Review of Heart-Lung Transplantation at Stanford

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Long-term survival after heart-lung transplantation was first achieved in 1981 at Stanford and a total of 217 heart-lung transplantations had been performed by June 2008. This review summarizes Stanford's cumulative experience with heart-lung transplantation, demonstrates the progress that has been made, and discusses past and persistent problems. Diagnostic tools and treatment options for infectious diseases and rejection have changed and patient survival markedly improved over the almost three decades. Eight patients lived longer than 20 years. Further options to treat infections and strategies to control bronchiolitis obliterans syndrome, the main causes of early and long-term mortality, respectively, are required to achieve routine long-term survival.

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The first reported clinical heart-lung transplantation (HLTx) was performed by Cooley in 1968 in a two-month-old child with complete atrioventricular canal defect and pulmonary hypertension [1]. The patient did not survive the surgery. Two more HLTx were performed by Lillehei in 1969 [1] and Barnard in 1971 [2] in adult patients with emphysema and cor pulmonale. Unfortunately, both patients died of infection after 8 and 23 days, respectively. In March 1981, after laboratory studies in monkeys and after cyclosporine was introduced to heart transplantation in December 1980, long-term survival of clinical heart-lung transplantation was first achieved at Stanford [3]. The number of heart-lung transplants performed thereafter rapidly increased over the following years [4] and the indications were expanded from pulmonary vascular disease to include patients with parenchymal lung disease [5]. Several years later, isolated lung transplantation emerged as a viable option and successful long-term survival was reported for pulmonary fibrosis in 1986 [6]. Preliminary success for chronic obstructive pulmonary disease became public in 1989 [7]. The number of heart-lung transplants reported to the International Society for Heart and Lung Transplantation (ISHLT) subsequently decreased during the 1990s and has been steady in the 2000s at 75 to 90 operations per year [4]. This article summarizes our 27-year experience with clinical heart-lung transplantation, outlines the improvements in survival over the years, and analyzes the major transplant-related complications.

Material and Methods

Patients

The Stanford Transplant Database and medical records of all heart-lung transplants performed at Stanford University Medical Center between March 1981 and June 30, 2008 were reviewed. Pediatric and adult patients were included. Human leukocyte antigen-A (HLA-A) and HLA-B typing was routinely done in all donors and recipients and HLA-DR typing was introduced in 1987. The study was approved by the Stanford Institutional Review Board and individual consent for the study was waived.

Listing criteria for HLTx evolved over time. Primary pulmonary hypertension (PPH) and congenital heart disease with or without concomitant Eisenmenger's syndrome were the initial diagnoses and remained the most common diagnoses over time. The first HLTx for cystic fibrosis (CF) was performed in 1988, the first HLTx for emphysema in 1989. Isolated lung transplantation (LTx) started in 1989 at Stanford and became an alternative option for patients with end-stage lung disease. The decision to list patients with PPH for HLTx rather than for bilateral LTx was made depending on the right heart function and its predicted recovery after isolated LTx. The first patient with sarcoidosis involving both the heart and the lungs underwent HLTx in 1994. Patients with end-stage parenchymal lung disease and acquired heart disease were usually deemed unsuitable candidates for HLTx.

Operative Technique

A median sternotomy incision was used in most patients. The bilateral thoracosternotomy ("clamshell") incision was only used in selected patients in whom significant pleural adhesions were expected. Before 1987, organ donors were transferred to Stanford for organ recovery. Later, distant graft procurement was routinely used. Implantation was performed according to the operative technique originally described in 1981 [8] and was modified toward bicaval anastomoses in 1992.

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Abbreviations and Acronyms

BOS = bronchiolitis obliterans syndrome
CF = cystic fibrosis
CMV = cytomegalovirus
EMBx = endomyocardial biopsy
HLTx = heart-lung transplantation
HLA = human leukocyte antigen
ISHLT = International Society for Heart and Lung Transplantation
LTx = lung transplantation
MM = mismatches
PPH = primary pulmonary hypertension
RATG = rabbit antithymocyte globulin
TBBx = transbronchial biopsies

Immunosuppression and Antimicrobial Prophylaxis

IMMUNOSUPPRESSION. Methylprednisolone (10 mg/kg, 500 mg max) was given intraoperatively and postoperatively (5 mg/kg, 125 mg max, 3 doses). From 1981, cyclosporine was the mainstay of the immunosuppressive therapy. Doses were titrated to target levels of 150 to 250 ng/mL within the first 12 weeks after transplantation and 100 to 150 ng/mL thereafter. Azathioprine was loaded preoperatively with 2 to 4 mg/kg and was continued at 2 mg/kg, adjusted to white cell counts greater than 5,000 cells/mm^3. Prednisone was tapered to 0.2 mg/kg by 6 weeks. Polyclonal rabbit antithymocyte globulin (RATG) or polyclonal horse antithymocyte globulin (ATGAM; Upjohn Co, Kalamazoo, MI) was used for induction therapy until 1987. Between 1988 and 1993, the monoclonal antibody OKT3 (Ortho Pharmaceutical Corp, Raritan, NJ) or RATG was used based on the availability of RATG. After 1993, RATG was used routinely and, since 2007, daclizumab was used for most cases. In 2006, mycophenolate mofetil replaced azathioprine and tacrolimus replaced cyclosporine. Tacrolimus target levels were 10 to 15 ng/mL early posttransplant and 8 to 12 ng/mL after 6 months.

CYTOMEGALOVIRUS (CMV) PROPHYLAXIS. Beginning in 1987, intravenous ganciclovir was used for 6 weeks when positive CMV antibody titers were found in the recipient or the donor. Since 1996, patients also received 7 doses of intravenous CMV immunoglobulin (CMV-IG) over the first 4 months. Since 2001, patients continue on oral valganciclovir for the first postoperative year. Acyclovir is used for CMV D−/R− patients.

PNEUMOCYSTIS PROPHYLAXIS. Pneumocystis jiroveci prophylaxis was initiated in 1988 using trimethoprim and sulfamethoxazole. Monthly pentamidine inhalations or, after 2000, atovaquone have been used in patients with sulfa allergy.

FUNGAL PROPHYLAXIS. To prevent oropharyngeal candidiasis, topical nystatin troches have been used since 1981. Since July 1993, aerosolized amphotericin B has been administered throughout the posttransplantation hospital stay. Figure 1 depicts immunosuppressive and antimicrobial prophylaxis regimens across the different eras of HLTx.

Follow-Up

Patients have been closely followed by the Stanford posttransplant team. Surveillance for rejection was initially performed by endomyocardial biopsy (EMBx) and, starting in 1988, by serial transbronchial biopsies (TBBx) [9]. Initially, TBBx with lavage were performed electively at 1-week to 2-week intervals after HLTx. Over the years, the intervals between TBBx increased, and in the 1990s, TBBx were scheduled at 2, 4, 8, and 12 weeks and then at 6 and 12 months after transplant. Currently, we perform surveillance TBBx at 6 weeks, 3, 6, and 12 months posttransplant or if clinically indicated. In the 1990s and early 2000s, recipients underwent EMBx twice in the first 6 months and annually thereafter. We now perform EMBx only if clinically indicated.

Acute cellular lung rejection equal to or greater than ISHLT grade A2 on TBBx or heart rejection equal to or greater than ISHLT grade 2R (formerly grade 3A) on EMBx were treated with 500 to 1,000 mg intravenous methylprednisolone for 3 days followed by a 2-week predisone tapering schedule. Persistent rejection was managed with cytolytic agents, total lymphoid irradiation, and (or) methotrexate. The incidence of death, rejection requiring steroid pulse therapy, infection, bron-

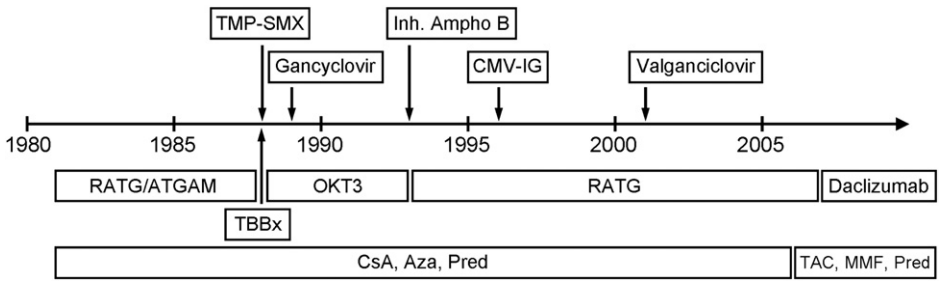

Fig 1. This timeline shows major changes in immunosuppressive therapy and antimicrobial prophylaxis regimens over almost three decades of heart-lung transplant. (Aza = azathioprine; CMV-IG = cytomegalovirus/immunoglobulin; CsA = cyclosporine A; Inh. Ampho B = inhaled amphotericin B; MMF = mycophenolate mofetil; OKT3 = monoclonal antibody OKT3; Pred = prednisone; RATG = rabbit antithymocyte globulin; RATG/ATGAM = rabbit antithymocyte globulin/antithymocyte globulin; TAC = tacrolimus; TBBx = transbronchial biopsies; TMP-SMX = trimethoprim /sulfamethoxazole.)