First Pediatric Heart Transplantation From a Pediatric Donor Heart in Japan

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Background: Since the revision of the Japanese Organ Transplantation Act, children younger than 15 years old can donate their organs after brain death.

Methods and Results: A teenage boy with endstage restrictive cardiomyopathy underwent the first heart transplantation with a pediatric donor heart in Japan on April 12, 2011. He had a good postoperative clinical course and no histological rejection episodes. His waiting period was relatively short (237 days) compared with adult patients, because of the pediatric patient-first policy for a pediatric donor heart.

Conclusions: To increase pediatric heart transplantation in Japan, further enlightenment of the general population about pediatric organ donation is desirable. (Circ J 2012; 76: 752–754)

Key Words: Cardiomyopathy; Pediatrics; Transplantation

Orthotopic heart transplantation (HTx) has been gradually increasing in Japan since the first HTx was performed in Osaka University Hospital in February 1999. However, because of the long waiting period for HTx, long-term support of that patient with ventricular support system was needed.1 Until continuous flow assist devices could be approved, and the postoperative prognosis thus improved,2 the results of HTx would be unsatisfactory. Moreover, children under the age of 15 years could not donate their organs after brain death until the Japanese Organ Transplantation Act was revised on July 17, 2010, because in Japan only persons who had given written consent for organ donation after brain death could donate their organs. Prior to the case reported here, only 4 teenage HTx had been performed, using adult donor hearts.

After renewal of the Act, organs can be donated after brain death by consent of the patient’s relatives, if he or she did not deny organ donation, allowing children younger than 15 years of age to donate.

Before issuing the revised Act, new guidelines for organ allocation were made and because of the beneficial effects of pediatric donor hearts on survival after pediatric HTx, the pediatric patient-first policy from a pediatric donor heart was made the same as the policy of the United Network for Organ Sharing. Briefly, within each heart status, a heart retrieved from a pediatric organ donor less than 18 years of age shall be allocated to a pediatric heart candidate (ie, less than 18 years old at the time of listing) before the heart is allocated to an adult candidate.

We report the first pediatric HTx with a heart from a donor under 15 years of age in Japan.

A teenage boy was admitted to Osaka University Hospital on April 12th 2011 by helicopter transportation from his local hospital. In April 2007, he fainted for the first time in his life, because of complete atrioventricular block. He underwent VDD mode pacemaker implant at his local hospital. Histological examination of the right ventricular myocardium revealed chronic myocarditis. Because there was progressive worsening of his clinical condition over the next few years, implantation of a pacemaker for cardiac resynchronized therapy was attempted, but it failed because another pacemaker lead could not be placed in a suitable site in the coronary sinus. In July 2009, he was admitted for acute renal failure accompanied by dehydration and diarrhea. Since then, he repeatedly showed digestive symptoms of heart failure and was admitted to his local hospital. The highest level of B-type natriuretic peptide was 4,200 pg/ml. In April 2010, continuous dopamine administration at a dose of 3 μg·kg⁻¹·min⁻¹ was started, but despite inotropic support he was diagnosed by cardiac catheterization as having restrictive cardiomyopathy with left ventricular systolic dysfunction. In August 2010, he was listed for HTx because of advanced restricted cardiomyopathy. He was waiting for HTx at his local hospital.

On April 12th 2011, the donor information was brought to Osaka University Hospital: the donor was between 10 and 15
years old, the donor heart’s function was good for transplantation (EF 69%), and the weight ratio of the donor and the recipient was −5%. The next day, HTx was performed with the bicaval method. The total ischemic time was 220 min. The waiting period for HTx had been 237 days.

The immediate postoperative course was good and he was extubated on postoperative day (POD) 1; 3 doses of methylprednisolone (125 mg) were given intravenously on the day of operation and POD 1 on each day. A triple oral immunosuppression regimen with tacrolimus, mycophenolate mofetil and prednisolone was started on POD 1. The tacrolimus target trough level was 10–15 ng/ml for the first week after HTx. No induction therapy was used. From POD 4, the serum creatinine level and his weight gradually increased, and on POD 8 the patient required continuous hemodiafiltration (CHDF) and mechanical respiratory support because of progressive dyspnea (Figure). Tacrolimus was discontinued because of its nephrotoxicity, and a chimeric monoclonal antibody against the interleukin-2 receptor α-chain, basiliximab, at a dose of 20 mg was given intravenously on POD 9 to spare the use of calcineurin inhibitors (CNI) during recovery of renal function. After the serum creatinine level decreased to 1 mg/dl, mechanical ventilation was discontinued on POD 11 and CHDF on POD 12. Oral administration of cyclosporine instead of tacrolimus was started, at a low initial dose, on POD 16, and the dose was gradually increased to give a blood trough level of approximately 250 mg/ml. After rehabilitation, the patient was discharged in good clinical condition on POD 50. Echocardiographic examination showed excellent biventricular EF. There were no clinical or histological episodes of rejection during the postoperative course. The serum creatinine level was 0.8 mg/dl at discharge.

Discussion

In Japan, HTx has increased since the revised Organ Transplant Act enforcement in July 2010; 34 HTx were performed in the 10 months after the revision of the Act, whereas only 69 had been done in the nearly 13 years after the old Act was first issued. Of the 103 HTx performed in Japan, only 5 patients have died after HTx and the 10-year survival after HTx is more than 95%, which is much better than the outcomes from the data of the International Society for Heart and Lung (ISHLT) Registry.

Only a limited number of teenage pediatric HTx were performed in Japan, because children younger than 15 years old could not donate their organs after brain death under the old Organ Transplant Act. Worldwide, since the ISHLT registry was started in 1982, the number of pediatric HTx has gradually increased.\(^3\) In recent years, the number has remained stable at approximately 450 per year, and a total of 8,575 pediatric HTx was reported before 2008. Overall survival was approximately 40% for patients up to 20 years after transplantation. The median survival was 18.3 years for infant recipients, 15.5 years for childhood-age recipients, and 11.3 years for adolescents. Moreover, HTx outcomes have improved era by era, even in sicker children who may have been excluded previously.\(^4,5\) It is certain that HTx is the major treatment for severe heart failure, even in the pediatric population.

When cyclosporine is the primary CNI, a significantly greater percentage of patients are treated for rejection than occurs with tacrolimus. Patients receiving cyclosporine at discharge have a 45% incidence of rejection in the first year compared with 27% for those discharged with tacrolimus therapy, ac-
According to the ISHLT Registry, therefore, we chose a triple immunosuppressive regimen based on tacrolimus. In Japan, no drugs for induction therapy after HTx are approved for use by the Government, so no induction was done initially. Because CHDF and mechanical ventilation were required in the present case, because of acute renal failure, tacrolimus was discontinued and anti-IL2R antibody was used to reduce the use of CNIs. After renal function was restored, we switched to cyclosporine. CNIs are still the basis of immunosuppressive therapy in HTx, but there are numerous side effects, such as renal failure, hypertension, hyperlipidemia, etc. Acute nephrotoxicity occurs soon after the onset of administration of CNIs, and the nephrotoxicity is dose-dependent and characterized by acute vasoconstriction of kidney arterioles and arteries. Additionally, renal dysfunction is frequently seen under the condition of pretransplant heart failure. The present patient had mild renal dysfunction prior to HTx, because of the high central venous pressure (25mmHg) caused by the restrictive cardiomyopathy. As his reserve capacity of renal function may have been decreased during the posttransplant period, CNIs caused additional deterioration in renal function, and CHDF was required as a result. In the case of deteriorated renal reserve capacity before HTx, other immunosuppressive regimens such as induction therapy and/or mammalian target of rapamycin inhibitors (mTORi) might be recommended. Primary induction therapy using an IL2R-antagonist, which is not approved for use in Japan after HTx, might be better for avoiding renal insufficiency. The trend for induction therapy with polyclonal antilymphocyte/antithymocyte globulin or IL2R-antagonist has increased recently, with more than 70% receiving it in 2009. These medicines for induction therapy should be covered by insurance for HTx in Japan as soon as possible. On the other hand, CNI-free immunosuppression after cardiac transplantation using MMF and the mTORi, sirolimus, showed a good clinical course in the absence of acute rejection in a patient with impaired renal function. In Japan, the mTORi, everolimus, is already approved for use after HTx. However, as mTORi have several side effects, such as impairment of wound healing, hypercholesterolemia, inhibition of sperm production and so on, we did not chose everolimus as the first choice after pediatric HTx.

On issuing the revised Act, the pediatric patient-first policy from a pediatric donor heart was made the same as the policy of the United Network for Organ Sharing. Therefore, the patient waited only 237 days for HTx, whereas the recent average waiting period for an adult donor heart with the same blood type was 1,008 days.

In conclusion, we successfully performed the first pediatric HTx from a pediatric donor heart under the pediatric patient-first policy in Japan. However, most pediatric patients requiring HTx die within a year while waiting. To increase pediatric HTx in Japan, further enlightenment of pediatric organ donation, establishment of pediatric emergency systems, intensive care systems, and pediatric mechanical circulatory support systems are needed. We desire that a pediatric HTx will soon be carried out in a young child, especially one who is less than 10 years old.

References