Medical Complications After Renal Transplantation

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With better control of adverse immunological events during early post-renal transplantation period, graft loss caused by rejection has significantly been reduced and successful transplantation is common. There are increasingly more elderly as well as patients with multiple co-morbidities received renal allografts. As a result, renal transplant recipients may develop a spectrum of complications related to the transplantation, the immunosuppression, their underlying disease or the previous uremia state.

There were 71 deaths among 999 transplant recipients followed up in Hong Kong with transplant operation between 1st January 1995 and 31st December 2000. The major causes of death were: Cardiac 14.1%; CVA 4.2%; Infection 35.2%; Liver failure 16.9% (14.1% related to HBV); Malignancy 8.5%; Suicide 1.4% and Unknown 19.7%. The causes of graft failure among 132 recipients were: Technical/Vascular 12.9%; Died with functioning graft 30.3%; Missing/Defaulted 0.8%; Non-functioning 6.1%; Non-Immune failure 3%; Original disease recurrence 4.5%; Acute rejection 22.7%; Chronic rejection 8.3%; Hyperacute rejection 1.5% and Unknown reasons 9.9% respectively. (Data from the Hong Kong Renal Registry).

Complications Affecting Graft Function

The medical causes of early graft dysfunction include a broad spectrum of diagnosis encompassing acute rejection, acute tubular necrosis, or drug toxicity.

Acute tubular necrosis can be minimized by careful management of fluid status and the avoidance of prolonged warm and cold ischaemic time during organ procurement.

Rejection Hyperacute rejection occurs within minutes or hours of graft revascularization and is due to the presence of pre-existing cytotoxic antibodies in the recipient's blood reacting with antigens on the transplanted kidney leading to rapid allograft destruction with extensive thrombosis and acute inflammatory infiltrates. Sensitive cross-matching prevents this complication. Accelerated acute rejection occurs sooner than expected by the first exposure to antigens and occurs within 7-10 days after transplant. The recipient has both memory T cells and B cells/plasma cells capable of producing anti-graft response. The recipient may have been sensitized to HLA antigens by multiple blood transfusions, multiple pregnancies or previous transplants. Current or prior circulating anti-HLA antibodies are detected by routine PRA screening done by the Tissue Typing Laboratory. Hyperacute and accelerated acute rejection are not prevented by medications. Acute cellular and vascular rejection accounts for most of the immunological graft loss. The risk of acute rejection is greatest during the first 2 months after transplantation, diminishing significantly afterwards. Nowadays acute renal allografts rejection seldom presents with the "classic" triad of fever, oliguria and a tender, swollen graft. The most common presentation of acute rejection is a modest, asymptomatic rise in the serum creatinine level and the diagnosis can be confirmed by renal biopsy. High dose pulse steroids can reverse 75% of first acute rejections and antibody treatment with OKT3, ALG or ATG may be required for recurrent or refractory rejections. Switching from cyclosporine to tacrolimus or adding mycophenolate mofetil (MMF) in patients who have not previously received it, have been shown to be effective treatment of refractory rejections.

Chronic rejection or chronic allograft nephropathy is an important cause of long-term graft loss. The pathogenesis is poorly understood. Poor early graft function; acute rejection episodes (especially multiple or occurring after 6 months); suboptimal immuno-suppression; histocompatibility mismatch
and medical noncompliance are the major risk factors for chronic rejection. The most common time of presentation is during the second post transplant year though it can still present after more than 10 or 20 years, and is most often characterized by progressive graft dysfunction. Proteinuria and hypertension occur in at least 70% of patients who have chronic rejection. Reversal or arrest in the progressive deterioration in renal function is seldom possible.

**Drug toxicity** Both calcineurin-inhibitors, cyclosporine and tacrolimus, produce nephrotoxicity. Acute elevation in serum creatinine level that reverses with dose reduction may occur, apparently caused by renal vasoconstriction. Chronically, cyclosporine and tacrolimus can induce a tubulointerstitial fibrosis with characteristic afferent arteriolar hyalinosis. Moreover, both agents can also induce haemolytic-uraemic syndrome, which is usually associated with elevated drug levels, and cause deterioration in allograft function.

**Recurrent disease in the renal transplant** Recurrence of original disease accounts for 4.5% of allograft failures. Patients usually present with deterioration in renal function, proteinuria, hypertension, active urinary sediments or a combination of these. They may also be asymptomatic. Renal biopsy is required to establish the diagnosis. The use of immunofluorescence staining and/or electron microscopic examination may be required. Mesangiocapillary glomerulonephritis type II, Henoch-Schonlein purpura, IgA nephropathy, primary focal segmental glomerulosclerosis, Mesangiocapillary glomerulonephritis type I, and membranous nephropathy, anti-GBM nephritis etc tend to recur after renal transplantation, with the chance of recurrence in descending order. Certain metabolic disorders like diabetes, amyloidosis, oxalosis and cystinosis do recur after transplant.

**De novo diseases** These include de novo membranous nephropathy leading to heavy proteinuria or nephrotic syndrome. The occurrence of anti-GBM antibody disease in transplant recipients with Alports syndrome may represent the sensitization of the recipient to antigenic components in the donor kidney GBM during the transplantation process and the antigens had not previously been recognized.

Pre-renal, renovascular as well as obstructive causes of renal allograft dysfunction need to be ruled out in cases of post-transplant deterioration in renal function.

**Complications Secondary to Immuno-suppressive Therapies**

**Drug side effects** Corticosteroids are commonly used in the induction and maintenance phase of immunosuppressive therapy and also in the management of acute rejections. In addition to the side effects associated with immunosuppression, steroids commonly induce cushingoid features, skin thinning, osteoporosis, avascular necrosis of bone as well as diabetes. Azathioprine may cause bone marrow suppression leading to leucopenia, anaemia and thrombocytopenia and megaloblastoid changes. There is an increased risk of malignancy, hepatotoxicity and hair loss. Calcineurin inhibitors, cyclosporine and tacrolimus may induce nephrotoxicity, neurotoxicity (especially tremor), diabetes, hypertension, hyperkalaemia, hyperuricaemia and hypomagnesaemia. Skin changes such as hirsuitism, gingival hypertrophy, hypertension and hyperlipidaemia are more common with cyclosporine whereas tremor and glucose intolerance are more common with tacrolimus. Mycophenolate Mofetil can induce diarrhoea. It may also cause leucopenia and perhaps mild anaemia. Rapamycin and its analogs may cause hyperlipidaemia and thrombocytopenia.

**Infection** Infection is the most important cause of early morbidity and mortality following transplantation. It is closely linked to the degree of immunosuppression and thus to the frequency and intensity of rejection and its therapy. Moreover, infection with cytomegalovirus (CMV) has been implicated in the development of rejections in both clinical and experimental settings and late acute rejection has been ascribed to clinically covert CMV infection. Infections after renal transplantation are best categorized according to their usual time of occurrence following transplantation. Infections that occur shortly after transplantation are usually from common bacteria or nosocomial infections.
involving the urinary tract, respiratory tract or surgical wound. Infections between 1 and 4 post transplant months, at the height of immuno-suppression, are typically opportunistic infections cause by viruses like CMV, Epstein-Barr virus (EBV), Varicella-zoster virus (VZV); parasites like pneumocystis, toxoplasma sp.; bacteria like Nocardia, listeria, mycobacterium spp. and fungal organisms like aspergillus, mucor and cryptococcus. Infections that occur late (after 3 or 4 months) may be persistent infections, opportunistic infections or infections associated with malignancies. Common organisms that are involved in late infections include CMV, VZV, Cryptococcus, HBV, HCV, and the malignancy associated viruses like EBV, herpes simplex virus HHV-8. Liver failure secondary to hepatitis B virus (HBV) infection or reactivation is a significant cause of death among recipients who are HbsAg positive.

Malignancies Immunosuppression increases the risk for malignancy. The overall incidence of post renal transplant malignancies in Hong Kong was 2.4% and the risk ratio was 4.8 when compared with the general population. (Chau et al., Hong Kong Journal of Nephrology, 2000; 2(2):84-90). The risks for transplant recipients are related to the dose, duration and type of the nonsteroidal immunosuppressants, and in part on the ability of these agents to promote the growth of various oncogenic viruses, such as papillomaviruses, HSV and EBV. The relative risk for occurrence is high with Kaposi sarcoma, non-Hodgkin's lymphoma (PTLD or post transplant lymphoproliferative disorders), carcinoma of vulva or anus and skin cancer. Malignancy may occur at any time after transplantation. However, some are more likely to occur earlier after transplantation and these include PTLD and Kaposi sarcoma. The incidence of malignancy continues to increase throughout the late post-transplantation period and the cumulative incidence of non-skin malignancy may reach 33% 30 years after transplantation.

Complications Affecting the Patient, Increasing the Morbidity and Mortality

Cardiovascular complications Patients with end-stage renal disease are predisposed to cardiovascular complications and the prevalence of coronary heart disease is even greater in renal transplant recipients especially if they are diabetic and old (>60 y.o.). Hyperlipidaemia is common after renal transplantation. Cyclosporine as well as corticosteroid therapies clearly contribute to the hyperlipidaemia and hypertension. Management of renal transplant recipients includes the pharmacological as well as the non-pharmacological correction of hypertension and hyperlipidaemia. Coronary as well as cerebral vascular risk factors need to be evaluated and modified if present. Patients at risk should have their coronary heart disease identified earlier and managed proactively. They are advised to have their blood pressure and hyperlipidaemia under good control, to abstain from smoking, to reduce excess body weight and to have regular exercise.

Haematologic complications There is an initial burst of erythropoietin at the time of engraftment but does not result in erythropoiesis. A second burst occurs at about 1 month post-transplant and is normally followed by effective production of erythrocytes. Anaemia after renal transplant may be the result of diminished iron store and is unable to respond to the erythropoietin production by the allograft. Treatment with Azathioprine or MMF may lead to bone marrow suppression. Neutropenia may be due to the dose related marrow suppression by drugs like Azathioprine or MMF or an idiosyncratic response to a number of drugs that are used. Neutropenia may also be the manifestation of systemic infection by viruses, fungi or mycobacteria. Post-transplant erythrocytosis (PTE) is the persistently elevated haematocrit level of >51%. It affects 5-19% of post-transplant recipients, usually presents within the first 2 years in those with excellent graft function. Hypertension and thromboembolic events have been reported. Current therapy is based on the use of angiotensin II receptor blockers and ACE inhibitors.

Gastrointestinal complications Gingival hyperplasia can be a severe and aggravating problem in renal transplant recipients and is related to the use of cyclosporine, poor dental hygiene, dental prosthetics and the use of drugs like phenytoin. Esophagitis may be caused by Candida albicans as well as HSV type I and CMV. Both MMF and tacrolimus can cause bloating, nausea, vomiting and
diarrhoea. However, diarrhoea may also be caused by a variety of organisms including CMV, Strongyloides sp., Clostridium difficile (toxin), other parasites and enteric pathogens.

**Liver disease** Liver disease may be responsible for 8-24% of the late mortality. Acute liver dysfunction may be caused by acute viral hepatitis (HAV, HBV, HCV, CMV, HSV, HHV-6, EBV), medications (notably Azathioprine, cyclosporine, acetaminophen and antibiotics), and etiologies (e.g. alcohol) that can be associated with chronic active hepatitis, cirrhosis or carcinoma of liver. The patient as well as graft survival for HbsAg positive recipients are inferior when compared with those who are negative. The use of Lamivudine, a nucleoside analog that interferes with reverse transcriptase activity of HBV, has been shown to be effective in reducing HBV DNA to undetectable level. However, the emergence of resistant strains is a long term concern. A more rapid progression of liver disease has been reported in renal transplant recipient who are HCV-positive especially in those who are older with ALG therapy. The graft as well as patient survivals are also inferior when compared with those HCV-ve subjects. However, HCV-positive transplant recipients appear to have better survival than those HCV-positive patients on dialysis.

**Musculoskeletal and metabolic complications** Mild hypercalcaemia associated with persistent hyperparathyroidism is not uncommon post-transplant. Persistent hyperparathyroidism may occur, often the result of continuous autonomous production of parathyroid hormone requiring total parathyroidectomy with or without auto-implantation. Osteoporosis with progressive loss of bone mineral density may occur after renal transplant. Two persistent contributing factors include corticosteroid treatment and the female gender. Avascular necrosis and gout may complicate the post-transplant course. Episodic bone pain in the knees and/or ankles may occur in patients on cyclosporine. The pain is usually worse at night or with recumbency and may be relieved by upright position or walking.

Post-transplantation diabetes mellitus (PTDM) may complicate the post-transplant course in 5-10% of calcineurin based immunosuppressive therapy. The onset of PTDM may be within 3 weeks to more than 20 years after transplantation. Diabetic nephropathy has been reported in patients who develop de novo PTDM.

**Ocular complications** The most common ocular complication in renal transplant recipients is posterior subcapsular cataract secondary to corticosteroid treatment. However, Ophthalmic herpes zoster, retinitis by CMV or toxoplasmosis, enophthalmitis by invasive sinus infection may progress rapidly with devastating consequences and require immediate attention. Regular ophthalmologic examinations should be routine in renal transplant recipients, especially if they are diabetic.

**Conclusion**

Renal transplantation results in excellent rehabilitation and better quality of life among patients on renal replacement therapies. A delicate balance should be maintained between the amount of immunosuppression to prevent allograft rejection and the side effects that are related to medications as well as immunosuppression. Proactive management in the prevention of cardiovascular and metabolic complications may further reduce the post-transplant morbidity and mortality in the future.