

## **HEART TRANSPLANTATION SELECTION, EVALUATION, MEDICAL THERAPY**

Key words: heart failure, cardiac transplantation, selection of recipients, post-transplant care, immunosuppressive therapy, post-transplant complications, post-transplant survival

Cardiac transplantation is a treatment reserved for patients with advanced heart failure, correctly, complexly and maximally-treated by conventional methods, which is expected to have major benefits in improving the quality of life and life expectancy.

In our country, 64 heart transplant surgeries were performed between November 1999 and February 2011. In 2011, 100,000 heart transplants were performed in 388 transplant centers worldwide.

Since 2005, the etiology of heart diseases leading to cardiac transplantation in most cases has been represented by non-ischemic cardiomyopathy, ischemic cardiomyopathy in a lower percentage and re-transplantation in a small number of cases.

The average age of transplanted patients (adults) (according to ISHLT-International Society of Heart and Lung Transplantation) is 54, whereas the average age of donors is 35 years.

The mean time of graft cardiac ischemia is estimated at 180 +/- 80 minutes (3 hours +/- 1.5 hours).

The immunosuppressive therapy used in patients with cardiac transplant is the double or triple combination of: calcineurin inhibitors (tacrolimus used in 73% of cardiac transplants or Cyclosporine used in less than 20% of the cases), Mycophenolate mofetil (used in 85%) and prednisone (used 1 year post-transplant in 80%, and 5 years post-transplant in 51% of the patients).

Post-transplant survival period is currently estimated at 11 years in 50% of the patients. There are about 100 patients worldwide with 25-year survival post-cardiac transplant.

The main causes of post-heart transplant mortality are: cardiac graft failure, multiple organ failure, infections, acute rejection, heart allograft vasculopathy, renal failure, malignant diseases.

Our study, based on the group of patients with heart transplant performed in the Institute of Cardiovascular Diseases and Transplantation of Tg. Mures between 1999 and 2011, followed two essential parts of the heart transplant activity:

I. Selection and evaluation of transplant recipients

II. Post- cardiac transplant care

For the assessment of the patients included on the waiting list for cardiac transplantation in our center we established a standard protocol, comprising 30 compulsory investigations.

In June 2011 the list of recipients for heart transplantation included 119 evaluated patients, from 32 counties plus Bucharest (a total of 41 counties), 79% from urban and 21% from the rural area. 72% had non-ischemic cardiomyopathy and 28% presented ischemic cardiomyopathy; 73% were over 40 and 27% were under the age of 40.

Forty-three heart transplants were performed in our center between November 1999 and February 2011.

The average age of the heart transplant patients is 36 years, the average age of donors is 26.

In our study the etiology of cardiomyopathy leading to heart transplant is: 77% non-ischemic cardiomyopathy and 23% ischemic cardiomyopathy.

The mean graft ischemia of the heart was 155 minutes with a minimum of 83 minutes and a maximum of 228 minutes.

The immunosuppressive medication in patients with heart transplantation in our center is represented by: 67% Tacrolimus; 13% Cyclosporine; 100% Mycophenolate mofetil; Prednisone: 0 months - 5%, 3 months - 11%, 6 months - 66%, 1 year - 18 %.

Survival as the success rate of surgery is 90.7% and 88.8% survival at 1 year, 71.4% survival at 5 years, 60% survival at 10 years. In our study the mean survival (calculated according to Kaplan Meyer curves) is of 8 years. The overall survival of the whole group regardless of the time elapsed since heart transplant surgery is 74.3% (29 of the 39 patients were alive upon the conclusion of the study in 2011).

The causes of death in our study were: multiple organ failure (2 cases), neoplasia (2 cases), cardiac rejection and allograft vasculopathy (1 case), TB infection (1 case), sudden death (1 case), renal (1 case), noncompliance to treatment (1 case), brain trauma (1 case).

**Post-cardiac transplant care** includes: routine ECG and echocardiography monitoring as well as monitoring the main possible complications: diabetes mellitus, renal failure, acute rejection, allograft vasculopathy, infections, arterial hypertension and dyslipidemia, neoplastic diseases, bone complications, and as an assessment of transplant activity is the estimation of post-transplant survival and post-transplant life quality.

**Routine monitoring** is meant to assess the status of cardiac transplant patients and early detection of specific complications of cardiac post-transplant condition in order to initiate the appropriate therapy and achieve the primary objective of the transplant activity – i.e. long survival with a high quality of life.

The basic elements of routine monitoring are: cardiologic examination, monitoring of immunosuppressive therapy, monitoring of areas of medical pathology according to highest possible complications: neurology, psychiatry, pneumophthysiology, gastroenterology, nephrology, metabolic diseases, infectious diseases, malignant diseases, bone diseases.

**ECG monitoring:** is meant to assess the heart rate and arrhythmias. Heart rate is increased in transplant recipients due to transplanted heart denervation; in our study group the average heart rate at one year post-cardiac transplant is 100bpm.

Supraventricular arrhythmias are markers of cardiac rejection while ventricular arrhythmias are not considered markers of rejection. Atrial flutter was a marker of acute cardiac rejection in two cases and atrial fibrillation in other two cases.

**Transthoracic echocardiographic monitoring:** its purpose is the assessment of heart graft functionality and early, noninvasive diagnosis of cardiac rejection. In our group, we have established a statistically significant correlation between survival and EF (ejection fraction) of the LV (Left ventricle) and RV (right ventricle) both early and late after heart transplant. The diagnosis of cardiac rejection was determined by ultrasound criteria of reduced LV and RV EF and presence of pericardial effusion.

**New onset diabetes mellitus (DM)** after heart transplant was detected by routine monitoring of post-transplant blood glucose and fasting glucose. 1 year after heart transplant 25% of patients had new-onset diabetes (given that the presence of diabetes is a contraindication of heart transplant in our center).

We determined as favorable factors for diabetes the following: the recipient age over 40, BMI (body mass index) over 25, tacrolimus and prednisone therapy. We obtained a statistically significant relation between the presence of diabetes and development of arterial hypertension (AHT) in patients with heart transplant.

**Post-transplant renal failure** was diagnosed by GFR monitoring (glomerular filtration rate). We recorded a GFR reduction in time to one third for the patients in our group, with two cases of advanced renal failure requiring hemodialysis, with one case requiring renal transplant. The predisposing factors for renal failure in our group were: transplant recipient age, time since transplant, male sex, presence of hypertension, diabetes and tacrolimus therapy.

**Cardiac rejection** was established as definite clinical diagnosis, also through echocardiography and EMB (endomyocardial biopsy). We diagnosed 19 episodes of acute rejection in the entire group, confirmed by EMB, most of them 1<sup>st</sup> degree ISHLT in the first year of evolution, and only 10% 3<sup>rd</sup> degree ISHLT. We established a correlation between acute rejection and vasculopathy of the cardiac allograft. Ischemic heart disease was associated with a higher score of rejection.

**Infectious complications** are multiple and of various forms. Chronic CMV infection did not influence survival in our study, but it was considered a contributing factor to heart allograft vasculopathy. Major infectious complications with an impact on life quality were complications such as the lung abscess - with obscure and Aspergillus fungal etiology. Pulmonary tuberculosis was a fatal infectious complication.

**Hypertension and dyslipidemia** are frequently encountered complications in patients with solid organ transplantation. In our study there was an incidence of 40% post-transplant hypertension at 6 months, mainly in male patients over 40 years, having ischemic cardiomyopathy before the heart transplant. Hypercholesterolemia is encountered in over 50% of the transplant patients and hypertriglyceridemia in 37% at 6 months of post-transplant evolution. They required lipid-lowering therapy with statins and fibrates. Cyclosporine is responsible for a more pronounced effect on lipid metabolism in our group.

**Malignant complications** encountered were represented by two cases of hepatocellular carcinoma with a brief and fatal evolution.

**Bone complications** are a major factor in the quality of post-heart transplant life.

Quantification of **life quality** according to standard protocols still remains a goal for our activity in cardiac transplantation. Our group of heart transplant patients in 2011 was composed of: 24 retirees on medical grounds, 5 patients enrolled in education, and 6 employees.

By using Kaplan Meyer curves we obtained a survival rate of 94.9% after the first month, 82.5% at 3 years, 72.8% at 4 years, 62.4% at 6 years and 31.2% at 11 years. We obtained an estimated average survival value of 8 years (6.3 years – 9.8 years, 95% CI).

According to these results we consider that cardiac transplantation in our center is integrated in the ISHLT standards and follows a trend of improvement, our objective being represented by the establishment of a center able to provide this therapy as a real opportunity to a larger number of patients with advanced heart failure that is irreducible by classical methods.