

phatases that are haplodeficient in the del(5q) clone.⁷ The key role of phosphatases in the regulation of ligand–receptor signaling might explain the broad range and lineage dependency of the biologic effects of immunomodulatory drugs.

Lenalidomide and the immunomodulatory drugs stand as prime examples of potentially dangerous chemical compounds that have been granted a second life with powerful therapeutic applicability. Like the mythical phoenix that was reborn from its own ashes, lenalidomide and the immunomodulatory drugs carry exciting potential.

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Lung Transplantation in Cystic Fibrosis — Primum Non Nocere?

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Cystic fibrosis is one of the most common autosomal recessive diseases. It causes intestinal, pancreatic, and progressive lung dysfunction, which is ultimately lethal. In 1989, the first specific cystic fibrosis gene defect on chromosome 7 was described, and its function was determined shortly thereafter. The cystic fibrosis gene codes for the cystic fibrosis transmembrane regulator (CFTR) protein, a chloride channel that controls chloride and, indirectly, sodium transport across epithelial cells.

When CFTR function is lost, excess sodium and chloride are resorbed from the airway lumen, leading to dehydration of the luminal contents and increased fluid viscosity of the airway lining. These abnormalities and the ensuing ciliary dysfunction lead to a cycle of infection, inflammation, and obstruction, causing irreversible bronchiectasis and pulmonary parenchymal destruction.¹ A better understanding of the molecular causes of cystic fibrosis has led to improved treatments such as oral antipseudomonal antibiotics, recombinant human DNase, hypertonic saline, and newer forms of chest physiotherapy. As a consequence, the predicted median survival of patients with cystic fibrosis has increased from the mid-teens in the 1970s to 36.5 years in 2006.²

Despite improved therapies, cystic fibrosis lung

disease progresses relentlessly, and eventually therapies are exhausted. It is in this setting that lung transplantation has become an alternative. A basic tenet regarding lung transplantation is that it extends life. In this issue of the *Journal*, a startling article by Liou et al.³ challenges this tenet with regard to children with cystic fibrosis. A previous study by Aurora et al.⁴ concluded that lung transplantation conferred a survival advantage in children with cystic fibrosis, and most workers in transplant centers have encountered patients in whom the results of transplantation seem nothing short of miraculous. However, another recent study by Liou et al.⁵ raised the question of whether a survival advantage is conferred in patients younger than 18 years of age. This study has led to heated controversy.^{6,7} In the current study, the authors show that only 5 of 514 patients on the waiting list for lung transplantation would have a prolonged life expectancy because of the procedure, whereas 315 would have a significant risk of harm associated with the procedure.

One of the difficulties of choosing suitable candidates for lung transplantation is finding the point of equipoise — that is, the point at which the patient's predicted life expectancy is less than his or her predicted survival after transplantation.

In the United States, the median survival of children with cystic fibrosis after lung transplantation is 2.84 years, and survival at 5 years is 32.9%, somewhat less than that reported for all patients with cystic fibrosis and for recipients of lung transplants for other conditions. The predicted 5-year survival of all patients on the waiting list for lung transplantation, according to the current model of Liou et al., was 57%. Thus, it is not surprising that transplantation afforded no survival advantage. Indeed, in an earlier study in which children were not considered separately from adults,⁸ Liou et al. showed that lung transplantation enhanced survival when the predicted survival was 30%. What is surprising in the current study is that no lower threshold of either predicted survival or low forced expiratory volume in 1 second (FEV₁) was found that would predict a survival benefit for transplantation. However, only 32 of the 514 children studied had a predicted 5-year survival of less than 30% at the time of their placement on the waiting list, and the power to analyze this sample is correspondingly small.

Do children who undergo lung transplantation do worse than children who do not because there are differences in the initial severity of their disease or because of the transplantation itself? Patients were carefully matched for severity on a number of important criteria. However, the relative risk associated with transplantation would be higher if patients who underwent transplantation became sicker or if patients who did not undergo transplantation became healthier or their lung function remained stable or improved after they were placed on the waiting list for lung transplantation. The procedure is often deferred if the condition of children who are on the waiting list is stable; indeed, patients who are referred to transplant centers often undergo intensive pulmonary and nutritional resuscitation as a way to prepare them for transplantation, and this may result in their deferral, at least temporarily. Thus, in this study, the patients who ultimately underwent transplantation may have been sicker than the patients who did not, predisposing them to worse outcomes.

This study was performed at a time when lung allocation was based on the patient's length of time on the waiting list for an organ. Under the current United Network for Organ Sharing (UNOS) allocation system, which began in 2005, the priority of transplant recipients over the age of 11 years

is assigned according to a combination of factors, including the severity of illness. This system has resulted in a decreased waiting time for the sickest recipients. Thus, conclusions that are based on the old UNOS allocation system may not be applicable to the current one.

What of the risks of the transplantation itself? For each patient, Liou et al. calculated a transplantation "hazard factor," which is the relative risk of death associated with the procedure. A hazard factor of more than 1 indicates that transplantation would be harmful; a hazard factor of less than 1 indicates that it would be beneficial. According to the authors' model, the predicted hazard factor is primarily based on two variables: first, *Staphylococcus aureus* infection is beneficial before transplantation, but disadvantageous after transplantation, and second, older age has no effect before transplantation but is disadvantageous after transplantation. The first phenomenon may be related to immune suppression after transplantation, and the second may be related to a lower rate of adherence to post-transplantation medical regimens among the teenage population.⁹

If there is no survival advantage associated with transplantation, what about quality of life? The authors had only limited data on this outcome, and they used medical complications and the number of hospitalization days before and after transplantation as surrogates for better information. Of these measures, only the number of hospitalization days after transplantation decreased. However, medical complications, as the authors readily admit, may not reflect quality of life. For example, quality-of-life scores that use domains such as symptoms, activity limitations, and emotional function may have poor physiological correlations.¹⁰ Future studies should incorporate well-accepted quality-of-life measurement tools, as well as documentation of adherence to post-transplantation medical regimens, which can profoundly affect survival.

The implications of the current study are that transplantation may not improve survival for children with cystic fibrosis, and if it does, it would be expected to do so only in patients whose predicted 5-year survival is less than 30% or whose predicted median survival is less than 3 years. These survival projections are lower than those for many patients who are being referred for transplantation now. It will be important to readdress this issue with the new lung allocation system,

which may decrease the waiting time and waiting-list mortality for candidates of lung transplantation and increase post-transplantation survival. In the meantime, patients with cystic fibrosis and their parents need to be informed that although transplantation may improve quality of life, it may not improve survival. This information is sure to make an already difficult decision more difficult still; cystic fibrosis centers must have the resources to provide appropriate social and psychological support to help families make the best choice.

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