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Review Article

Cardiac Transplantation in Pediatrics: Drugs and Treatment

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ABSTRACT

Heart transplantation is a standard treatment for some pediatric patients with end-stage cardiac disease. With advances in surgical technique, postoperative care, and immunosuppression, survival has increased significantly and, in most cases, can reach 15 to 20 years. The most common indication for heart transplantation in children is cardiomyopathy, followed by complex congenital heart diseases. An irreversible increase in pulmonary vascular resistance is an accepted contraindication to transplantation, although an accepted value for IRVP remains controversial. Graft survival depends on ongoing immunosuppression. It is also common for patients to take several other medications to treat or prevent transplant complications. Corticosteroids, such as prednisolone and methylprednisolone, cause a decrease in peripheral blood lymphocytes. Antiproliferative agents, such as mycophenolate mofetil (MMF) and azathioprine (AZA), inhibit purine metabolism, resulting in dysfunctional DNA synthesis in lymphocytes. Both can be administered orally or by intravenous infusion. Posttransplant hypertension is general and is partly due to the side effects of steroids and calcineurin inhibitors. Most patients require at least one antihypertensive agent. Cardiac allograft vasculopathy (CAV) has a major impact on the long-term prognosis of transplant patients. Current medical management of VAC is limited. The introduction of mammalian target of rapamycin inhibitors has shown promise in slowing disease progression.

INTRODUCTION

Heart transplantation is a standard treatment for some pediatric patients with end-stage heart disease.[1] With improved surgical techniques, organ procurement and preservation strategies, immunosuppressive medications, and more sophisticated monitoring strategies [2], survival after transplantation has increased over time.

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However, rejection, infection, renal failure, posttransplant lymphoproliferative disease, and vasculopathy after cardiac allograft still prevent long-term survival.[3,4] Heart transplantation is considered the final treatment option for patients with end-stage heart disease. The first pediatric heart transplant was performed in 1968[5] in a 3-week-old patient with tricuspid atresia from an anencephalic donor. The annual report of the International Society for Heart and Lung Transplantation (ISHLT) highlighted that pediatric heart transplant cases have increased significantly since the publication of the first registry report in 1982, and that 550 pediatric patients have received heart transplants each year and continue to do so.[6] Heart transplantation improves prognosis and quality of life of children with end-stage heart disease. Thanks to advances in surgical technique, postoperative care, and immunosuppression, survival has increased significantly and, in most cases, can reach 15 to 20 years. The most common indication for heart transplantation in children is cardiomyopathy, followed by complex congenital heart disorders.[7] The prognosis after heart transplantation is largely determined by complications resulting from rejection or medication-related complications. Primary transplant failure, acute rejection, coronary vasculopathy, infections, and the development of malignancies are the main causes of death. Despite a decrease in the incidence of graft rejection following improved immunosuppressive protocols, coronary vasculopathy remains the leading cause of long-term death after transplantation, and treatment options are limited.[8] Heart transplantation is an established therapy for children with end-stage heart failure. The initiation of ciclosporin in the 1980s has significantly enhanced quality of life and survival. In recent decades, approximately 4,000 to 4,500 heart transplants have been performed each year worldwide (195 in the UK in 2015).[9] This includes 450-500 paediatric cases (30-40 in the UK per year) and the proportion remains relatively stable. Children under 2 years of age and adolescents are the most frequently transplanted age groups. In children, the two most common indications for transplantation are dilated cardiomyopathy and congenital heart disease. [10] There is an increasing number of patients suffering from heart failure after palliative surgery for congenital heart disease, especially after palliative surgery with a single ventricle strategy.[11]

Indications and contraindications for heart transplantation

Indications

Some children with heart failure have an unacceptable quality of life and are severely limited in their ability to perform daily activities despite maximum medical treatment. Some patients also require intravenous infusion of inotropic drugs or mechanical circulatory support to maintain adequate tissue perfusion. Children with congenital heart disease who are not suitable for surgery or with incurable arrhythmias may also be considered suitable for transplantation. If no organs are available, the progressive nature of the disease eventually leads to death.[12]

Contraindications

An irreversible increase in pulmonary vascular resistance is an accepted contraindication for transplantation, although an accepted value for IRVP remains controversial. Patients with active infection or malignancy, significant genetic or metabolic disorders with multiorgan involvement, severe irreversible pulmonary, renal, or hepatic failure, uncertain neurologic prognosis, and significant behavioral problems that increase the risk of dangerous treatment noncompliance after transplantation are also relative contraindications for heart transplantation.[13]

TRANSPLANT LIST

Transplant Evaluation

Patients with end-stage heart disease are referred to transplant centers for evaluation by members of the transplant team, including a transplant cardiologist. [14] The evaluation consists of a number of tests and clinical examinations designed to assess their initial condition and inform families about the relative benefits and harms of heart transplantation. This results in a multidisciplinary decision regarding eligibility and timing of inclusion on the waiting list.[15] Parents and their children are also involved in the decision-making. A patient is accepted on the waiting list only if a heart transplant appears to be the best option. In some cases, alternative treatment, such as intensified medical or surgical intervention, may be recommended. Pre-transplant testing.[16] Patients undergo blood tests, samples, ECG, 24-hour ECG, ECHO, stress, abdominal ultrasound, and chest X-ray.

DRUGS USED IN TRANSPLANT PATIENTS

Graft survival depends on ongoing immunosuppression. It is also common for patients to need to take multiple other medications to treat or prevent transplant complications.[17] Despite recent improvements in patient survival rates, side effects caused by these agents remain a significant concern.

Immunosuppressive Drugs

There are probably almost as many immunosuppressive drug protocols as there are transplant units worldwide. Below is a discussion of the medications used, although a universal immunosuppression strategy is a source of ongoing debate. No randomized trials of immunosuppression have yet been conducted in the pediatric population, although efforts to establish an international trial are underway.[18]

Corticosteroids

Corticosteroids, namely prednisolone and methylprednisolone, cause a reduction in peripheral blood lymphocytes. Steroids inhibit T-cell proliferation and the expression of genes encoding interleukins 1, 2, and 6. If no rejection is detected during a routine biopsy, doses are gradually reduced to a maintenance dose, then discontinued (at our center, generally after 3 months). Adverse effects include electrolyte imbalances, hypertension, hyperglycemia, growth retardation, osteoporosis, myopathy, redistribution of body fat, acne, and hirsutism.[19]

Antiproliferative agents

Antiproliferative agents, such as mycophenolate mofetil (MMF) and azathioprine (AZA), inhibit purine metabolism, resulting in dysfunctional DNA synthesis in lymphocytes. Both can be administered orally or by intravenous infusion. The use of mycophenolate mofetil may be limited by adverse gastrointestinal symptoms (such as diarrhea, constipation, vomiting, and abdominal pain) that usually respond to dose reduction.[20] Other side effects include tremors, leukopenia, thrombocytopenia, hyperglycemia, and hypercholesterolemia. The main side effects of azathioprine include myelosuppression (leukopenia, anemia, and thrombocytopenia) and hepatotoxicity.[21]

Calcineurins

Calcineurin inhibitors include tacrolimus and cyclosporine. The incidence of rejection is significantly lower with tacrolimus than with cyclosporine and therefore tacrolimus is the preferred agent at our institution. Tacrolimus inhibits the biochemical transcription pathway of genes encoding IL-2 and IL-2 receptors. It therapeutic index is narrow and requires monitoring of drug level. It is administered orally or intravenously. Toxicity usually presents as nephrotoxicity, hypertension, convulsive encephalopathy, glucose intolerance, and nausea. Cyclosporine is a second-line immunosuppressive drug and can cause hypertension, hirsutism, tremors, and nephrotoxicity.[22]

Mammalian target of rapamycin (mTOR) inhibitors

mTOR inhibitors such as sirolimus and everolimus also block IL-2, but their mechanism of action is different from calcineurin inhibitors. They have low nephrotoxicity and are used in patients with chronic renal failure. Studies suggest that early use of these antiproliferative agents reduces the incidence of cardiac allograft vasculopathy [23] in the first year, but they have been disappointing in preventing poor outcomes in follow-up studies. Their effect on children remains unknown.

Immunosuppressive antibodies

Immunosuppressive antibodies are used as induction agents and lead to a high degree of immunosuppression immediately after transplantation, when the risk of rejection is highest. They allow the introduction of calcineurin inhibitors when renal function is stable and thus reduce their nephrotoxicity. T-cell diminishing agents can also be used in the treatment of severe rejection. Administration of the antibodies may cause an anaphylactic reaction, fever, or chills.[24] Basiliximab is a monoclonal antibody that blocks the T-cell response to interleukin 2, but does not cause T-cell depletion, administered in two doses 4 days apart as an induction drug with an effect lasting 4 to 6 weeks. Antithymocyte globulin is an animal polyclonal antibody that blocks T-cell membrane proteins, resulting in profound T-cell depletion. It serves as both an induction therapy to initiate immune suppression and a maintenance therapy to prevent organ rejection.[25]

Other commonly used medications

Posttransplant hypertension is usual and is partially due to the side effects of steroids and calcineurin inhibitors. Most patients require at least one antihypertensive agent. Prophylaxis against CMV, fungi, and pneumocystis is required for several months after transplantation in all patients. Lipid-lowering medications, such as pravastatin, are used in some settings before discharge. Prevention of cardiac allograft vasculopathy is related not only to the cholesterol-lowering effect but also to the supposed anti-inflammatory properties.

Non-compliance with drug therapy can lead to irreversible rejection with graft loss. If the transplant was performed at a very young age, patients may not fully appreciate the need for immunosuppressive medication and may discontinue it as soon as they feel well. Experience shows that adolescent girls are at greater risk.[26]

OUTCOME AFTER HEART TRANSPLANTATION

The general prognosis after heart transplantation is good in most cases, but it is limited by some potential complications. The improvement in functional capacity is remarkable, and it is generally difficult to distinguish successful heart transplant recipients from their normal peers. In the early years of the heart transplant program at GOSH, only about half of the patients survived for 10 years.[27] With advances in immunosuppression, intensive care, and medical knowledge, the prognosis has improved. In the UK, the 30-day, 1-year and 5-year paediatric survival rates are 96%, 90% and 84% respectively. Currently, it is realistic to expect a median survival of 15 years after heart transplantation. Primary graft failure (PGF) Primary graft failure (PGF) is a serious problem that presents as severe cardiac dysfunction immediately after surgery for which there is no identifiable secondary cause. It is the main contributor of death in the first 30 days after transplantation.[28]

Primary Graft Failure (PGF)

Primary graft failure is thought to likely result from catecholamine toxicity, pro-inflammatory mediators, and ischemia-reperfusion injury that causes calcium overload and oxidative stress. Donor, recipient, and methodological factors play important roles in the development of primary graft failure. In general, organs from younger

donors are believed to have more reserve and are less likely to fail.[29]

INFECTION

Transplant patients are highly susceptible to life-threatening infections during the first year after surgery, which can lead to hospitalization and death. Several factors influence the occurrence and type of infectious complications. The immune system weakened by immunosuppression has a reduced ability to fight not only common bacteria and viruses, but also rare opportunistic pathogens. Notably, CMV can be transmitted from a CMV-positive donor to a CMV-negative recipient through the transplanted organ. For this reason, prophylaxis against CMV, pneumocystis, and mold is necessary for several months after transplantation. In addition, nosocomial infections such as catheter-related sepsis or ventilator-acquired pneumonia are also common in the intensive care setting.[30] It is important that patients are vaccinated as early as possible in the course of the disease, as live vaccines are contraindicated after transplantation. The highest risk of viral infection occurs approximately 6 to 8 weeks after transplantation. Cytomegalovirus (CMV) infection is common in the pediatric transplant population, but CMV mortality is low. Human CMV patients- HIV negative people who receive an organ from an HIV-positive donor are at the increased risk of developing infection. Although some studies have suggested that CMV infection plays a role in rejection, CAV, and PTLD, there is insufficient evidence to support this hypothesis. Positive CMV serology at the time of transplantation has not been associated with death or the development of CAV.29 Other common viral infections include Epstein-Barr virus (EBV), herpes simplex virus, varicella-zoster virus, and influenza virus. EBV is another human herpesvirus that causes a spectrum of diseases with limited therapeutic options; this can range from infectious mononucleosis to PTLD with limited treatment options. Varicella infection should be treated with acyclovir, and administration of varicella-zoster immunoglobulin within 48 hours of exposure is indicated as a preventive measure.[31]

Cardiac allograft rejection

Cardiac allograft rejection is a direct immune response against HLA antigens in the donor heart that are recognized as foreign. Non-HLA antigens can also cause rejection, but this is thought to be less common. Hyperacute rejection is currently rare and occurs when a patient is highly sensitized to the donor (positive donor-specific match).[32] Donor-specific anti-HLA antibodies are routinely monitored after transplantation. Transplant rejection often occurs several months post-surgery, but can arise at any point during the recipients life-time. Recipient sensitization from previous transplants, blood transfusions, pregnancy, use of homograft's, and ventricular assist devices play an important role and increase the risk of antibody-mediated rejection episodes. The process may present with symptoms of heart failure, arrhythmias, and may lead to subsequent destruction of the graft. There are two main types of rejection reactions. The initial type of rejection is known as acute cellular rejection. During this process, the graft is directly damaged by T lymphocytes.[33] The second type of reaction is antibody-mediated rejection. Here, antibodies bind to donor-specific HLA molecules in the allograft. This leads to complement activation, inflammation, and cell lysis. Maintaining compliance with life-saving treatment is essential and can be challenging during adolescence, especially when complications and increased mortality are observed in a developing child or a recently transplanted adolescent. Psychological intervention in the transplant department is essential to manage the mental health of post-transplant recipients.[34]

Cardiac allograft vasculopathy

Cardiac allograft vasculopathy (CAV) has a major impact on the long-term prognosis of transplant patients. Despite significant reductions in the incidence of acute rejection and improvements in early survival with new immunosuppressive drugs, the incidence of CAV has not improved significantly. The pathogenesis of CAV is related to cellular and antibody rejection, CMV infection, and risk factors for heart disease. Unlike atherosclerotic plaques that tend to be focal rather than circular, CAV is a diffuse concentric hyperplasia of the intima of the coronary arteries of the graft. Symptoms can range from a regional wall motion abnormality detected on echocardiography to sudden cardiac death. Myocardial ischemia may not cause chest pain due to lack of reinnervation of the transplanted heart. Therapeutic options for CAV are very limited, but can be reduced with the routine use of statins and the introduction of proliferation signaling inhibitors such as sirolimus. Current medical management of CAV is limited. The introduction of mammalian target of rapamycin inhibitors has shown promise in slowing disease progression. Statins are also useful and safe for use in children.[35] In pediatric patients with focal stenosis of the coronary arteries, percutaneous coronary stent placement via catheter has been proven to be a safe and effective treatment option. For severe and progressive CAV, treatment is limited to re-transplantation in some cases.

Escalation of immunosuppression does not slow the process, and revascularization is rarely successful. In advanced stages of the disease, heart re-transplantation is the only effective treatment. Re-transplantation rates are disappointing, with less than a 10% chance of re-transplantation.[36]

Development of malignant tumors

The development of malignant tumors is also a long-term problem and is related to the use of chronic immunosuppression and infection with oncogenic viruses; EBV and HPV. The peak incidence of malignancy usually occurs during the first year after transplantation, when the highest levels of immunosuppression are needed to prevent rejection. Post-transplant lymphoproliferative disease (PTLD) associated with EBV infection is more common, occuring in 5% of transplanted children. Fortunately, responses to treatment are good and rarely contribute to post-transplant mortality.

It is important to note that heart transplant patients have higher rates of cancer than other solid organ recipients because the heart requires one of the highest levels of immunosuppression. In children, PTLD is the most common form of malignancy and usually responds to reduction of immunosuppression and treatment with rituximab. Skin carcinomas, kidney tumors, and liver tumors can also be seen more frequently in the adult population.[37]

Acute and chronic renal failure

Heart transplantation is often complicated by acute and chronic renal failure, which can significantly impact patient survival. This is primarily due to low cardiac output before transplantation and nephrotoxicity of transplant drugs. In rare cases, patients require kidney transplantation.[38]

CONCLUSIONS

Heart transplantation remains a life-saving and life-improving treatment option for children with end-stage heart disease. Despite the complexity and challenges associated with pediatric heart transplantation, advances in medical technology, immunosuppressive regimens, and surgical techniques have significantly improved outcomes.

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