Chapter 19

Rare indications for lung transplantation

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Summary

Lung transplantation is a suitable treatment to improve survival of patients with various end-stage pulmonary diseases. Lung transplantation is an orphan therapy with an annual incidence of approximately five procedures per million inhabitants in most Western countries. Orphan lung diseases account for ~5% of all indications. Lymphangioleiomyomatosis (LAM), obliterative bronchiolitis and pulmonary manifestations of connective tissue diseases are the major indications among these.

Some of these orphan diseases have systemic manifestations that may lead to special post-transplant problems and must be investigated carefully before transplantation. Typical post-operative complications in LAM include intraoperative intra-thoracic bleeding, chylothorax, pneumothorax, and bleeding of angiomyolipomas. In Langerhans' cell histiocytosis X, extra-pulmonary manifestations in the bones and pituitary gland may progress after transplantation. Some orphan diseases typically recur in the allograft, but these recurrences may be asympto-matic. Long-term results of large volume centres demonstrate improving results after lung transplantation. Bronchiolitis obliterans syndrome and infections are the main causes of death. Survival of patients with orphan diseases is similar to patients receiving transplants for other diseases or even superior.

Keywords: Bronchioloitis obliterans, Langerhans' cell histiocytosis, lung transplantation, lymphangioleiomyomatosis, recurrence

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There is no uniform accepted definition for orphan disease. One suggested definition is a disease affecting fewer than five people per million individuals. Since the first successful lung transplantation in 1983, the number of transplantations has increased internationally until now. Presently, transplantations are stagnating at ~2,700 per year worldwide [1]. Lung transplantation itself is therefore a rare therapy performed in most European countries with an annual incidence of approximately five procedures per million inhabitants [2]. There is still a shortage of donor organs so that every seventh patient on the waiting list in Europe and the USA dies before a donor organ is available.

Due to the paucity of data, most recommendations for candidate selection and management of transplant candidates with orphan lung diseases are based on expert opinion and case series. Knowledge of candidate selection, timing, transplant outcome and specific problems for these diseases has increased over the years in large transplant centres.

Lung transplantation is also a therapeutic option for respiratory failure resulting from certain systemic diseases (*e.g.* lymphangioleiomyomatosis (LAM), Langerhans' histiocytosis X and systemic sclerosis) with limited extrapulmonary disease. These indications account for ~5% of all lung transplant procedures [1]. Therefore, worldwide experience is relatively small. Nevertheless, lung transplantation for these rare diseases is an accepted therapeutic option in selected patients.

Occasionally diagnosis of an orphan lung disease is made post-transplant after histopathological examination of the explanted lung. This is explained by the clinical dilemma when patients with end-stage lung diseases are evaluated and possibilities for invasive testing are limited. This subset of patients can be accepted as candidates unless the history and findings are suggestive of a malignant disease and if significant extrapulmonary disease can be safely excluded.

In orphan lung diseases, extrapulmonary manifestations are common and it is important to remember that systemic manifestations of orphan diseases deteriorate after lung transplantation and impose additional risks.

In this chapter, the issues of lung transplantation and the unique problems and specific considerations of orphan lung diseases will be discussed with regard to lung transplantation.

General selection criteria

Lung transplantation is indicated for various non-malignant pulmonary diseases with limited long-term prognosis and resistance to other therapeutic options, or when no other therapy is available. The primary goal of lung transplantation is to provide a survival benefit. Several retrospective studies have demonstrated that lung transplantation confers such benefit in patients with advanced cystic fibrosis and idiopathic pulmonary fibrosis. Nevertheless, lung transplantation is still a palliative rather than curative treatment for most patients. The patient's quality of life should also be taken into account when the need for a lung transplant is assessed, but owing to the shortage of donor organs it is not currently possible to support transplantation solely for quality of life purposes.

Early referral for consideration of a transplant is important to allow for careful assessment, preparation and patient education before active listing. Typical candidates are less than 60 yrs of age, have signs of respiratory failure (supplemental oxygen) and have no significant comorbidity. Their estimated 5-yr survival rate should be <50% because expected post-transplant survival is ~60%. The primary diseases before transplantation are distributed according to their incidence and natural course among the general population. The major indications of emphysema, cystic fibrosis and idiopathic pulmonary fibrosis account for 80% of all lung transplants performed worldwide since 1995. In the last 10 yrs, already ~50% of the recipients internationally were aged >50 yrs.

Orphan lung diseases account for ~5% of all indications; LAM (1.0%), obliterative bronchiolitis (0.9%), and connective tissue diseases (0.8%) are the leading diseases.

Follow-up after lung transplantation is complex and requires a high level of cooperation by the patient.

Lung transplantation remains a complex therapy with a significant risk of perioperative morbidity and mortality; therefore, it is important to consider the overall sum of contraindications and comorbidities. A consensus of contraindications and indications are summarised in table 1 [3].

Most often, the sum of concomitant problems and relative contraindications rather than absolute contraindications are the reason why a candidate is staged as not suitable for lung transplantation.

Table 1. Transplant indications and contraindications

General indications
Clinically and functionally advanced pulmonary disease
Reduced life expectancy (estimated 5-yr survival rate <50%)
No therapeutic alternatives
Restricted quality of life
High patient motivation
Absolute contraindications
Malignancy in the last 2 yrs (a 5-yr disease-free interval is indicated in breast and colorectal cancer), with the exception of non-melanotic skin cancer
Extrapulmonary organ failure (*e.g.* heart, liver or kidney)
Incurable chronic extrapulmonary infection, significant chest wall/spinal deformity
Documented nonadherence or inability to follow-up
Absence of a consistent or reliable social support system
Psychiatric or psychological conditions associated with the inability to cooperate or comply with medical therapy
Substance addiction (*e.g.* alcohol, tobacco or narcotics)
Relative contraindications
Aged >65 yrs
Critical or unstable clinical condition (*e.g.* shock, mechanical ventilation or extracorporeal membrane oxygenation)
Severely limited functional status with poor rehabilitation potential
Colonisation with highly resistant or highly virulent bacteria
Severe obesity (body mass index >30 $kg \cdot m^{-2}$)
Severe or symptomatic osteoporosis

Adapted from [3].

Procedure and outcome

Three different surgery procedures are available. 1) Single lung transplantation: one lung is transplanted but the second remains. 2) Bilateral or double-sided lung transplantation: both lungs are sequentially transferred. 3) Heart–lung transplantation: the heart and both lungs of the donor are transplanted *en bloc*. Bilateral transplantation is mandatory if bronchiectasis is present, because a source of infection by the natural lung would remain if only one lung were transplanted. Bilateral transplantation is often also preferred for pronounced pulmonary hypertension and because of the greater functional reserves. Single transplantation is frequently used in older patients for fibrosing lung diseases and to reduce the operative risk. Heart–lung transplantation is chosen in the case of surgically non-correctable congenital heart disease or the concomitant occurrence of progressive lung disease and heart disease.

Perioperative (3-month) mortality is generally between 10 and 15%. Long-term survival rates are regularly published by large registries and transplant centres [1, 4, 5]. These transplant centres reported a 5-yr survival rate of >60% (The International Society for Heart and Lung Transplantation (ISHLT) registry 1994–2008: 52%) and a 10-yr survival rate of >40% (ISHLT registry 1994–2008: 29%) [1]. More than 1 yr after transplantation, chronic organ dysfunction (bronchiolitis obliterans syndrome) and infections are the main causes of death.

Disease-specific considerations

Lymphangioleiomyomatosis

LAM is a rare disorder, and LAM patients account for only 1% of all transplant recipients [1]. Sporadic LAM affects one in 400,000 adult females [6]. It affects females of reproductive age and is characterised by proliferation of abnormal smooth muscle cells. In the lung this may lead to progressive cystic degeneration of the lung parenchyma, chylous pleural effusions and pulmonary haemorrhage. Airflow

limitation is the most important functional feature and the primary determinant of exercise limitation in patients with LAM. Pulmonary function testing at evaluation usually shows an obstructive pattern in LAM. Pulmonary hypertension is uncommonly associated with the disease. Extrapulmonary manifestations include cell proliferation along abdominal lymphatics, renal angiomyolipomas and uterine leiomyomas. In a recent survey of patients undergoing transplantation for LAM, most had severe airway obstruction and were transplanted with a mean forced expiratory volume in 1 s (FEV_1) of 27% and diffusing capacity of the lung for carbon monoxide of 26% predicted.

Early studies suggested that LAM patients had a poor long-term prognosis after onset of symptoms, but more recent studies have documented 10-yr survival rates of between 40 and 78% [7, 8]. Increasing awareness and growing knowledge with earlier diagnosis, consecutive therapy and referral for lung transplantation may explain these differences. In 43 patients an annual decline in FEV_1 was 118 mL [9]. Internationally, criteria for candidate referral (New York Heart Association functional class III or IV) and transplantation (reduced exercise maximal oxygen uptake $<$50% predicted and hypoxaemia at rest) for LAM patients were proposed [3].

Extrapulmonary manifestations may affect post-operative success and therefore should be known prior to transplantation. Imaging studies to rule out renal angiomyolipomas and retroperitoneal lymphadenopathy are mandatory before transplant. Pre-transplant nephronsparing surgical techniques or embolisation should be applied for symptomatic angiomyolipoma. Nephrectomy is disadvantageous due to the fact that renal failure caused by immunosuppressive toxicities is frequent after transplant. Impaired wound healing and long half-life is of concern with sirolimus, so discontinuation of this drug for LAM patients admitted to the transplant waiting list is recommended. Out of 61 European LAM patients who underwent transplant in the period 1997–2007, renal angiomyolipomas were found in 33% and hepatic angiomyolipomas in 3%, retroperitoneal lymph nodes in 13%, brain lesions in 11% and uterine LAM in 13% [10]. 79% had a history of pneumothorax.

In 2008, an international survey on the results of lung transplantation for LAM in 21 transplantation centres on 61 patients was performed [10]. Estimated 1- and 3-yr post-transplant survival was favourable compared with other indications with 79% and 73%, respectively, in Europe and even better in a USA registry analysis (1- and 3-yr post-transplant survival 86% and 75%, respectively) [10, 11]. In most experienced centres double lung transplantation for LAM is preferred given the risk of pneumothorax in the native lung. Chylothorax is a typical complication of lung transplantation in a LAM patient. Therapy of chylothorax consists of drainage, total parenteral nutrition, a diet containing medium-chain triglycerides, thoracic duct ligation, pleurodesis or pleurectomy. Patients with asymptomatic angiomyolipomas $\leqslant$4 cm in diameter may be followed up annually by ultrasound or computed tomography (CT). If the lesions are $>$4 cm, they should be followed up every 6 months. An increased risk of renal cell cancer has been described in patients with tuberous sclerosis complex and angiomyolipoma. Theoretically, renal cancer might also occur in LAM patients especially under immunosuppression after transplant. In the case of bleeding angiomyolipoma after transplantation, conservation of the kidney should be attempted with selective embolisation whenever possible. Recurrence of LAM after transplantation, usually diagnosed by imaging studies, has been described in 7% of recipients with LAM [10]. Clinical impact of recurrence is low and most patients die from other causes [12].

Recommended indications for transplantation in LAM patients are FEV_1 $<$30% pred with one of the following: hypoxaemia (partial pressure of oxygen (P_{O_2}) $<$55 mmHg) at rest; impaired endurance capacity (6-min walking test $<$300 m); and recurrent pleural complications. Possible complications in LAM patients are previous pleurodesis or pleurectomy with adhesions that may cause intraoperative bleeding, recurrence of LAM after lung transplantation, post-operative pleural complications (chylothorax) and abdominal disease complications.

Langerhans' cell histiocytosis X

Langerhans' cell histiocytosis X is clinically characterised by a broad spectrum of disease manifestations ranging from disseminated disease in children to localised disease in adults affecting lungs,

bones, or the pituitary gland with granuloma formation as the histological hallmark. There is an estimated prevalence of 1–2 people per 100,000 individuals. Pulmonary Langerhans' cell histiocytosis accounts for only 0.2% of all lung transplants. Pulmonary manifestation can occur at any age and 90–100% of patients are smokers. Presenting symptoms include dry cough, dyspnoea on exertion and pneumothorax. Pulmonary function testing at evaluation usually shows a mixed obstructive and restrictive pattern. The biopsy specimen with specific immunostaining of the Langerhans' cells with S100 and CD1a is the gold standard for the diagnosis.

The classic high-resolution CT (HRCT) finding consists of the simultaneous presence of nodules, cavities and cysts with thin and thick walls interspersed in normal parenchyma. Typically, the costophrenical angle is spared. The natural history of the disease is variable. Smoking cessation is essential and in 25% of patients spontaneous resolution occurs and in 50% there is stabilisation of lung function. Long-term abstinence from smoking should be documented biochemically (cotinin tests) before evaluation and listing.

Immunosuppressive therapy is rarely used in pulmonary forms in adults. Lung transplantation is an established option for therapy in advanced progressive lung disease. Lung function testing may show an obstructive, restrictive or mixed pattern, and diffusion capacity is severely reduced in nearly all progressive patients.

Severe secondary pulmonary hypertension often develops in these patients due to intrinsic pulmonary vascular disease, in which the pulmonary circulation is involved independently of the small airway and the lung parenchymal injury. Long-term improvement of pulmonary hypertension may be obtained using bosentan in patients with pulmonary Langerhans' cell histiocytosis and vasoactive therapy may be considered in individual cases [13]. The median survival of patients with pulmonary Langerhans' cell histiocytosis X is ~13 yrs [14]. Guidelines for referral and transplantation also include criteria for Langerhans' cell histiocytosis X patients [3].

At evaluation for transplantation, nonpulmonary manifestations should be considered. Hypothalamopituitary abnormalities in adult patients are common and might be missed. Diabetes insipidus is the earliest hormonal deficiency.

Recurrence is established by HRCT or transbronchial biopsy (including immunostaining with CD1 or S100). Usually, at the time of recurrence, lung function has deteriorated with a fall in FEV_1 and vital capacity and most of these patients have restarted smoking after transplantation [15]. Abstinence from smoking is therefore essential to prevent recurrence of disease in the allograft. Although there is a considerable recurrence rate of the disease of ~20%, lung transplantation is a therapeutic option in patients refractory to other therapies and with recurrent pneumothoraces. Recommended indications for transplantation in patients with Langerhans' cell histiocytosis X are FEV_1 <30% pred with one of the following: hypoxaemia (P_{O_2} <55 mmHg) at rest; impaired endurance capacity (functional class III/IV); and pulmonary arterial hypertension without response to vasoactive agents. Possible pitfalls in candidates with Langerhans' cell histiocytosis X are previous surgery, recurrence after lung transplantation, continuous smoking or illicit drug abuse, and bone and hypothalamopituitary abnormalities (*e.g.* diabetes insipidus).

Obliterative bronchiolitis

Obliterative bronchiolitis is a rare but important respiratory illness because of irreversibility and progressive course leading to respiratory failure. Obliterative bronchiolitis is common among lung transplant recipients and thus reflects chronic organ dysfunction. Shortness of breath is the major symptom and the typical physiological finding is airflow obstruction that is nonresponsive to an inhaled bronchodilator agent. The chest radiograph is usually normal or may show hyperinflation. The chest CT scan shows air trapping on expiratory films and thickened small airway walls. Obliterative bronchiolitis is generally non-responsive to steroids and lung transplantation might be a successful option. Bronchiolitis obliterans is a rare and potentially fatal complication in

connective tissue disorders. The fibrotic constrictive bronchiolar lesion has been described in rheumatoid arthritis, Sjögren's syndrome, scleroderma and lupus erythematosus [16].

Obliterative bronchiolitis may occur in 9% of patients after haematopoietic stem-cell transplantation (HSCT) and reflects pulmonary chronic graft *versus* host disease [17]. Severe chronic graft *versus* host disease confers a 5-yr survival of only 15%. The clinical syndrome is termed bronchiolitis obliterans syndrome and is staged according to the degree of airflow obstruction. A recent publication indicates that selected patients receiving solid organ transplantation after HSCT have a remarkably good overall survival and organ survival rate, and lung transplantation should be considered in selected patients with single respiratory failure after HSCT [18]. Recommended indications for transplantation are FEV_1 <30% pred with one of the following: hypoxaemia (P_{O_2} <55 mmHg) at rest and recurrent hospitalisations for respiratory complications. Possible complications in HSCT recipients with obliterative bronchiolitis include: uncontrolled fungal or mycobacterial infections; hypogammaglobulinaemia; severe extrapulmonary manifestations of chronic graft *versus* host disease (especially liver, gut and skin); and severe wasting (body mass index (BMI) <17 $kg \cdot m^{-2}$). Possible pitfalls in patients with obliterative bronchiolitis and connective tissue diseases are extrapulmonary manifestations and recurrence early post-transplant (personal communication).

Diffuse parenchymal lung diseases with connective tissue disease

Clinically significant interstitial lung disease (ILD) occurs in 25% of patients with systemic sclerosis, 7–30% of patients with dermatopolymyositis and 5% of patients with rheumatoid arthritis. Nonspecific interstitial pneumonia (NSIP) is the predominating histopathological pattern in systemic sclerosis and dermatopolymyositis; a pattern of usual interstitial pneumonia (UIP) is frequently seen in rheumatoid arthritis. ILD may occur in Sjögren's syndrome, possibly associated with thin-walled cysts. Proposed provisional criteria for lung dominant connective tissue disease are: 1) an NSIP, UIP or desquamative interstitial pneumonia (if no smoking history) pattern, as determined by lung biopsy specimen or suggested by HRCT; 2) insufficient extrathoracic features of a definite connective tissue disease designation; 3) no identifiable alternative aetiology for interstitial pneumonia; and 4) autoantibodies (*e.g.* antinuclear antibodies >1:320, rheumatoid factor >60 $IU \cdot mL^{-1}$, anti-Scl-70 and anti-Jo-1) or at least two histopathology features (lymphoid aggregates with germinal centres, extensive pleuritis, prominent plasmacytic infiltration or dense perivascular collagen) [19]. The antisynthetase syndrome consists of an ILD with arthritis, myositis, fever, mechanic's hands and Raynaud phenomenon in the presence of an antisynthetase autoantibody, most commonly anti-Jo-1. The ILD is generally of UIP or NSIP pattern and resembles idiopathic pulmonary fibrosis or systemic sclerosis-related lung disease. Very few data are available concerning lung transplantation in this setting. Even under immunosuppressive therapy myositis may reoccur.

Diffuse parenchymal lung diseases and/or pulmonary hypertension associated with connective tissue disease are rare indications (0.5%) for lung transplantation. The manifestations of the connective tissue diseases are highly variable, and patients should be evaluated individually to assess extrapulmonary disease. In general, evidence of quiescent systemic disease is recommended, and any evidence of active vasculitis should preclude referral. Currently the most common of the connective tissue diseases with ILD referred for lung transplantation is systemic sclerosis with a prevalence of 30–70 cases per million individuals.

Systemic sclerosis is an autoimmune disease characterised by multiorgan involvement resulting in significant morbidity and mortality. Pulmonary complications are now the leading causes of death while in earlier years it was scleroderma renal crisis. There are two major types of lung disease in scleroderma, with different clinical associations and pathogenesis. ILD is more common in patients with diffuse cutaneous systemic sclerosis and is often complicated by the development of pulmonary hypertension [6]. Isolated pulmonary arterial hypertension, histologically similar to idiopathic pulmonary hypertension [7], is more common in patients with limited cutaneous

systemic sclerosis. In 59 patients with systemic sclerosis a significantly reduced survival in patients with combined pulmonary hypertension and interstitial lung disease (n=39, 3-yr survival of 39%) compared to patients with systemic sclerosis and isolated pulmonary hypertension (n=20, 3-yr survival of 64%) was demonstrated [20]. Systemic sclerosis potentially has multiple organ system involvement, including the gastrointestinal, cardiac, renal and pulmonary systems. Severe involvement of the gastrointestinal tract and severe renal disease and cardiac disease (excluding pulmonary hypertension) are contraindications to lung transplantation [21]. In several single-centre reports similar survival 1 yr post-transplantation was demonstrated when compared with other indications [22, 23].

Recommended indications for transplantation in diffuse parenchymal lung diseases with connective tissue diseases are: forced vital capacity <50% predicted with one of the following: hypoxaemia (P_{O_2} <55 mmHg) at rest and pulmonary arterial hypertension. Possible pitfalls in diffuse parenchymal lung diseases with connective tissue diseases include: severe involvement of the gastrointestinal tract (history of aspiration and severe swallowing difficulties), renal disease and cardiac disease (except pulmonary hypertension), and severe wasting (BMI <17 $kg \cdot m^{-2}$).

Other rare indications

Pulmonary alveolar proteinosis (PAP) is a rare lung disease with an estimated prevalence of one case per million individuals. In PAP, abnormal accumulation of surfactant occurs within the alveoli, interfering with gas exchange. Causes of death in PAP are mainly infections (up to 20%) and respiratory failure (~80%). Overall, survival rates exceed 80% at 5 yrs post-transplant, but a subset of patients do not respond to whole lung lavage and will develop respiratory failure. Double lung transplantation is a therapeutic measure employed in congenital forms of PAP, when whole lung lavage was unsuccessful, when PAP is associated with other fibrosing lung conditions or when recurrent pneumothorax is a recurrent complication. Physicians involved in lung transplantation programmes should be informed that PAP can recur in the transplanted lungs and may be heralded by the appearance of small rounded opacities seen on the chest radiograph [24].

Pulmonary alveolar microlithiasis (PAM) is a rare disease characterised by intra-alveolar calcium deposits. The aetiology of the disease is still unknown. More than half of the patients are asymptomatic; dyspnoea, cough and chest pain were reported in the other cases. The course of the disease is slow but patients usually die as a result of cardio-respiratory failure. There are some case reports describing successful lung transplantation in PAM [25, 26].

Inherited deficiency of surfactant protein-B (SP-B) results in refractory respiratory failure that is lethal in the newborn period. More than 25 mutations have been identified in patients with SP-B deficiency. Lung transplantation for infants was first performed in the early 1990s and has permitted survival of infants who previously would have had intractable pulmonary parenchymal or vascular disease. A single-centre report covering a period of 12 yrs reported the experience of lung transplantation for infants with SP-B deficiency and compared the outcome with that of infants (<1 yr of age) who underwent lung transplantation for other pulmonary disease. Infants with SP-B deficiency undergoing lung transplantation had similar survival, pulmonary function and developmental progress when compared with infants undergoing lung transplantation for other reasons. Although lung transplantation is a complex procedure and has long-term limitations, it continues to be the only intervention available for infants with SP-B deficiency [27].

Conclusion

Lung transplantation is indicated for various non-malignant pulmonary diseases with limited long-term prognosis, resistance to other therapeutic options, or when no alternative therapy is available. Orphan lung diseases account for ~5% of all indications. LAM, obliterative bronchiolitis and pulmonary manifestations of connective tissue diseases are the major indications among these.

However, lung transplantation has some drawbacks because not all patients are eligible for transplantation as factors such as age and comorbidities may pose an unacceptably high risk. In addition, patients with end-stage lung disease often become critically ill and may not survive until a donor organ is available. Lung transplantation creates new medical problems and the life-expectancy after this operation remains limited.

Orphan lung diseases as indications for lung transplantations have some special aspects compared with the classical underlying diseases. Evidence for candidate selection and transplant management of patients with orphan diseases are limited, most recommendations are based on expert opinion and small case series. Some of these orphan diseases have systemic and extrapulmonary manifestations which may lead to special post-transplant problems and must be investigated carefully before transplantation. Typical post-operative complications in LAM include intraoperative intrathoracic bleeding, chylothorax, pneumothorax and bleeding of angiomyolipomas. Some orphan diseases typically recur in the allograft, but recurrences may be asymptomatic. In addition, immunosuppressive therapy may affect disease progression in organs other than the lung.

Long-term results of large volume centres demonstrate improving results after lung transplantation. Bronchiolitis obliterans syndrome and infections are the main causes of death. Survival of patients with orphan diseases is similar to patients transplanted for other diseases or even superior (*e.g.* LAM).

Statement of interest

None declared.

References

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