Outcome after pediatric heart transplantation: two decades of a single center experience

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Abstract

Background: Twenty years after the first successful pediatric heart transplantation (HTx), the long-term outcome of this population is still unknown. Current study analyzes our results in pediatric HTx population.

Methods and results: Between 1985 and 2005, we performed 604 HTx. Forty-three patients (7%) were less than 18-years old and six patients were less than 1-year old. Mean age at HTx was 9.7 ± 6.3 years (38 days–18 years). Indications were: cardiomyopathy in 33 patients (76%), congenital in 9 (21%), tumor in 1 (3%). Chronic immunosuppression was Cyclosporine A and Azathioprine-based. Overall survival at Kaplan–Meier analysis (CI 95%) was 82.5% at 1-year post-HTx, 73.5% at 5 years, 72.2% at 10 years, 62.1% at 15 years, and 49.3% at 20 years, respectively. We had 14 deaths (32%): 7 within the first year after HTx (early mortality, EM), 7 occurred later (late mortality, LM). Causes of EM were: graft failure (43%), acute rejection (43%) and post transplant lymphoproliferative disease (14%). Causes of LM were: neoplasms (57%), infection (28%), graft vasculopathy (15%). At late follow-up, cardiac function, somatic and psychoaffective development were normal. Fifteen patients (34%) developed neoplasms, nine patients (21%) hypertension, and three patients (8%) developed kidney dysfunction. Neoplasms were found to be an independent predictor of outcome (p = 0.039) (OR = 7).

Conclusions: Overall survival in the pediatric population is better than adults’ population (62.1 vs 48% at 15 years after HTx). Neoplasms were the main comorbidities and causes of LM: at multivariate analysis, their incidence was related with hematic Cyclosporine A levels after 10 years from HTx (p = 0.01).

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1. Introduction

Heart transplantation (HTx) is currently the ‘gold standard’ treatment for patients with end-stage heart failure refractory to medical or conventional surgical therapy. Following the first successful pediatric HTx 20 years ago [1], the worldwide experience has constantly increased showing substantial differences from adult transplantation as far as indications and results. Nevertheless the long-term outcome of this young population still remains unknown [2,3].

The aim of this study is to report our 20-year experience with pediatric HTx patients.
Table 1
Indications for heart transplantation in our patients

<table>
<thead>
<tr>
<th>Cardiomyopathy</th>
<th>76%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dilated: Twenty case</td>
<td></td>
</tr>
<tr>
<td>Restrictive: eight cases</td>
<td></td>
</tr>
<tr>
<td>Hypertrophic: four cases</td>
<td></td>
</tr>
<tr>
<td>Arrhythmogenic right ventricle: one case</td>
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</tbody>
</table>

Status post cardiac surgery

- Fontan circulation: five cases
- Others: four cases

Primary cardiac tumor

- Cardiac fibroma: one case

Table 2
Description of congenital HTx recipients

- 1. Tetralogy of Fallot
- 2. Ebstein’s anomaly
- 1. Double-inlet left ventricle
- 1. Pulmonary atresia with IVS
- 2. Hypoplastic left heart syndrome
- 1. Double-outlet right ventricle, unbalanced
- 1. Transposition of great arteries, mitral atresia

adopted while in 17 (43%) cases a bicaval technique was preferred. In the remaining three patients (7%), with pulmonary arteriolar resistance greater than 6 WU/m², we performed heterotopic HTx: in two cases as left ventricle-bypass, in one case as biventricular bypass.

Combined heart and kidney transplantation from the same donor were performed in two female recipients, 3- and 15-years old, respectively, affected by severe renal failure due to congenital kidney disease. Forty-three donors were used (24 male, 19 female), mean age was 13.8 ± 12 years, and mean weight was 41 ± 25 kg. Due to poor donors’ availability, in an urgent HTx, a donor—recipient weight mismatch of 300% (12 kg donor—4 kg recipient) was successfully accepted.

The causes of donor’s death were: head trauma (55%), intracranial bleeding (26%), multiple trauma (13%), cerebellar tumor (3%), anoxia (3%).

Mean cold ischemia time was 188 ± 66 min (range 58—320 min). Among the 43 donors, 6 (14%) were ‘marginal donors’ because they presented one or more of the following conditions [4]:

- Left ventricular ejection fraction (LVEF) <45% and/or left ventricular hypertrophy and/or valvular disease at trans-thoracic echocardiographic examination.
- A cumulative dosage of inotropic drugs infusion greater than 15 mcg/kg/min.

Table 3
Description of Associated Diseases in congenital patients

- Assist device: four cases
- Anal atresia, perineo-scrotal fistulae, hypospadias: one case
- Left nephrectomy in Wilms tumor: one case
- Retina disorders, neurosensorial hypoacusia, pseudoacanthosis nigricans: one case
- Juvenile nephropathies: one case
- Nephrosis syndrome: one case
- Pulmonary artery resistance > 6 U/m²: three cases

* Patient underwent heart and kidney transplant.

Standard post-HTx regimen of immunosuppression included Cyclosporine A (4—40 mg/kg/day) and Azathioprine (0.5—3 mg/kg/day). Steroids were used only in selected cases.

In the first year after HTx, Cyclosporine A levels were kept between 150 and 300 ng/ml. Since the second year, Cyclosporine A levels were kept between 80 and 180 ng/ml. Azathioprine doses were adjusted on white blood cell count (total WBC ranging from 5000 to 6000). We used chronic steroids only in patients with episodes of refractory rejection. In order to reduce side effects of immunosuppressive therapy, this standard protocol was tailored on each patient: at 1-year follow-up 23% of patients were already in single therapy (CyA), and 19% still under steroid therapy; after 5 years 43% were in single therapy (CyA), and only 9% still used steroids. After 10 years half population was treated with monotherapy (CyA), and no patient had chronic steroid therapy. Induction therapy was adopted in 10 patients (26%): OKT3 in 2 patients, Thymoglobulin in 4 patients and Lymphoglobulin in 4 patients. Acute rejection episodes were treated by intravenous steroids (10 mg/kg i.v. for 3 days).

Diagnosis of acute rejection episodes was based on both clinical (non-specific malaise, fever with gallop rhythm) and non-invasive instrumental methods (ECG, ECHO). Endomyocardial biopsies were reserved to unclear cases [5]: the youngest patient who underwent biopsy weighed 4 kg. Vascularopathy was detected by means of bi- or tri-annual coronaryography.

For statistical purposes, graft function was assessed evaluating left ventricular ejection fraction (LVEF) by means of ECHO at 3 months and 1, 5, 10, 15 years post Htx.

Kidney function was monitored on a regular basis: data on Creatinine serum level at 1 and 3 months and at 1, 5, 10, 15, 20 years, respectively, were recorded as well as data on liver function (AST (U/l), ALT (U/l), and total bilirubin (μmol/l)).

Somatic growth was evaluated by plotting weight and height of each patient at follow-up visit on Tanner-Whitehouse tables. All measurements ranging between two standard deviations from the average (between the 3rd and 97th percentile) were considered as normal.

3. Statistical analysis

Data are expressed as mean values ± SD for continuous variables, as frequency with percentage for categorical variables. Differences between means of continuous variables were tested by unpaired Student t-test as appropriated. Frequencies were compared using chi-square or Fisher exact test analysis when the expected value of cell was <5.

Cumulative survival curves were constructed according to the Kaplan—Meier methods. The contribution of variables to death rate was evaluated by univariate and multivariate logistic regression analysis.

The following variables: cold ischemic time, causes of donors’ death, use of marginal donors, immunosuppressive regimen, CyA doses (calculated as C0 trough levels), incidence of acute rejection and CAV (detected with serial
predictors, maintaining into the model variables with \( p \) value \( < 0.1 \). The univariate and multivariate odds ratio (OR) and their corresponding 95% confidence intervals (CIs) were calculated. A \( p \)-value \( < 0.05 \) was considered significant. Data were analyzed with SPSS for Windows, release 10 (SPSS Inc, Chicago, Illinois).

4. Results

The overall mortality was 32% (14 patients): 11 were males and 3 females, with age ranging from 1 to 31 years. There were seven deaths (50%) within the first-year of follow-up (early mortality). The main causes of early deaths were: acute rejection in three patients (43%), graft failure in three patients (43%) and post transplant lymphoproliferative disease (PTLD) in one patient (14%). There were seven deaths (50%) after the first year post-HTx (late mortality). In our experience late mortality accounts for less than 1% per year of follow-up.

The causes of late deaths were: neoplasms in four patients (57%), infections in two patients (28%), severe graft vasculopathy in one patient (15%).

Actuarial survival by Kaplan–Meier (CI 95%) analysis was 82.5% at 1-year post HTx, 73.5% at 5 years, 72.2% at 10, 62.1% at 15 years, 49.3% at 20 years. (Fig. 1).

Graft function analysis showed a mild increase of LVEF in the first five years post-HTx and then a slight reduction that became more evident after the 10th year: mean LVEF was 69.6% at 3 months post HTx, 69.5 at 1 year, 72% at 5 years, 69.6% at 10, and 63% at 15 years, respectively.

Mean incidence of acute rejection at 1-year follow-up was 0.4 episodes/patient.

All infections requiring treatment were analyzed: infection rate was 0.6 episodes per patient. There were two late deaths due to myocarditis: one was caused by CMV and one by Toxoplasma Gondii.

Fifteen patients (34%) developed one or more neoplasms, among them five died, respectively 8 months, 3, 8, 13, 16 years post HTx (three patients for lymphoproliferative disorders, one patient for leukaemia, one patient for CNS neoplasm). Among the other 10 patients, a 13-year old child developed a non-Hodgkin liver lymphoma that fully healed at 15-year follow-up after 12 cycles of chemotherapy. A 12-year old girl required surgery because of bleeding due to a uterine fibroma. Three female patients transplanted at the age of 6, 12, and 18 years, suffered for a breast adenoma after 7, 6, 4 years post HTx, respectively. After surgical exeresis they are still followed-up with serial soft-tissue echograms. A 3-year old baby had an EBV related PTLD 2 years after HTx, treated to resolution with reduction of immunosuppressive and antiviral therapy.

Another patient had three different tumors: in situ epidermoid carcinoma of the lips 4 years after HTx, a lips papilloma 1 one year later and an EBV related PTLD 2 years after. The neoplasms were treated by surgical exeresis of the lips tumor and immunosuppressive therapy reduction. At 6-year follow up the patient is still alive.

Two patients, transplanted at 2 and 8 months of age developed an EBV related PTLD 3 months and 15 years after HTx, respectively. Both patients did not respond to immunosuppression reduction and required chemotherapy and antibodies against CD20+ receptor. A patient transplanted at the age of 14 years developed a vulvar papilloma 15 years after HTx that was surgically treated. Graft vasculopathy occurred in four patients (9%) 1, 6, 9, 13 years after HTx, respectively.

In order to assess the long-term effects of immunosuppression on multiorganic performance we have studied serum creatinine (CRE) in all our patients: CRE was within normal ranges (\(<60\,\mu\text{mol/l}\)) in 35% of patients, there was a mild kidney dysfunction (\(61 < \text{CRE} < 120\,\mu\text{mol/l}\)) in 22% of the cases, and only 12% of patients had moderate to severe kidney impairment (CRE \(> 200\,\mu\text{mol/l}\)) (Fig. 2).

None of our patients required hemodialysis. As far as liver function is concerned, a mild increase (within 20% above normal values) in AST, ALT and Serum bilirubin was observed in 70% of cases, whereas in 30% of cases their values were exceeding of 20% the normal range. Nevertheless in all cases INR, serum albumin and total proteins were within normal values.

Nine patients (21%) suffered from hypertension requiring drug therapy. Neoplasms were the only independent predictor of outcome \((p = 0.039)\). Marginal donors showed only a trend for increase in cardiac death \((p = 0.08)\).

5. Discussion

HTx in pediatric age has been proved to be a valid therapy for end-stage cardiomyopathies when no conventional...
therapeutical alternatives are available. Long-term results are satisfactory in terms of either survival and quality of life [6]. Moreover, in our series, overall survival rate of pediatric patients is better than the adults’ one (62.1 vs 48% at 15 years after HTx). At the moment of HTx, 14 patients (34%) were under the 3rd percentile of weight: HTx led to a complete recovery of somatic growth and cognitive skills in all patients, as observed at last follow-up. According to ISHLT Registry report 2006 [6], the indication to HTx and the severity of illness at the time of heart transplantation are relevant risk factors for early survival: in our experience, congenital diseases were associated with worst early survival (30% early deaths in congenital subgroup vs 12% in the remaining patients) while they did not affect late outcomes (16% late deaths in congenital subgroup vs 18% in the others).

Early mortality accounted for half of all deaths. Main causes of early mortality were represented by acute rejection and graft failure. It is interesting to note that all these patients had well known pre-HTx risk factors [6]: four patients were on mechanical circulatory support and three patients were on high-dosage inotropic support. Our experience confirms that, in this era of donor shortage, the timing of waiting-list entrance appears to be crucial, before worsening of hemodynamic performance occurs [6,7].

Main cause of late mortality in our series was represented by neoplasms, followed by infections and vasculopathy. Interestingly acute rejection had no influence on the causes of late mortality.

Occurrence of neoplasms is a well-recognized complication of solid organ transplantation [6—8]. Prevalence of different types of neoplasms in transplanted patient is 3—20 times higher than a control population [8].

After HTx, non-melanoma skin cancer and PTLD are the types with higher incidence. For skin cancer patients’ age greater than 40 years and immunosuppressive therapy levels are proved risk factors [9].

Our experience with paediatric HTx patients confirms a prevalence of PTLDs (53.3%) on all the other types of neoplasms, and a low skin cancer incidence (13%).

In our multivariate analysis, the correlation between the immunosuppressant therapy, with or without corticosteroids and neoplasms insurgence is not statistically significant \( (p = 0.15) \), while \( p \)-value becomes statistically significant \( (p = 0.01) \) when we correlate the hemat C0 through levels of Cyclosporine A and neoplasms insurgence after 10 years from transplant (Fig. 3).

In patients in which neoplasm has already been diagnosed there is a trend between hematic Cyclosporine A levels and survival \( (p = 0.05) \) (Fig. 4).

To explain the higher incidence of PTLD in HTx patients when compared to non-immunosuppressed population, an activation of oncogenic viruses (Epstein-Barr virus, HHP8 and HPV) has been hypothesized [10].

Our results seem to confirm these data: B-Lymphocyte phenotype is the only form that we have observed in our patients, the majority of them were EBV-linked (75%). We had an early PTLD insurgence (<12 months) in two cases: one of them had induction therapy with OKT-3 and this is in keeping with reports referring a higher PTLD incidence in patients treated with this drug [11]. Anyway, the small number of patients of our cohort treated with induction therapy using different drugs (OKT3 in two cases, Lymphoglobulin in four cases, Thymoglobulin in four cases) does not allow any statistical inference on its association with PTLD.

In our experience higher haematic C0 through levels of Cyclosporine A were related to higher incidence of neoplasms \( (p = 0.001) \).

The introduction of new immunosuppressive agents, i.e., Everolimus, in adult patients, plays an important role in preventing acute and chronic rejection with low Cyclosporine A dosage [12]; moreover its antiviral role could lower the incidence of EBV and HHP8 infections, which can be considered responsible of PTLDs activation.

As far as infections are concerned, remarkably, both fatal infections observed in our patients were recurrences of myocarditis. In those two patients HTx was indicated because of dilated cardiomyopathy following biopsy proven myocarditis. After HTx, in one of these patients we detected the same viral genome being responsible of both native heart and donor heart myocarditis.

Overall incidence of graft vasculopathy in our population is lower than that of the international experience (9 vs 11.4% at 5 years), although our data may be limited [6].

As reported in other studies, avoiding the use of steroids in chronic immunosuppression might be responsible for lower vasculopathy occurrence [14,15].
Heterotopic technique was used in patients with high arteriolar pulmonary resistances (RVPO > 6 U/m²) and transpulmonary gradient > 15 mmHg: two patients with restrictive and one patient with hypertrophic myocardiopathy. In this subgroup (follow up period 8 ± 1 years), this technique was effective in avoiding right ventricular graft failure, all patients are now alive with a satisfactory quality of life at a follow-up of 8 ± 1 years [16].

Although a large donor recipient weight mismatch has been referred as cause of cerebrovascular incidents [17], none of our patients had the 'Big Heart Syndrome'.

The normal graft function observed along all the follow-up period was not related to recipients' age at the time of HTx. The incidence of major complications and comorbidities was lower than in the adult population: hypertension occurred in nine patients (21%) but it is remarkable that six of these patients were transplanted with a heart from an oversized donor (mean donor–recipient weight ratio = 1.6 ± 0.5). Hypertension did not occur in the two combined heart–kidney transplants. There was no new-onset of diabetes mellitus. Incidence of neoplasms still remains a major issue (34%), although their mortality is low (33% of all cases) at long-term follow-up and healing rate is good. It is interesting to highlight that in our series we observed an increase of the rate of neoplasm in association with high haematic CO through levels of Cyclosporine A over a prolonged period of time. This correlation might suggest the need of lowering CyA levels in our study we found CyA levels to be higher in the subgroup of patients with higher rejection scores. In adult HTx a late reduction of immunosuppression could be a relatively safe procedure, the same can not be stated for pediatric patients, where recurrence of acute fatal rejections is a well known complication [6]. Thus we suggest a reduction of CyA dosages and the concomitant start-up of other immunosuppressive drugs. The introduction of new immunosuppressant agents [13–19], (i.e., mycophenolate, everolimus), prevents acute and chronic rejection with low Cyclosporine A dosage, and it could play a crucial role in preventing these severe complications in the pediatric population.

References