

LONG-TERM CARE FOR THE HEART TRANSPLANTED PATIENT

ANCA SGLIMBEA¹, MARIA MIHAELA OPRIS², MIHAELA ISPAS³, LILIANA GOZAR⁴, HORATIU SUCIU⁵

^{1,2,4,5}University of Medicine and Pharmacy Tîrgu-Mureş, ³Cardiology Clinic Tîrgu-Mureş

Keywords: cardiac transplantation, child, follow-up

Abstract: Cardiac transplantation has completely demonstrated its efficacy as a final therapy for the patient with intractable heart failure, regarding both survival and quality of life. Nevertheless, the transplanted patient turns into an "eternal patient", due to the necessity of clinical and laboratory follow-up on a long term basis. The authors are presenting their personal experience concerning long time follow-up of the only small child in Romania receiving a transplanted heart. Follow-up period extends from the discharge from the hospital over 21 months posttransplantation and refers to the dynamic of the clinical and biological evolution and their impact on medication. Finally, the authors propose a follow-up protocol for the patient with this type of pathology, which includes all aspects of the day-to-day life of a child in this age group: life and activity behaviour, active and passive prophylaxis, medication etc.

Cuvinte cheie: transplant cardiac, copil, follow-up

Rezumat: Transplantul cardiac, ca terapie finală în managementul pacientului cu insuficiență cardiacă intratabilă, și-a dovedit cu prisosință eficiența, atât în ceea ce privește supraviețuirea, cât și referitor la calitatea vieții. Cu toate acestea, pacientul transplantat devine un "pacient veșnic", având în vedere necesitatea supravegherii clinice și monitorizării de laborator a la long. Autorii prezintă experiența personală referitoare la îngrijirea pe termen lung a singurului copil mic beneficiar de transplant de cord din România. Follow-up-ul se extinde pe perioada de la externare până la 21 de luni posttransplant și prezintă în dinamică evoluția clinică, datele biologice și de laborator, precum și reflecția acestora în ajustarea medicației. În final, autorii propun un protocol de urmărire a pacientului cu această patologie, care să includă toate aspectele vieții unui copil de această vârstă: regim de viață și activitate, profilaxie activă și pasivă, medicație etc.

Transplantation for intractable heart failure is nowadays a treatment with a well established efficacy and results, both on short and long term. At the same time, the transplanted child becomes a long-term "patient", as it needs a close and proper surveillance, due to the postoperative therapy. This postoperative care plays an important part in the long-term outcome of these children.

The aim of this article is to present our experience with postoperative management and outcome of our first, and, to date, only heart transplanted small child.

Our patient, a 3½ years old girl, with severe heart failure (class IV NYHA), secondary to idiopathic dilated cardiomyopathy, was transplanted in January 2011, receiving an iso-group, iso-Rh heart. Intraoperative and postoperative intrahospital evolution were positive, with the exception of developing a left intraatrial thrombus, which was treated first with heparin, and afterwards with clopidogrel for 6 weeks, with complete resolution of the thrombus. There was the thought of a differential diagnosis with the suture lines in the left atrium but the change of the echocardiographic aspect of the assumed thrombus with time brought us to the conclusion that a thrombus was indeed present. The little girl was catheterized at 5 weeks posttransplantation, the result being ISHLT grade 0 (no signs of rejection). She was released 6 weeks after transplantation,

weighing 10 kg, with a normal clinical exam, HR- 120/min, BP 110/70 mmHg (under medication). Her treatment included three orally given immunosuppressants: Tacrolimus 2x1 mg (blood tacrolimus levels at release were 8 ng/ml), Myfortic 2x230 mg (absolute lymphocyte number at release = 2400/mm³) and Prednisone.

The treatment also included pneumocystis carinii prophylaxis with Biseptol 2x7,5 mg po, anticytomegalovirus prophylaxis with Gancyclovir (Valcyte) 1x225 mg po, antifungic prophylaxis with Diflucan 1x50 mg po, along with gastric ulcer prophylaxis with Nexium 1x10 mg po.

Follow-up includes a period of 21 months, with periodically scheduled control visits, monthly for the first year, afterwards at 3-month period. Each visit included complete physical exam, blood analysis (blood count, blood smear, C reactive protein, BUN, creatinine, liver enzymes, cholesterol triglycerides, uric acid, blood glucose, blood ions, arterial blood gases, tacrolinemia, BNP, urine exam), EKG and echocardiography.

The clinical examination was normal, besides of obvious signs of infection, as noted underneath. Heart rate remained between 100- 120bpm. Blood pressure was kept in the normal range with an association of Diltiazem and Captopril, the later one could have been stopped 10-month postoperatively.

¹Corresponding author: Mihaela Opris, Str. Dr. Victor Babeş, Nr. 12/14, Tîrgu-Mureş, România, E-mail: m_opris2000@yahoo.com Tel: +0744 626571

Article received on 16.11.2012 and accepted for publication on 12.12.2012
ACTA MEDICA TRANSILVANICA March 2013;2(1):224-226

CLINICAL ASPECTS

The growth parameters showed a gain in weight of 6-6.5 kg in 21 months, raising from less than the 5th percentile for age at transplantation (10 kg), to the 40th percentile for age at 21 months posttransplantation. Laboratory tests showed no signs of organ damage. RGF could not be determined, due to laboratory problems. On EKG, we monitored arrhythmias, ST-T changes, changes in R and S wave voltages. None of such modifications were encountered during the follow-up period.

Echocardiography included the usual measurements of cardiac structures in M mode, the assessment of systolic biventricular function by ejection and shortening fraction, as well as MAPSE and TAPSE, the assessment of diastolic biventricular function in 2D and tissue Doppler mode, monitoring myocardial structure modifications, pericardial effusions, thrombi, pulmonary artery pressure estimation and any heart structure or function changes. No echocardiographic changes were encountered during the follow-up period, other than those associated with child's normal growth. Approximately one year after transplantation, a control endomyocardial biopsy was performed, which showed no signs of rejection.

Immunosuppression continued as a three medication association for 7 months. After 7 months, during which the dose of Prednisone was tapered, the drug was stopped. The original plan was to stop Prednisone after 6 months, but this was not possible due to a severe upper respiratory tract infection during this period. Tacrolimus dosage was adjusted in order to maintain tacrolimus blood levels in the range between 8-12 ng/ml, in the first 6 months and 5-8 ng/ml afterwards. In fact, her levels were less stable in the first 7 months, extending from 6 to 12 ng/ml, but definitely more stable afterwards, around 5-6 ng/ml. Myfortic, initially at a dose of 2x230 mg, aimed to have an absolute lymphocyte number less than 2500/mm³, was reduced after a severe gastroenteritis to 2x180 mg and remained at this dose, with an absolute lymphocyte number ranging between 1700- 2500/mm³.

Biseptol was stopped 6 months posttransplantation. valcyte was ended at the same time with prednison, 7 months postoperatively. The girl received immunoglobulins once, monthly for 3 months after transplantation. During this period, she also had varicella, but as she had just received a regular immunoglobulin- perfusion and, on the other hand, she seemed to have had varicella as an infant, no further therapeutic measures were taken.

During the follow-up period of 21 months, the child developed only two more severe infections, along with a few simple respiratory tract infections, the latter being treated at home. One month after discharge, the girl developed an upper respiratory tract infection, with a prolonged evolution, nasal secretions persisting for weeks after the resolution of the infection.

No germ could be isolated from cultures, but blood count, C reactive protein and blood smear suggested a viral infection, with bacterial suprainfection. The infection was treated with antibiotics and symptomatic medication, along with oestrone as an antiemetic drug, which was able to control vomiting caused by the great amount of nasal and tracheal secretions, thus immunosuppressive therapy continued to be given orally in proper doses. No cardiac problems were encountered during this infection. The second infectious episode was a gastroenteritis with loose stools and vomiting, probably of viral etiology. The treatment was symptomatic, but the prolonged evolution and vomiting obliged us to add methylprednisolon for three days, along with a slight reduction of the dose of myfortic.

At 21 months posttransplantation, the therapy included Tacrolimus 1.5-0-1 mg, alternatively with 1.5- 0- 1.5 mg, Myfortic 2x180 mg, Diltiazem 2x5 mg.

Discussion. There are two major objectives in the long-term care of a child with a heart transplantation:

- a) Maintaining an efficient immunosuppression, in order to avoid rejection episodes;
- b) Reduction of side effects of immunosuppressive medication to minimum.

A) Most immunosuppressive regimens employed in the long-term therapy of heart transplant recipients consist of a combination of agents that affect different pathways in the activation of the T-cell.

There are several combinations used in different centres, depending on experience. Most centres use for the beginning a triple combination: prednison+ciclosporine or tacrolimus+ azathioprin or mycophenolat.

At discharge from the hospital, posttransplantation, prednisone is usually given orally, in a dosage of 0.8 mg/kg/d, once daily. This dose is tapered over 6 months, in steps of 0.1 mg/kg/3 weeks. There are centres which stop prednisone even earlier, at 2 months (Giessen), the reason being the fact that coronary vasculopathy is caused by steroids.

Cyclosporine (Sandimmun) is given orally, in 2 or 3 doses (depending on age), the aim being a blood level of 200-300 ng/ml in month 1 to 6, and 100- 200 ng/ml in month 7 to 24.

There is a major concern of continuing oral administration of this medicine even during gastrointestinal events, as reaching desired blood levels after stopping the medicine is extremely difficult. Proper hydration is a cornerstone of the therapy. Side effects include: gum hyperplasia (proper dental hygiene is very important), neurodermitis, increase of uric acid, psychosis. Interactions of several medicines with cyclosporine must be known (e.g.: macrolides are given in 10% of usual dose when associated with cyclosporine).

The alternative for cyclosporine is tacrolimus (prograf). The desired blood levels are 8-12 ng/ml in the first 6 months and 5-8 ng/ml afterwards. If levels are over 24 ng/ml, one dose is skipped. Compared with, cyclosporine, tacrolimus has a greater incidence of neurological side effects, hyperglycemia (in 30% of cases- irreversible diabetes mellitus), alopecia, gastrointestinal effects, while cyclosporine causes more often increased blood pressure, hyperlipidemia, hypertrichosis, gum hyperplasia. Incidence of renal failure, hyperkalemia and hypomagnesaemia is equally caused by both drugs.

Azathioprin (imurek) is tailored to reach an absolute lymphocyte number of less than 2500/ml. If this cannot be reached, the dose can be increased up to 10 mg/kg, and if this dose is not effective, the recommendation is to switch over to mycophenolat. The usual dose is 1-2 mg/kg/day. If neutropenia of less than 1000/ml appears, the dose should be reduced. There seem to be two different population types concerning metabolism of azathioprin: some patients need doses of 1-2 mg/kg/day, while others reach the desired effect only after 8-10mg/kg/day.

Mycophenolat (Cellcept) can be used as an alternative to Azathioprin. The desired effect is the same: absolute lymphocyte number less than 2500/ml. The side effects include: gastrointestinal, fever, loss of appetite. Blood level determination is possible, but not very useful. If gastrointestinal problems are very severe, this total dose can be given in 3 amounts. An alternative is myfortic (360 mg myfortic equal 500 mg cellcept).

CLINICAL ASPECTS

Newer immunosuppressants, like everolimus or sirolimus are less nephrotoxic; they have antiproliferative properties, which make chronic rejection less often.

B) The side effects of immunosuppressive medication:

1) Infection prophylaxis

- a) For bacterial infections: Perioperative cefazolin is recommended;
- b) Prophylactic cytomegalovirus (CMV) treatment is given if the donor and/or the receptor are CMV positive, or the status of the donor is unknown (in Romania, this is the most often situation). The medicine used is valgancyclovir orally. CMV-PCR should be performed once weekly. If reactivation occurs, the infectionist should be asked for advice;
- c) Pneumocystis carinii prophylaxis is performed with biseptol, in different regimens: Zurich recommends 30 mg/kg/day given twice daily in three consecutive days of the week, until prednidolon < 0.5 mg/kg/day and T cells in FACS < 200/microl (which we could not perform in our labs);
- d) Antifungal prophylaxis is made with amphotericine B 10% suspension 4x1 ml. If there is increased building activity around the patient: itraconazol syrup 5 mg/kg/day, once daily;
- e) Immunoglobulins should be given 0.4 g/kg/day over a 3 hour perfusion once per month for the first 3-6 months;
- f) If in contact of varicella or measles, specific immunoglobulins should be given in the first 96 hours, unless a regular immunoglobulin perfusion has not been received recently;
- g) Vaccination should be performed with inactivated vaccines- 6 months after transplantation; titter control after 2- 3 months. After cessation of steroids, activated vaccines can be also given;
- h) Hygiene: isolation is recommended until discharge from the hospital (minimum 4 weeks single room, mouth protection and cloth protection). Visits are allowed only for parents. At home, no mouth protection is needed, but until 6 months posttransplantation (or steroids over 0.1 kg/day), mouth protection is required outdoors. No play in sand or with earth is allowed, as well as no swimming in pools, attending large crowds. Hand disinfection is always required.

2) Specific recommendations:

- Food: During the first 6 months posttransplantation, food is recommended to have a low bacterial, high fiber, low cholesterol and lipid content. After 7 months, the intake of food is free, except some types of cheese, uncooked meat, eggs and grapefruit juice;
- Prophylaxis of gastric ulcer with omeprazol as long as steroids > 0.5 mg/kg/day;
- Prophylaxis of osteoporosis with oral calcium (500 mg/day) and vitamin D (cholecalciferol 400U/day);
- Dental hygiene is important for prevention of infections and gum hyperplasia;
- Anticoagulation is recommended only in the presence of a largely increased left atrium; aspirin is an option in case of coronary artery sclerosis;
- L-thyroxin is recommended in all infants, after blood analysis of TSH, T3 and T4;
- Rehabilitation, even for the whole family, in centres adapted to the age of the child;
- Sun protection with proper cloth and sun blocker;

- Routine discussion and explanations with/for the patient and family.

Periodical follow-up is directed towards the timely diagnosis and treatment of rejection or side effects of chronic medication. Outpatient follow-ups include clinical exam, blood analysis, echocardiography and EKG.

The diagnosis of rejection is based on clinical signs (fever, malaise, irritability, alter hemodynamics, arrhythmias), echocardiographic modifications (increase in cardiac wall dimensions, with heterogenic increased echogenicity of the myocardium, pericardial fluid), ECG signs of altered amplitude and repolarisation (negative T waves in V5 and V6), increase of troponin levels and active lymphocyte subpopulations, relevant signs on endomyocardial biopsy (inflammation). Heart biopsy should be obtained before starting the therapy, but in some centres, infants are excepted by this recommendation, the treatment being started without biopsy.

The treatment is based on the severity of the rejection, as shown by ISHLT scale: from grade 0 (no rejection), through grades 1A, 1B, 2, 3A, 3B, 4. Grades 0 and 1 need no therapy, grade 2 only needs increases of the dose of immunosuppressive medication, while grades 3 and 4 need steroid therapy and the increase of immunosuppressive medication.

Tumours and lymphoproliferative diseases should be sleeked for actively.

Coronary artery vasculopathy is associated with known risk factors: subclinic rejection, hiperlipidemia, CMV infection, lipid absorption abnormalities (rarely), which should be diagnosed and corrected.

The therapy of a child who received a transplanted heart is a long targeted teamwork, which needs a substantial support from a good laboratory. This is because the aim of this therapy is a normally living child for a normal lifespan.

Acknowledgement:

This paper is partially supported by the Sectoral Operational Programme Human Resources Development, financed from the European Social Fund and by the Romanian Government under the contract number POSDRU/89/1.5/S/60782.

REFERENCES

1. Pediatric Heart transplantation protocol. June 2002 - <http://lomalindahealth.org/common/legacy/ih/pedproto.pdf>
2. The ISHLT Guidelines for the Care of Heart Transplant Recipients. J Heart Lung Transplant. 2012;29(8):914-956.
3. Pietra BA, Boucek MM. Immunosuppression for pediatric heart transplantation in the modern era. Progress in Pediatric Cardiology. 2005;11:115-129.