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ORIGINAL ARTICLE

A comparison of CF and non-CF school-age children undergoing lung transplantation

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Summary

Cystic fibrosis (CF) is a genetic disorder resulting in a chloride channel (CFTR) defect characterized by multi-organ damage. The primary cause of morbidity and mortality is end-stage obstructive lung disease. Lung transplantation is a treatment option, but is complicated by the risks of acute rejection, Bronchiolitis Obliterans syndrome (BOS) (graft dysfunction), and serious infection. This study sought to assess survival free from three major complications, namely BOS, acute rejection, and serious infection and also to compare overall survival among school-age CF transplantation recipients to non-CF recipients. We limited consideration to school-age children because they comprise a unique cohort in terms of linear and graft growth, immunity, pharmacokinetics and infection exposure as compared with infants, adolescents and adults. The OPTN national database was searched for period between January 1997 and August 2006 for children between 6 and 10 years of age undergoing lung transplantation. Children with CF were compared with non-CF recipients with regard to occurrence of BOS, infection-related hospitalizations, and acute rejections. Kaplan–Meier analyses were used for statistical comparisons of the two cohorts. There were 50 CF patients and 37 non-CF patients available for analysis from the OPTN database. Up to 5 years post-transplant, there were no statistically significant differences between CF and non-CF patients in overall survival, and survival free from BOS, acute rejections, or serious infections defined as those requiring hospitalization. Despite having an underlying systemic disease based on defective CFTR, CF school-age children receiving a lung transplant do not demonstrate more major complications or lower survival than non-CF children.

Introduction

Bronchiolitis Obliterans syndrome (BOS) remains a major cause of morbidity and mortality among all lung transplant recipients regardless of age or diagnosis [1]. The onset of BOS in the lung transplant patient has been linked to the development of irreversible airflow obstruction and reduced survival [2]. The International Society of Heart and Lung Transplantation (ISHLT) registry includes information on the occurrence of BOS in children under the age of 18 years. The ISHLT estimate of 5-year BOS incidence is approximately 34% among transplanted children [3]. Cystic fibrosis (CF), a genetic disease resulting in multi-system luminal obstruction and chronic bacterial colonization of the sinuses and airway, is the most frequent indication for lung transplantation in children under the age of 18. CF is caused by a chloride channel defect and thus the disease is not cured by lung transplantation. After transplantation, all CF patients undergoing lung transplantation still have CF and continue to be treated for nonpulmonary manifestations of the disease. Therefore, comparison with patients who

have their disease treated and cured by the transplantation is of importance.

Most of the CF recipients are over the age of 14 years and therefore pediatric studies typically include a large number of adolescent patients [4]. No prior national publications have exclusively studied primary school-age CF transplant patients as a unique population distinct from infants, adolescents and adults. Most pediatric transplant studies and registries do not separately report statistics on school-age children, but rather as part of the 'pediatric' population, defined as those patients under the age of 18 years. The school-age group is distinct in its pattern of growth, stage of immune development, host responses, pathogen exposures and altered pharmacokinetics [5,6]. Normal children under the age of 6 have a dynamic immune development such as lower CD4 cells when compared with older children. Other considerations in defining the age range studied included that children older than 5 years are able to perform reproducible standard pulmonary function tests. This study examined school-age (6–10 years) CF lung transplant patients in terms of important transplantation conditions that are associated with reduced survival such as BOS, acute rejection and serious infection (i.e. those requiring hospitalization) when compared with non-CF transplanted school-age children.

Methods

Patient demographics

Lung transplant patients between the ages of 6–10 years were identified using the organ procurement and transplantation network (OPTN) national database for the period between January 1997 and August 2006. There were no US centers or regions excluded from analysis. No patient or center identifiers were included. Patient information included CF status, gender and age. School-age, for the purposes of this study, was defined based on a number of considerations including immune cell development, ability to perform pulmonary function tests, and hormonal changes distinct from adolescents, infants and adults.

OPTN database

The OPTN's secure transplant information database contains all national data on the candidate waiting list, organ donation and matching, and transplantation. The 2007 Annual Report of the US Organ Procurement and Transplantation Network and the Scientific Registry of Transplant Recipients contains data that is current and is sponsored by the Department of Health and Human Services, Health Resources and Services Administration, Healthcare Systems Bureau, Division of Transplantation, Rockville, MD; United Network for Organ Sharing, Richmond, VA; University Renal Research and Education Association, Ann Arbor, MI. The use of the OPTN database includes all reported data from major centers nationally.

Clinical parameters and definitions

Each center is responsible for reporting clinical parameters relating to each transplant patient, which are amalgamated in the national database. In particular, the centers report, on a per patient basis, occurrence of (i) Bronchiolitis Obliterans/BOS using ISHLT definitions, (ii) serious infections defined as those requiring hospitalization, and (iii) Clinical diagnosis of Acute rejection (any grade), post-transplant. The time from date of transplantation to occurrence of BOS, acute rejection, and serious infection was used as the definition for subsequent analysis and figures.

Statistical methods

Summary statistics for continuous data are reported as means and standard deviations. Comparisons between CF and non-CF patients relating to occurrence of BOS, serious infections, and acute rejection episodes, were made with Kaplan–Meier curves and associated log rank statistics. In this regard, times of occurrence were calculated as (date of event) – (date of transplant). Individuals not experiencing particular events were considered censored at time (date of last follow-up) – (date of transplant).

Results

Patient demographics

There were a total of 87 transplant recipients between the ages of 6–10 years of age who were reported to the OPTN database between January 1997 and June 2006. Among these, 50 (26 F/24 M) had the diagnosis of CF. The remaining 37 (18 F/19 M) had a variety of diagnoses including: pulmonary fibrosis, pulmonary vascular disease and bronchopulmonary dysplasia. The mean ages were comparable in each group with a mean of 8.5 years (±1.3) and 8.2 years (±1.4) in the non-CF group.

Clinical development of complications

Kaplan–Meier (KM) curves were generated for the three endpoints outlined

Beonchiolitis obliterans syndrome. There were no statistically significant differences between the two groups in the reported rates of BOS. In Fig. 1 we display the KM curves

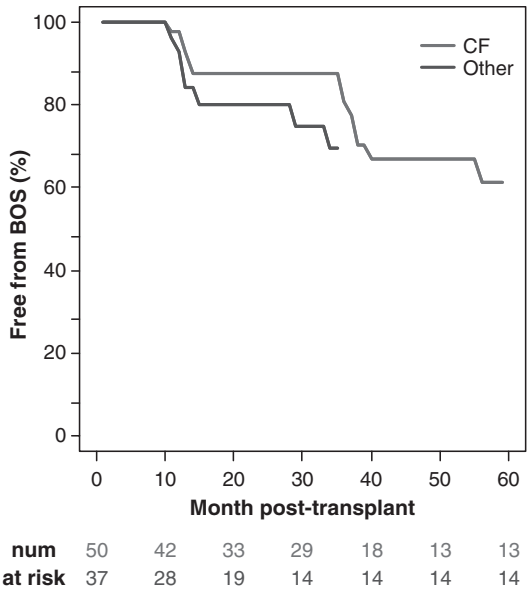

Figure 1 Kaplan–Meier (KM) curves for Bronchiolitis Obliterans syndrome (BOS)-free survival among cystic fibrosis (CF) and non-CF patient cohorts. The observed differences in BOS-free survival did not achieve statistical significance (log-rank $P = 0.18$).

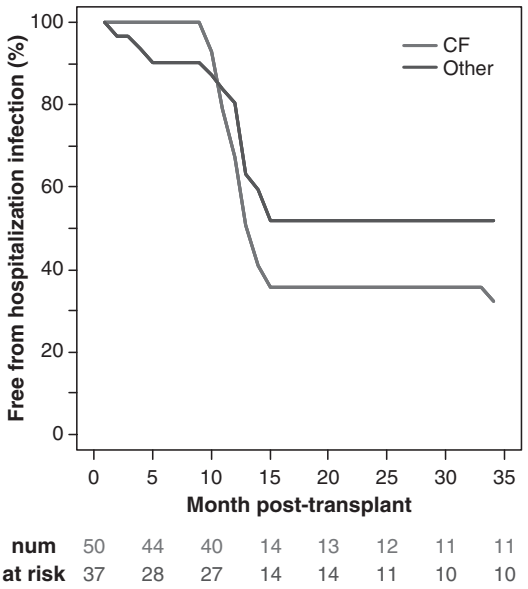

Figure 2 Kaplan–Meier (KM) curves for rejection-free survival in the two cohorts of cystic fibrosis (CF) and non-CF school-age lung transplant recipients. The observed differences in occurrence of acute rejection were not statistically significant (log-rank $P = 0.11$).

for BOS-free survival in the two cohorts, CF and non-CF school-age lung transplant recipients. The observed differences in BOS-free survival did not achieve statistical significance (log-rank $P = 0.18$).

At the end of year 1, there were five CF (12%) and five (19%) non-CF patients who carried the diagnosis of BOS. At the end of year 3, there were seven CF (28%) and eight non-CF (47%) with BOS; 18 CF patients remained free from BOS at the end of 3 years. At 5 years, nine CF (60%) and five non-CF patients (50%) remained free from BOS.

Acute rejection. In Fig. 2, we show the KM curves for rejection-free survival in the two cohorts of CF and non-CF school-age lung transplant recipients. The observed differences in occurrence of acute rejection were not statistically significant (log-rank $P = 0.11$).

Three CF patients (21.4%) and three non-CF (25%) patients had at least one episode of acute rejection by the end of year 1.

Hospitalization for infection. In Fig. 3, we give the KM curves corresponding to the durations of hospitalization for infection in the two patient groups studied. The observed differences in hospitalization rates were not statistically significant (log-rank $P = 0.08$).

Twenty-seven CF (81.8%) and 14 non-CF (82.3%) were hospitalized for infection during year 1 following

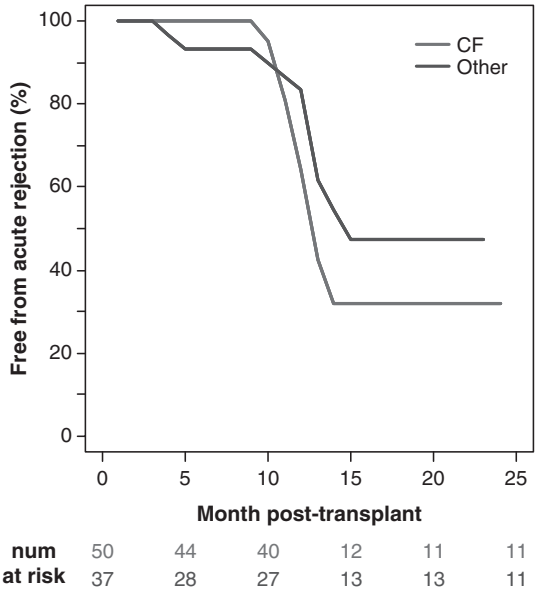

Figure 3 Kaplan–Meier (KM) curves corresponding to the durations of hospitalization for infection in the two patient groups studied. The observed differences in hospitalization rates were not statistically significant (log-rank $P = 0.08$).

lung transplantation. At 3 years: 16 (84.2%) CF/six (66.6%) non-CF patients were hospitalized and at 5 years: eight (80%) CF; non-CF: two or 66% had infections

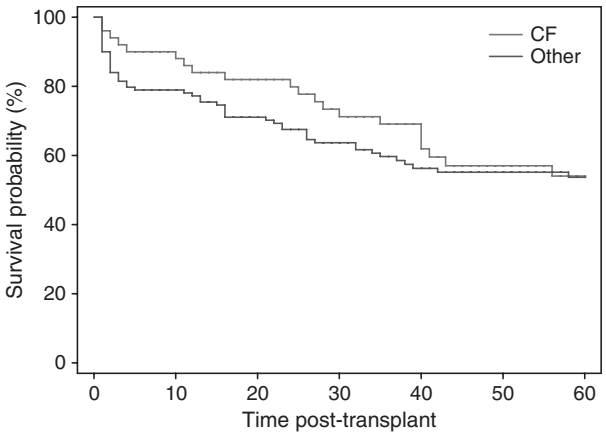

Figure 4 Kaplan–Meier (KM) curves corresponding to overall survival in the two cohorts studied. The observed differences were not statistically significant (log-rank $P = 0.73$).

requiring hospitalization. While CF patients consistently had a higher rate of hospitalization in all the time periods studied, it did not reach statistical significance. In Fig. 4, we show the KM curve corresponding to overall survival post transplantation. There were no statistically significant differences found between the two groups studied (log-rank sum $P = 0.73$).

Discussion

This study shows for the first time, that among school-age children with CF, there is no significant difference in the 1-, 3- and 5-year rates of common complications or overall survival, following lung transplantation, compared with non-CF children of similar gender and age. Specific major complications studied included BOS, AR, and hospitalization for infection. The latter two complications are considered potential risk factors for BOS. Survival free of these three complications was not significantly different among CF versus non-CF patients. While single-center pediatric studies have been published, the results may not reflect national findings. This study is unique in investigating only school-age lung transplantation recipients, using a well-accepted, frequently cited searchable national database. School-age children are a unique group in terms of growth, infection exposure patterns and immune development. It is well established that there is less compliance among adolescents, and that in very young patients the immune system is still developing. School-age children generally display more linear somatic growth and fewer infections compared with infants and lack the hormonal variations of the adolescent patient [5,6]. School-age children should be considered as a specific age group when considering transplantation complications. For the purposes of this study, recipient ages ranging from 6 to 10 years were included for analysis. Therefore, this study analysed the transplantation outcomes in this age group specifically.

Bronchiolitis Obliterans syndrome is a serious complication following lung transplantation and is linked to poor survival [2]. Major risk factors include acute rejection and infection episodes, which may cause epithelial damage and subsequent cellular events which result in the obliteration of the airway [7]. According to our study, in school-age CF children with severe disease necessitating lung transplantation, there were no statistical differences detected at 1, 3 and 5 years in the survival free from BOS, or the rates of BOS, compared with the non-CF recipients. Lung transplantation in the CF patient does not cure the genetic multi-system disease, but offers a viable alternative in the management of the disease. When compared with non-CF lung transplant recipients in this specific age range, the survival free from BOS was similar. There was a trend between 20–40 months of better survival free from BOS among the CF patients, but this did not reach significance.

Other studies of CF lung transplantation recipients have shown important considerations in the postoperative complications such as diabetes, sinus infections and nutritional requirements among this population. CF does not in itself appear to be a risk factor for the development of BOS. One important difference in the management of the CF patient remains that the sinuses and trachea can serve as a reservoir for bacterial infection of the lower airway [7,8]. Our results indicate that survival free from serious infection, reflected by hospitalization rates for infection did not vary significantly compared with the non-CF population. There was a trend toward greater hospitalization rates after the first year among CF patients, but this did not reach statistical significance. Some studies suggest that innate immunity is impaired in the CF lung transplant recipient and this possibly could be another explanation of higher infection rates. Toll like receptor (TLR4) heterozygotes may be associated with reduced onset of BOS based on a study of 170 lung transplant patients [9,10].

There are many challenges to the management of the Pediatric transplantation patient, and organ allocation to adolescents and infants have excellent short-term but less optimal long-term results [11,12]. Some of the challenges in the management of pediatric transplantation patients include different etiologies of organ failure, development of the immune system, surgical technical complexities, high rates of gastro-esophageal reflux, altered pharmacokinetics of commonly used immunosuppressive agents [13,14]. Nutritional management in the CF child is another possible factor complicating outcome, but studies

have indicated improvement in post-transplantation nutritional parameters [15].

In order to perform an analysis of a particular age group, individual centers may not have the number of patients necessary. Thus, the OPTN database provided a useful, reliable source for statistical analysis of pediatric transplantation data. The drawbacks of a national database, previously cited, include reliance upon individual centers to report accurately to OPTN [16]. As the study is retrospective yet analytic, only parameters entered in the OPTN database can be included. The advantages of using a national database include that the data is compiled from numerous centers across geographic and regional areas. As reporting from centers increases, studies can be expanded to include greater numbers of patients.

In conclusion, despite genetic differences in chloride channel CFTR function and resultant upper airway colonization with bacteria, CF school-age children receiving a lung transplantation prior to adolescence neither demonstrate lower survival nor higher rates of BOS, AR and serious infection compared with the non-CF children during the 5 years following transplantation.

Authorship

AD: performed the study and wrote paper, helped analyse data. JK: statistical analysis of data.

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References

1. Scott JP, Higenbottam TW, Sharples L, *et al.* Risk factors for obliterative bronchiolitis in heart-lung transplant recipients. *Transplantation* 1991; **51**: 813.
2. Burton CM, Carlsen J, Mortensen J, Andersen CB, Milman N, Iversen M. Long-term survival after lung transplantation depends on development and severity of bronchiolitis obliterans syndrome. *J Heart Lung Transplant* 2007; **26**: 681.
3. Aurora P, Boucek M, Christie J, *et al.* Registry of the ISHLT 2007. *J Heart Lung Transplant* 2007; **26**: 1223.
4. Hadjilliadis D. Special considerations for patients with cystic fibrosis undergoing lung transplantation. *Chest* 2007; **151**: 1224.
5. Behrman R, Klegman R, Jenson H eds. *Nelson Textbook of Pediatrics*, 16th edn. Philadelphia, PA: W.B. Saunders, 2001: 594–5.
6. Behrman R, Klegman R, Jenson H eds. *Nelson Textbook of Pediatrics*, 16th edn. Philadelphia, PA: W.B. Saunders, 2001: 50–52.
7. Husain AN, Siddiqui MT, Holmes EW, *et al.* Analysis of risk factors for the development of bronchiolitis obliterans syndrome. *AJRCCM* 1999; **159**: 829.
8. Dosanjh A, Lakhani S, Elashoff D, Chin C, Hsu V, Hilman B. A comparison of microbiologic flora of the sinuses and airway among cystic fibrosis patients with maxillary antrostomies. *Pediatr Transplant* 2000; **4**: 182.
9. Palmer SM, Burch LH, Trindade AJ, *et al.* Innate immunity influences long-term outcomes after human lung transplant. *AJRCCM* 2005; **171**: 780.
10. Bonvillain RW, Valentine VG, Lombard G, La Place S, Dhillon G, Wang G. Post-operative infections in cystic fibrosis and non-cystic fibrosis patients after lung transplantation. *J Heart Lung Transplant* 2007; **26**: 890.
11. Pahl E, Naftel DC, Kuhr MA, *et al.* The impact and outcome of transplant coronary disease in a pediatric population: a nine year multi-institutional study. *J Heart Lung Transplant* 2005; **24**: 645.
12. Ibrahim JE, Sweet SC, Flippin M, *et al.* Rejection is reduced in thoracic organ recipients when transplanted in the first year of life. *J Heart Lung Transplant* 2002; **21**: 311.
13. Wells A, Faro A. Special considerations in pediatric lung transplantation. *Semin Respir Crit Care Med* 2006; **27**: 552.
14. Benden C, Aurora P, Curry J, Whitmore P, Priestley L, Elliott M. High prevalence of gastroesophageal reflux in children after lung transplantation. *Pediatr Pulmonol* 2005; **40**: 68.
15. Beck C, Lin A, Robbins RC, Dosanjh A. Improvement in nutritional and pulmonary profiles of CF lung transplant patients. *Nutr Clin Pract* 1997; **12**: 40.
16. Sweet SC, Wong HH, Webber SA, *et al.* Pediatric transplantation in the United States 1995–2004. *Am J Transplant* 2006; **6**: 1132.

