Registry Report on Heart Transplantation in Japan (June 2016)

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The Japanese Organ Transplant Act came into effect in October 1997 and the first heart transplant (Htx) procedure under this Act was performed in February 1999.1 The number of procedures increased steadily to around 10 per year, but then rose sharply to 44 in 2015 after a revision of the Act in July 2010.1,3

However, the number of Htx procedures remains low in international terms and the mean waiting period exceeded 1,150 days at the end of June 2016 because of a rapid increase in newly registered patients on the waiting list. A bridge to transplantation (BTT) using a left ventricular assist device (LVAD) plays a greater role than before in managing the listed patients, and the total number of CF-LVAD implantation patients enrolled in the Japanese registry for Mechanically Assisted Circulatory Support (J-MACS) increased to 656 at the end of June 2016. Because of the severe organ shortage, more marginal donor hearts are being transplanted than in other developed countries, but the outcomes of patients with these marginal hearts have not been well reported. This report is based on the latest statistics of Htx recipients and donors compiled by the Committee of Heart Transplantation Registry of the Japanese Society for Heart Transplantation, which were correct as of June 30, 2016, to clarify the effects of recipient or donor factors on patient survival after Htx.

Results

The Japanese Htx statistics were analyzed in terms of the number of cases, recipient status, donor status, waiting status and period, type of procedure, immunosuppressive therapy regimen, and recipient outcomes with respect to return to society and survival rates. Survival rates were calculated using the Kaplan-Meier method.

Number of Htx Performed

The first Htx performed under the Organ Transplant Act took place in February 1999,1 and as of June 30, 2016, the total was 284 procedures. Figure 1A shows the general trend over this period. The effect of the amendments is plain to see; the maximum number was 11 in 2008, but after the amendments this rose to a high of 44 in 2015.

There is a 2-stage screening process for registering for Htx with the Japan Organ Transplant Network (JOT). Firstly, the potential recipient must be certified as suitable by the relevant medical institution. Approval is then required from the Heart Transplant Candidate Registry Committee of the Japanese Circulation Society. The Heart Transplant Candidate Registry Committee was set up in 1997, when the Organ Transplant Act came into effect. The number of newly referred patients was initially around 40–60 cases per year. After the amendments came into force, however, applications rose sharply, to over 160 per year (Figure 1B). Since May 2015, 3 institutions [National Cerebral and Cardiovascular Center, (NCVC), Osaka University and University of Tokyo] with experience of more than 50 Htx procedures can register a candidate on the waiting list based on their own assessment of suitability for Htx.3 JOT has been processing Htx applications since October 1997. Active waiting candidates have risen sharply from 8 in 1997 to 35 in 1999, 100 in 2007, and 512 at the end of June 2016. Initially, only 3 institutions were authorized to perform Htx procedures in Japan: NCVC, Osaka University and Tokyo Women's Medical University. Six more have been added: University of Tokyo, Kyushu University, Saitama Medical University (now Saitama Medical University International Medical Center), Tohoku University, Hokkaido University and Okayama University, which brought the total to 9. In addition, when the amendments to the Organ Transplant Act were introduced, allowing organ harvesting from infants and children, 3 institutions were authorized to perform Htx on children up to 10 years of age: NCVC, Osaka University and University of Tokyo. Tokyo Women's Medical University was added to this list in 2013, bringing
Analysis of Htx Patients

Of the 284 Htx recipients, 210 (74%) are male. Age has ranged from 1 to 66 years, with an average age of 38.1 years. In Japan, ideally Htx should be performed before 60 years of age, but because of the long waiting times, some recipients are over 60 by the time the procedure is performed. In February 2013, the recommended age ceiling was lifted to less than 65 years and patients older than 60 and less than 65 years were permitted to register as Htx candidates. We can expect to see more Htx procedures in patients aged 55 years and older as a result.

Figure 2 illustrates underlying diseases among Htx recipients. Dilated cardiomyopathy (DCM) is the most common at 187 cases (66%), followed by dilated-phase hypertrophic cardiomyopathy (dHCM) (31 cases, 11%) and ischemic cardiomyopathy (23 cases, 8%). It is interesting to note that the proportion of ischemic cardiomyopathy is relatively low compared with most Western countries, probably because of the 65-year upper age limit for listing as a Htx candidate.

Waiting Status

Each Htx candidate is assigned a status that reflects the candidate’s medical urgency for transplant. A candidate who is currently supported with mechanical circulatory support or mechanical respiratory support, or who requires continuous inotrope administration and has stayed in the intensive care unit (ICU), is assigned Status 1. Other
candidates are assigned Status 2. Of the 284 procedures, only 1 was a Status 2 patient aged less than 10 years; all others were Status 1. Only 19 of the Status 1 cases (7% of the total) were receiving intensive care with continuous intravenous infusion of inotropes.

The other 263 cases were on BTT with a LVAD. Figure 3A shows the types of LVAD used prior to Htx: 6 cases were implanted with both left and right VAD and the others with a LVAD alone. Figure 3B shows the breakdown of pretransplant treatment regimens for patients awaiting Htx. The Nipro-Toyobo extracorporeal LVAD was initially the most commonly used for BTT. After insurance coverage for BTT was extended to CF-LVAD, in 2015 there were 5 extracorporeal devices installed, including a Berlin Heart in an infant patient, as well as 38 CF-LVADs (81%).

Figure 4 shows the average Status 1 waiting time in days, for both continuous intravenous inotrope infusion and LVAD cases. The Status 1 waiting time was initially around

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**Figure 3.** (A) Heart transplantation by year and pretransplant condition (up to June 30, 2016). (B) Left ventricular assist devices (LVAD) implanted prior to heart transplantation (up to June 30, 2016). NCVC, Nipro VAD. Dura/Jarvik, Jarvik/Jarvik, NCVC/NCVC, HVAD/HVAD and NCVC/Jarvik mean bi-ventricular VAD (right VAD/left VAD).

**Figure 4.** Heart transplantation recipients waiting as Status 1 by year and pretransplant condition and mean Status 1 waiting time by year (up to June 30, 2016). LVAD, left ventricular assist device.

**Figure 5.** Immunosuppressive regimens after heart transplantation before and after revision of the Organ Transplant Act (up to June 30, 2016). ATG, antithymocyte or lymphocyte globulin; AZP, azathiopurine; CsA, cyclosporin A; MMF, mycophenolate mofetil; OKT3, anti-CD3 monoclonal antibody; PRD, prednisolone; Tac, tacrolimus.
For myocardial protection, Celsior was used in 253 cases, followed by University of Wisconsin (12), Modified Collins (9), St. Thomas (7) and Bredshnieder (3). Thus, Celsior has been the most commonly used and was used in 95% of recipients in 2014. The most common Htx procedure was LVAD bridging periods for 263 cases ranged from 21 to 1,738 days, with an average of 936 days.

**Myocardial Protection Fluids and Htx Procedures**

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modified bicaval (243 cases: 86%), which was introduced by Kitamura et al, followed by Lower Shumway (36), bicaval (3), total heart (1) and dextrocardia (1).

Immunosuppressive Therapy

There were 80 cases of use of antibody agent for induction therapy or sparing of calcineurin inhibitor. Initially, anti-CD3 monoclonal antibody (OKT3) (n=6) and antithymocyte globulin (n=7) were used, although basiliximab has become increasingly popular in recent years. After the legislative amendments there were 67 cases. In 2015, induction therapy was used in 14 of 44 cases (32%).

The initial immunosuppressive regimen in all cases comprised a combination of calcineurin inhibitor [either cyclosporin A (CyA) or tacrolimus (Tac)], antimetabolites and steroids. Tac is becoming more popular, and currently accounts for 80% of the total (Figure 5). Azathioprine was used as the antimetabolite in the first 3 cases only, with mycophenolate mofetil (MMF) as the more common choice. Everolimus (Certican) was never used in the initial stage, only being introduced as an alternative to MMF in the event of complications such as postoperative coronary artery lesions, renal disorder, malignant tumor or MMF intolerance.

Survival Rates and Return to Society for Htx Recipients

Figure 6A shows survival rates among the 284 Htx recipients in Japan. The survival rates at 5, 10 and 15 years after the transplant are 92.7%, 89.6%, and 81.8%, respectively, which are better than those from the International Society for Heart and Lung Transplantation registry report. A total of 21 recipients have died, with the cause attributable to infection (8 cases, including 1 case of cryptococcal meningitis), multiple organ failure (3), fatal cardiac dysrhythmia (2), single cases each of postoperative coronary artery lesion, bladder cancer, gastric cancer, renal failure, graft dysfunction, post-transplant lymphoproliferative disorder and 2 with unknown cause. Two recipients survived for longer than 15 years, with the maximum survival time being 17 years. At the time of the study, 3 Htx recipients were hospitalized and the remaining 260 were accessing outpatient services. Including housewives and part-time workers, more than 150 recipients had reintegrated successfully into society. There is no significant difference in patient survival by underlying heart disease (Figure 6B). Broken down by age group, the survival rate after 10 years is only 60.8% for transplant recipients aged 55 or older at the time of the procedure, a statistically significant discrepancy from the other groups (P=0.0038 log rank test) (Figure 6C).

Although the Organ Transplant Act was revised in July 2010, brain-dead organ donation is still extremely less popular in Japan than in other developed countries. To increase heart availability, special strategies to assess and manage donors have been established since 2002. Briefly, special cardiac transplant surgeons or physicians (so-called medical consultants: MCs) are sent to a procurement hospital to evaluate whether the heart can be transplanted and to stabilize hemodynamics and respiratory function using antidiuretic hormone and frequent bronchofiberoscopy in collaboration with physicians in the procurement hospital. By these efforts, 287 (75%) of 384 donor hearts (including 3 heart-lung transplantations) were transplanted. Although 20 heart grafts from donors aged 60 or older at the time of the procedure were transplanted, there was no significant difference in patient survival by donor age group (Figure 6D).
The most common cause of brain death of the donor was subarachnoid hemorrhage (95), followed by anoxia (58), head trauma (53), cerebral hemorrhage (29), post-resuscitation (19), cerebral infarction (5) and others. Interestingly, there is no cause of brain death of the donor (Figure 6E). These data suggest that the MCs may play a great role in increasing donor heart availability and in improving the outcomes of cardiac recipients from old donors or donors who died of post-resuscitation or anoxia in Japan.8

**Pediatric Htx**

Children under 15 years of age were not allowed to donate their hearts after brain death until the *Organ Transplantation Act* was revised on 17th July in 2010,9 because only persons who had given written consent for organ donation after brain death could donate their organs.7 Therefore, young children could not undergo Htx in Japan and many Japanese children went abroad to undergo the procedure.

After revision of the Act in July 2010, children became able to donate their organs if their family accepted and, in fact, 17 children donated organs up to the end of June 2016 (Figure 7A). The first procedure in 2000 took place using an adult female donor under the original version of the *Organ Transplant Act* (Figure 7B). As the amendments, which explicitly place the priority on the condition of the recipient when harvesting organs from minors less than 18 years of age, have prompted an increase in the number of procedures in children listed less than 18 years of age, 19 procedures have been performed in pediatric recipients under 18 years of age from 8 adult and 11 pediatric donors. Eleven of the 19 recipients were boys aged from under 1 to under 18 years of age from 8 adult and 11 pediatric donors. DCM is also the most common in pediatric Htx recipients. DCM is also the most common in 15 cases, followed by single cases of dHCM, post-myocarditis cardiomyopathy, restrictive cardiomyopathy (RCM), and DCM combined with RCM. Because of the severe shortage of organ donation for children, 14 underwent LVAD implantation prior to Htx (Figure 8B).

**Conclusions**

The number of Htx performed annually in Japan rose sharply after the *Organ Transplant Act* was amended, with 215 procedures performed over a period of just 6 years. However, the number of procedures remains relatively low in global terms, while the waiting time has extended to more than 1,150 days. After insurance coverage was extended to include BTT using CF-LVAD in April 2011 there was an increase in Htx applications, reflecting a renewed interest in BTT. Although amendments to the *Organ Transplant Act* have cleared the way for organ harvesting from child donors in Japan,7 the number of pediatric cases is still relatively low. Htx in a BTT patient with an extracorporeal pediatric LVAD has been performed each year (2014, 2015 and 2016). The introduction of pediatric LVADs is being promoted in Japan with the aim of boosting the number of Htx in children.

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**References**