Cardiac Transplantation in Hong Kong

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Heart failure is a common condition causing significant mortality and morbidity. Although the majority of patients can be stabilized on medical therapy, those patients who remain in end-stage heart failure refractory to medical therapy or conventional cardiac surgery, such as valvular replacement or coronary artery bypass surgery, may be considered for heart transplantation. The first heart transplantation in Hong Kong was performed in 1992. From December 1992 to March 2001, a total of 30 patients underwent orthotopic cardiac transplantation at Grantham Hospital. In this article, we review the result of our Heart Transplant Program with particular attention on the survival, functional capacity and complications after transplantation.

The current age limit for heart transplantation in our program is 60 years, with rare exceptions up to 65 years. All potential heart transplant recipients undergo detailed cardiac assessment for diagnosis and risk stratification, including echocardiogram, cardiac catheterization, gated equilibrium radionuclide angiocardiography and 6-minute walk assessment. One of the mandatory tests for the ambulatory patients is the cardiopulmonary exercise testing with ventilatory gas exchange, which can distinguish exercise limitation due to cardiac or non-cardiac causes and can identify the high-risk patients in need of heart transplant. A peak oxygen consumption of <14 ml/kg/min predicts poor survival and is an indication for heart transplantation. Right heart catheterization with nitroprusside is performed every 6-12 months pre-transplant to exclude significant irreversible pulmonary hypertension, which can adversely affect the outcome of heart transplant. Detailed non-cardiac investigations are also performed to exclude any possible contraindications, such as co-existing end-organ failure, human immuno-deficiency virus infection, hepatitis, malignancy and systemic illnesses that may recur in the transplant allograft. Psychological assessment for psychosocial problems and non-compliance with medical advice is also an important part of the evaluation. After being interviewed by our multidisciplinary heart transplant team, the patients are then put on the waiting list for heart transplantation.

A suitable heart donor with certified brain death should be under the age of 60 years with normal electrocardiogram and echocardiogram and without significant transmissible disease such as the human immunodeficiency virus, hepatitis or certain malignancies. For those donors over the age of 50 years and with known risk factors for ischaemic heart disease, no significant coronary artery disease must be demonstrated on coronary angiogram. When a suitable heart donor becomes available, matching of the appropriate recipient is performed with regard to the blood group (matching similar to blood transfusion), body size (donor body weight >=75% of the recipient body weight), urgency for transplant and length of waiting time. In those patients with pre-formed lymphocytotoxic antibodies (positive reaction against test panel of reactive antibody) due to previous blood transfusions or pregnancy, a negative lymphocytotoxic screening test of recipient serum specific for the donor must be demonstrated.

For immunosuppression, the transplant recipients receive cytolytic therapy for induction, in the form of OKT3 (murine monoclonal anti-CD3 antibody) or ALG (anti-lymphocyte globulin), for the first 10-14 days after transplant. Methylprednisolone is given for the first 24 hours after transplant and prednisolone is started after termination of administration of OKT3. Initial maintenance immunosuppression consists of triple therapy, namely corticosteroid, azathioprine and cyclosporine A. The dose of prednisolone is gradually reduced at 3 months after transplant with an aim to stopping it altogether by one year. Azathioprine is given at 4 mg per kg before transplant and then at 1-2.5 mg/kg/day, the dose being adjusted to keep the white cell count between 4 and 6 x 10^9/L. This may be substituted for mycophenolate mofetil if the patient is sensitive to or is intolerant of.
azathioprine. Cyclosporine A is started when the renal function of the patient is stable and the dose is adjusted according to the therapeutic level.

All transplant patients are followed up closely after discharge from hospital for allograft function, complications after transplant and rehabilitation. Echocardiogram is performed regularly for presence of pericardial effusion and allograft function. Surveillance for cellular rejection is done by performing endomyocardial biopsy at regular intervals after transplant, initially every 2-4 weeks for the first 3 months, then monthly from the 3rd month to the 6th month, then every 2-3 months from the 6th month to the 1st year and then every 6-2 months afterwards. Moderate or severe rejection (International Society of Heart and Lung Transplantation classification grade 2 or above) is treated with augmentation of immuno-suppression. For routine prevention of infections, each post-transplant patient is given antifungal mouth preparations and low-dose acyclovir against herpes simplex for the first year. For cytomegalovirus (CMV) mismatch (donor positive, recipient negative) cases, the incidence of CMV infection is very high and may be reduced by prophylactic therapy with anti-CMV immunoglobulins (Cytogam). Routine surveillance for CMV reactivation is performed by measuring the CMV pp65 antigen level and rising level of the antigen is treated pre-emptively with intravenous ganciclovir before the manifestation of symptoms. At each annual study after transplantation, each patient undergoes a comprehensive assessment including blood tests, functional capacity assessment, echocardiogram, coronary angiogram, endomyocardial biopsy and cardiac catheterization.

From December 1992 until March 2001, a total of 30 cases of heart transplantation were performed at Grantham Hospital. Orthotopic heart transplantation using either standard technique with anastomosis of donor and recipient right atria or bi-caval anastomosis was employed. The mean ischaemic time for transplant was 159±39 minutes. At March 2001, the mean follow-up period was 36±25 months. The average ages of the recipients and donors are 47±11 years (range 19-65) and 39±14 years (range 14-61), respectively. The majority of the patients, 80% of recipients and 70% of donors, are of the male gender. Seven out of the 30 recipients (23%) were receiving inotropic therapy as in-hospital patients at the time of transplantation, including two patients who were on multiple intravenous inotropic agents as well as intra-aortic balloon pump. The commonest cause for end-stage heart failure requiring transplantation is valvular heart disease (32%), followed by ischaemic heart disease (27%) and dilated cardiomyopathy (27%). Congenital heart disease accounted for 7% and arrhythmogenic right ventricular dysplasia accounted for the remaining 7% of cases. This is in contrast to the U.S. data published by the United Network for Organ Sharing (UNOS), which showed that ischaemic heart disease is the commonest cause for heart transplantation in the U.S., with valvular heart disease accounting for only a small minority of end-stage heart failure. The probable reasons are that rheumatic heart disease is still a common condition in this locality and that coronary artery disease is less common in Chinese patients. The waiting time for heart transplantation is variable. The waiting time for group O recipients is 5.8±4.6 months versus 4.5±3.9 months for non-group O recipients. The causes for brain death in the heart transplant donors are head trauma (57%), cerebrovascular accident (36%) and brain tumours (7%).

The average size of the donors is 58±8 kg while the average size of the recipients is 56±10 kg. Therefore potential recipients over 80 kg would be expected to wait much longer than the average 55 kg patient for a donor of suitable body size. Unlike renal transplantation, there is no consensus on the survival benefit of human leukocyte antigen (HLA) loci on the outcome of heart transplantation. Therefore prospective matching of HLA loci is neither indicated nor possible in view of the small size of our donor and recipient pools. Retrospective analysis of our donors and recipients showed poor matching of the HLA loci. Out of 6 HLA loci, the numbers of patients for 0, 1, 2, 3 and ≥3 matched loci are 10, 13, 3, 4 and 0, respectively.

Out of the 30 recipients, 29 (97%) were successfully discharged from hospital. Four patients (13%) required temporary renal dialysis after transplant. Although half of the recipients had previous
sternotomies, only two patients (6%) required re-operation for haemostasis. The mean length of hospital stay was 29±19 days. At March 2001, 25 patients are still alive and are in New York Heart Association (NYHA) functional class I or II. There were four transplant-related deaths, one at day 4 from right heart failure, one at 6 weeks from severe cellular rejection and another at 5 months from vascular rejection. One died of allograft failure at 15 months post-transplant following reduction of immunosuppression for post-transplant lymphoproliferative disease in the brain. There was one non-transplant-related death due to suicide at 5 months. The survival rates at one, three and five years were 86%, 81% and 81%, respectively and are comparable to the UNOS data for a similar period (from 1991 to 1998). By March 2001, nineteen patients completed their first year follow-up assessment and all showed a significant improvement in the their NYHA functional class (from 3.5±0.5 to 1.2±0.4, p<0.001), exercise capacity as determined by the 6-minute walk (from 344±129 metres to 519±90 metres, p<0.001) and the left ventricular ejection fraction (22±11% to 68±7%, p<0.001). More than half of these patients (10 out of 19) had returned to work. Three other recipients were housewives and one was a college student. Only five patients were either unemployed or retired.

The two major complications after heart transplant are rejection and infection. Although rejection is commonest in the first few months after transplant, it can occur any time when the dose of corticosteroids is being gradually reduced after 3 months. The number of rejection episode per patient-year is 0.50. Apart from the usual post-cardiac surgery infections, such as wound and chest infections, the heart transplant recipients are also at risk from opportunistic infections, including CMV, fungal infections, mycobacterium tuberculosis, atypical mycobacterium and herpes zoster. One patient developed Epstein-Barr virus (EBV)-related post-transplant lympholiferative disease in the brain, the histology of which showed monoclonal B-cell lymphoma positive for EBV polymerase chain reaction. Other complications include hypertension, hypercholesterolaemia, diabetes, renal impairment, osteoporosis, sinus node dysfunction and transplant vasculopathy. Treatment of osteoporosis is difficult and therefore in high risk patients, especially those who cannot be weaned off corticosteroids because of recurrent rejections, prevention is given by oral calcium supplements and, in post-menopausal patients, by hormone replacement therapy.

Cardiac transplantation improves the functional status and is life-saving for some patients with refractory end-stage heart failure. With careful selection and follow-up of patients, satisfactory survival and outcome may be achieved. However, widespread use of cardiac transplantation in treatment of end-stage heart failure is limited by the shortage of donors, the cost and the complications associated with the immunosuppressive therapy. Referral to specialized centres for evaluation of advanced heart failure should be done early before contraindications to transplantation, such as failure of other major organs, develop.