REVIEW ARTICLE

Lung Transplantation : Management and Complications

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ABSTRACT

Lung transplantation has become an accepted treatment modality for end stage lung disease including emphysema, fibrosing alveolitis, cystic fibrosis, pulmonary hypertension and bronchiectasis. Despite the use of potent immunosuppressive drugs, acute rejection occurs frequently, especially in the first few weeks and months after transplantation. Bacterial, viral and fungal infections frequently occur in lung transplant recipients. Rapid diagnosis and adequate treatment of infections is needed. The side effects with the use of long term immunosuppressive agents includes renal toxicity, hypertension, neurotoxicity, hyperlipidemia, leucopoenia, hyperglycaemia, weight gain, osteoporosis and malignancy. However, obliterative bronchiolitis (OB) which is regarded as a chronic rejection process remains the dominant cause of morbidity and mortality in the long-term survivors of lung transplantation. This article focuses on the postoperative and long term management of lung transplant recipients.

Key words : Lung transplantation; Bronchiolitis *obliterans;* Rejection; *Immunosuppression.*

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INTRODUCTION

Since its first successful performance three decades ago, lung transplantation has become an accepted treatment modality for end stage lung disease including emphysema, fibrosing alveolitis, cystic fibrosis, pulmonary hypertension and bronchiectasis. It has reached the present state because of developments in surgery, patient selection and management, as well as availability of potent immunosuppressive agents. Despite the use of these potent immunosuppressive drugs, acute rejection occurs frequently, especially in the first few weeks and months after transplantation. Bacterial, viral and fungal infections frequently occur in lung transplant recipients. Rapid diagnosis and adequate treatment of infection is needed. Furthermore, prophylactic anti-infectious treatment to be given. Donor and recipient selection and surgical approaches have been a subject of a previous review'. The side effects with the use of long term immunosuppressive agents includes renal toxicity, hypertension, neurotoxicity, hyperlipidemia, leucopoenia, hyperglycaemia, weight gain, osteoporosis and malignancy. However, obliterative bronchiolitis (OB) which is regarded as a chronic rejection process remains the dominant cause of morbidity and mortality in the long-term survivors of lung transplantation. This article, therefore, focuses on the postoperative and long-term management of lung transplant recipients.

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POSTOPERATIVE MANAGEMENT

A majority of lung transplants can be performed without cardiopulmonary bypass. patients are postoperatively usually extubated within 24 hours after transplantation. Standard ventilation and weaning techniques are used except in special circumstances. After single lung transplantation (SLT) for COPD , positive end-expiratory pressure (PEEP) is not used because it tends to hyperinflate the more compliant native lung. Rarely split ventilation using a double lumen tube and two ventilators may be needed. After SLT or bilateral lung transplantation (BLT) done for other indications, low level PEEP is a standard part of postoperative support. Pulmonary capillary wedge pressure should be kept as low as possible, consistent with adequate urine output and systemic blood pressure. Vasopressor, inotropic and diuretic drugs are often used concomitantly to achieve this balance. Colloid solutions or blood products are preferable to crystalloid solutions for volume replacement.

Induction Immunosuppression

Patients receive IV methyl prednisolone (1000-1500 mg.) peri transplantation followed by oral prednisolone, which is initiated at 1 mg/kg and tapered over four weeks to a daily maintenance dose of 0.25 mg/kg. Immunosuppressive drugs are selected and designed to suppress lymphocyte function and inflammatory reactions, irrespective of the organ transplanted. The classical immunosuppressive regimen in lung transplant recipients consists of cyclosporine , aza thioprine and prednisolone. In recent years patients have been randomized to receive either azathioprine or mycophenolate mofetil (MMF). In some centers, tacrolimus has replaced cyclosporine as primary immunosuppressive agent. Currently, about 80% of patients undergoing lung transplantation receive cyclosporine based immunosuppressive regimen, azathioprine is administered in 75% of recipients whereas short and long-term therapy with prednisolone is given to 95% patients[2]. Approximately 15% receive mycophenolate mofetil (MMF), early or late after transplantation[2]. Induction therapy with cytolytic agents such as antithymocyte globulin or OKT3 has been used for many years. However, some centers do not favour this policy because of a higher incidence of viral infections, and the risk of developing lymphoproliferative disorders[2]. An overall benefit in survival has not been proven in patients treated with cytolytic agents as induction therapy.

Maintenance Immunosuppression

Most patients beyond the first year of transplantation are treated with triple drug immunosuppression consisting of cyclosporine/tacrolimus, azathioprine/MMF and prednisolone. Cyclosporine administration also presents particular problems in CF patients because of absorption problems. Since the doses to maintain adequate levels are usually higher, cyclosporine, in patients with CF is usually administered in three divided doses rather than two divided doses as done in other patients. The combination of different drugs seems to be a more effective regimen for suppression of acute rejection episodes compared with single or dual drug regimens. However, the optimal immunosuppressive regimen has to be individually determined. Recently, MMF and tacrolimus have been introduced. Although tacrolimus appears to have reduced the number of acute rejection episodes, there are limited data regarding the influence on survival, infectious episodes, or broncholitis obliterans syndrome (BOS). MMF has been considered an alternative to azathioprine because both affect B lymphocyte function. Currently, a number of studies are being conducted to look at the specific influence of MMF on the incidence of chronic rejection. Tacrolimus and/or MMF are often used in patients with refractory rejection.

Mycophenolate Mofetil (MMF)

Mycophenolate mofetil (MMF) is the ester prodrug and is rapidly hydrolysed in *vivo* to mycophenolic acid, the active compound. Gastrointestinal side effects have been shown to subside with longer use[3]. The efficacy of MMF

in reducing the incidence of rejection by 50% after cadaver renal transplantation has been established when compared to azathioprine[4-6]. In patients with renal allograft rejection refractory to antilymphocyte globulin, additional treatment with MMF in combination with cyclosporine resulted in a 45% reduction in graft loss and death six months after enrollment in the study[7]. Improved survival has been observed in heart transplant recipients treated with MMF compared to azathioprine[8]. A lower incidence of biopsy proven rejection during treatment with MMF has been reported during the first 12 months after lung transplantation[9]. Although not statistically significant, the prevalence of BOS at one year in the azathioprine treated group was twice as high (36%) as in the group treated with MMF (18%).

Tacrolimus (FK 506)

Although structurally different from cyclosporine, tacrolimus has a similar mode of action. Both a large US study and a European multicentre trial have shown the superiority of tacrolimus based therapy over cyclosporine in reducing the incidence and severity of rejection up to one year after liver transplantation[10,11]. However, no difference was found in terms of graft and patient survival. When the efficacy of tacrolimus was compared to cyclosporine in lung transplant recipients, acute rejection occurred less frequently in the tacrolimus group (89% *versus* 100% at six months), and fewer courses of methyl prednisolone were required[12,13]. The long-term results of this study reported a markedly reduced incidence of biopsy proven OB in the tacrolimus treated group (21.7% *versus* 38%) with a trend towards improved survival[14]. In patients with recurrent or persistent acute rejection, the incidence and severity of acute rejection declined significantly after maintenance immunosuppressive treatment was changed from cyclosporine to tacrolimus[14]. Tacrolimus has also been used as rescue therapy for BOS. However, no improvement in lung function could be found although the rate of decline decreased[15]. Studies are on going to assess if tacrolimus is superior to cyclosporine in its neoral form.

Sirolimus (Rapamycin)

Sirolimus inhibits not only the proliferation of lymphocytes, but also of mesenchymal and endothelial cells[16-18]. In animal models, it has been shown to markedly inhibit the fibroproliferative response to transplantation[19,20]. Preliminary data in renal transplant recipients seem to confirm its efficacy, but a high number of withdrawals from the study due to side effects were noted [21,22]. Data comparing rapamycin or a rapamycin derivative with azathioprine in patients at risk for BOS in a randomised controlled multicentre trial should be available soon.

IL-2-receptor Antibodies

New blocking antibodies directed towards different cell receptors involved in the stimulation of alloreactive lymphocytes are currently being developed. From the results of two randomised, placebo controlled trials it appears that the humanised anti-IL-2-receptor antibodies are effective in reducing the incidence of rejection after kidney transplantation [23,24]. Results of randomised trials following lung transplantation have not yet been reported.

Inhalation of Immunosuppressants

Treatment of biopsy proven OB refractory to enhanced immunosuppression treated with aerosolised cyclosporine resulting in histological improvement and a reduced rate of decline in FEV_1 compared with pre treatment values has been reported[25]. Similar results in patients with refractory acute allograft rejection have been reported by the same group[26,27]. Randomised studies with larger patient numbers should clarify the value of this immunosuppressive approach.

Antibiotic and Antifungal Therapy

Patients receive antibiotics according to the sensitivity of organisms grown from the donor or the recipient in the peri-operative period or

board-spectrum antibiotics until cultures are available. If *Aspergillus* species is isolated, treatment with itraconazole should be considered. Most centers routinely provide prophylactic therapy against *Pneumocystis curinii* infection and hence its occurrence is now rare. The usual drug used in patients who are not allergic to sulfa products is trimethoprim-sulfamethoxazole combination (160:800 mg) administered as one double strength tablet twice weekly on Monday and Friday. Most patients receive nebulised amphotericin (10 mg/day) post operatively until they are discharged from the hospital. In patients having positive *Aspergillus* cultures inhalation with amphotericin B is continued after discharge or other antifungal agents commenced.

Antiviral Prophylaxis

The most effective strategy for cytomegalovirus (CMV) prophylaxis in seronegative recipients is the use of seronegative donors and screened blood products. CMV infection usually occurs 3-4 weeks from the time of transplantation. This allows a potential window of opportunity to make some intervention to either prevent or modify the disease. Acyclovir, valacyclovir, ganciclovir and hyperimmune globulins have been used for prophylaxis as well as therapeutic agents for CMV disease. We use intravenous ganciclovir prophylaxis (5mg/kg/day) three times a week, in patients who are CMV seropositive and receive a seropositive donor *i.e.* CMV mismatch for 10 weeks post transplant. Some centers use oral ganciclovir for CMV prophylaxis. However, the bioavailability of the oral form is very low and more than eight tablets of ganciclovir have to be taken daily. Post transplant lymphoproliferative disease (PTLD) is a serious, often fatal complication after solid organ transplantation. Primary Epstein-Barr virus (EBV) infection is a major risk factor for PTLD, particularly in EBV naïve patients who seroconvert post lung transplantation. All our EBV naive lung transplant recipients receive life long prophylaxis with valacyclovir 500-1000 mg/day or ganciclovir 1000 mg three times a day (Mon/Wed/Fri).

Nutrition

End stage lung diseases are often associated with cachexia, which is a risk factor for perioperative complications. All our patients undergo nutritional counselling when they are **on** the pre transplant list as well as post transplantation (steroid induced weight gain may be a problem). Preoperatively patients are encouraged to eat high calorie food and excessive number of calories because of nutritional depletion accompanying their end stage lung disease. Enteral feeding *(via* gastrostomy) is advised in patients who have difficulty in consuming an adequate oral diet. In patients with cystic fibrosis (CF) malnutrition is multifactorial. The usual malnutrition seen in end-stage respiratory failure is complicated by exocrine pancreatic enzyme insufficiency Adult CF patients also may have islet cell deficiency with diabetes mellitus and may require insulin supplementation. Early treatment of osteoporosis, which is often presents in patient with end-stage lung diseases due to physical inactivity or steroid therapy, should be addressed.

Monitoring : Lung Function Testing and Bronchoscopy

Lung function gradually improves and usually reaches a plateau during the first three months after surgery. After heart-lung and bilateral lung transplantation, lung volumes are expected to reach predicted values for the recipient[28]. A sustained decline of 10 or more in the FEV, signals a potentially significant problem[29]. All patients receive a hand-held personal spirometer which is used to monitor and chart the FEV, twice a day.

The utility and safety of transbronchial lung biopsy (TBB) for diagnosis of clinically suspected acute rejection and infection has been demonstrated[30]. When performed for a clinical indication, it has a high overall positive rate (63-83%) and a good sensitivity for detecting acute rejection[30-33]. However, the sensitivity of TBB in the detection of OB has been inconsistent and a negative transbronchial biopsy does not

exclude OB[34]. The practice of periodic TBB for surveillance in asymptomatic, clinically and physiologically stable recipients varies among centers[35]. We perform surveillance TBB at 3 and 6 weeks, and 3, 6 and 12 months post transplantation. After the first year following transplantation, TBB is performed in the presence of symptoms or fall in lung function. It is our practice to obtain bronchial washing specimens for microbiology and cytology purposes every time a bronchoscopy is performed.

COMPLICATIONS

Ischaemic Reperfusion Injury

Early graft dysfunction is an acute lung injury with increased vascular permeability that is presumably related to preservation and ischaemia-reperfusion, and may be amplified by cardiopulmonary bypass[36]. Treatment is supportive. Optimal fluid and hemodynamic management is needed. Inhaled nitric, extracorporeal membrane oxygenation (ECMO) and ventilatory support are used[37,38].

Rejection

The incidence of acute rejection is the greatest within the first 100 days after transplantation, steadily declining after the first year[39]. The practice of diagnosing and treating acute rejection based on clinical criteria may run the risk of subjecting the patient to unnecessary high doses of steroids and may have additional deleterious effects if the underlying cause of the clinical symptoms is infective in origin. TBB offers a safe and accurate means of diagnosing acute rejection. The histologic hallmark of acute rejection is the presence of perivascular lymphocyte infiltrates, which in more severe cases, spill over into the interstitium and alveolar air spaces[40]. Perivascular infiltrates must be interpreted cautiously, if infection is present. Since airway inflammation has many causes, its implications on a biopsy specimen depend on the clinical correlation[41]. However, histological bronchiolitis is significantly associated with the development of OB. Treatment of acute rejection consists of a three-day course of 10–15 mg/kg/day of intravenous methyl prednisolone. In case of moderate or severe rejection a tapering oral pulse of prednisolone follows the IV pulse of steroids. After treatment for rejection there is a considerable incidence of persistent rejection or CMV pneumonitis in follow up transbronchial biopsies performed within six weeks [42].

Obliterative bronchiolitis is thought to be the pathological hallmark of chronic rejection. It is characterised by a clinical syndrome of progressive dyspnea and airflow obstruction. It is manifested histologically as a fibroproliferative process targeting the small airways, leading to submucosal fibrosis and luminal obliteration. As discussed earlier, histological confirmation of OB by TBB has a low sensitivity. Hence, the concept of the "bronchiolitis obliterans syndrome" (BOS) has developed, the diagnosis of which is based on demonstration of airflow limitation on serial lung function tests. BOS is defined as an otherwise unexplained and sustained fall in the forced expiratory volume in one second to a level of 80% or less of the peak value after transplantation[43]. It is uncommon in the first six months following transplantation, but its prevalence increases steadily thereafter to a prevalence of 60-70 per cent in those who survive five years[44]. The pattern of change of lung function in OB is often a fall followed by a plateau, which may persist for a variable time [45]. It is not known why one individual develops OB that progresses relentlessly and another develops OB that obtains a plateau. Standard chest radiographs are not much of a help, but high resolution computed tomography may demonstrate decreased peripheral vascular markings, peripheral bronchiectasis, and evidence of air trapping on expiratory images[46,47]. Acute pulmonary allograft rejection has been identified as the major risk factor for the development of OB[48]. Other proposed risk factors include CMV infection, airway ischaemia and HLA mismatching[44,49]. The treatment of chronic rejection has focused on augmentation of immunosuppression[50]. Single center

studies have examined the utility of inhaled cyclosporine, tacrolimus, MMF, methotrexate, cyclophosphamide, cytolytic therapy with OKT3 or ATG, photophoresis, plasmapheresis, and total lymphoid irradiation[15,25,51-56]. The multiplicity of agents tried underscores their lack of universal efficacy, and speaks strongly in favour of multicenter trials to guide management. Many centers perform surveillance biopsies in the first year to identify asymptomatic rejection. Retransplantation remains the only cure for established severe OB[57].

Infection

The rate of infection among lung transplant recipients is several times higher compared to recipients of other organs and this is most likely related to the exposure of the allograft to the external environment[58]. *Bacterial pneumonia* is common in the early period after transplantation and treatment should be based on culture and susceptibility results available from current or most recent specimens. Bronchoalveolar lavage provides excellent samples for culture purposes, and protected brush specimens have also been employed usefully[33]. The common organisms isolated include Pseudomonas *aeruginosa* and *staphylococcus* species including methicillin resistant *Staphylococcus aureus* (MRSA). The fourth generation cephalosporins, aminoglycosides and fluoroquinolones are used in the combined treatment of Pseudomonas infection, which is typically seen in CF patients. Vancomycin is the drug of choice to treat MRSA infection and teicoplanin may be used in cases of renal insufficiency. The lower respiratory tract of transplant recipients with BOS often becomes colonised with *Pseudomonas* species, and recipients with BOS are at increased risk of bacterial pulmonary infection[59].

Cytomegalovirus disease can be manifested as pneumonitis, gastritis, colitis or hepatitis. It usually occurs in the second or the third month after transplantation. Pneumonitis is a common form of presentation and may pose a dilemma as its clinical presentation may easily mimic that of acute rejection. CMV infection is characterised by active replication and shedding of CMV and may be asymptomatic. CMV disease is defined by the presence of typical inclusion bodies in the tissue or cell preparations. A definitive diagnosis of CMV pneumonitis can be made by the demonstration of CMV inclusions in the lung biopsy or bronchoalveolar lavage specimens. The prevalence of CMV disease is low in seronegative recipients who have been matched with seronegative donors[60]. However, among the recipient negative and donor negative group, those who acquire a primary CMV infection, disease has been diagnosed in approximately 80 per cent. The prevalence of CMV disease is around 60% in other serology combinations, *viz* recipient negative and donor positive, recipient positive and donor negative, and recipient positive and donor positive. Patients developing CMV disease are treated with ganciclovir 10 mg/kg/day in divided doses for two weeks followed by 10 mg/kg/day single dose three times a week for the following two weeks. Foscarnet is also effective against CMV, and is the best alternative for ganciclovir resistant infection or in presence of severe bone marrow depression.

The reported prevalence of pulmonary *Aspergillus* infection in lung transplant recipients is in the range of 20 to 40 per cent[59,61]. The spectrum of disease encompasses colonisation, bronchitis, locally invasive and disseminated aspergillosis. *Aspergillus* bronchitis is the more common form seen in lung transplant recipients and the diagnosis is usually made by a combination of bronchoscopic findings and isolating the organism on bronchoalveolar lavage or sputum specimen. Biopsy confirmation is needed for a definitive diagnosis of invasive aspergillosis. However, a clinical diagnosis may be justified if *Aspergillus* is isolated from an appropriate culture specimen in the presence of a consistent clinical picture. It may infect the airways more diffusely, causing mucosal oedema, ulceration, and formation of pseudomembranes[62]. Although usually responsive to oral itraconazole or to intravenous or inhaled amphotericin B, airway infections with *Aspergillus* in rare cases been associated with wide spread dissemination and with fatal erosion into the pulmonary artery[62]. *Aspergillus* infection is a frequent compli-

cation in patients with OB. Use of a liposomal preparation of amphotericin has the advantages of targeted delivery and less nephrotoxicity. Although *Candida* is a frequent fungal infection, often isolated from respiratory tract specimens, it usually does not cause pneumonitis and other forms of presentation include wound infection and mediastinitis. This infection can be treated with fluconazole or amphotericin. Infection with *Scedospsrium apiospermium (Pseudoallescheria boydii)* and *Scedosporium prolificans (Scedosporium inflatum)* has mainly been described in patients treated with high dose chemotherapy, autologous or allogenic bone marrow transplantaion[63,64]. So far we have had seven recipients who had infection with *Scedosporium apiospermium,* eradication of which proved difficult. However, under combined treatment with itraconazole and fluconazole this opportunistic infection did not disseminate[65].

Pulmonary and extra-pulmonary mycobacterial infection is relatively common after lung transplantation and may be an unrecognised cause of graft dysfunction. Early treatment of cutaneous lesions is associated with excellent control; however, graft dysfunction may be permanent. In our reported series of mycobacterial infections in lung and heart-lung transplant recipients, 23 were diagnosed with mycobacterial infection in 25 sites, including 19 pulmonary and six extra-pulmonary sites. The most often isolated micro-organism was *M. avium*[66]. Therapy for non tuberculous mycobacteria consisted of clarithromycin, rifampicin, ciprofloxacin and or ethambutol. Although drug toxicity and interactions with immunosuppressive agents were not infrequent, the majority of these infections were managed successfully.

Major Airway Complications

Airway complications are a continuing problem in lung transplantation and are reported in 7% to 14% of patients[67-69]. The lung is the only solid organ transplant in which the systemic arterial blood supply is not routinely anastomosed to the graft. After isolated lung transplantation, viability of the donor bronchus relies exclusively on retrograde collateral blood supply from the pulmonary circulation". However in the case of heart-lung transplantation, the tracheobronchial blood supply may be adequate through coronary to bronchial artery collateral circulation explaining the lower anastomotic complication rate in this group[71]. Early dehiscence has a very high fatality and very limited success with reoperation or retransplantation [57] Balloon dilatation is a safe method for dilating airway stenosis and can be performed *via* the flexible bronchoscope. However in up to 75% of airway stenosis post lung transplantation, stent placement in addition to a dilatation procedure is required[72]. Nitinol stents may be used in the future because of the ability to adapt well to the bronchial wall[73]. Laser therapy is effective for removing granulation tissue or fibrous webs. Significant bronchomalacia often requires stent placement to maintain airway patency, but difficulties may arise in case of long segments with malacia.

Renal Complications[74]

The major renal complications encountered in lung transplant recipients include nephrotoxicity induced by cyclosporine or tacrolimus. Vasoconstriction at the afferent renal arterioles is primarily responsible for the observed reduction in the giomerular filtration rate. Acute tubular necrosis postoperatively may occur due to a combination of factors including cyclosporine, hypotension, infections and nephrotoxic drugs. Chronic nephrotoxicity from cyclosporine occurs virtually in all patients following lung transplantation. The majority of the increase in the creatinine is observed in the first six months. The management of worsening renal failure consists of reducing the dose of cyclosporine or tacrolimus and eliminating other nephrotoxic drugs. Calcium channel blockers and thromboxane synthesis inhibitors such as picotamide and pentoxyphylline have been reported to have beneficial effects in patients with cyclosporine induced nephrotoxicity.

Hypertension

Hypertension is a recognised side effect of

cyclosporine and steroid administration after transplantation. Morrison et *al*[75] have reported an incidence of 66% in previously normotensive patients and that the time to onset of hypertension in lung transplant recipients is delayed, compared with that in other organ transplants. The drugs commonly used to treat hypertension in the lung transplant recipients are calcium channel blockers and ACE inhibitors.

Diabetes'*

Hyperglycaernia due to use of corticosteroids is a common problem encountered after lung transplantation, and tacrolimus has been associated with the development of diabetes. Patients with cystic fibrosis are at particular risk because of underlying pancreatic insufficiency. The treatment consists of dietary modifications, weight loss if hyperglycaemia occurs in association with obesity, and insulin. Oral hypoglycaemic agents should be used with caution because significant and prolonged hypoglycaemia may ensure if patients have hepatic dysfunction.

Osteoporosis

As survival continues to improve with the advent of improved therapies, osteoporosis and atraumatic fractures are increasing being recognised as long term complications of lung transplantation. Patients who undergo lung transplantation have a large number of risk factors for osteoporosis both pre-and post-operatively. Diminished mobility, hypoxaemia, and corticosteroid therapy may all play a role in bone demineralisation in patients with emphysema, pulmonary fibrosis and pulmonary hypertension[76]. Patients with cystic fibrosis have pancreatic insufficiency, reduced vitamin D, and calcium absorption, reduced sex hormone production, and increased serum levels of catabolic cytokines, which predispose to osteoporosis[77]. Following lung transplantation large doses of immunosuppressants including corticosteroids and cyclosporine, and prolonged bed rest may further contribute to bone demineralisation[78-79]. Patients at risk of osteoporosis are treated with oral calcium supplements and those with osteoporosis with calcitriol or alendronate sodium.

Malignancy

Solid organ transplant recipients have an increased incidence of cancer. The diverse lymphocytic diseases that arise after transplantation are referred to collectively as post-transplantation lymphoproliferative disorders and have been closely associated to EBV infection. Use of continuous prophylactic antiviral therapy in EBV seronegative patients can prevent the development of PTLD[80]. The overall frequency of PTLD in solid organ transplants including lung transplants have been reported between 1.8% to 20 per cent[81-83]. Most cases develop in the first year after transplantation, though some appear later. The lung allograft has been the most common site of involvement, presenting clinically as focal or multi focal nodules or pleural effusion. Management involves reduction in the intensity of maintenance immunosuppression and high dose antiviral therapy[80]. Adjuvant therapy includes surgical excision, radiation therapy, chemotherapy, alpha interferon, lymphokine activated killer cells and anti-B cell monoclonal antibodies[59,84-86]. In lymphomas appearing late after transplant, there may be no viral association and, hence, a role for chemotherapy.

The most common non-lymphoproliferative tumours recorded by the Cincinnati Tumor Transplant Registry were cancers of the skin and lips[87] and the incidence of squamous cell carcinoma of the skin was particularly elevated. In locations on the body, which have had a high level of sun exposure, organ transplant recipients had a 21-fold greater likelihood of developing skin cancer than people in the local population. Kaposi's sarcoma occurred in 6% of organ transplant recipients and it was confined to the skin in 61% of cases. Kaposi's sarcoma is associated with herpes virus 8 infection, which can be transmitted via transplanted organs[88]. Other cancers that occur with greater incidence in the transplant population include carcinoma

of the cervix, the anogenital area, and the hepatobiliary system.

Hyperlipidemia

Serum lipids are elevated in many patients after lung transplantation and this has not been studied in detail in this population. Hyperlipidemia has been studied extensively in renal and heart transplant recipients and in a multivariate analyses, has been ascribed to the effects of corticosteroids and cyclosporine[89-92]. The lipid abnormalities involve elevation in total cholesterol and triglycerides[74]. Dietary modification should be attempted and efforts should be made to curtail obesity after transplantation through exercise and education. The 'statins' (HMG-Co-A-reductase inhibitors) are the drug of choice and despite infrequent reports of myopathy arising from the use of these drugs with cyclosporine, they are generally efficacious and well tolerated[93,94].

Haematological Complications

Azathioprine can cause a dose-related suppression of bone marrow function by inhibiting dihydrofolate reductase. Leucopenia is the most common abnormality, although anaemia and thrombocytopenia may ensue. This effect may be exacerbated by the use of trimethoprim, also a dihydrofolate inhibitor. Reducing the drug dosages or temporarily ceasing it when the white cell count falls below 4.0 and folic acid supplementation are effective therapy in most cases. Chronic anaemia in most lung transplant recipients is multifactorial and includes iron deficiency, decreased erythropoetin levels, azathioprine, MMF, cyclosporine and tacrolimus associated with the haemolytic uraemic syndrome.

Diaphragmatic Paralysis

It is an uncommon but not rare complication of single as well as bilateral lung transplantation. This occurs as a result of injury to the phrenic nerve in the course of the operation. These patients may require a longer period of time to be weaned from mechanical ventilation post-operatively. However, it does not seem to be associated with long term deleterious effects on the lung function.

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