cyclophosphamide. One patient (case 9) was receiving CSA. Eight of nine patients had positive CMV serologic status.

Seven patients underwent thoracoscopic lung biopsies. Two patients had UIP, four patients had fibrotic nonspecific interstitial pneumonia (NSIP), and one patient had nondiagnostic small bullae. Two patients who did not undergo lung biopsy had IPF diagnosed on the basis of typical findings on a CT scan.

**Donor Data and Graft Size**

Among the 18 living donors, 4 were the brothers of recipients, 4 were sons, 3 were sisters, 3 were daughters, 2 were husbands, 1 was a father, and 1 was a mother. The average height and weight of the right-side donor were 175.4 cm and 83.9 kg, and those of the left-side donor were 161.7 cm and 57.9 kg, respectively. The total FVC of the two grafts was estimated to range from 55.5 to 102.0% (average, 72.1%) of the predicted FVC of the recipient. Four patients received an ABO-identical LDDL, and five patients received an ABO-compatible LDDL with a minor ABO mismatch. All but one donor had positive CMV serologic status. One patient (case 7) with negative CMV status received CMV-positive grafts.

**Transplant Procedure**

The duration of cardiopulmonary bypass was 257 ± 18 min. Cardiopulmonary bypass was successfully removed from all nine patients at the end of the procedure. The ischemic time of the right graft was 180 ± 9 min, and that of the left graft was 127 ± 8 min.

**Early Postoperative Course**

There was one early death (11%) due to severe acute rejection. The patient (case 9) continued to do well until 4 days after LDDL, when unilateral acute rejection developed in the right graft. Augmented immunosuppressants (bolus injection of steroid, FK plus MMF, and OKT3) failed to control the acute rejection and the patient died on day 16.

The operative morbidity of the remaining eight recipients included bleeding from chest wall requiring rethoracotomy, gastroesophageal reflux, transient left recurrent nerve palsy, CMV enteritis, and compression fracture of the lumbar vertebra in one patient. Three patients required reintubation and tracheostomy. There were no airway complications in the 18 bronchial anastomoses. During the first month, acute rejection occurred at an average rate of 1.7 episodes per patient. CSA plus AZA was switched to FK plus MMF in five patients due to repeated episodes of acute rejection. With the exception of

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**Table 1—Preoperative Vital Data of the Nine Patients With IIP**

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age, yr/Gender</th>
<th>VC, L</th>
<th>% Predicted</th>
<th>Oxygen</th>
<th>Pa\textsubscript{O}\textsubscript{2}, mm Hg</th>
<th>Pa\textsubscript{CO}\textsubscript{2}, mm Hg</th>
<th>Type of Steroid/Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>38/female</td>
<td>0.46</td>
<td>16.5</td>
<td>5 L/min</td>
<td>173.1</td>
<td>55.1</td>
<td>PDS/15 mg/d</td>
</tr>
<tr>
<td>2</td>
<td>53/female</td>
<td>0.47</td>
<td>17.9</td>
<td>NIPPV (100%)</td>
<td>96.7</td>
<td>39.8</td>
<td>MPD/1 g/d</td>
</tr>
<tr>
<td>3</td>
<td>29/female</td>
<td>1.01</td>
<td>33.8</td>
<td>10 L/min</td>
<td>123.9</td>
<td>44.7</td>
<td>PDS/50 mg/d</td>
</tr>
<tr>
<td>4</td>
<td>44/male</td>
<td>1.65</td>
<td>44.5</td>
<td>NIPPV (100%)</td>
<td>93.7</td>
<td>59.9</td>
<td>PDS/30 mg/d</td>
</tr>
<tr>
<td>5</td>
<td>42/female</td>
<td>1.08</td>
<td>38.7</td>
<td>4 L/min</td>
<td>55.1</td>
<td>52.2</td>
<td>PDS/35 mg/d</td>
</tr>
<tr>
<td>6</td>
<td>55/female</td>
<td>0.46</td>
<td>19.0</td>
<td>7 L/min</td>
<td>98.2</td>
<td>51.6</td>
<td>PDS/50 mg/d</td>
</tr>
<tr>
<td>7</td>
<td>13/male</td>
<td>0.53</td>
<td>18.0</td>
<td>1 L/min</td>
<td>52.7</td>
<td>50.4</td>
<td>None</td>
</tr>
<tr>
<td>8</td>
<td>52/female</td>
<td>1.35</td>
<td>50.0</td>
<td>3 L/min</td>
<td>83.3</td>
<td>82.1</td>
<td>PDS/30 mg/d</td>
</tr>
<tr>
<td>9</td>
<td>51/female</td>
<td>1.11</td>
<td>42.7</td>
<td>3 L/min</td>
<td>91.9</td>
<td>47.2</td>
<td>PDS/15 mg/d</td>
</tr>
</tbody>
</table>

*NIPPV = noninvasive positive pressure ventilation; PDS = prednisone; MPD = methylprednisolone.
†Three patients (cases 4, 5, 8) were too sick to undergo pulmonary function testing prior to transplantation, so VC measured > 9 mo prior to transplant was used as preoperative data.
one patient (case 4), in whom transient CMV enteritis developed, no patient experienced infectious complications. Case 4 was CMV positive and received CMV-positive grafts. For the eight survivors, duration of mechanical ventilation required was 11.8 ± 2.6 days, ICU stay was 18.6 ± 2.9 days, and hospital stay was 60.2 ± 8.7 days.

Pathologic Examination of the Excised Lungs

Excised lungs were fixed in formalin, and at least 10 histologic specimens were made from both the right and left lung. Sections stained with hematoxylin-eosin and elastica Masson were evaluated by a pathologist (I.Y.) and classified according to American Thoracic Society/European Respiratory Society international multidisciplinary consensus classification of the IIPs.19 Pathologic diagnoses of the excised lungs were advanced stage of UIP in six patients and fibrotic NSIP in three patients.

Functional and Radiographic Assessment

Functional assessment at 3 months after transplantation is summarized in Table 2. Although VC was limited at 3 months, arterial oxygen tension on room air and systolic pulmonary artery pressure were excellent. Seven patients could not walk before transplantation, but their 6-min walking distance became 342 ± 27 m at 3 months. VC improved gradually and reached 2.03 ± 0.20 L (71.4% of predicted) at 1 year (Fig 1). Unilateral bronchiolitis obliterans developed in one patient (case 1) 10 months after transplantation, resulting in marked reduction of FEV1. By switching the immunosuppressant to FK plus MMF followed by OKT3 administration, this patient’s FEV1 reached plateau in 8 months.

Radiographic change was dramatic in all eight survivors, as shown in Figure 2. Fully expanded grafts filled the chest cavity, leaving no detectable dead space.

Recipient Survival

At the time of final data analysis in February 2005, the mean time from transplant to final analysis for the nine patients was 21.7 months (range, 10 to 48 months). Except for one early death due to acute rejection, there have been no late deaths among the eight operative survivors during the observation period (Table 3).

Donor Outcome

One donor required rethoracotomy due to bleeding from the chest wall; however, none of the donors required blood transfusion. All 18 donors have returned to their previous lifestyles during the observation period.

Discussion

IPF is a progressive and fatal disease characterized by radiographically evident interstitial infiltrates predominantly affecting the lung bases and by progressive dyspnea and worsening of pulmonary function.1–3 It has been shown that IPF is generally unresponsive to medical treatment, including the use of steroids and cytotoxic agents,20,21 and patients have an extremely limited prognosis with a median survival of 2.8 years.22 Cadaveric lung transplantation has been demonstrated to be a viable option in these patients.4,5 When compared to the natural course of IPF, the survival benefit conferred by cadaveric lung transplantation in patients with IPF has been strongly suggested.6,23,24 However, among patients awaiting lung transplantation, patients with IPF have demonstrated to have the highest mortality rate while waiting cadaveric donors because of the rapid progression of the disease and the severe scarcity of

Table 2—Early Functional Data of the Eight Recipients (3 mo)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Mean ± SEM</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>VC, L</td>
<td>1.58 ± 0.10</td>
<td>1.15–2.05</td>
</tr>
<tr>
<td>VC, % predicted</td>
<td>56.5 ± 3.9</td>
<td>41.4–69.7</td>
</tr>
<tr>
<td>PaO2, mm Hg</td>
<td>92.8 ± 3.2</td>
<td>82.9–115.0</td>
</tr>
<tr>
<td>Systolic pulmonary artery pressure, mm Hg</td>
<td>24.4 ± 1.6</td>
<td>20–33</td>
</tr>
<tr>
<td>Six-minute walk, m</td>
<td>342 ± 27</td>
<td>250–460</td>
</tr>
</tbody>
</table>
available cadaveric donors. Among the 63 patients registered in the Japan Organ Transplantation Network from our institution, only 4 patients with non-IPF received cadaveric lung transplantation during the past 3 years with an average waiting time of 657 days, whereas all 6 patients with IPF on the waiting list died within a year after registration without receiving lung transplantation.

LDLLT was developed at the University of Southern California (USC) as a procedure for patients considered too ill to await cadaveric lung transplantation. Because a limited amount of lung tissue is implanted, this procedure seems to be best suited for children and small adults, and has been applied most exclusively to patients with cystic fibrosis. LDLLT has been expanded to include pediatric patients with primary pulmonary hypertension, bronchiolitis obliterans, and adult patients with IPF. In a report from the USC on 123 patients receiving LDLLT, the primary indication for transplantation was cystic fibrosis (84%). Despite the critical condition of many of these patients, the overall actuarial survivals of 70%, 54%, and 45% at 1, 3, and 5 years, respectively, were comparable with those of bilateral cadaveric lung transplantation reported by the International Society for Heart and Lung Transplant registry. Encouraged by the USC group, we began to apply the procedure to a wide range of pathophysiology both for pediatric and adult patients. We have reported our early and intermediate results with this procedure. We now have performed LDLLT in 31 patients with various lung diseases, 9 of whom were patients with IPF.

Contraindications to cadaveric lung transplantation include current high-dose systemic corticosteroid therapy because it may increase airway complications and various types of infection, although low-dose pretransplantation corticosteroid therapy (<20 mg/d of prednisone) is acceptable. We have accepted high-dose systemic corticosteroid therapy, as high as 50 mg/d of prednisone, in LDLLT. Excellent bronchial healing was observed in all 18 anastomoses, and no serious infectious complications were encountered. Various factors, such as short donor bronchial length, high blood flow in the small grafts implanted, and well-preserved lung parenchyma with short ischemic time, may contribute to the better oxygen supply to the donor bronchus, resulting in excellent bronchial healing in LDLLT. Six patients were receiving additional immunosuppressive drugs such as CSA, AZA, and cyclophosphamide before transplantation, in addition to steroids. Administration of γ-globulin during and after transplantation may be effective in preventing infectious

Table 3—Outcome of Recipients After Receiving LDLLT

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age, yr/Gender</th>
<th>Follow-up</th>
<th>Outcome</th>
<th>Daily Living</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>38/female</td>
<td>48 mo</td>
<td>Alive</td>
<td>Mild restriction due to bronchiolitis obliterans</td>
</tr>
<tr>
<td>2</td>
<td>53/female</td>
<td>43 mo</td>
<td>Alive</td>
<td>No restriction</td>
</tr>
<tr>
<td>3</td>
<td>29/female</td>
<td>23 mo</td>
<td>Alive</td>
<td>No restriction</td>
</tr>
<tr>
<td>4</td>
<td>44/male</td>
<td>21 mo</td>
<td>Alive</td>
<td>No restriction</td>
</tr>
<tr>
<td>5</td>
<td>42/female</td>
<td>18 mo</td>
<td>Alive</td>
<td>No restriction</td>
</tr>
<tr>
<td>6</td>
<td>55/female</td>
<td>12 mo</td>
<td>Alive</td>
<td>No restriction</td>
</tr>
<tr>
<td>7</td>
<td>13/male</td>
<td>11 mo</td>
<td>Alive</td>
<td>No restriction</td>
</tr>
<tr>
<td>8</td>
<td>52/female</td>
<td>10 mo</td>
<td>Alive</td>
<td>No restriction</td>
</tr>
<tr>
<td>9</td>
<td>51/female</td>
<td>16 d</td>
<td>Died</td>
<td></td>
</tr>
</tbody>
</table>
complications in these immunocompromised recipients. The use of γ-globulin was personally suggested by the USC group.

The amount of tolerable size discrepancy between donors and recipients in LDLLT is currently unknown. The use of significantly undersized grafts is potentially problematic because it could result in poor ventilation due to a large dead space remaining.28 However, these IIP patients had small chest cavities due to the nature of the restrictive lung disease. Although the average graft size was estimated to be 72.1% of the normal recipient’s lung, none of the nine IIP recipients experienced any space problems after LDLLT. Their pulmonary function was sufficient to provide normal daily activities without need for oxygen inhalation. It should also be noted that their pulmonary arterial pressure became normal within 3 months after receiving LDLLT.

The classification of IIPs has evolved recently. Most patients with IPF show the features that fulfill the histopathologic criteria for UIP, the most common histologic type of IIP. In 1994, Katzenstein and Fiorelli introduced the concept of NSIP as a category of IIP.29 Among IIP patients, a histologic diagnosis of NSIP was associated with a significantly better prognosis than UIP.21,30 However, NSIP has a broad spectrum of histologic findings and a variable prognosis. It has been reported that a histologic diagnosis of fibrotic NSIP was associated with a significantly worse survival rate than cellular NSIP, and a long-term survival rate similar to UIP.31,32 In the present report on nine IIP patients, histologic section of the excised lung tissue revealed advanced stage of UIP in six patients and fibrotic NSIP in three patients. Preoperative histologic diagnosis of NSIP by lung biopsy needs to be interpreted with caution and does not necessarily denote a good outcome.33

To our knowledge, LDLLT for IPF had been previously reported only by the USC group.12 In their 123 patients undergoing LDLLT, 5 adult patients had IPF. Two of five patients were alive 1.8 years and 8.6 years after transplantation, respectively, whereas three patients died 27, 45, and 70 days after transplantation from Aspergillus species infection, idiopathic thrombocytopenic purpura, and bacterial pneumonia, respectively. In our nine patients with IIP, there was one early death (11%) and no late death with a follow-up period of 10 to 48 months despite severely compromised pretransplant pulmonary function and high-dose steroid treatment.

It has been recommended that symptomatic IPF patients should be referred to a transplant center in any of the following circumstances: VC < 60 to 70% of predicted, pulmonary hypertension, or resting hypoxia.16 In the present nine IIP patients, the average VC was only 31.2% of predicted; all but one showed pulmonary hypertension (systolic pulmonary artery pressure > 35 mm Hg), and all were markedly hypoxic without oxygen inhalation. It was obvious that they would likely not have lived long enough to receive an organ from a cadaveric donor in Japan, where the average waiting time is approximately 2 years. Although our experience in LDLLT for IIP is still limited in numbers and in length of the observation period, the 89% survival rate is encouraging. These early follow-up data support the option of LDLLT in patients with advanced IIP, including UIP and fibrotic NSIP, who would die soon otherwise.

References