Should Patients Choose Lung Transplantation or Optimal Drug Therapy?
— The Clinical Situation in the Treatment of Pulmonary Arterial Hypertension in Japan —

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Idiopathic and heritable pulmonary arterial hypertension (I/HPAH), previously called primary pulmonary hypertension, is a rare, progressive and refractory disease. In the supportive therapy only era, the prognosis for I/HPAH patients was poor, with a 3-year survival of 48% and 5-year survival of 34%. However, recent advances in pulmonary vasodilators have greatly improved these

Figure. Adult lung transplantation Kaplan-Meier survival by major diagnosis (transplants: January 1992–June 2017) published by The International Society for Heart and Lung Transplantation (ISHLT). Survival rates were compared using the log-rank test statistic. Only pairwise comparisons statistically significant at P<0.05 are shown. A1ATD, α-1 antitrypsin deficiency; CF, cystic fibrosis; COPD, chronic obstructive pulmonary disease; IIP, idiopathic interstitial pneumonia; ILD, interstitial lung disease; IPAH, idiopathic pulmonary arterial hypertension. (Reproduced with permission from ISHLT.)
patients’ clinical symptoms and outcomes since the introduction of the first PAH therapeutic agent, epoprostenol, and the recent REVEAL registry indicated the amended 5-year survival of 68% in newly diagnosed IPAH patients.\(^2\,^3\)

Certainly, the outcome of treatment for PAH has improved, but patients in World Health Organization function classes (WHO-FC) III and IV, despite adequate targeted therapies, have a high risk for right heart failure and death. For these critically ill patients, lung transplantation (LT) is required to cure PAH. As in the USA and Europe, PAH patients in Japan have also benefited from advances in targeted therapies. Because of the Japanese universal insurance system and subsidy for medical expenses for intractable diseases, many Japanese patients can receive adequate medical therapy, including triplet combination therapy and high dosage of parenteral prostacyclin (epoprostenol or treprostinil). Thus, many Japanese PH experts have been actively treating PAH patients with the aim of normalizing hemodynamics. These aggressive therapeutic strategies might have contributed to the good treatment results shown in several Japanese trials. That is, Japan PH Registry data, which included 189 consecutive PAH patients from 2008 to 2013, demonstrated a high 3-year survival rate of 88.2% among overall PAH patients, and the retrospective study of 141 I/HPAH patients at 3 PH centers from 1992 to 2012, which indicated a mean survival time from treatment initiation of 14.7±0.8 years (95% confidence interval, 13.1–16.3 years) with 1-, 3-, 5-, and 10-year survival rates of 97.9%, 92.1%, 85.8%, and 68.5%, respectively.\(^4\) The latter study also reported that baseline heart rate and heart rate, 6-minute walk distance (6MWD), mean pulmonary arterial pressure (mPAP), and cardiac index (CI) after treatment were significant determinants of survival.\(^5\)

LT is the ultimate therapeutic option for advanced PAH patients, because it can reduce pulmonary vessel resistance (PVR) and relieve right heart failure immediately. The recent recommendation suggests immediate consult to the LT facility when a PAH patient displays inadequate response to maximum medical therapies, including prolonged WHO-FC III or IV with severe hemodynamics (CI <2.0 L·min\(^{-1}\)·m\(^{-2}\), right atrial pressure >15 mmHg), 6MWD <350 m, or signs of right heart failure.\(^6\) However, the number of brain dead donors is so small that the waiting period for LT is about 3 years and extending year by year. We usually think LT is necessary for PAH patients when right heart failure occurs even with high doses of parenteral prostacyclin. However the 3-year waiting period is too long for decompensated PAH patients to get LT while in good physical condition. As a result, we clinicians are becoming more likely to register PAH patients for LT at an earlier stage.

LT is a radical treatment for PAH, and its results are not necessarily good. The International Society for Heart and Lung Transplantation (ISHLT) published the 2019 annual report on life prognosis of LT from January 1992 to June 2017. In 1,944 IPAH patients, the 1-, 3-, and 5-year survival rates were 74.3%, 64.2%, 56.1% and 41.4%, respectively (Figure). And IPAH patients had higher mortality risk in the first 3 months after LT than other major diagnoses.\(^7\)

In Japan, LT had been performed in 75 IPAH patients by the end of January 2017. The perioperative mortality rate was 13.3% and 5-year mortality survival rate was 82.4%.\(^8\) General risk factors of death after LT are bronchiolitis obliterans syndrome, infection and malignancies. In addition, left heart failure immediate after LT is related to early post-transplant death of PAH patients, presumed to be caused by the rapid physiological changes that acute normalization of PVR which increases cardiac output and left ventricular filling. These facts often bother us about whether to transplant as soon as possible or continue current medical treatment in PAH patients.

In this issue of the Journal, Akagi and colleagues\(^8\) investigate and compare the clinical course and hemodynamic changes after LT registration in 57 PAH patients. The patients were divided into 3 groups by clinical outcome (LT, death and survival): 27 patients underwent LT (48%), 21 patients (37%) died during the waiting period, and 9 patients (15%) survived long term. Of 57 patients, 34 (8 Survival, 13 LT and 13 Death) underwent right heart catheterization after LT registration. Comparing follow-up intervals and hemodynamic changes among the 3 groups, the 8 patients in the Survival group had a significantly longer follow-up and greater decrease in mPAP than the patients in the other 2 groups, despite baseline characteristics being similar other than interval from diagnosis to adding epoprostenol. As a result, the authors conclude that early introduction of epoprostenol infusion after the diagnosis of PAH could induced a marked decline in PAP, which contributed to long-term survival of PAH patients even after LT registration. This study included many patients enrolled before 2005 who only had epoprostenol for PAH treatment. Therefore, these patients were registered for LT before the treatment was sufficiently strengthened. These days, it is common to receive maximum drug treatment at the time of LT registration. It should be noted that it is necessary to determine whether a long-term prognosis with a PAH drug can be expected before LT registration. One report also refers to PAP as a prognostic factor in I/HPAH patients, in which the achievement of mPAP <42.5 mmHg predicts significantly better long-term survival than mPAP ≥42.5 mmHg after optimal medical treatment.\(^9\) It is important for the outcome for PAH patients to predict the necessity and appropriate timing of LT. A recent study demonstrated that prolonged use of extracorporeal membrane oxygenation support after LT successfully improved postoperative mortality and the 90-day, 1-, 3-, and 5-year survival rates were 92.7%, 90.2%, 87.4% and 87.4%, respectively.\(^10\) In order to improve the outcome of PAH treatment, it is necessary to reform the trinity of (1) optimal therapeutic strategy before LT registration, (2) shortening the waiting period after registration, and (3) improving perioperative and postoperative mortality after LT.

Disclosure

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References


