Heart transplantation

Kalp transplantasyonu

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ABSTRACT

End-stage heart failure is still associated with a decrease in both quality and prognosis of life and one- year survival of these patients is below 50%. Heart transplantation remains the final therapeutic option for the treatment of irreversible end-stage heart failure in all age groups with adequate success rates. Survival of patients who underwent heart transplantation has improved incrementally in recent years, with 86% survival in the first year and over 50% survival at 10 years. Approximately 50% of patients live for more than 10 years after heart transplantation and 25% of patients live for more than 18 years. Improvement of the quality of life is an other benefit, while the patients were in NYHA class III-IV preoperatively, nearly all of them have an improved functional status with NYHA class I-II after transplantation. However, discrepancy between the number of candidates and number of available donors is still the major problem for the applicability of heart transplantation.
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Key words: Heart transplantation, immunosuppression, rejection, cardiac allograft vasculopathy, endomyocardial biopsy

ÖZET

Son dönem kalp yetersizliği, yaşam beklentisi ve hayat kalitesinde belirgin azalma ile seyreden klinik bir tablodur. Son dönem kalp yetersizlikli hastaların bir yıllık yaşam beklentisi %50 'den daha azdır. Kalp transplantasyonu, son dönem kalp yetersizliği olan tüm yaş gruplarındaki hastalarda, yeterli başarı oranıyla uygulanabilecek en uygun tedavi seçeneğidir. Son yıllarda, kalp transplantasyonu yapılan hastaların yaşam beklentilerinde belirgin bir artış vardır. Günümüzde kalp transplantasyonu sonrası 1 yıllık yaşam beklentisi %86 ve 10 yıllık yaşam beklentisi %50'nin üzerine yükselmiştir. Hastaların yaklaşık %50'si 10 yıldan uzun süre ve %25'i 18 yıldan uzun süre yaşarlar. Hayat kalitesindeki düzelme kalp transplantasyonunun bir başka faydasıdır. Preoperatif fonksiyonel kapasitesi NYHA klas III-IV olan hastaların tamamına yakını transplantasyon sonrası NYHA klas I-II'dir. Transplantasyon bekleyen adayların sayısı ile uygun donor sayısı arasındaki uyumsuzluk kalp transplantasyonunun uygulanabilirliğini kısıtlayan en önemli sorundur. *(Anadolu Kardiyol Derg 2008; 8: Özel Sayı 2; 131-47)*
Anahtar kelimeler: Kalp transplantasyonu, immünsüpresyon, rejeksiyon, kardiyak allogreft vaskulopati, endomiyokardiyal biyopsi

Introduction

Heart transplantation is a widely accepted therapy for most patients under 65 years of age with advanced heart failure who remain symptomatic with the expectation of high intermediate term mortality, despite optimal heart failure medications. Heart transplantation should be reserved for those patients most likely to benefit in terms of both life expectancy and quality of life. With over 30 years of experience, heart transplantation has been the most scrutinized and intensively studied therapy for advanced heart failure (1). Today, the better understanding of immune mechanisms in allograft rejection and the subsequent development of new immunosuppressive treatment regimens, improved postoperative follow-up care management and new donor organ preservation and transport systems, dramatically improves survival rates for heart transplant recipients. Recent data from the International Society for Heart and Lung Transplantation (ISHLT) registry (2) have shown that the overall graft half-time (time at which 50% of those transplanted remain alive) has been increasing steadily, now reaching over 10 years (2).

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History

The first successful clinical heart transplantation in a human was performed in 1967, by Dr. Christian Bernard, in Cape Town, South Africa (3). These early efforts in heart transplantation were thwarted by the infancy of cardiopulmonary bypass and a lack of understanding of the immune system. A majority of these transplant patients died, because of acute rejection and infection in the first years. The clinical use of cyclosporine as an immunosuppressive agent revolutionized the field of heart transplantation in 1983. Recipient survival rates improved, thus producing an explosive increase in the number of transplant centers offering heart transplantation. The ISHLT registry (2) has reported total 80106 recipients with heart transplantation and 3341 recipients with heart-lung transplantation through June, 2007 (4).

In Turkey, through 31 October 2007, a total of 302 heart transplantations have been reported by the department of Health Ministry. Today, the number of centers performing heart transplantation is 12 in Turkey. In our country, the number of heart transplant candidates are increasing at rate of 10% per year and 7% of them are dying while on the waiting list. In the year of 2006, 225 new patients applied to the waiting list and the number of the performed heart transplantation was only 46 in the same year. In Turkey, the number of heart transplants performed per million population is only 0.6 (transplant /per million population) that much lower than in other European countries. This is 7.3 in USA, 6.1 in France and 5.0 in Germany (5).

Etiology

The majority of the heart transplant candidates have dilated or ischemic cardiomyopathy. Approximately, 44% of candidates have ischemic and 45% of candidates have dilated cardiomyopathy. The other group of conditions undergoing heart transplantation are congenital heart diseases and valvular heart diseases which could not be treated with surgical methods. Candidates for re-transplantation are few, approximately 2%.

In recent years, improvements in diagnosis and treatment of coronary artery diseases have provided early revascularization before deteriorating cardiac function in acute myocardial infarction and the coronary by-pass surgery could be performed safely in patients with poor ventricle function. Due to these developments, patients could be treated before developing ischemic cardiomyopathy and the proportion of patients with ischemic cardiomyopathy to heart transplant candidates has been declined to %35 over the years. Many studies indicate that patients with ischemic heart disease as the etiology for heart failure have a worse prognosis than patients with nonischemic cardiomyopathies. Ischemic cardiomyopathy was identified by multivariable analysis as a risk factor for sudden out-of-hospital death (6). Thus, if other clinical and hemodynamic variables are similar, patients with ischemic cardiomyopathy should be listed earlier in their disease course than patients with other forms of dilated cardiomyopathy.

Indications/contraindications and recipient evaluation

In general, patients selected for heart transplantation should have an expected 1-year survival less than 50% with current medical therapy and have severe reduction of quality of life secondary to cardiac symptoms that cannot be relieved with nontransplant therapy (1). General recommendations regarding indications for heart transplantation are listed in Table 1.

Patients are evaluated for transplantation after referral by a cooperating cardiologist. At the initial evaluation, a mutual long-term working relationship between patient, relatives, and the team is established. The evaluation includes the tests summarized in Table 2. The listing decision involves a recommendation by the team and decision by the patient. The complexity of the evaluation process mandates a team approach (7).

The number of available donor hearts severely limits the epidemiologic impact of heart transplantation. Because of the huge discrepancy between the number of patients and the number of available donors, the mortality of patients while on the waiting list is currently estimated at 10% per year. The thoracic organ waiting list is stratified by 3 levels (United Network of Organ Sharing-UNOS Policy 3.7.3). Status 1a is defined by the need for ICU care with high dose inotropes or mechanical assistance including intraaortic balloon pump. The candidates who have a chronic mechanical assist device or who are inotrope dependent are granted status 1b. All other patients with compensated heart failure managed as outpatients are status 2.

The contraindications for heart transplantation are based on an assessment of comorbid medical, social, and psychological conditions that are associated with reduced outcomes after transplantation. Some of these conditions represent absolute contraindications, but most (depending on severity and associated risk factors) are considered relative contraindications, reflecting institutional and physician differences. The general contraindication is, presence of any noncardiac condition that would itself shorten life expectancy or increase the risk of death from rejection or complications of immunosuppression (Table 3).

Because of the numerical disparity between recipients and donors for heart transplantation, most of the heart transplant candidates in relative contraindication group are not accepted for waiting list. Advanced age is a major criterion for primary elimination. However, as reported by the recent ISHLT registry (2), there is an increasing trend to perform transplantation in older patients (above 60 years); between 1982-1991, the ratio of heart transplanted recipients older than 60 was 10% whereas this ratio has increased to about 25% between 2002-2006. Often this was managed by the allocation of donor hearts to older patients by using an alternate list in which organs from donors that would otherwise remain unused because of some quality concerns, including older donor age. For example, older donors that were not used but seem to be otherwise satisfactory, has allocated to older recipients. On follow-up, these older recipients survival was shown to be equivalent to

Table 1. General indications for heart transplantation (Reproduced from ref. 1 with permission of Elsevier, Copyright 2004 by Elsevier)

Criteria for consideration of heart transplantation in advanced heart failure
Significant functional limitation (NYHA Class III–IV heart failure) despite maximum medical therapy
Refractory angina or refractory life-threatening arrhythmia
Exclusion of all surgical alternatives to transplantation, such as the following:
Revascularization for significant reversible ischemia
Valve replacement for severe aortic valve disease
Valve replacement or repair for severe mitral regurgitation
Appropriate ventricular remodeling procedures
Indications for heart transplantation determined by severity of heart failure despite optimal therapy
Definite indications
VO2 max <10 ml/kg/min
NYHA Class IV
History of recurrent hospitalization for congestive heart failure
Refractory ischemia with inoperable coronary artery disease and EF <20%
Recurrent symptomatic ventricular arrhythmias refractory to medical, ICD and surgical treatment
Probable indications
VO2 max <14 mg/kg/min (or higher with multiple other risk factors)
NYHA Class III–IV
Recent hospitalizations for congestive heart failure
Unstable angina not amenable to coronary artery bypass grafting, PTCA with EF <25%

EF-ejection fraction, ICD-implantable cardioverter-defibrillator, PTCA-percutaneous transluminal coronary angioplasty

standard list patients (8, 9). However some authors describe a significant mortality in the alternate list group, outcomes were significantly better than the natural history of end-stage heart failure (10, 11).

Donor selection/evaluation

All potential heart donors must be evaluated by systemic examination, especially for cardiac pathology. Prolonged hypotension during and after brain death (persistent systolic blood pressure <60 mmHg more than 3 hours) and prolonged use of high dose inotropes (dopamine or dobutamine >20 mcg/kg/minute) can impair cardiac functions. Nonspecific ST-T wave changes on electrocardiogram, may occur due to electrolyte imbalance, hypothermia and catecholamine release associated with brain death and these changes can disappear after transplantation of donor heart. However, the existence of pathological Q waves is accepted as contraindications (12). Donors who have a significant smoking or persistent hypertension history must be screened for coronary artery disease with cardiac catheterization.

Examination by echocardiography remains the best initial screening mechanism for potential donors. A normal ejection fraction (EF>50%) with normal valvular structure and function and an absence of left ventricular hypertrophy are indicators of an excellent heart for transplantation. Minimal abnormalities detected by echocardiography, such as minimal tricuspid or mitral regurgitation, minimal pericardial effusion, marginal left ventricular hypertrophy or reduced ejection fraction may also be indicators of an acceptable organ depending on the history of the donor and the status of the recipient (status 1a-b, 2). In instances in which the recipient is in extremis, a less than ideal donor heart may be accepted in order to save the patient's life. Common donor heart contraindications are listed in Table 4.

Optimal management of the hemodynamic, metabolic, and respiratory status of the donor is essential and includes the use of a pulmonary artery catheter to monitor euvolemia and normal cardiac output. Hormonal resuscitation is strongly recommended for metabolic perturbations: management with insulin, corticosteroids, triiodothyronine, and arginine vasopressin has been shown to be beneficial in donors and could be used to detect reversible cardiac dysfunction.

The number of available donor hearts severely limits the applicability of heart transplantation, over the years. In some countries, approximately 50% of all waiting list patients will never receive a transplant because of extended waiting periods and shortage of organs. At this point, expanding the donor pool becomes crucial. Evidence exists that certain 'standard' donor criteria can be significantly liberalized to increase the available donor pool by accepting 'Marginal Donors' who would, under conventional transplant guidelines, be declined as potential organ donors (13). These extended

Table 2. Evaluation protocol for heart transplant candidates (Reproduced from ref. 1 with permission of Elsevier, Copyright 2004 by Elsevier)

General
Complete history and physical examination
Nutritional status evaluation[a]
Blood chemistries including liver and renal profiles
Hematology and coagulation profile
Serum electrolytes
Lipid profile
Urinalysis
24-hour urine for creatinine clearance (and protein if diabetic or urinalysis positive for protein[a])
Nuclear renal scan with measurement of effective renal plasma[a]
Pulmonary function testing with arterial blood gases
Ventilation-perfusion scan[a]
Stool for heme (X3)
Mammography[a]
Prostate-specific antibody (PSA)[a]
Abdominal ultrasound study (liver, pancreas, gall bladder, and kidney evaluation)
Carotid ultrasound
Social evaluation
Psychiatric evaluation
Neuropsychiatric evaluation (neurocognitive evaluation)[a]
Dental evaluation
Sinus X-Ray films[a]
Cardiovascular
Electrocardiogram
Chest radiograph, (PA and lateral)
Two-dimensional echocardiogram with Doppler study
Exercise test with oxygen consumption (peak Vo2)
Right-heart catheterization with detailed hemodynamic evaluation
Shunt series[a]
Left-heart catheterization with coronary angiography[a]
Myocardial biopsy[a]
Radionuclide angiogram (gated blood pool study)[a]
Nuclear imaging study for myocardial viability (thallium-201 or positron emission tomography)[a]
Holter monitor for arrhythmias (if ischemic cardiomyopathy)[a]
Immunology
ABO blood type and antibody screen
Panel reactive antibody (PRA) screen
Human leukocyte antigen (HLA) typing (if to be listed for transplantation)
Infectious Disease Screening
Serologies for hepatis A, B, and C; Herpes virus, human immunodeficiency virus (HIV), cytomegalovirus (CMV), toxoplasmosis, varicella, rubella, Epstein-Barr virus, venereal disease research laboratory (VDRL), Lyme titers[a], histoplasmosis and coccidioidomycosis complement-fixing antibodies[a]
Throat swab for viral cultures (CMV, adenovirus, Herpes simplex virus)[a]
Urine culture and sensitivity[a]
Stool for ova and parasites[a]
PPD (purified protein derivative) skin test with controls (ie, mumps, dermatophytin, histoplasmosis, and coccidioidomycosis[a])
[a]Only performed if appropriate or indicated

Table 3. Contraindications to heart transplantation

Absolute Contraindications
Age >65 years
Irreversible pulmonary hypertension (pulmonary vascular resistance >6 Wood units)
Significant chronic renal impairment* (creatinine>2mg/dl or creatinine clearance <50 ml/min)
Significant chronic hepatic impairment (bilirubin>2.5 mg/dl or transaminases >2x normal)
Active systemic infection, HIV/AIDS
Severe peripheral vascular or cerebrovascular disease
Severe diabetes mellitus with end-organ damage
Active or recent malignancy
Systemic diseases such as amyloidosis, collagen vascular disease or sarcoidosis
Relative Contraindications
Acute pulmonary thromboembolism or infarction
Active ulcer disease
Active diverticulitis
Excessive obesity (more than about 140% of ideal body weight)
Severe osteoporosis
Psychiatric instability refractory to expert intervention
History of recurring alcohol or drug abuse
Previous demonstration of repeated noncompliance with medication or follow-up

*Transplantation may also be advisable as combined heart-kidney transplant

Table 4. Donor contraindications

Age >50 years
Cardiac contusion secondary to the thorax trauma
Diffuse coronary artery disease
Documented myocardial infarction
Documented other heart disease
Refractory ventricular arrhythmias
Hemodynamic instability with out high dose inotrope
Malignancies (except central nervous system)
Refractory generalized infection

criteria include advanced donor-recipient size match, donor age, donor heart dysfunction, donor heart structural changes, donor malignancies, and donor infection (Table 5). These 'Marginal Donors' may be used selectively in certain higher risk recipients.

Expansion of traditional donor criteria in terms of donor age became a standard very early in numerous centers. In early practice, most institutions excluded donors >40 years of age with extended comorbidities. Over time, organ shortage led to increasing acceptance of more marginal, especially older aged donors, such as alternate recipient list for 'old for old program'. Latest evidence indicates that even hearts of donors older than 50 years of age result in equivalent survival (14, 15), although some authors report increased early mortality and decreased recipient survival with older donor hearts (16). Therefore, in each instance, the risk of accepting an older donor heart must be weighed against the risk of remaining on the waiting list. According to the registry of ISHLT database (2), in 1980s, the ratio of donors older than 50 was %1-2, in 1990s %5-9, whereas it has increased to %15-20 in 2000s.

Surgical technique

The standard heart transplantation technique was developed by Lower and Shumway and it depends on the anastomosis of donor atrial cuff with recipient atrial cuff and remained the primary method of heart transplantation for nearly 30 years (17). Several problems have been noted in the allograft that are thought to be related to this bi-atrial cuff technique: dyssynchrony between donor and recipient atria leading to tricuspid and mitral regurgitation and reduced right ventricular filling, increased trauma to the sinus node leading to a lowered rate of postoperative normal sinus rhythm, and technical difficulties with obtaining endomyocardial biopsies via right heart catheterization (18). These findings led to the modification in which anastomoses were performed between the superior and inferior vena cava of the donor and recipient leaving the right atrium intact.

The most notable technical modification has been the substitution of the bicaval anastomoses for the earlier atrial-to-

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Table 5. Acceptance criteria for heart transplantation using marginal donors (Modified from Massad MG. Current Trends in Heart Transplantation. Cardiology 2004; 101: 79-92)

Age up to 65 years
Undersizing or oversizing by more than 20% body weight
Prolonged hospitalization
History of chest trauma
Open cardiac massage
Elevation of myocardial enzyme levels
Prolonged cardiopulmonary resuscitation (>5 min)
Transient hypotension (>30 min)
High-dose vasopressor requirement
Wall motion abnormalities by echocardiography
Long-distance procurement (>1000 miles)
Persistent conduction disturbances
Cold ischemia time up to 4–5 h
Bypassable one- or two-vessel disease
Correctable valvular dysfunction by echocardiography

atrial cuff technique (19). Using the bicaval technique, several retrospective analyses have shown an improvement in allograft performance; cardiac index has increased in the early period of transplantation, requirement for inotropes was less frequent and tricuspid valve regurgitation has seen less than bi-atrial cuff technique (20, 21). The disadvantages of bicaval technique are stenosis in the anastomosis and the extension of ischemia time. Recent data from the ISHLT registry (2) have shown that there was no statistical difference in survival rates between biatrial and bicaval techniques in heart transplantation performed between 1999-2005.

Immunosuppressive treatment

Survival of patients who underwent heart transplantation has improved incrementally in recent years. The improved survival benefit is a result of newer immunosuppressive drug regimens with better understanding of immune mechanisms in allograft rejection, drug-drug interactions, and other comorbid conditions in these patients. The aim of immunosuppressive regimen is to find the optimal trade off between over-immunosuppression and under-immunosuppression therapy. The main goal is to avoid and control rejection of the allograft (22).

Immunosuppressive drugs result in three categories of outcomes: the desired immunosuppressive effects, the adverse effects of immunodeficiency such as infection and malignancy, and the non-immune toxicities such as diabetes, hypertension, and renal insufficiency. All immunosuppressive drugs contribute to increased risk of infection, with the probable exception of interleukin-2 receptor (IL-2R) antagonists. Malignancy is another significant problem after cardiac transplantation. All immunosuppressive drugs contribute to the risk of malignancy, with the possible exception of steroids. Data in animals suggest that the antigrowth properties of a new immunosuppressive drug, sirolimus, may result in fewer malignancies. The cumulative amount of immunosuppression, especially with OKT3 and polyclonal anti-lymphocyte preparations, is positively correlated with the risk of malignancy (23). Immunosuppression regimens are generally defined as induction, maintenance, and rejection regimens.

Induction therapy

Induction therapy is intense perioperative immunosuppressive therapy that originally designed to induce tolerance to the graft. Antidonor responses are typically most vigorous shortly after the transplantation when stimuli such as donor brain death, ischemia/reperfusion, and surgical trauma increase donor antigen expression, which augments the recipient's immune response. The benefits of induction therapy are a marked reduction in rejection in the early postoperative period when graft dysfunction and renal dysfunction are problematic. Induction therapy also allows later introduction of calcineurin inhibitors, thus avoiding exacerbation of renal dysfunction. Disadvantages of induction therapy are the increased risk of infection, malignancy, or both and increased cost (23).

The immunosuppressive drugs using for induction therapy are summarized in Table 6. Anti-lymphocytic drugs use is limited because of an increased incidence of serious allergic and potentially life-threatening reactions, including serum sickness and cytokine release syndrome (particularly with the monoclonal antibody OKT3). Use of OKT3 may be associated with an increased risk for subsequent humoral rejection.

The use of antilymphocytic preparations is slowly being affected by the newer and possibly safer IL-2R antagonist preparations. This group consists of two main drugs: daclizumab and basiliximab. Both are synthetic, humanized monoclonal antibody preparations that bind to the α-subunit of IL- 2 receptor on activated T lymphocytes and inhibit IL-2 binding competitively, resulting in immunosuppression (22). Both agents are FDA approved for induction therapy for heart transplant patients, and there are no case reports of any serious side effects using the drugs. A randomized study by Carlsen et al. (24), showed no significant difference in the incidence of acute rejection between daclizumab and thymoglobulin, however, more side effects with thymoglobulin were noted such as cytomegalovirus (CMV) infections. Kobashigawa et al. (25), showed no increase in mortality, infections, or death by use of daclizumab. Daclizumab remains a popular choice in many centers for induction therapy after heart transplantation. Basiliximab has shown similar efficacy and safety as compared with daclizumab after heart transplantation (26).

Recent data from the ISHLT registry (2) have shown that there was an overall increased trend toward perioperative IL-2R antibodies used of the late years. The use of polyclonal anti-lymphocytic preparations has remained nearly stable, whereas the perioperative use of OKT3 as an induction agent has been significantly decreasing. Also, there was an

increased trend of using no induction therapy in some heart transplant centers, nearly over half of the patients had no induction therapy in the last seven years. For the 5 year survival rate, there was no statistical difference between the patients who had an induction therapy or no induction therapy, however, OKT3 used patients had the lowest rate (Fig. 1).

Maintenance therapy

In the absence of the ideal immunosuppressive drug, maintenance immunosuppression is achieved with combinations of immunosuppressive agents. Combination therapy is intended to minimize the side effects of a single drug while maintaining adequate overall immunosuppression. These immunosuppres-

Table 6. Immunosuppressive drugs for induction therapy (Modified from ref. 23)

Drugs	Trade Name	Dosing	Monitoring
Polyclonal anti-lymphocyte			• ATGAM requires skin test before first dose.
-ATGAM	ATGAM	10-15 mg/kg/d iv for 3-14 d	• Premedication is required
-ATG	Thymoglobulin	1.5 mg/kg/d iv for 3–14 d	• Monitoring is done by following CD3 counts
	ATG fresenius	2-5 mg/kg/d iv for 7–14 d	• Repeating daily dose when CD3+ cells increase may decrease number of daily doses
Monoclonal anti-lymphocyte			
- Muromonab CD3	Orthoclone, OKT3	5 mg/d for 7–14 d	• Premedication is required • Monitoring is done by following CD3 counts • HAMA may result in an increase of CD3+ cells.
IL-2R Antagonist			
-Daclizumab	Zenapax	1 mg/kg/d within 24 h of transplantation and q 14 d for 4 additional doses	• IL-2R + lymphocytes may be measured but are not generally followed clinically • Premedication is not required
-Basiliximab	Simulect	20 mg within 2 h of surgery and 4 d postoperatively	

ATG-antithymocyte globulin, ATGAM-antithymocyte gamma-globulin, HAMA-human antimouse antibodies, IL-interleukin

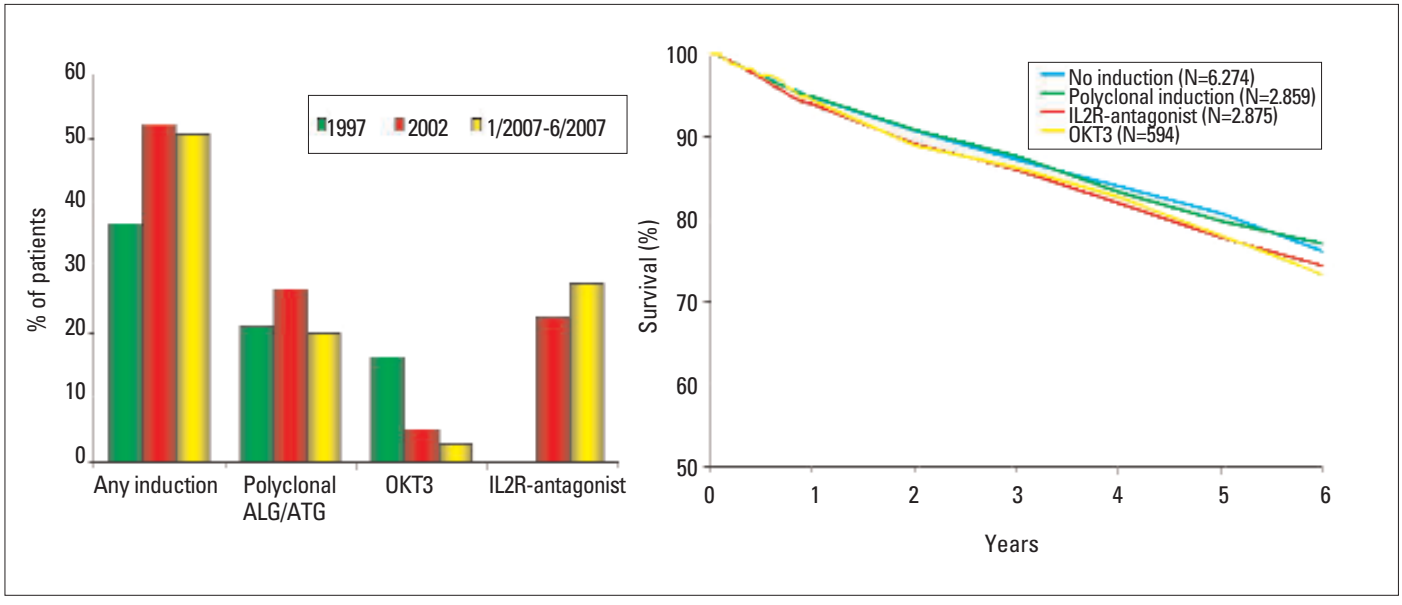

Figure 1. Types of induction therapy by year (Transplants: 1997, 2002 and 1/2007-6/2007) and survival by induction type of transplant between 2000-2006. Registry of the International Society for Heart and Lung Transplantation: twenty-fifth official adult heart transplant report-2008. ((Reproduced from ref 2. with permission of Elsevier. Copyright 2008 by International Society for Heart and Lung Transplantation)

ATG-antilymphocyte globulin, ATG-antithymocyte globulin, IL-interleukin, OKT3 -monoclonal anti-human C3 antibody

sive drugs can be grouped together in 4 major groups: 1) Corticosteroids, 2) Calcineurin inhibitors, 3) Antiproliferative agents, 4) TOR (target of rapamycin) inhibitors. The immunosuppressive drugs using for maintenance therapy are summarized in Table 7.

Maintenance therapy is generally considered a triple combination therapy with a calcineurin inhibitor, an antiproliferative agent and steroid. In recent years, most transplant centers have replaced the routine use of azathioprine with mycophenolate mefetil (MMF). In a study by Kobashigawa et al. (27), compared MMF with azathioprine in combination with cyclosporine and steroids have shown that MMF was associated with a reduction in mortality at 1 year (6.2% versus 11.4%, p=0.031) and a reduction in rejection requiring treatment (65.7% versus 73.7%, p=0.026). Hosenpud et al (28) reported, patients treated with MMF have an actuarial survival benefit (1 year, 96% versus 93%; 3 year, 91% versus 86%; p=0.0012). In conclusion, MF is more potent and beneficial than azathioprine with causing less myelosuppression and conferring more renal protection in the management of heart transplant patients. Today, MMF is the predominant antiproliferative agent used in nearly 75% of patients at 1 year (Fig. 2).

A newer antiproliferative agent mycophenolate sodium (MPS, Myfortic), is an enteric-coated analog of MMF, engineered to improve the tolerability of this drug class, especially by reducing the gastrointestinal side effects in patients. Myfortic is currently approved for use in renal transplant patients but not yet in heart transplantation (22).

For a long period, cyclosporine (CSA) has been used as first-line therapy for immunosuppression in heart transplant

Table 7. Immunosuppressive drugs for maintenance therapy

Drugs	Trade Name	Dosing	Monitoring	Side Effects
Corticosteroid -Prednisone -Prednisolone Methylprednisolone		Intraop. 500-1000 mg(iv). 5-7 mg/kg/d in 3 divided doses over next 24 h (iv). Tapered from 1 to 0.3 mg/kg/d at 3-6 mo to 0.1 mg/kg/d at 6 mo (po) Discontinue 6-12 months	No monitoring	Cushingoid appearance, hypertension, hyperglycemia, dyslipidemia, peptic ulcer formation, pancreatitis, personality changes, cataract formation, osteoporosis
Calcineurin inhibitors -Cyclosporine (CSA)	-Gengraf -Sandimmune-neoral	4-8 mg/kg/d in 2 divided doses (po) 1-2 mg/kg/d (iv)	Blood Level (ng/ml) 0-3 mo-----350-400 3-6 mo-----300-350 6-12 mo-----200-250 >12 mo-----100-150	Nephrotoxicity, hypertension, hyperglycemia, hyperuricemia, dyslipidemia, tremor, paresthesias, gingival hyperplasia, hypertrichosis
-Tacrolimus (TAC) (FK 506)	-Prograf	0.05-0.1 mg/kg/d in 2 divided doses (po) 0.01-0.02 mg/kg/d (iv)	0-1 mo----- 17-23 1-3 mo----- 15-20 3-12 mo----- 10-15 >12 mo----- 5-10	Hypertension, hyperlipidemia, hirsutism and gingival hyperplasia incidence is lower than cyclosporine
Antiproliferative -Azathioprine	-Imuran	1-2 mg/kg/d (po or iv) in 2 divided doses	Dose decreased if leucocytes <3000-4000	Bone marrow depression, hepatotoxicity Gastrointestinal upsets.
-Mycophenolate mofetil (MMF)	-Cellcept	2x (0.5-1 gr) /d (po or iv)	Mycophenolic acid (MPA) blood level 2.5-5 µg/ml (not necessary)	Bone narrow depression is lower
TOR inhibitors -Sirolimus -Everolimus	-Rapamune -Certican	2.0 mg/d (po) 1.5-3 mg/d in 2 divided doses (po)	Blood level 5-15 ng/ml 3-8 ng/ml	Delayed postsurgical wound healing, pleural and pericardial effusions, leukopenia, thrombocytopenia male hypogonadism

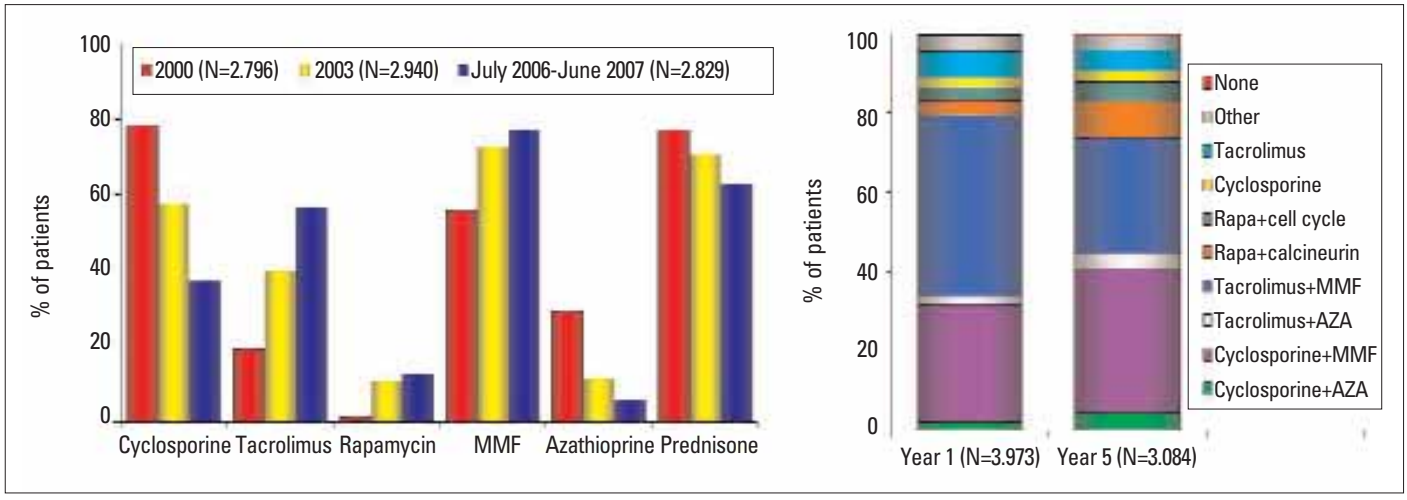

Figure 2. Drugs for maintenance therapy by year (Transplants: 2000, 2003 and 7/2006-6/2007) and drug combinations at time of follow-up 1/2005 – 6/2007. Registry of the International Society for Heart and Lung Transplantation: twenty-fifth official adult heart transplant report-2008. (Reproduced from ref 2. with permission of Elsevier. Copyright 2008 by International Society for Heart and Lung Transplantation)

AZA - azathioprine, MMF - mycophenolate mofetil, Rapa - rapamycin

patients and tacrolimus (TAC) has been reserved for patients at high risk for rejection and those with preexisting renal dysfunction. Numerous studies have made comparisons between CSA and TAC. Taylor et al (29), compared TAC with CSA in combination with azathioprine and steroid. Patient and graft survival were not different between the two groups (89% for TAC, 91% for CSA, p>0.05), serum cholesterol, low-density lipoprotein cholesterol (LDL), high-density lipoprotein cholesterol (HDL) and triglycerides were significantly higher in the CSA group. The incidence of diabetes at 1 year was similar. More CSA-treated patients were treated for hypercholesterolemia (71% vs. 41% at 12 months, p=0.01), and more CSA-treated patients developed new-onset hypertension that required pharmacologic treatment (71% vs. 48%, p=0.05). However, there was no significant difference in acute organ-rejection rates between the two groups.

In a large European multicenter study (30) compared TAC-based vs. CSA-based immunosuppression in combination with azathioprine and corticosteroids in 314 heart transplant recipients reported no significant difference for patient/graft survival at 18 months (92.9% for TAC, 89.8% for CSA, p>0.05). The overall incidence of nephrological disorders was not different between the two groups (58.6% vs 61.1%, p>0.05). Significant differences emerged between groups for these clinically relevant adverse events: new-onset diabetes mellitus was higher in TAC group (20.3% vs. 10.5%); post-transplant arterial hypertension (65.6% vs. 77.7%) and dyslipidemia (28.7% vs. 40.1%) were higher in CSA group. Incidence of first biopsy proven acute rejection of grade ≥1B (54.0% vs. 66.4%, p= 0.029) and grade ≥3A (28.0% vs. 42.0%, p=0.013) at month 6 was significantly lower for TAC vs. CSA, proved TAC-based immunosuppression provided superior prevention of moderate-to-severe acute, and recurrent acute rejection compared with CSA-based therapy (30).

Kobashigawa et al. (31) compared 343 heart transplant recipients receiving steroids and either TAC+SRL (sirolimus), TAC+MMF or CSA+MMF. Biopsy proven ≥3A rejection or hemodynamic compromise rejection requiring treatment showed no significant difference at 6 months (TAC+MMF 22.4%, TAC+SRL 24.3%, CSA+MMF 31.6, % p=0.271) and 1 year (p=0.056), but it was significantly lower in the TAC+MMF group when compared only to the CSA+MMF group at 1 year (23.4% vs. 36.8%; p=0.029). Differences in the incidence of any treated rejection were significant (TAC+SRL 35%, TAC+MMF 42%, CSA+MMF 59%; p<0.001). Median levels of serum creatinine and triglycerides were lower in the TAC+MMF group. The TAC+SRL group encountered fewer viral infections but more fungal infections and impaired wound healing. The authors suggested that the TAC+MMF combination appears to offer more advantages than TAC+SRL or CSA+MMF in heart transplant patients. In conclusion, there has been an increase of using TAC instead of CSA as the most common calcineurin inhibitor used after heart transplantation in the past few years.

The registry of ISHLT 2008 heart transplantation report (2) estimates that at 1 year 45.6% of recipients were on a combination of TAC and MMF (with or without corticosteroids), whereas 29.9% of patients were on a combination of CSA and MMF (with or without corticosteroids). The patients used TAC+MMF for maintenance therapy have a less percentage of rejection in the first year than CSA+MMF used patients. Overall, 23.7% of recipients have experienced rejection within 1 year (received a rejection treatment or no treatment) in TAC+MMF using group vs. 34.8% of recipients in CSA+MMF group (p=0.0001) (Fig. 2).

Nowadays, newer maintenance therapy regimens are being used which replace TOR inhibitors, sirolimus or everolimus, for either a calcineurin inhibitor or an antiproliferative agent. This group is known for their complications with delayed postsurgical wound healing and significant increase in the incidence of symptomatic pleural and pericardial effusions; therefore, they are not used as a first-line agent immediately after transplantation surgery (32). Keogh et al. (33) showed that the use of sirolimus in heart

transplant patients decreased the number of patients experiencing acute rejection by 50%, and also showed a decrease in the development of transplant vasculopathy at 6 months and 2 years after transplantation. In a study of 634 heart transplant recipients, CSA+everolimus was significantly more effective than CSA+azathioprine for preventing efficacy failure (death, graft loss, acute rejection grade ≥3A or rejection associated with hemodynamic compromise) at 6th, 12th and 24th months. The overall incidence of cardiac allograft vasculopathy (CAV) was significantly lower in the everolimus group. The change in intravascular ultrasonography (IVUS) measured parameters of CAV, including maximal intimal thickness and intimal volume, was significantly smaller in everolimus group. The frequency of CMV infection was lower in everolimus treated patients. Everolimus facilitated the use of reduced dose CSA without compromising immunosuppressive efficacy (34, 35).

Acute rejection

Rejection occurs against to the donor organ via multiple immune mechanisms' activation. Despite the developments of immunosuppressive therapy it has been reported that rejection was responsible for 17-30% of deaths at 1 year after transplantation. Acute rejection is frequently seen in the first three months, however, it can also develop at any time after transplantation. In the early 1980s, 70% to 85% of heart transplant recipients experienced acute rejection in the first 6 months after transplantation. More recently, documented incidence of acute rejection within the first 6 postoperative months is 40% to 70% (36). However, the clinical aspect of acute rejection is generally asymptomatic. Symptoms can be evaluated in three categories: 1) Nonspecific symptoms-fatigue, loss of weight, fever, anorexia; 2) Symptoms of cardiac irritation-sinus tachycardia, pericardial rub, new-onset atrial flutter or fibrillation, diagnosed of a new or increased pericardial effusion by echocardiography; 3) Low cardiac output symptoms-tiredness, palpitation, dyspnea, orthopnea, paroxysmal nocturnal dyspnea, jugular venous distention, gallop rhythm, hepatomegaly, peripheral edema and hypotension.

Endomyocardial biopsy (EMB)

Endomyocardial biopsy (EMB) is still the gold standard for diagnosis of acute rejection since it was first used in 1973. EMB is performed with a bioptome introduced from internal jugular, subclavian or femoral vein to sample the right ventricular septal wall. The major cause of failure in diagnosis is obtaining inadequate material. It is recommended that an absolute required minimum for evaluation is 3 biopsy pieces, each of which must contain at least 50% myocardium and exclude a previous biopsy site or scar. The rejection can be diagnosed with 95% to 98% sensitivity in these cases.

The frequency of EMB varies highly between different institutions. In our institution, biopsies are performed on postoperative 2nd, 4th , 8th and 12th weeks for the first 3 month, than on 6th and 12th month. We are performing EMB with coronary angiography yearly after the second year. If rejection is diagnosed, the patient is treated and undergoes repeat biopsy after 1 to 2 weeks. With regular and frequent endomyocardial biopsy, the rejection, if exist, can be detected at early stage and can be treated with minimal damage within the heart.

In 1990, the registry of ISHLT published a standardized international grading system for acute rejection. In 2004, under the direction of the ISHLT, a working group revised this that portraying a more clinically and histologically functional grading system (37). Grade 2 rejections resolve without treatment in the majority of cases prompted to include grade 2 rejection with the revised mild rejection category and the old grade 3A has been reclassified as grade 2R in the new grading scheme (Table 8).

Several noninvasive modalities have been investigated over the years as potential candidates for the detection of allograft rejection. Despite the development of these techniques, the EMB is still the gold standard, as noninvasive methods are associated with low specificity for the diagnosis of rejection.

Table 8. ISHLT standardized EMB grading scheme (Reproduced from Ref. 37 with permission of Elsevier, Copyright 2005 by International Society for Heart and Lung Transplantation)

Grade	Description (1990)	Grade	Description (2004)
0	No rejection	0R	No rejection
1A	Focal (perivascular and/or interstitial) lymphocytic infiltrate without myocyte necrosis	1R, mild	Interstitial and/or perivascular infiltrate with up to 1 focus of myocyte damage
1B	Diffuse but sparse lymphocytic infiltrate without myocyte necrosis		
2	One focus only with aggressive lymphocytic infiltrate and/or focal myocyte injury	2R, moderate	Two or more foci of infiltrate with associated myocyte damage
3A	Multifocal aggressive lymphocytic infiltrates and/or focal myocyte necrosis	3R, severe	Diffuse infiltrate with multifocal myocyte damage (±edema, ±hemorrhage, ±vasculitis)
3B	Diffuse, inflammatory process with myocyte necrosis		
4	Diffuse, aggressive, polymorphous infiltrate with necrosis (±edema, ±hemorrhage, ±vasculitis)		

Imaging techniques to determine rejection include echocardiography and magnetic resonance imaging (MRI). Increased wall thickness with myocardial edema that occurred during rejection can be seen with MRI but it's only determinative for advanced rejection (38). Echocardiographic left ventricular mass index, systolic and diastolic performance, the ratio of the peak early to late mitral valve annulus velocity (Emax/Amax) and isovolumic relaxation time can differ between rejecting and non-rejecting groups (39). Newly developed mitral insufficiency and pericardial effusion can be correlated with rejection. Echocardiographic findings may be helpful but limited by low specificity.

Myocardial edema associated with the rejection process result in electrical conduction abnormalities. This phenomenon has led to the development of devices implanted during transplantation for telemetric monitoring of intramyocardial electrocardiograms. Changes in the ventricular evoked response amplitude obtained during ventricular pacing have been correlated with rejection. This technique has a sensitivity of 80%, specificity of 50%, and a negative predictive value of 97% (40).

A variety of circulating markers have been studied in allograft rejection. B-type natriuretic peptide (BNP) is produced in response to cardiac stress. In a recent study, acute rejection episodes (ISHLT grade 2 or greater) were associated with marked BNP increases and a significant decrease was associated with successful treatment in the majority of patients. The BNP monitoring was, however, associated with only a moderate diagnostic accuracy (41).

Another novel non-invasive marker for the rejection is breath methylated alkane contour. Rejection is accompanied by oxidative stress that degrades membrane polyunsaturated fatty acids, evolving alkanes and methylalkanes, which are excreted in the breath as volatile organic compounds, which can be collected and analyzed by gas chromatography and mass spectroscopy. The test has a sensitivity of 78.6% but a specificity of only 62.4% for the detection of ISHLT grade 3 rejection (42).

The Cardiac Allograft Gene Expression Observation Study (CARGO Trial) is a multicenter study that aimed screening for genetic markers to determine a gene expression profile which may be representative of the rejection process. Microarray technology was used to screen for a number of candidate genes that were expressed in cardiac allograft rejection as determined by routine endomyocardial biopsy. The selected genes were then examined in peripheral leucocytes using polymerase chain reaction from blood samples obtained at the time of endomyocardial biopsy. The technique has a high negative predictive value (for grade ≥3A rejection above 99%) for the diagnosis of acute rejection (43). This method of detection of acute rejection is currently being employed at a number of transplant centers.

Acute rejection therapy

Despite the standardization and evaluation of endomyocardial biopsies, the treatment of acute rejection shows variety and individuality. Treatment decision may be taken according to the clinical symptoms, histological findings, and hemodynamic changes. The type of therapy generally depends on timing after transplantation, the severity and the protocols of individual centers. Therapy may include intravenous or oral steroids, monoclonal or polyclonal antilymphocyte agents or an increase (e.g., increasing levels of CSA, TAC, MMF) or change (eg., switching CSA to TAC or MMF to everolimus) in current therapy.

The standard practice in heart transplantation has been routine treatment for biopsy grade 3A or higher and employs intravenous steroids as a first line therapy. Symptomatic patients (e.g., presenting with fever, arrhythmias, hemodynamic compromise) are often treated despite lesser grade biopsy results. Because 25% of non-treated patient's rejection score progress to from grade 1B to grade 3A in the first 6 months after transplantation, asymptomatic grade 1B rejection is treated with augmented immunosuppression (increase in calcineurin and/or steroid dose) in some centers. Grade 2R or moderate rejection (grade 3A as per the old ISHLT scale) can be treated with oral or intravenous high-dose pulse steroid therapy for 3 to 5 days. Grade 3R or severe rejection (grade 3B or 4 as per the old ISHLT scale) is usually treated with a course of oral or intravenous high-dose pulse steroid therapy for 3 to 5 days, along with either an increase in the dose of immunosuppression drug or a substitution of the immunosuppressive therapy. A monoclonal or polyclonal antilymphocyte agent is often used in patients with evidence of hemodynamic compromise (hypotension, low cardiac output, or reduced left ventricular ejection fraction) (22).

Recurrent or severe episodes of acute rejection have been correlated with the development of allograft vasculopathy. Later graft damage may occur due to these repetitive mild rejection attacks and these patients' survival rates are lower than patients without rejection.

Infective diseases

Because of the successive transplantation can be achieved only with adequate immunosuppression, infections are the most important mortality and morbidity causes in this patient group. The scanning of the recipient and donor before transplantation in terms of infective diseases has viable importance for preventing possible complications and eliminating ineligible recipients and donors. Transplantation should not be performed if the donor is positive and recipient is negative for HIV and Hepatitis B virus infection. In terms of Hepatitis C virus positivity the transplantation decision should be taken according to emergency of transplantation and recipient age (44).

Transplanted patients often do not present with typical signs and symptoms of infection because of their immunodeficiency state. Even though significant progress in prophylaxis has been made, as much as 20% of deaths in the first year of posttransplant may be attributed to infections and the attendant complications. Infections can be evaluated in three time periods; first month (early post-transplantation period), between 1-6 months and late post-transplantation period (>6 month).

Early post-transplantation period can be considered as nosocomial phase and infections in this period are due to catheters insertion and incision area, and nosocomial pneumonia are predominant. The most frequent bacterial agents are staphylococcus and gramnegative bacteria. The major infectious agent in viral causes are herpes simplex viruses, which can reactivate in seropositive patients. Prophylactic usage of acyclovir decreases the frequency of herpes infections in this period.

Transplantation related classical infections are usually seen between 1st and 6th months. Patients are susceptible to infection with reactivated viruses such as herpes simplex virus (HSV), Epstein-Barr virus, and most notably CMV. In addition, opportunistic infections such as Pneumocystis carinii pneumonia (PCP) and infections because of Nocardia and Aspergillus might become clinically apparent. Listeria and fungi are typically seen in this period. In this period, the activation of latent infections due to immunosuppression can develop. Mycobacterium tuberculosis has special importance for our country. The most affected areas are lungs, gastrointestinal system, urinary system, skin and surgical area (45). Routine prophylaxis against CMV, HSV, and PCP is now commonly used, which reduces the risk of these infections. Current recommendations suggest one tablet of trimethoprim–sulfamethoxazole 3 to 7 times a week. This regimen helps prevent infections with PCP, Toxoplasma, and Nocardia. Nystatin oral solution is commonly used to help treat oral candidiasis and gastrointestinal colonization (3 to 14 days of treatment) in posttransplant patients.

After 6 months, the heart transplant patients are generally at risk for community-acquired pathogens, especially those causing pulmonary infections. Opportunistic infections are less common. A small portion of transplanted patients continues to be plagued with chronic infections such as hepatitis B and C virus, CMV, and even papilloma virus.

Cytomegalovirus infections

The most important infective pathogen after transplantation is CMV. It is a virus in Herpes viridae family and the only known reservoir (host) is human. The contagious needs close contact between people. This infection is usually asymptomatic in healthy people. However, in solid organ recipients it is frequently seen in first 3 months when the immunosuppression is maximum. Cytomegalovirus infection is a major cause of morbidity and mortality in transplanted patients, with 26% incidence of seroconversion of CMV IgG-negative recipients after heart transplantation from IgG-positive donors within the first 3 months and 75% within the first year after transplantation (46). Cytomegalovirus is the cause of multiple complications, including acute viral syndrome, pneumonitis, gastroenteritis, hepatitis, retinitis, myocarditis, chronic allograft rejection and endothelial dysfunction (47).

Serologic tests have no value in diagnosis. Diagnosis can be made by demonstration of viremia and tissue invasion. The tests used in diagnosis are histological evaluation of tissues, detection of CMV antigenemia in blood samples, viral culture or CMV PCR tests. Generally, there are two approaches to prevent CMV infection: 1) Prophylaxis - initiating antiviral agent to all patients or high-risk patients; 2) Preventive therapy-initiating antiviral therapy when CMV replication is detected.

Oral valganciclovir, high dose acyclovir or valacyclovir therapy can be initiated for prophylaxis. If significant viremia is detected during follow-up with PCR or antigenemia on preemptive therapy, parenteral ganciclovir 2x5 mg/kg/day for 2-3 weeks is given until the viremia disappears.

Long-term complications in heart transplantation

With an important increase in post-transplantation survival, various long-term complications can be experienced, especially due to the use of immunosuppressive drugs. Table 9 shows the most frequent complications experienced fifth and tenth years in patient with heart transplantation between 1994-2006 (2).

Hypertension: Five years after transplantation, approximately 95% of patients suffer from hypertension. Development of hypertension mostly depends on calcineurin inhibitors and corticosteroid usage and cardiac denervation. The TAC has shown to confer a slightly lower incidence of

Table 9. Cumulative prevalence of morbidities in survivors at 5 and 10 years post-transplant (follow-ups: 1994 - 2006) (Data from ISHLT registry -2008 available at http://www.ishlt.org/registries/quarterlyDataReport.asp)

Outcome	Within 5 years	Total N	Within 10 years	Total N
Hypertension	%93.8	(N=8.266)	%98.5	(N=1.586)
Renal Dysfunction	%32.6	(N=8.859)	%38.7	(N=1.829)
Abnormal creatinine <2.5 mg/dl	%21.2		%24.4	
Creatinine >2.5 mg/dl	%8.4		%8.2	
Chronic dialysis	%2.5		%4.9	
Renal transplantation	%0.5		%1.2	
Hyperlipidemia	%87.1	(N=9.237)	%93.3	(N=1.890)
Diabetes mellitus	%34.8	(N=8.219)	%36.7	(N=1.601)
Allograft vasculopathy	%31.5	(N=5.944)	%52.7	(N=896)

hypertension compared with CSA (30). The latter causes hypertension via direct sympathetic stimulation, direct vascular effect and neurohumoral activation and indirectly might worsen renal function, which can further impair blood pressure control.

Salt restriction is the first step in hypertension treatment. The first medical choice is calcium channel blockers. Diltiazem reduces the cost of immunosuppressive therapy because it elevates cyclosporine levels. Angiotensin-converting enzyme (ACE) inhibitors (enalapril, ramipril) are also used. Generally, the combination of ACE inhibitor and calcium channel blocker is used. The third medication option is, if the patient's renal functions are normal, diuretics. Alfa-adrenergic blockers may be used in treatment resistant hypertension. Carvedilol must be the first choice if β-blockers will be used.

Chronic renal insufficiency: The major risk factor of renal failure is usage of calcineurin inhibitors in immunosuppressive therapy. The other risk factors are DM, hypertension, systemic atherosclerosis and pre-existing compensated renal failure due to heart failure. Renal functions are impaired by 20% at first year of heart transplantation in 20% of patients who use CSA as immunosuppressive agent. At fifth year 8.4% of patients' serum creatinine levels raise above 2.5 mg/dl and in 3% of all patients will progress to end-stage renal disease requiring hemodialysis or renal transplantation. It is imperative to continue monitoring for renal insufficiency as it has direct effect on several drug levels and dosages and may exacerbate many drug-drug interactions.

Diabetes mellitus (DM): DM can be attributed to the use of corticosteroids, however calcineurin inhibitors also contribute to diabetes. The TAC is associated with a higher incidence of posttransplant diabetes than CSA (30).

Hyperlipidemia: The basic causes of hyperlipidemia are inappropriate nutrition, genetic predisposition and immunosuppressive therapy (48). The CSA elevates serum cholesterol levels by reducing the bile acid synthesis from cholesterol and inhibiting lipoprotein lipase activity. On the other hand, corticosteroids induce acetyl-CoA-carboxylase activity, free fatty acid synthesis, hepatic synthesis of very low-density lipoprotein cholesterol (VLDL) and HMG-CoA reductase activity so that total cholesterol, triglyceride and LDL cholesterol levels elevate whereas HDL cholesterol levels decrease. Hyperlipidemia is seen in more than 85% of patients five years after transplantation. The most preferred and suggested agent in transplant patients is pravastatin. Pravastatin has been shown to have the lowest incidence of rhabdomyolysis and proved to provide a significant reduction in the progression of CAV in heart transplant patients (49). If the patient's liver function tests are normal it should be started with 10 mg initial dose in hospital. Six week after, if the liver enzymes are still within normal limits dose can be raised up to 20 mg. Three mounts later, the goals of triglyceride <200 mg/dl, LDL<100 mg/dl and HDL >40 mg/dl should be achieved with 40 mg pravastatin. If this blood lipid goal levels couldn't be obtained with pravastatin it can be substituted with atorvastatin. A week after transplantation, empiric statin therapy is suggested if there is no any specific contraindication.

Bone complications: Osteoporosis is an important morbidity factor, especially in postmenopausal women, using corticosteroids as an immunosuppressive agent. Two years after transplantation, 20% of patients have severe osteoporosis on the neck of femur and 28% of patients-on lumbar vertebrae. Vertebral compression fractures have been reported in 10% to 30% of patients who had severe osteoporosis Avascular necrosis of femoral head can be seen due to long-term usage of corticosteroids (50).

Malignancies: Malignancies play a major role as cause of death after cardiac transplantation. In the long-term course after cardiac transplantation, the risk of malignancies is 1-2% per year. This risk is 10-100 fold higher than the risk in age-matched control population. Malignant tumors of the skin and lymphomas are the most frequent types, but any solid organ tumor may occur (Table 10). The mechanisms of neoplasia are; deterioration in immune function and regulation, the synergic affect of immunosuppressive drugs, exceeding use of immunosuppressive agents and oncogenic viruses. Azathioprine may cause skin cancer and the use of OKT3 is responsible for increased incidence of post-transplantation lymphoproliferative disease (PTLD) (51). The major oncogenic viruses are Ebstein-Barr virus (EBV) and Human papilloma virus. The EBV-induced PTLD develops because of abnormal proliferation of lymphoid cells. It is seen more frequently (24-33 times) in pre-transplant EBV seronegative recipients than in seropositive recipients and also seen more often in recipients who take cytolytic therapy like OKT3.

Table 10. Malignancies after heart transplantation (Data from ISHLT registry-2008 available at http://www.ishlt.org/registries/quarterlyDataReport.asp)

		1 year follow-up	5 years follow up	10 years follow up
Malignancy (-)		(97.1%) 20441	(84.9%) 7780	(68.1%) 1264
Malignancy (+) (all kinds)		(2.9%) 612	(15.1%) 1389	(31.9%) 592
Malignancy Type	Cutaneous	282	937	360
	Lymphoma	142	127	38
	Other	132	359	108
	Unknown type	56	39	126

Gastrointestinal (GIS) complications: In the first 3-5 years, GIS complications are seen in about 15-30% of patients. Corticosteroids may cause development of peptic ulcer, intestinal perforation, bleeding and pancreatitis.

Ocular complications: Due to inverse affects of steroids used in immunosuppressive therapy cataract and glaucoma may develop. The CMV is the most responsible infection in retinitis.

Cardiac allograft vasculopathy (CAV)

Despite the improvements in long-term outcomes of heart transplantation, cardiac allograft vasculopathy is still the major cause of mortality, approximately 20% of all deaths, after the first years of transplantation (2).

Cardiac allograft vasculopathy is a complicated interplay between immunologic and non-immunologic factors resulting in repetitive endothelial injury and a localized sustained inflammatory response. Endothelial injury is followed by intimal hyperplasia and the proliferation of vascular smooth muscle cells. It is a progressive condition characterized by diffuse, concentric thickening of the epicardial and intramyocardial coronary arteries. The obstructive process can progress to near-complete occlusion of the coronary arteries causing micro- and macro-infarctions. The histological findings differ from those seen in typical atherosclerosis, with a uniform pattern of near-luminal occlusion by neointimal proliferation, fewer early accumulations of extracellular lipid, and infiltrates of T cells that encircle the entire vessel (52).

Cardiac allograft vasculopathy can begin soon after transplantation developing rapidly in a matter of months or years. Its incidence is reported to be 10-15% for every each year and it is seen in almost half of the patients by 5 years after transplantation. The exact etiology of CAV is not well defined but certain predisposing factors have been identified, including immunological mechanisms with alloreactive T cells and the humoral immune system, and non-immunologic factors such as older donor age, injury due to ischemia or reperfusion, hyperlipidemia and infections particularly CMV infections (53). Patients are usually asymptomatic. Coronary angiography and intravascular ultrasound (IVUS) are the first steps in diagnosis. Annual coronary angiography is performed for diagnostic and surveillance purposes. With coronary angiography, especially diffuse narrowing and occlusion in middle and distal coronary arteries, and abrupt distal vessel obliteration can be visualized. Abrupt occlusion in secondary branches constitutes "pruned-tree" appearance.

Intravascular ultrasound is a more sensitive diagnostic tool for early disease stages. It can visualize the all three layers of artery. Because of the catheter's diameter is smaller than 1 mm, the catheter can be advanced into all 3 major coronary arteries' distal parts. In more than 50% of the patients who have normal coronary angiography results, there is a significant intimal thickening demonstrated by IVUS. The allograft vasculopathy criteria with IVUS is that being 0.3 mm or above of the intimal thickening. The determination of coronary flow reserve using an intracoronary Doppler wire further complements IVUS in the evaluation of allograft vasculopathy. Because abnormalities in flow reserve most often reflect microvascular disease, this analysis is particularly important to detect early stage disease (54). Serum IL-2 levels and cardiac isoenzymes, dobutamine stress echocardiography, radionuclide scintigraphy and ultrafast computerized tomography can be also used in diagnosis of CAV.

Several pharmacological agents, including the calcium channel blocker diltiazem, statins such as pravastatin, and newer antiproliferative immunosuppressive agent everolimus have been used to slow down the progression of CAV.

Long term patient follow-up after heart transplantation

Patients should be followed after heart transplantation with EMB: 2nd, 4th, 8th and 12th weeks for the first 3 month, on 6th and 12th month and then once a year. Table 11 shows follow-up procedures for patients with heart transplantation.

Table 11. Follow-up post-transplant patients

Investigation	Frequency
Blood research at excrement	Once a year for all patients over 50 years of age
Colonoscopy or/with sigmoidoscopy	Once three years for all patients over 50 years of age
Prostatic touch	Once a year for men after 50 years of age
PSA (prostate specific antigen)	Once two years for all patients over 50 years of age
Mammography	Once a year for women after 35 years of age
Pelvic examination/pap smear	Once a year for women after 35 years of age
Chest radiography	Once every six months
Dermatological investigation	Once a year
Blood cholesterol levels	Once every six months
Bone densitometry	Once a year
Ophthalmic investigation	Once a year
Examination of teeth	Once every six months

Expected survival and life quality after heart transplantation

Success of heart transplantation is evaluated in according to survival rates and long-term outcomes. One-year survival is reliable for early succession. Comparing the major causes of death for the first year with the following years, it is clearly observed that they differ from each other. According to the registry of ISHLT 2008 report (2), it is obviously seen that the major mortality cause in the first 30 days after transplantation is primary graft failure. In the first year, the most frequent causes are rejection and infections. After the first year, malignancies and cardiac allograft vasculopathy are the major mortality reasons (2) (Table 12).

Nowadays, most of the heart transplantation centers report survival of heart transplant patients with over 95% in the first month and 86% survival in the first year after transplantation. According to the ISHLT 2008 data (2), the average half life of 74267 patients with heart transplantation between 1982 and 2006 was 10 years. It was reported that in the first year, 5 years, 10 years and 15 years, the survival rates were 82%, 69%, 51% and 33% in these patients' follow-up (2).

Due to increased experiments in heart transplantation, new immunosuppressive medications and developments in diagnosis and treatment of rejection, in recent years, the patients' expected survivals also increase significantly. From the ISHLT 2008 data (2), medial half life of patients who have experienced heart transplantation between 1982 and 1991 was 8.9 years whereas it has increased to 10.3 years for the patients experienced transplantation between 1992 and 2001. The life quality should also be taken into account when assessing the success of heart transplantation. The life quality is assessed with functional performance, psychosocial, physical and mental situations. The expected one year survival of the candidates of the heart transplantation is about %50 while life quality may be worsened by severe heart failure symptoms. After transplantation, in more than 90% of patients symptoms of failure disappear or reduce to minimum. While nearly all of the patients were in NYHA class III-IV preoperatively, they have an improved functional status with NYHA class I-II after transplantation (2).

Conclusion

Despite improvements in medical treatment and alternative surgical approaches such as coronary revascularization in ischemic cardiomyopathy, valve reconstruction and ventricular restoration in dilated cardiomyopathy, heart failure is still the major cause of death. Heart transplantation is a widely accepted therapy for the treatment of the end-stage heart failure and can be performed with adequate success rates. Nowadays, most transplantation centers are reporting a survival rate above 85% at one year and 50% to 60% at ten years. The survival benefit after heart transplantation is a result of a better understanding of immune mechanisms, development of new immunosuppressive drug regimens, improved postoperative follow-up care and organ preservation methods. The success rates lead to a widespread initiation of transplant programs and an enlargement of waiting lists. However, heart transplantation is limited by the huge discrepancy between the number of available donors and the number of patients suffering from end-stage heart failure. At this point, expanding the donor pool becomes crucial and standard donor criteria can be significantly liberalized to

Table 12. Cause of deaths in heart transplant patients (deaths: 1992-2006) (Data from ISHLT registry -2008 available at http://www.ishlt.org/registries/quarterlyDataReport.asp)

CAUSE OF DEATH	0-30 days (N=3.006)	31 days-1 year (N=2.722)	>1-5 Years (N=3.992)	>5-10 Years (N=4.054)	>10 years (N=2.107)
Allograft vasculopathy	%1.7	%4.7	%15.0	%14.3	%14.7
Acute rejection	%6.4	%12.4	%7.4	%1.7	%1.2
Lymphoma	%0.1	%2.0	%4.6	%4.8	%3.5
Malignancy (other)	%0.0	%2.1	%14.3	%18.5	%18.6
CMV(+) infection	%0.1	%1.2	%0.5	%0.1	%0.0
Infection (non CMV)	%13.1	%32.9	%11.3	%10.9	%10.1
Primary failure	%26.7	%7.2	%5.3	%4.6	%2.0
Graft failure	%15.1	%11.2	%16.6	%14.3	%14.7
Technical	%7.8	%1.0	%0.9	%0.9	%0.9
Other	%5.4	%6.4	%8.4	%8.4	%8.3
Multiple organ failure	%11.8	%9.8	%5.5	%7.6	%9.0
Renal Failure	%0.7	%0.9	%2.6	%5.6	%8.2
Pulmonary	%4.4	%4.0	%4.6	%4.2	%4.7
Cerebrovascular	%6.7	%4.1	%3.3	%4.1	%3.9

CMV - cytomegalovirus

increase the available donor pool by accepting 'marginal donors' who would normally be rejected. Limitations in organ donation also lead to increase researches on alternative treatment methods. There are ongoing investigations on new medications, assisted circulation devices, dual-chamber pacing, genetic therapy methods and xenograft transplantation.

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