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The Organ Transplant Law came into effect in October 1997 and the first heart transplantation under this law was performed in February 1999.1 The number of heart transplantations slowly increased thereafter to approximately 10 per year, but then rose sharply to just under 40 per year following revision of the transplant law in July 2010. In 2013, more Japanese patients underwent heart transplant procedures in Japan than overseas for the first time. This trend continued in 2014, suggesting that heart transplants are increasingly regarded in Japan as a viable option for the treatment of patients with advanced heart failure.2–4

However, the number of heart transplant procedures remains low in international terms and waiting times are still long. Patients on the waiting list are often obliged to make do with a bridge to transplantation (BTT) using a left ventricular assist device (LVAD). Previously, only extracorporeal LVADs were available, but in April 2011 insurance coverage was extended to continuous flow type implantable LVADs, which are more compact and enable at-home treatment. As a result, implantable LVADs are becoming increasingly widely used. This report is based on the latest statistics compiled by the Japanese Society for Heart Transplantation, current as of December 31, 2014.

Statistics of Heart Transplantations and Organ Harvesting From Brain-Dead Donors in Japan

Organ harvesting from brain-dead donors has been performed since 1999 under the Organ Transplant Law in Japan. Initially there were approximately 5 cases per year; this figure doubled over the period 1999–2008, before dropping off somewhat from 2009 through to July 2010, when the abovementioned revision were made. Amendments to the transplant law caused a sharp rise in donations under brain death to over 40 per year, reaching 50 in 2014.

The first heart transplant from a brain-dead donor was performed under the newly introduced Organ Transplant Law in February 1999. The number of heart transplants per year rose from 3 initially to 5, then to nearly 10. After the legislative amendments it rose to 30 and then 37 per year (Figure 1).

Most of the early VADs used for BTT were extracorporeal devices, with implantable devices used mainly for clinical research or experimental trials of at-home treatment. The extension of insurance cover to compact non-pulsatile flow implantable LVADs in April 2011 as a form of BTT treatment has led to increased use of this type of VAD.

Results

Heart transplant statistics in Japan were analyzed in terms of the number of cases, recipient status, waiting status and period, types of transplant procedure, immunosuppressive therapy regimen, and recipient outcomes in terms of return to society and survival rates. Survival rates were calculated using the Kaplan-Meier method.

Number of Heart Transplantations Performed

The first transplant procedure performed under the Organ Transplant Law took place in February 1999, and as of 31 December 2014, the total was 222 procedures. Figure 1 shows the general trend over this period. The effect of the revision is plain to see; previously, the maximum figure was 11 in 2008, but after the law was amended this rose to a high of 37 in 2013 and 2014. Looking at the effect of the revisions to the transplant law in another way, only 69 procedures were performed in the 11.5 years between 1999 and mid-2010, whereas 152 procedures have been performed in the 4.5 years since.

There is a 2-stage screening process for registering for a heart transplant with the Japan Organ Transplant Network (JOTNW).5 Firstly, the potential recipient must be certified as suitable by the relevant medical institution. Approval is then required from the Heart Transplant Candidate Registry
Heart Transplantation in Japan (1999-2014)

Committee of the Japanese Circulation Society, which was established in 1997 when the Organ Transplant Law came into effect. The number of applications was initially around 40–60 cases per year, later climbing to around 70 cases per year. After the revisions came into force, however, applications rose sharply, to over 100 per year, mainly because of a general increase in transplant procedures and the extension of health insurance coverage to at-home BTT treatment regimens using non-pulsatile flow type implantable LVADs. In 2014, there were more than 140 applications. Several institutions with considerable experience with heart transplant procedures are now considering setting up applicant registration systems based on their own assessments of suitability for heart transplantation, and introducing an in-house system of determining suitability to be implemented at the time of the actual procedure.

The JOTNW has been processing heart transplant applications since October 1997. Applications have risen sharply from eight in 1997 to 35 in 1999, 100 in 2007, 158 in 2010, 231 in 2012 and 361 in 2014.

Initially only 3 institutions were authorized to perform heart transplant procedures in Japan: the National Cerebral and Cardiovascular Center, Osaka University, and Tokyo Women’s Medical University. Six more have been added (Tokyo University, Kyushu University, Saitama Medical University (now Saitama Medical University International Medical Center), Tohoku University, Hokkaido University and Okayama University), bringing the total to 9. In addition, when the Organ Transplant Law was amended to allow organ harvesting from infants and children, 3 institutions were authorized to perform heart transplants in children up to 10 years of age: the National Cerebral and Cardiovascular Center, Osaka University and Tokyo University. Tokyo Women’s Medical University was added to this list in 2013, bringing the total to 4. To date, Osaka University has performed 2 heart transplants in children under 10 years of age, one of whom had been on BTT using an extracorporeal LVAD in 2014. As of December 31 2014, Osaka University had performed the most procedures (66), followed by the National Cerebral and Cardiovascular Center (63), Tokyo University (50), Tokyo Women’s Medical University (15), Kyushu University (10), Tohoku University (10), Saitama Medical University International Medical Center (5), Hokkaido University (2) and Okayama University (1).

Analysis of Patients
The total population of 222 heart transplant recipients comprises 161 (73%) males and 61 (27%) females. Their ages ranged from <10 to 66 years old, with an average age of 37.9 years (Figure 2). The most common age bracket was 30–54 years.

Three procedures were performed in recipients under 10 years of age. The procedure in 2000 took place under the original Organ Transplant Law. The revisions, which explicitly give 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 of children listed less than 18 years of age.

The donor age was <10 years in 1%, 10–19 years in 4%, 20–29 years in 14%, 30–39 years in 19%, 40–49 years in 28%, 50–59 years in 26% and ≥60 years in 7%. The proportion of donors aged <40 years is less than 40%.

In Japan, ideally a heart transplant 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 65 years, and patients older than 60 and less than 65 years were permitted to register as heart transplant candidates. We can expect to see more heart transplants in patients aged ≥55 years as a result.

Figure 3 illustrates the underlying diseases in heart transplant recipients.
Waiting Status

Figure 4 shows the breakdown of pretransplant treatment regimens for patients awaiting transplant procedures. Of the 222 recipients, only 1 was a Status 2 aged under 10 years; all others were Status 1.

Only 18 of the Status 1 cases (8% of the total) were receiving intensive care with continuous intravenous infusion of recipients. Dilated cardiomyopathy is the most common at 141 cases (64%), followed by dilated phase hypertrophic cardiomyopathy (27 cases, 12%) and ischemic cardiomyopathy (19 cases, 9%). It is interesting to note that the proportion of ischemic cardiomyopathy is relatively low compared with most Western countries.
Heart Transplantation in Japan (1999-2014)

Figure 4. Pretransplant status of heart transplant recipients in Japan.

Figure 5. Types of ventricular assist devices used as bridge to transplant in Japan (before and after revision of Organ Transplant Law).
Figure 6. Number of heart transplants performed and mean waiting duration for status 1 candidates by year in Japan (status 2 pediatric patient was excluded).

Figure 7. Cumulative survival rates of heart transplant recipients in Japan (vs. global average in ISHLT report).

inotropes. The other 203 cases (91%) were on BTT with a VAD. The Nipro-Toyobo extracorporeal VAD was the most commonly used VAD for BTT. After insurance coverage for BTT was extended to continuous flow implantable LVADs, there was a marked increase in LVAD bridging cases, in excess of 50% from 2013 onwards. In 2014, there were 6 extracorporeal devices installed, including 1 in a patient <10 years of age, as well as 30 non-pulsatile flow type implants (81%). Figure 5 shows the types of LVAD used prior to transplant procedures.

Figure 6 shows the average Status 1 waiting time in days, for both continuous intravenous infusions of inotropes and LVAD cases. Status 1 waiting time was initially around 200 days, increasing to 600 days in 2001, over 800 days in 2003 (when no heart transplants were performed at all), and around 900 days thereafter. Long waiting times have not improved, despite the increased number of procedures performed since the legislative revisions. VAD bridging periods for 203 cases ranged from 21 to 1,738 days, with an average of 893 days.
Heart Transplantation in Japan (1999–2014)

Myocardial Protection Fluids and Transplant Procedures

For myocardial protection, Celsior was used in 194 cases, followed by Modified Collins (9), UW (9), St. Thomas (7) and Bredshneider (3). Celsior is by far the most commonly used (in 95% of recipients in 2014).

The most common transplant procedure was modified bicaval (190 cases), followed by Lower Shamway (28), bicaval (2), total heart (1) and dextrocardia (1). The modified bicaval technique, developed in Japan, was used in 86% of transplant procedures.

Immunosuppressive Therapy

There were 72 cases of induction therapy. Initially, OKT3 (muromonab-CD3) and antithymocyte globulin were used, although basiliximab (Simulect) has become increasingly popular in recent years. After the legislative amendments, induction therapy was used in 50 cases. In 2014, induction therapy was used in 14 of 37 cases (38%).

The initial immunosuppressive regimen in all cases involved a combination of calcineurin inhibitor (CNI; either cyclosporin (CyA) or tacrolimus (Tac)), antimitabolites and steroids. Tac is becoming more popular, and currently accounts for 69% of the total. Azathioprine was used as the antimitabolite in the first 3 cases only, with mycophenolate mofetil (MMF) now the common choice. In 2014, triple therapy comprising Tac, MMF and steroids was used in 89% of cases. Everolimus (Certican) was not used initially, only being introduced as an alternative to MMF in the event of complications such as postoperative coronary arterial lesions, malignancy or MMF intolerance. MMF is also replaced by everolimus in cases of renal dysfunction to minimize CNI toxicity.

Survival Rates and Return to Society for Transplant Recipients

Figure 7 shows survival rates for the 222 heart transplant recipients in Japan. The survival rate at 10 years after the transplant is an impressive 89.3%, better than for the International Society for Heart and Lung Transplantation registry.8,9 A total of 16 recipients have died, with the cause attributed to infection (7 cases, including 1 case of cryptococcal meningitis), multiple organ failure (2), and 1 case each of post-transplant coronary artery disease, gastric cancer, renal failure, fatal arrhythmia, graft dysfunction, post-transplant lymphoproliferative disorder, and cause unknown; 2 recipients survived for longer than 15 years, with a maximum survival time of 15 years and 8 months. At the time of the study, 6 heart transplant recipients were inpatients, with another 200 accessing outpatient services. Including housewives and part-time workers, 122 recipients had successfully reintegrated into society. Broken down by age group in Figure 8, the survival rate after 10 years is only 69.5% for transplant recipients aged ≥55 the time of the procedure, significantly lower than for the other age groups. In future, a study of the condition of both donors and recipients in this age bracket would be useful.

Conclusions

Survival rates for Japanese heart transplant recipients are favorable despite relatively older donors, long waiting times, and the high rate of BTT cases.7,8 The rate of heart transplants performed per year rose sharply after the Organ Transplant Law was revised, with 152 procedures performed over a period of just 4.5 years, including 37 in both 2013 and 2014. In 2013, more patients received heart transplants in Japan than overseas. However, the number of procedures remains relatively low in global terms, while the waiting time is around 900 days. It has been at this level since 2005, when the only viable BTT option was an extracorporeal LVAD, and heart transplants were generally deemed unviable for patients with terminal cardiac failure. In April 2011, insurance coverage was extended to include BTT using compact continuous flow implantable LVADs, suitable for at-home treatment. This meant that they could be installed and monitored by medical facilities that did not have the capacity to provide heart transplants, leading to an increase in heart transplant applications, reflecting a renewed interest in BTT. A further boost in LVAD BTT applications was seen after February 2013, when the recommended age limit for heart transplant recipients was raised from <60 years to <65 years. In light of the expected increase in elderly heart transplant recipients in the coming years,
further research into the low survival rates for recipients aged ≥55 is required. 

Although the revised Organ Transplant Law cleared the way for organ harvesting from child donors in Japan, the number of pediatric cases is still low. A heart transplant was performed on a pediatric patient on BTT with an extracorporeal LVAD in 2014. The introduction of pediatric LVADs is being promoted in Japan, with the aim of boosting the number of heart transplants in children.

Addendum

In-house systems of determining suitability for heart transplantation were commenced on May 1, 2015 at 3 transplant hospitals (National Cerebral and Cardiovascular Center, Osaka University, and Tokyo University).

References


Appendix

The authors acknowledge the following members of the Cardiac Transplantation Committee of the Japanese Circulation Society and the transplant hospitals.

Hiroshi Itoh, MD, PhD (Okayama University); Yasuhiko Usui, MD, PhD (Nogoya University); Shunichi Ogawa, MD, PhD (Nippon Medical School); Masahumi Kitakaze, MD, PhD (National Cerebral and Cardiovascular Center); Koichiro Kinugawa, MD, PhD (Tokyo University); Hiroaki Shimokawa, MD, PhD (Osaka University); Shunii Sano, MD, PhD (Okayama University); Hiroaki Shimokawa, MD, PhD (Tohoku University); Issyo Shiraishi, MD, PhD (National Cerebral and Cardiovascular Center); Kenji Sunagawa, MD, PhD (Kyushu University); Hiroyuki Tsutsui, MD, PhD (Tokyo Women’s Medical University); Hiroshi Niinami, MD, PhD (Saitama International Medical Center); Nobuhisa Hagiwara, MD, PhD (Tokyo Women’s Medical University); Kenichi Fukuda, MD, PhD (Keio University); Toyosato Maruhara, MD, PhD (Nagoya University); Yasuhiro Maejima, MD, PhD (Tokyo Medical and Dental University); Taro Sasaki, MD, PhD (Tokyo Medical and Dental University); Kenji Yamazaki, MD, PhD (Tokyo Women’s Medical University); Satoshi Saito, MD, PhD (Tokyo Women’s Medical University); Ryui Tomima, MD, PhD (Kyushu University); Tadahisa Tanoue, MD, PhD (Kyushu University); Shigeyuki Nishimura, MD, PhD (Saitama International Medical Center); Atsushi Iguchi, MD, PhD (Saitama International Medical Center); Yoshio Matsui, MD, PhD (Hokkaido University); Tomonori Ooka, MD, PhD (Hokkaido University).