Lung Transplantation for Idiopathic Pulmonary Arterial Hypertension
Steps in the Right Direction

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In the past decade, there have been remarkable advances in the medical management of patients with idiopathic pulmonary arterial hypertension (IPAH). These therapies have improved the quality of life, saved many lives, and, in some cases, obviated the need for lung transplantation. However, the reality is that the majority of patients with IPAH, even with access to the best medical therapy, continue to progress and will require lifesaving lung transplantation.

1. Optimizing medical care of IPAH patients: This is a large and growing field in which major advances have been made with the development of intravenous infusion therapies of prostacyclin and related analogs and other vasoactive drugs. As further research is conducted in the fundamental pathophysiology and underlying mechanisms of IPAH, additional advances have been and continue to be made with the development of oral and inhaled therapeutic pharmacological formulations. Advanced molecular therapies such as gene therapy and cell therapy directed at correcting the underlying defects are the hope on the horizon.

2. Optimize timing of listing for transplant: Initially, after the introduction of effective medical therapy for IPAH, many patients were taken off lung transplant waitlists (appropriately so) because their condition improved significantly. Many patients were never considered for transplant because they were effectively treated medically from the time of diagnosis. The honeymoon ended as it became evident that many patients would become refractory to medical therapy and begin to deteriorate much more rapidly such that they often could not make it to transplant. The effect of the prostaglandin analogs on platelet function, in combination with warfarin anti-coagulation, made these patients even higher risk surgical candidates, because these lung transplants are done on cardiopulmonary bypass and the ensuing coagulopathy led to significant issues with perioperative hemorrhage and primary graft dysfunction. The recognition these issues led to changes in anticoagulation management practice, which has decreased the bleeding risks. Furthermore, it has become general practice in experienced centers to have IPAH patients assessed for possible lung transplantation early on in their disease course so that they can be promptly listed if they begin to deteriorate. This is especially important in those patients who present in a significantly symptomatic state or who deteriorate very rapidly. With a limited supply of donor organs, one can see that this might exacerbate the problem of waitlist mortality in this particular patient population that cannot afford to wait. One can also appreciate then, that when the United Network for Organ Sharing Lung Allocation Score (LAS) was initially introduced, this caused some concern regarding the potential for placing IPAH patients on the list at a disadvantage. The LAS score was designed with the intent to optimize the use of the scarce resource, donor lungs, by the allocation of lungs to patients who have the best potential for a good outcome after transplantation, balancing mortality on the waitlist with survival probability after transplant.

To optimally treat patients with IPAH, the treating physicians in the IPAH and lung transplant community need to (1) optimize medical care, (2) optimize timing of listing for transplant, and (3) optimize management on the lung transplant waitlist to maximize the likelihood of successful lifesaving lung transplantation in the context of available donor organs and current listing guidelines and practices.

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patients with IPAH that were rapidly deteriorating had few options and had an excessive waitlist mortality.

Patients with IPAH tend to die of progressive right heart failure or sudden cardiac death from secondary related arrhythmias when the heart just cannot pump any more against the high resistance of the diseased pulmonary vascular bed. An historical option used to palliate patients was the use of an atrial septostomy. Creating an atrial septostomy would decompress the pressure on the right heart for a period of time, but eventually led to death from biventricular failure secondary to hypoxic perfusion (right to left shunting) of the coronary circulation of the already failing heart. Another option that was sometimes used was extracorporeal lung support (ECLS) instituted in a venoarterial perfusion conformation, usually femoral vein to femoral artery. This has the benefit of supporting the circulation of the severely decompensated patient, but often is not successful in that it does not effectively address the right heart failure and the very high pulmonary vascular resistance faced by the heart of a patient with end-stage IPAH.

We described the use of ECLS in a unique fashion for IPAH patients.1 We placed the Novalung (Novalung, Germany) membrane parallel to the pulmonary circulation, cannulating the pulmonary artery and the left atrium (right superior vein or left atrial appendage) to effectively create a pulmonary artery-left atrium shunt. The right ventricle provides the pumping action, and, hence, this membrane is used in a pumpless fashion to effectively create a shunt that also oxygenates the blood while offloading the right ventricle by providing a low-resistance (6 mm Hg at 1.5 L/min flow across the membrane) path for the ejection of blood from the right heart. Since the introduction of this technology, we have decreased the lung transplant waitlist mortality for IPAH patients in the Toronto Lung Transplant Program from 22% to 0%.2 ECLS bridging to lung transplantation is an effective therapeutic option that will likely play an increasing role in successfully managing patients on the lung transplant list, to decrease not only waitlist mortality, but also post–lung transplant survival. These patients can be extubated and ambulatory on ECLS and, as such, with successful pulmonary artery-left atrium bridging come to surgery in far better condition with a recovered right ventricle and recovery of hepatic and renal congestion/failure.2

Malldi and colleagues have studied, in a competing-outcomes analysis, the cumulative incidence of lung transplant and mortality for wait-listed patients in the period preceding and after the introduction of the United Network for Organ Sharing LAS.3 The authors have duly acknowledged the limitations of inferences made from the study of registry data. The most important bottom line is that, in this analysis, the LAS system does not appear to have specifically disadvantaged patients with IPAH. In fact, to the contrary, this analysis reports that, despite of the fact that IPAH patients in the post-LAS era had worse comorbidities (reflected in higher LAS scores), at 2 years, the incidence of lung transplant as a competing outcome was higher (39% versus 18%), the incidence of death on the waitlist was lower (23% versus 31%), and furthermore the posttransplant survival was improved (80% versus 65% at 2 years). These encouraging statistics support the contention that the LAS is functioning as intended to prioritize sicker patients for transplant and to get these patients to transplant sooner. That lung transplant incidence doubled but post–lung transplant survival did not increase likely reflects that the patients are still very sick, or sicker, when they get to transplant.

This registry analysis, however, is not able to account for significant changes in practice that have occurred over the same time period. Importantly, the United Network for Organ Sharing registry data do not collect data related to ECLS bridging to lung transplant. The finding that IPAH patients on the waitlist fare better in medium to large centers potentially alludes to this. Specialized centers with increased experience likely have knowledge of and access to progressive IPAH medical therapies and ECLS technologies for bridging patients. The LAS scoring system was intended to be a modifiable scoring system based on the analysis of real data over time. Clearly, this analysis and adjustment needs to be done to increase the fidelity of the scoring system. The authors have raised provocative questions regarding the role of the cardiac index and donor-recipient sex matching that need to be evaluated in more detail. We will also need to look at how to allocate LAS points to patients on a ventilator versus on ECLS.

Conclusions

Major advances have been made in the treatment of patients with IPAH. Although tremendous improvements have been achieved with medical therapy, the majority of patients will require lung transplantation. Our goal should be to continue to study the underlying mechanisms of this disease to develop therapies to prevent or treat IPAH and to maximize the access of all patients to donor lungs. Thankfully, the implementation of the LAS system appears to have improved the incidence of lung transplant, and the waitlist mortality overall is also reduced. The association of improved outcomes in higher-volume centers in dealing with complex patients is once again borne out. Although this study is reassuring in that it appears that the LAS is doing what it was intended to do, the improvements in the parameters reported in this study clearly cannot all be attributed to the impact of the implementation of the LAS system. As outlined, it is possible that the major advances in care that have occurred have had a significant effect and that the impact of the LAS itself may not be as large.

Disclosures

None.

References


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