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Malignant Neoplasms in Kidney Transplantation

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1. Introduction

Renal transplantation is the preferred renal replacement therapy for patients with end stage renal disease (ESRD) as this modality provides better quality of life, improved overall survival, and lower treatment cost than dialysis. Malignancy is a known complication among transplant recipients, and is likely to become even more common in these patients as donation criteria are extended to allow older donors, the age of patients on waiting list is increased, and transplant recipients live longer (Gallagher et al, 2010). However still there is a continuous struggle to keep the delicate balance between reducing the immunosuppression and maintaining the graft survival. Majority of post-transplant morbidity and mortality is related to immunosuppression. Post-transplant patients are subjected to high rate of infections, medication nephrotoxicity, cardiovascular disorders, and development of malignancies. The life expectancy in kidney transplant patients is only half of that in general population. Although cardiovascular diseases are the most common cause of death in patients with functioning graft, malignancy is a significant cause of mortality. Malignancy is the third most common cause of death in renal transplant recipients after cardiovascular events and infections. There is a substantial three to five fold increase in the incidence of malignancy after solid organ transplantation as compared to the general population. Moreover the cancer incidence is also higher in transplant recipients than that seen in dialysis patients (Rama & Grinyó, 2010). As the risk of acute rejection and subsequent organ loss diminished due to the introduction of better immunosuppressive agents, infection and malignancy incidence has increased. Recently the life-threatening infections have also been declining due to the more judicious use of immunosuppressive agents and improved treatment regimen for infections. As cardiovascular diseases poses the greatest risk to the long-term graft and patient survival, efforts are being undertaken to reduce these risks by the use of less atherogenic immunosuppressive regimens, aggressive treatment of hyperlipidemia and better blood pressure control. Based on these observations it is estimated that malignancy will surpass cardiovascular complications as the leading cause of death post-transplant within the next 2 decades (Buell et al, 2005).

2. Epidemiology

There are several factors that lead to development of malignancy among transplant recipients. These include impaired immunosurveillance of tumor cells, DNA damage and impaired DNA repair mechanism, exposure to oncogenic viruses, and upregulation of cytokines that may promote tumor growth such as vascular endothelial growth factor, transforming growth factor β 1 (TGF- β 1), and interleukin-10. Certain neoplasms have a much higher incidence in post-transplant patients such as skin cancers including squamous cell carcinoma, basal cell carcinoma, merkel cell cancer, and melanoma, kaposi's sarcoma, lymphoma, carcinoma of oropharynx, anogenital cancer, liver cancer, in-situ carcinoma of cervix, renal cell carcinoma, and several sarcomas. In contrast, solid tumors that are most commonly seen in general population such as breast, colorectal, prostate, and invasive cervical cancer have only a modest increase in post-transplant patients. The largest study on the rate and types of malignancies was on 35,000 first time renal transplant recipients of deceased and living donor kidney transplants. As compared to the general population, the incidence of tumors was found to be as follows (Kasiske et al, 2004):

- 2 fold increase: most common solid tumors in general population such as breast, colon, prostate, lung, ovary, stomach, pancreas, and esophagus.
- 3 fold increase: testicular and bladder carcinoma.
- 5 fold increase: melanoma, leukemia, hepatobiliary, cervical, and vulvovaginal tumors.
- 15 fold increase: renal cell carcinoma.
- 20 fold increase: nonmelanoma skin cancer, non-Hodgkins lymphoma(NHL), and kaposi's sarcoma (KS).

Certain malignancies tend to occur at a higher rate in transplant recipients as compared to patients on transplant waiting list (Morath et al, 2004). These include non-melanoma skin cancer (2.6 fold), melanoma (2.2 fold), KS (9 fold) NHL (3.3 fold), oral cancer (2.2 fold), and renal cell carcinoma (39% higher) (Kasiske et al, 2004). Malignancy development is 2-4 fold more common in heart transplant than renal transplant patients as a result of increased immunosuppression required in heart transplantation. In general, the post-transplant carcinomas tend to behave more aggressively and have a worse outcome. The incidence of second primary cancer is similar to that of the first malignancy with an exception of non-melanoma skin cancer with recurrent Squamous cell carcinoma. Malignancies develop in 15-20% of transplant recipients after 10 years. After 20 years of immunosuppressive therapy, approximately 40% of recipients develop cancer. However the real incidence still could be underestimated as follow-up is usually short in many patients (Pita-Fernandez et al, 2009).

The average latency of malignancy development after transplant is approximately 3-5 years. Different tumors have a distinct time interval between transplant and tumor presentation (Brennan et al, 2011):

- Kaposi's sarcoma : 13-21 months
- Lymphomas: 32 months. The risk is highest during the first year when the immunosuppression is intense and the risk of viral infection is highest.
- Epithelial carcinomas (including skin): 69 months
- Anogenital region carcinomas: 84-112 months. The latency is longer in children transplant recipients who may develop tumors during adulthood.

3. Common malignancies in transplant recipients

3.1 Skin carcinomas

Non-melanoma skin cancers such as squamous cell and basal cell carcinomas are common after transplant. They account for approximately 37% of all cancers, and can result in significant morbidity and mortality rate of 5-8%. As compared to general population, the transplant recipients develop these tumors 15-20 years earlier with an average time of development of 4-9 years post-transplant. The incidence of these tumors can vary between different geographic locations. Risk factors include increase age, male gender, fair skin, HLA A11, B27, and DR7, presence of HPV, use of cyclosporine, or Azathioprin, sun exposure, and the geographic location. Rapamycin has been reported to potentially decrease the risk of developing these tumors after transplant (Comeau et al, 2008). The overall incidence of skin cancer rises progressively as transplanted graft longevity increases with a cumulative risk increase from 7.5% to 28.6% after 5 years and 15 years respectively. The anatomic distribution of these tumors in transplant recipients is similar to the general population. The development of skin cancer is also strongly related to the patient's age and sex at the time of the transplantation (Naldi et al, 2000).

3.1.1 Squamous cell carcinoma (SCC) and basal cell carcinoma (BCC)

Non-melanoma skin cancers are the commonest tumors following solid organ transplant. They are reported to occur approximately 8 years after renal transplant in recipients aged 40 years or younger, and 3 years post-transplant in recipients 60 years and older. SCC and BCC account for more than 90% of these tumors. The risk of SCC is 60-250 times greater than the general population whereas the risk of BCC is 10 times higher. Interestingly, SCC is more common than BCC in transplant patients which is in contrast to the general population where the ratio of BCC:SCC is 4:1. Both tumors generally occur at a younger age, involve multiple sites, behave more aggressively, and tend to recur after treatment. The most important risk factors are prior exposure to ultraviolet radiation, and for SCC, development of premalignant lesions such as Bowen's disease, premalignant keratosis and warts, and keratoacanthoma.

3.1.2 Melanoma

The risk of developing melanoma is 3.6 times greater than in the general population. The risk is positively associated with increasing age at transplant, and use of depleting anti-lymphocyte antibodies. On the other hand, increasing time since transplant, female sex, and non-Caucasian race are associated with a reduced risk of melanoma development.

3.1.3 Merkel cell carcinoma (MCC)

MCC is an aggressive neuroendocrine carcinoma of skin which has an even more aggressive outcome in transplant patients. It is more common in transplant recipients with an average of 7 years post-transplant and mean survival of 18 months after diagnosis. Merkel cell polyomavirus (MCV) is believed to be a contributing factor.

3.1.4 Carcinomas of anogenital region

The incidence of these tumors is 100 fold higher in renal transplant recipients. These tumors often present as pigmented maculopapular lesions or warts. They tend to involve multiple

sites including anus, and or perianal skin, and external genitalia of both sexes. They are usually extensive, in particular in women, one third of whom have concurrent cervical cancer.

3.2 SCC of the eye

The incidence of SCC of the eye is 20 fold higher in transplant recipients than in the general population. The incidence is also higher in HIV patients.

3.3 Urinary tract malignancy

There is an increased risk of developing tumors of the native urinary tract in patients with an exposure to cyclophosphamide, analgesic nephropathy, and nephropathy-induced by Chinese herbs (Morath et al, 2004).

3.3.1 Renal cell carcinoma (RCC)

The incidence of RCC after renal transplant is increased by more than 15 fold. Primary RCC occurs in approximately 3% of the general population, and 4.6% of renal transplant patients. The risk is increased in African-Americans, men, older donor age of more than 50 years, recipient age at least 65 years, patients with microscopic hematuria, acquired cystic kidney disease, analgesic nephropathy, and longer pre-transplant dialysis interval. More than 70 % of these tumors arise in native kidneys with only few cases reported in allografts. Once a RCC is diagnosed in an allograft, it is crucial to know the origin of the tumor cells whether they are of donor or recipient origin. RCC originating from renal allograft can be distinguished from RCC of the native kidney. Most RCCs of native kidney present as incidental tumors (90%) that are of low-grade, low-stage, and have a good prognosis. Post-transplant RCCs, on the other hand, are multifocal in 40% of cases, and bilateral in 20%. Clear cell carcinoma is the most common subtype, although papillary subtype is seen more frequently than in non-transplanted patients. If the RCC develops 6 months after transplant, it is assumed to be de novo. Although multiple risk factors have been identified, the exact risk factor dependent screening protocol is yet to be determined (Klatte & Marberger, 2011, & Boix, et al, 2009, & Tydén et al, 2000).

3.3.2 Bladder carcinoma

Among the urologic malignancies that develop after transplant, bladder cancers are associated with worse prognosis, aggressive behavior, and high risk of recurrence than the general population. Most bladder carcinomas reported among solid organ transplant recipients are seen after kidney transplant. Yearly screening for non-glomerular hematuria is indicated in patients exposed to prolonged cyclophosphamide therapy due to the increased risk of bladder cancer. These patients should undergo cystoscopy as cytology may miss low grade lesions.

3.4 Lung carcinoma

In comparison to renal and liver transplant recipients, the incidence of lung tumors tends to be much higher in heart and lung transplant patients.

3.5 Kaposi's sarcoma (KS)

The incidence of KS is much higher in renal transplant recipients with a male predilection (male:female ratio of 3.3:1). It is caused by Human Herpes virus 8 (HHV-8) and is commonly seen in patients of Mediterranean, Arabic, Jewish, Caribbean, or African descent, mostly corresponding to the geographic distribution of HHV-8. The choice of immunosuppressive agent also plays a role in development of this entity as calcineurin inhibitors are associated with a higher risk of developing KS than other immunosuppressive agents. Clinical presentation is similar to the classic KS with angiomatous lesions involving the lower extremities. Approximately 90% of patients have cutaneous involvement with 10% showing visceral involvement which is associated with a worse prognosis. The incidence of visceral involvement is lower in renal transplant than in heart or lung transplant recipients.

3.6 Gastrointestinal (GI) carcinomas

Approximately 50% of GI malignancies affect the large intestine. Other organs at increased risk are liver, esophagus, and stomach (Lutz & Heemann, 2003). Colorectal carcinomas occur almost 3 times more frequently in renal transplant than age- and gender- matched general population. Significant risk factors include male gender, > 50 years of age, and the duration of immunosuppression (Nafar et al, 2009). GI malignancies have poor prognosis. Cancer survival by stage is also much worse in transplant recipients. The 5 year survival for localized cancer is 74% in transplant patients as compared to 90% in the general population.

3.6.1 Hepatocellular carcinoma

Infection with oncogenic hepatitis B and C viruses increases the risk of hepatocellular cancer. Transplant recipients with known hepatitis B and C cirrhotic liver disease should have serum alpha-fetoprotein (AFP) and hepatic ultrasound screen every 12 months (Kasiske et al, 2010). AFP has high specificity (>90%) but low sensitivity (20-60%) for detection of small hepatocellular carcinomas. The abdominal ultrasound, on the other hand, is more sensitive than serum AFP (80-85%) for detection of small hepatocellular carcinoma (1-5 cms in size). Patients with suspicious lesions should undergo contrast-enhanced CT (Brennan et al, 2011).

3.7 Post-transplant lymphoproliferative disorder (PTLD)

PTLD is characterized by abnormal proliferation of lymphoid cells with majority representing malignant lymphoproliferative lesions. The most recent 2008 WHO classification of PTLD stratifies the subgroups into monoclonal or polyclonal. These are further subdivided according to their morphologic features and characteristics to monomorphic, if cells are homogenous, or polymorphic if cells are heterogenous. (Table 1) (Mucha et al, 2010). PTLD varies from polyclonal B cell proliferation with normal cytogenetics and no evidence of immunoglobulin gene rearrangement to polyclonal B cell proliferation with early malignant transformation associated with clonal cytogenetic abnormalities and or immunoglobulin gene rearrangements to monoclonal B cell proliferation with malignant cytogenetic abnormalities and immunoglobulin gene rearrangements, the latter accounting for about 15% of cases (Nalesnik et al, 1988). 80-90% of these PTLDs representing B-cell malignancies are associated with EBV infection. Most PTLDs are of recipient origin with only few that are of donor cell origin. The recipient-origin

Early Leions	<ul style="list-style-type: none"> • Plasmacytic Hyperplasia • Infectious-mononucleosis like lesions
Polymorphic PTLD	
Monomorphic PTLD	<ul style="list-style-type: none"> • B Cell Neoplasms <ul style="list-style-type: none"> ○ Diffuse large B-cell lymphoma ○ Burkitt lymphoma ○ Plasma cell myeloma ○ Plasmacytoma-like lesions • T Cell Neoplasms <ul style="list-style-type: none"> ○ Peripheral T-cell lymphoma, not otherwise specified ○ Hepatosplenic T-cell lymphoma
Classical Hodgkins Lymphoma-type PTLD	

Table 1. Pathologic Classification of PTLD (Morgans et al, 2009).

PTLDs clinically present with a multisystem disease that occurs after an average of 76 months post-transplant. On the other hand, the donor-origin PTLDs are usually limited to the allograft, develop after an average of 5 months, and regress with reduction of immunosuppression. Although, most of these disorders are of B-cell origin, however T-cell derived lesions are rarely reported. Data obtained from United States Renal Data System related to 66,159 renal transplant recipients, reported the development of malignant lymphoid proliferation in 1.8% of patients over 10 year follow-up, with 70% representing NHL, 14% multiple myeloma, 11% lymphoid leukemias, and 5% Hodgkins lymphoma (HL) (Caillard et al, 2006). The incidence was higher in the first year. NHLs in these patients have a more aggressive clinical course with more extranodal involvement occurring in 30-70% of cases, and worse prognosis. The lymphoproliferative disorders occurring in post-transplant behave differently than those in general population. NHL accounts for 65% of lymphomas in the general population whereas it accounts for 93% in post-transplant patients. Most of these NHLs are large cell lymphomas, majority of B-cell origin. For early detection of these disorders, a high level of suspicion is required, and when diagnosed the management should be handled by an experienced team to overcome this life-threatening complication (Morgans et al, 2009). Although the prognosis varies with clonality and extent of disease, the overall survival rate ranges from 25-35%. Mortality with monoclonal malignancies has been reported to be as high as 80%. T cell lymphomas in general have an extremely poor prognosis. Additional prognostic factors associated with worse outcome are identified for PTLD that include the performance status of > 2 as per the Eastern Cooperative Oncology Group criteria and more than one site involvement. The International Prognostic Index useful in determining prognosis in immunocompetent patients with NHL, is less beneficial in this setting. Adverse prognostic indicators include the presence of hypoalbuminemia, and involvement of central nervous system (CNS) and bone marrow. Increase mortality rates have been associated with a diagnosis within 6 months versus after 6 months from surgery (64% versus 54%), increasing age, no surgical intervention (100% versus 55%), allograft plus other organ involvement versus allograft involvement alone (64% versus 31%), and multiple versus single sites (73% versus 53%) and the risks are additive (Friedberg et al, 2011).

4. Pathogenesis

Malignancy can develop in transplant recipients in three different ways (Morath et al, 2004):

- **De novo malignancy occurrence.** The risk is approximately 0.2%.
- **Recurrent malignancy in the recipient.**
- **Transmission of malignancy from the donor.** Despite all efforts to secure a safe organ for transplantation, transmission of diseases such as malignancies, and infections may occur. Donor transmission of solid cancers is an unlikely event (Pedotti et al, 2004). These tumors may represent metastasis from malignancies diagnosed in the donor at the time of transplant (Donor-transmitted malignancy) or tumors develop de novo in transplanted donor tissue (Donor-derived malignancy). The risk of cancer developing in recipients receiving kidney from a donor with known or incidentally discovered cancer is 45%. In a population based study by the United Network for Organ Sharing analysed 257 donors who donated 650 organs over a period of 33 months (Birkeland & Storm, 2002), both cadaveric and living-related donors were seen to have a concealed malignancy. In general, diagnosis of a malignant tumor in a donor is a contraindication for organ donation, except from those with in-situ carcinoma of cervix, low-grade cancers of skin, and primary tumors of CNS. CNS tumors may metastasize in less than 2.3% of cases with only few reports of transmission to recipients (Detry et al, 1997 & 2000 & Wallace et al, 1996).

4.1 Risk factors

Multiple factors are associated with development of de novo malignancy in transplant recipients. The risk of oncogenesis after transplantation is related to the types and duration of exposure to immunosuppressive therapy. Disruption of both antitumor immune surveillance and antiviral activity likely play a role. Chronic antigen stimulation from transplanted organs, repeated infections, or transfusion of blood products may overly stimulate a partially depressed immune system, resulting in the development of post-transplant lymphoproliferative disorder (Buell et al, 2005, Chapman and Campistol, 2007).

4.1.1 Immunosuppression

There is strong evidence that the intensity of immunosuppression after transplant affects the risk of post-transplant malignancy development. This observation is supported by the fact that the incidence of malignancy is higher in heart and lung transplant patients who routinely require more intense immunosuppression than renal transplant recipients. In addition, the risk of development of PTLD is highest in the first year post-transplant when the degree of immunosuppression is at its maximum. Episodes of graft rejection in the first year post-transplant increase the likelihood of developing a second malignancy most likely due to the increased level of immunosuppression required.

4.1.1.1 Calcineurin inhibitors (CNI)

Both cyclosporine and tacrolimus have been associated with increased levels of TGF- β that might lead to tumor growth since both agents have long been linked to the development of post-transplant malignancies including PTLD and solid organ cancers. Some authors suggest that tacrolimus is safer than cyclosporine in this regards. In addition, cyclosporine also

induces production of VEGF, thus promoting carcinogenesis, and enhances the apoptotic effect of taxol and INF-gamma on human gastric and bladder carcinomas (Buell et al, 2005). Patients receiving low dose cyclosporine have a lower incidence of malignancy development (19.8% versus 32%) in particular skin carcinomas. In animal model, cyclosporine and tacrolimus have a direct effect on the tumor cells, promote invasiveness, and facilitate metastases. Data suggest that the CNI promote metastatic spread of the pre-existing tumor cells rather than convert a non-malignant cell into a cancer cell (Suthanthiran, 2009).

4.1.1.2 Azathioprin

Azathioprine is an antimetabolite that has long been recognized as an etiologic agent in the development of neoplasia. It is in particular associated with increased incidence of non-melanoma skin cancer especially SCC. It also may lead to the development of myelodysplastic syndrome. Azathioprin has been reported to increase photosensitivity and also allows ultraviolet A to directly damage the DNA by intercalating DNA level, inhibiting repair splicing, eliciting codon misreads, and development of microsatellite DNA instability (Buell et al, 2005 & O'Donovan et al, 2005).

4.1.1.3 Antilymphocyte therapy

The use of anti-T-cell therapy (antilymphocyte serum or muromonab-CD3), but not IL-2 receptor antibodies, has been shown to predispose solid organ transplant recipients to EBV-associated PTLD. Transplant patients on monoclonal antilymphocyte antibody (anti-CD3) as the sole induction agent, show a 72% increase in the risk of PTLD, however despite this relation anti-CD3 has not been found to show any association in the development of other solid organ malignancies. Anti-CD52 appears safer with no increased risk of de novo malignancy development (Buell et al, 2005).

4.1.1.4 Sirolimus

Sirolimus, an inhibitor of the mammalian target of rapamycin (m-TOR), suppresses the growth and proliferation of tumors. It has antineoplastic effect mainly due to inhibition of p70 S6K, IL-10, cyclins, and vascular endothelial growth factors A and C, with direct inhibition of cell replication, induction of apoptosis, and inhibition of tumor angiogenesis. Some studies show a decreased incidence of malignancy in patients receiving Sirolimus than other immunosuppressive therapies. Post-transplant patients treated with Sirolimus appear to have a lower incidence of de novo malignancy when compared with a triple immunosuppressive regimen treated group (CNI, antimetabolite, and corticosteroids). In addition the use of Sirolimus in place of cyclosporine has been associated with complete regression of KS in the vast majority of renal transplant recipients (Buell et al, 2005). Newer sirolimus analogues, such as temsirolimus, have become a focus in pure oncological research for their antineoplastic effects on a variety of malignancies (Kapoor, 2008, & Campistol, 2007).

4.1.1.5 Mycophenolate Mofetil (MMF)

MMF impairs lymphocyte function by inhibiting enzyme inosine monophosphate dehydrogenase leading to purine biosynthesis block. Several cancers including leukemias and some solid tumors produce dramatic elevation of this enzyme. Some studies suggest that the risk of malignancy is not increased and even may be even decreased with MMF (Rama & Grinyó, 2010 & Brennan et al, 2011). Recent studies show a distinctive antineoplastic effect of MMF against colorectal and prostatic carcinomas, and its inhibiting

effect on the adhesion of colonic adenocarcinomatous cells to endothelial cells (Eng, 2005, & Leckel, 2003). The use of MMF is clearly associated with a distinctive decrease in the incidence of post-transplant PTLD (Buell et al, 2005).

4.1.2 Conventional risk factors

Exposure to ultraviolet radiation is associated with increased risk of skin cancer. Other common risk factors are also associated with development of post-transplant malignancy such as advanced age, smoking, and analgesic abuse. History of phenacetin abuse is associated with striking increase in urothelial carcinoma. Renal transplant recipients also have higher incidence of development of carcinomas in the native kidneys in particular if they have been on long term dialysis. The incidence is almost 100 times greater than expected and is in part related to ESRD, tubular hyperplasia, cyst formation, and in some cases malignant transformation.

4.1.3 Genetic factors

Transplant recipients who had history of invasive carcinoma before transplant have a higher risk (relative risk 2.38) of developing a second invasive carcinoma post-transplant. Some primary renal disorders such as von Hippel-Lindau disease are associated with higher risk of developing renal cell carcinoma that behave more aggressively. In addition, patients with Wiskott-Aldrich syndrome and Drash syndrome are also associated with an increased risk of carcinoma development in particular lymphoma and Wilms tumor.

4.1.4 Coexisting oncogenic viral infection

Certain viral infections are associated with increased predisposition of transplant patients to development of specific tumors. At least 4 viruses may be cocarcinogenic in transplant patients.

4.1.4.1 EBV

Most PTLDs are associated with EBV infection. EBV is a gamma herpes virus. It is present worldwide and EBV antibodies are seen in almost 90-95% of the population. In immunosuppressed patients, EBV infection can lead to cell transformation. Latent membrane protein-1 (LMP-1) of EBV has the major role in EBV-associated PTLD development as it engages the signaling proteins from tumor-necrosis-factor-receptor-associated factors (TRAFs) that lead to cell growth and transformation. There is increased risk of PTLD among EBV-seronegative recipients of EBV positive donors. The incidence of PTLD for EBV seronegative recipients is reported to be 24 times higher than EBV seropositive recipients. EBV negative PTLDs present much later (2324 days versus 546 days post-transplant), and have a much more virulent behavior (Friedberg et al, 2011).

4.1.4.2 HHV-8

All types of KS including classic, endemic, AIDS-related, and post-transplant KS are all associated with HHV-8 presence in tumor tissue. There is convincing evidence of transmission of HHV-8 from the donor to transplant recipients, with one study showing evidence of donor-derived tumor cells transmitted to transplant recipients. HHV-8 is necessary but not sufficient for KS development, with transplant related immune

dysfunction being an important contributing cofactor. Pretransplant antibody screening of recipients as well as donors in high seroprevalent areas may be useful. However seropositivity for HHV-8 is not always associated with increased risk of development of KS. Studies from Saudi Arabia show the proportion of patients with antibodies against HHV-8 is higher among patients who developed KS post-transplant than those who did not. In addition the incidence of KS is higher in patients with HHV-8 infection at the time of transplant than among those who did not have infection (15-28% versus <1%) (Diociauiti et al, 2000, & Cattani et al, 2001, & Regamey et al, 1998). A study from Saudi Arabia revealed 10 fold higher incidence of KS in Saudi transplant recipients than in Western countries. In addition, there was a markedly higher incidence of specific anti-HHV-8 antibodies in patients with KS as compared to those without it (92% versus 28%) (Qunibi et al, 1998).

4.1.4.3 Human papilloma virus (HPV)

There is an extremely diverse group of HPV subtypes that can be found in various benign, premalignant, and malignant skin lesions in transplant recipients. Multiple subtypes can be seen in a single lesion. HPV DNA is detected in 65-90% of skin tumors in transplant recipients. However a causative role of HPV in development of secondary skin cancers is not proven. Interestingly, HPV has been detected in normal hair follicles of transplant patients (Boxman et al, 1997, & Berkhout et al, 2000).

4.1.4.4 Merkel cell virus (MCV)

MCV is believed to be a contributing factor to MCC.

4.1.5 Geographic differences

Literature review shows widely variable relative frequency of the different types of post-transplant malignancies in different geographic areas. In Saudi Arabia the most common tumors in transplant recipients are KS, skin cancers (melanoma being more common in children than in adults), anogenital cancers, and lymphomas particularly in children (al-Sulaiman & al-Khader, 1994). In Japan the most common post-transplant tumors are those of digestive tract including stomach, liver, colon, and rectum. On the contrary, the incidence of lymphoma and skin tumors in Japan is low. In Australia the risk of skin cancer development is the highest, most likely due to the excessive sun exposure of the fair-skinned population. In South East Asia the frequency of liver cancer is high where hepatitis B and C infections are endemic. In United Kingdom lymphomas, renal cell carcinomas, bronchial cancer, and tumors of digestive tract are the most commonly encountered tumors in post-transplant recipients (Morath et al, 2004). In South Africa, the incidence of post-transplantation malignancy development is reported to be 5.6%, the commonest tumors being PTLT, followed by non-melanoma skin cancer, KS, gastrointestinal carcinoma, cervical cancer, and vulval cancer (Maharaj & Assounga, 2010). The Northern Italy Transplant program studied 3,521 patients over a 10 years period in 10 local Transplant centers. The average cancer incidence was 4.9%. The commonest tumors were KS, PTLT, renal and skin cancers followed by colorectal, breast, gastric, lung, and bladder carcinomas, and mesothelioma (Pedotti et al, 2003). In India, the incidence of malignancy after transplant is lower than the Western countries. PTLT is the commonest malignancy there especially in the first year followed by oropharyngeal cancer. Skin cancer incidence of both melanoma as well as non-melanoma cancer is much lower mostly attributed to the high cutaneous melanin content (Joshi and Jha, 2009).

4.1.6 Renal transplant tourism

Despite the international abandonment of commercial organ trafficking, many patients continue to travel to different countries to receive commercial transplants. Commercial cadaveric renal transplant was compared to domestic cadaveric renal transplant in China. The 10 year cumulative cancer incidence of the touring group, primarily of Taiwan origin, (21.5%) was significantly higher than the domestic group (6.8%). This might be related to older age at transplantation, more depleting antibody induction therapy, and omitted pre-transplant cancer screening. The graft and patient survival in transplant tourism group is inferior as compared to the domestic group. Hepatocellular and urothelial carcinoma were the most prevalent malignancies in renal transplant tourism patients from Taiwan when compared to Western patients. This can be explained by the high incidence of viral hepatitis in Taiwan and the use of Chinese herbal medications. The use of Chinese herbal medications containing aristolochic acid, which is associated with urothelial carcinoma development, facilitates diuresis and is a common practice in ESRD patients who do not accept dialysis. It is interesting that transplant tourism is considered to be an independent risk factor for post-transplant malignancy development (Tsai et al, 2011).

4.1.7 Blood groups

Types of blood groups does not seem to be related to increased incidence of cancer development (Pedotti et al, 2003).

4.1.8 Transplant center selection

Selection of a particular transplant centers does not appear to be related to an increase in incidence of cancer development (Pedotti et al, 2003).

4.1.9 HLA match

There is a strong influence of HLA matching on graft outcome (Opelz, 2001). However the association is indirect and related to the aggressive immunosuppression required for low degree HLA matching.

5. Incidence of post-transplantation malignancy in children

The pattern of malignancies that occur in pediatric post-transplant population is different from the adult post-transplant patients and the general pediatric population. In a study of 219 children who underwent renal transplant, 7.3% developed malignancy. The cumulative incidence of cancer development was found to be 1.9% at 1 year, 4.0% at 5 year, 6.9% at 10 years, and 10.2% at 15 years. The 10 years incidence of PTLD was 4.5% when the mortality rate was 25%. Other commonly encountered tumors in post-transplant children recipients are HL, Burkitt lymphoma, renal papillary carcinoma, thyroid papillary carcinoma, recurrent ovarian seminoma, and skin cancer. The occurrence of skin cancer is rare in children and usually occurs during early adulthood. Screening and early detection of these tumors in children is of great importance. In addition regular screening for EBV viral load is recommended for patients at risk for developing PTLD (Koukourgianni et al, 2010).

6. Transplantation in patients with pre-existing malignancy

The recurrence rate of malignancy is 22% in patients treated before transplantation and 27% in those treated after transplantation. There is however variability in recurrence rate according to the type of tumor (Barrett et al, 1993, & Trofe et al, 2004, & Kasiske et al, 2001):

- 0-10%: Localized renal cell carcinoma, cervical, testicular, and thyroid carcinoma, and Hodgkins as well as non-Hodgkins lymphoma.
- 11-25%: Wilm's tumor, and cancer of colon, uterus, prostate, and breast.
- Over 25%: Advanced renal cell carcinoma, bladder cancer, myeloma, sarcoma, and skin cancer including melanoma and non-melanoma skin tumors.

Patients with low risk tumors such as in-situ carcinoma, low grade bladder carcinoma, and basal cell carcinoma should have no waiting period for transplantation. Patients with tumors that have a high risk of recurrence such as melanoma, colorectal and breast cancer should wait for at least 5 years before transplantation. For most other tumors a delay of 2 years is often considered sufficient (Table 2) (Morath et al, 2004).

Type of Cancer	Recommendation (years)
Breast cancer	> 5 (> 2 for early disease)
Colorectal cancer	> 5 (> 2 for Dukes Stage A or B1)
Melanoma	> 5 (> 2 melanoma in situ)
Uterine cervical cancer	> 2 (> 5 for more advanced cervical cancer)
Renal cell carcinoma/Wilms tumor	> 2 (> 5 for large cancers; no wait for incidental tumor < 5 cm)
Bladder cancer	> 2
Kaposi sarcoma	> 2
Leukemia	> 2 (limited data to make recommendation)
Lung cancer	> 2
Lymphoma	> 2 (possibly > 5)
Prostate cancer	> 2 (possibly less for localized disease)
Testicular cancer	> 2
Thyroid cancer	> 2
Skin (nonmelanoma) cancer	0-2 (no wait for basal cell carcinoma)
Liver cancer	Unable to give recommendation
Myeloma	Unable to give recommendation

Table 2. Recommended Wait Time (Years) Based on Type of Cancer Before Listing for Transplantation (Kasiske et al, 2001).

7. Multiple independent primary cancers or second tumor in transplant recipients

Excluding the non-melanoma skin cancers, the risk of developing a second primary cancer is almost the same as the incidence of first cancer. The risk of developing a second primary in this group could be related to persistence of environmental risk factors associated with the first cancer such as tobacco, genetic factors responsible for development of second primary cancer, and individual susceptibility to carcinogens. A study of a network of cohort of transplanted patients shows the incidence of second primary cancer development to be 0.3%. The incidence of developing second primary cancer is 1-5%. Excluding skin cancers, transplant patients with first cancer diagnoses should follow regular screening procedures and do not appear to require a special program (Taioli et al, 2006).

Skin cancer is the commonest second malignancy among transplant recipients (Morath et al, 2004). The North Italy Transplant program reported the prevalence of second primary cancer to be 1.7% and development of multiple independent primary cancers arising in the same patient to have a prevalence of 3.6% (Pedotti et al, 2003). The risk of developing a second non-melanoma skin cancer is high in renal transplant recipients who developed a first non-melanoma skin cancer. The risk is, in particular, high of SCC but is also substantially increased for BCC. The risk is much lower for SCC in renal transplant recipients who present with BCC, however after the diagnosis of first SCC the subsequent risk for SCC appears to be the same. The 3 year cumulative risk is approximately 59% of non-melanoma skin cancers and 62% of subsequent SCC. The 3 year risk of BCC is 37% and the 5 year risk of subsequent BCC is 51%. Renal transplant recipients who develop SCC mostly develop SCC as subsequent skin cancer and recipients who have BCC as first malignancy mostly develop subsequent BCC. This difference could be related to the difference in the lifestyle as the risk of SCC is associated with chronic cumulative sun exposure whereas BCC is more associated with intermittent intense sun exposure. Longer time between transplantation and development of first SCC is also associated with an increased risk of subsequent SCC. The type of maintenance immunosuppression is the most important risk factor of subsequent development of SCC. Patients on Azathioprin have an approximately 3 times higher risk of subsequent SCC as compared to cyclosporine-based regimen. The duration of immunosuppression also influences the development of subsequent SCC after the first SCC. Sun exposure is an important risk factor for multiple lesions development. Fair skin of patients and light color of the hair and the eyes are predictive of multiple SCC development (Euvrard et al, 2006). Male sex is also a risk factor for multiple skin cancer development, especially the BCC. In addition, BCC is more commonly seen in living-related kidney transplant than the cadaveric kidney transplant recipients (Wisgerhof et al, 2010).

8. Prevention and screening for early detection

Regular cancer screening is recommended when a patient is considered for renal transplant. Screening and early detection of cancers should be incorporated into the pre-transplant evaluation of ESRD patients. Screening may also detect premalignant lesions quite early allowing for a timely intervention (Kiberd, 2005). The rising age and the prolonged duration on transplant waiting list increases patients' risk of being transplanted with an undetected malignancy (Morath et al, 2004). Careful screening should be performed for the recipient as

Target Organ or Cancer	Test*	Frequency	Age of Screening
Breast	Mammography	Every 1-2 years	> 40 years
Colon/rectum	Occult blood and Sigmoidoscopy or Colonoscopy	Annually Every 5 years Every 10 years	> 50 years > 50 years > 50 years
Prostate gland	Digital rectal exam PSA	Annually	> 50 years
Kidney	Imaging study†	Once	All patients
Bladder	Cystoscopy	Not routine	> 50 years and all high-risk patients
Uterine cervix	Pap smear Pelvic exam	Every 1-3 years	> 20 years or any sexually active patient
Testicle	History and physical exam	Once	All male patients
Kaposi sarcoma	History and physical exam HHV-8 assay	Once	All patients All high-risk patients
Skin	History and physical exam	Once	All patients
Melanoma	History and physical exam	Once	All patients
Liver	Imaging study†	Once, high risk annually	All patients
Lung	CXR	Once	All patients
Lymphoma	History and physical exam EBV assay	Annually	All patients
Leukemia	CBC	Annually	All patients
Myeloma	Immunoelectrophoresis	Once	> 50 years

PSA = prostate specific antigen; HHV-8 = human herpes virus 8; CXR = chest x-ray;

EBV = Epstein-Barr virus; CBC = complete blood count

*Abnormalities on screening tests may indicate the need for additional tests. For example, suspicious lung lesions on the chest x-ray should be followed up with a computed tomography scan.

†Ultrasound, CT scan, or magnetic resonance imaging scan.

Table 3. Possible Pretransplant Screening Strategies for the Potential Kidney Transplant Recipient (Kasiske et al, 2001).

well as the donor. The 2009 Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guidelines on monitoring and treatment of kidney transplant recipients were developed to help practitioners caring for these patients. These guidelines were based on evidence and systemic review of treatment trials. A set of recommendations were developed

for screening and risk assessment of renal transplant recipients (Kasiske et al, 2010). Patients with failed transplant returning to dialysis have a higher mortality than those on transplant waiting list (Cattran & Fenton, 1993).

The Clinical Practice Guidelines Committee of the American Society of Transplantation (AST) has published guidelines for outpatient evaluation of pediatric and adult kidney transplant candidates that include recommendations for screening and early detection of malignancies. Some of these recommendations are represented in Tables 3 and 4 (Kasiske et al, 2001 & Kiberd, 2005, & Kalble et al, 2009, & AST Kidney-Pancreas committee, 2009).

Target Organ or Cancer	Who	Test*	Frequency	Age of Screening
Breast	Selected*	Mammography	Every 1-2 years	> 40 years
Colon/ rectum	Selected*	Occult blood and Sigmoidoscopy or colonoscopy	Annually Every 5 years Every 10 years	> 50 years > 50 years > 50 years
Prostate gland	Selected†	Digital rectal exam PSA	Annually	> 50 years
Uterine cervix	Female	Pap smear Pelvic exam	Every 1-3 years	> 20 years or any sexually active patients
Kaposi sarcoma	All	History and physical	Annually	All high-risk patients
Nonmelanoma skin	All	History and physical	Annually	All patients
Melanoma	All	History and physical	Annually	All patients
Liver	Selected‡	Imaging study	High risk annually	All patients
Lymphoma	All	History and physical	As clinically indicated	All patients

PSA = prostate specific antigen

*Patients with good life expectancy and good allograft function

†Male patients at high risk, including black patients

‡Patients with cirrhosis

Table 4. Posttransplant Screening Strategies for the Kidney Transplant Recipient (Kiberd, 2005).

8.1 Skin and lip cancer

Introduction of patient education programs is recommended in particular in countries with high incidence of non-melanoma skin carcinoma secondary to high sun exposure. Patients should also be educated about their increased risk of such cancers especially if they are fair skinned, have high sun exposure level, or have prior history of skin cancer. Patients should reduce their sun exposure, perform self-examination, and have an annual skin and lip examination by qualified Health care provider. Oral acitretin should be given to patients with prior history of skin cancer to prevent development of new malignancy.

8.2 Non-skin cancer

The recommendations for transplant patients with moderately increased risk of developing non-skin cancer are non-specific. However they reinforce the same recommended screening strategies as for the general population. These include pap smear, self-breast examination, mammography, and colonoscopy. In addition annual liver ultrasound and α -fetoprotein monitoring is also recommended in patients with cirrhosis ((Rama & Grinyó, 2010).

8.3 PTLD

Since development of PTLD is related to the degree of immunosuppression, and infection with EBV and CMV, prevention largely relies on limiting patient exposure to aggressive immunosuppression, and anti-viral prophylaxis. There is a relatively high incidence of PTLD reported with introduction of tacrolimus and therefore rapid tapering of tacrolimus may limit the development of PTLD (Friedberg et al, 2011). In one review of PTLD in children, the incidence of PTLD development was 17% in children who received renal allograft with tacrolimus as compared to 4% in children who underwent aggressive tapering of tacrolimus (Shapiro et al, 1995). There is higher incidence reported of PTLD among EBV-seronegative recipients of EBV-seropositive donors that suggests that treatment of early EBV infection may decrease subsequent development of PTLD (Holmes et al, 2002 & Funch et al, 2005). In addition prophylactic antiviral therapy is also associated with a reduced risk of PTLD development. The use of prophylactic anti-CMV during the first 3-6 months after renal transplant significantly reduces the incidence of PTLD in the first year post-transplant but not in the subsequent 5 years (Kasiske et al, 2010, & Opelz et al, 2007).

8.4 Colorectal carcinoma

Community-level screening for colorectal carcinomas using fecal occult blood is now a standard practice in most developed countries. Studies in the general population have shown that the benefits of starting screening at a younger age were little and costly as compared to starting at age of 50. However renal transplant patients have an age-shifted increase in the risk of colorectal carcinoma and screening at a younger age in this population seems therefore justifiable (Wong et al, 2008).

9. Treatment

Reduction or cessation of immunosuppression is particularly useful in renal transplant recipients as loss of graft secondary to rejection is not a fatal event in this group as

compared to the heart, lung, or liver transplant recipients. Immunosuppression reduction may lead to spontaneous regression of some tumors such as some cases of PTLD, some skin cancers, KS, and donor-derived malignancies. In KS reduction of CNI may be particularly important. Despite the association of CNI and cancer development, some authors recommend discontinuation of antimetabolite and use of CNI and Prednisone as first line approach in transplant recipients with malignancy. This is because rejection is less likely to occur with double therapy (CNI and prednisone) than combination of antimetabolite and prednisone. An exception to this is the very well matched HLA transplant recipients with 0 HLA, B, or DR mismatch, in which the risk of rejection is low with the use of antimetabolite in combination with prednisone (Brennan et al, 2011, & Bosman and Verpooten, 2007).

9.1 Skin, non-melanoma carcinomas

Once a skin lesion is detected there is no evidence of benefits from stopping azathioprin . Treatment of these patients requires several strategies including preventive strategy, specific treatment, and medical adjunct therapy because these tumors may present with multiple lesions, and large areas of skin involvement. Despite this, dedicated surveillance programs are lacking for most patients. Surgery remains the mainstay of managing these tumors and it may be destructive in large or multiple skin tumors. Studies in immunocompetent patients show recurrence in almost 100% of cases with incomplete surgical excision and therefore tumors that are not completely excised should be treated by additional methods (Jemec & Holm, 2003).

9.1.1 SCC

Premalignant lesions can be treated with topical retinoids or in combination with low dose systemic retinoids. Although systemic retinoids reduce actinic keratosis and prevent development of new dysplastic lesions in transplant patients, the treatment is frequently discontinued due to drug adverse events such as mucocutaneous xerosis, pruritis, arthralgia, and hyperlipidemia. Once treatment is discontinued, the lesions tend to recur rapidly. Superficial cancers can be treated with cryotherapy or electrocautery and curettage. More aggressive local therapy is required for invasive SCC as they may have metastasis at presentation and are more likely to develop recurrence. These invasive tumors need surgical excision with negative margins. Although there are no clear established guidelines about margins of SCC excision, Mohs micrographic surgery is typically recommended for these high risk tumors especially those seen in cephalic location, a diameter of > 2 cms, or rapid growth. Metastasis in a single lymph node is considered potentially curable. Adjuvant radiation, systemic chemotherapy, and or immunotherapy are not of benefit. Several reports show beneficial effect to immune response modifier Imiquimod, however, the safety and efficacy of this agent has not been adequately assessed (Brennan et al, 2011).

9.1.2 BCC

Development of frequent BCCs should prompt reduction in immunosuppression. The management otherwise is similar to that in non-immunocompromised patients.

9.1.3 MCC

Although management of MCC is similar to that in non-immunocompromised patients, the overall prognosis is poorer in transplant patients as compared to the general population with 2 year survival of 44% versus 65-75%. Distant metastasis may regress temporarily with cyclosporine discontinuation (Brennan et al, 2011).

9.2 Skin, melanoma

Multiple strategies are required to treat melanoma including wide local excision with or without sentinel lymphadenectomy, and reduction of immunosuppression.

9.3 KS

Discontinuation of immunosuppression should be the first line of treatment as majority of patients with KS may show complete regression of the lesions. The disappearance of KS by reducing immunosuppression is about 17% with mucocutaneous disease and 16% with visceral involvement. Substitution of Sirolimus for cyclosporine has also been associated with complete regression (Stallone et al, 2005). Patients who do not regress spontaneously should be treated the same way as non-immunosuppressed patients are treated. In the CONVERT study, a randomized prospective study to evaluate the effect of conversion to sirolimus from CNI, displayed a significantly lower malignancy rate (3.8%) at 24 months compared with those who continued CNI based therapy (11%). An mTOR-inhibitor CNI-free regimen should be considered for transplant recipients at high risk for cancer development and for those who develop malignancies over the post-transplant course (Alberú, 2010, & Schena, 2009).

9.4 Anogenital carcinomas

Anogenital Intra-epithelial neoplasia / in-situ carcinomas are treated with laser therapy, topical fluorouracil, or electrocautery. Reduction of immunosuppression is beneficial and may lead to regression of the in-situ lesions. Invasive carcinomas, on the other hand, require wide local excision with inguinal lymphadenectomy for tumors that are >1 mm thick. Adjuvant therapy is given to only selected patients.

9.5 Bladder carcinomas

9.5.1 Non-muscle invasive bladder carcinoma

Bacillus Calmette-Guerin is still the only intravesical therapy that has shown a significant reduction in recurrence-free and possibly progression-free survival.

9.5.2 Muscle-invasive bladder tumor

The mean time between organ transplant and bladder tumor development is 2.8 and 4 years. Most patients presenting with muscle-invasive bladder carcinoma have extravesical disease or lymphadenopathy at the time of surgery. In general, there has been little to no improvement in the survival after radical cystectomy. A reasonable cancer-specific survival and renal allograft preservation is achieved after aggressive surgical therapy in only a few patients. (Wallerand et al, 2010).

9.6 Other solid organ tumors

The course of these malignancies is more aggressive than the general population and the outcome is mostly determined by the stage of tumor at the time of presentation. Visceral malignancies are treated with surgical intervention, chemotherapy, and radiation therapy. If chemotherapy is needed, azathioprine should be discontinued to avoid myelosuppression. Early invasive and in-situ carcinomas can be cured by surgery. The outcome is poor in advanced disease with majority of the patients dying within 1-2 months (Brennan et al, 2011).

9.7 Donor-derived tumors

If the cancer is shown to be of donor origin, reduction of immunosuppression should theoretically lead to rejection of the tumor. This has been shown to be effective in PTLD but the data is not very supportive in other solid organ tumors. In RCC with no metastatic disease, total transplant nephrectomy is curative, however the patient has to go back to dialysis. Some authors suggest nephron sparing surgery in non-metastatic RCC that are located peripherally and are < 4 cms in size. Recipients with metastatic RCC should be treated with transplant nephrectomy, reduction in immunosuppression, and immune therapy (Muruve & Shoskes, 2005).

9.8 PTLD

9.8.1 Reduction of immunosuppression

The most important treatment modality for PTLD is reduction of immunosuppression which allows restoration of the natural T-cell mediated immune response against EBV-infected B cells. The goal by reducing the immunosuppression is to find the correct dose that will allow restoration of the patient's immune response against the PTLD without causing rejection of the transplanted organ. Transplant rejection occurs in approximately 39% of transplant recipients regardless of whether they respond to treatment or not. The risk of rejection also varies with the type of transplanted organ, with highest risk among heart and lung transplant recipients. The reduction of immunosuppression has no standard approach and it has to be individualized for each patient depending on various characteristics such as transplant type, relative risk of transplant rejection, extent and severity of PTLD, and selection of immunosuppressive agents. In general, MMF and azathioprine are discontinued first and the doses of CNI and steroids are reduced. There are several predictive factors to response to reduction of immunosuppression. Interestingly, EBV serostatus does not predict response and therefore this modality of treatment should be used for both EBV seronegative as well as EBV seropositive patients. Multiple factors are associated with poor response that include lactate dehydrogenase level of > 2.5 times the upper limit of normal, bulky disease, multiple visceral sites being involved, and organ dysfunction. Patients lacking these features show a response rate to reduction of immunosuppression as good as 89% (Morgans et al, 2009). The vast majority of polyclonal lymphoproliferative lesions and EBV-related plasmacytomas show significant improvement or complete resolution by immunosuppression reduction. The response is best in patients with early onset disease in whom the level of immunosuppression is a major risk factor as compared to patients with late onset or extensive disease who are much less likely to benefit. One potential regimen for

patients who are severely ill and have extensive disease is to reduce prednisone and stopping all other immunosuppressive agents. For patients who are less severely ill and have only limited disease, one regimen is to reduce cyclosporine or tacrolimus and prednisone by at least 50% and the discontinuation of azathioprine or MMF. If necessary another 50% reduction of immunosuppression can be considered. Immunosuppressive regimens with the fewest possible toxic effects are desirable for transplant recipients. The ELITE-Symphony Study which is the largest prospective study in kidney transplantation evaluated the effects of standard dose versus low dose immunosuppression. The primary end point of the study was the estimated glomerular filtration rate and the secondary end points included acute rejection events and allograft survival. Over 3 years, daclizumab induction, MMF, steroids and low-dose tacrolimus proved highly efficacious, without the negative effects on renal function commonly reported for standard CNI regimens. (Ekberg et al, 2007, 2009).

9.8.2 Antiviral prophylaxis

Initially antiviral prophylaxis was used to eradicate EBV from the patient's system thereby preventing reactivation of any latent infection and abnormal cellular proliferation that may lead to PTLD. Currently there is no supportive evidence of antiviral therapy efficacy for treatment of PTLD. The nucleoside analogues acyclovir and gancyclovir inhibit the replication of multiple members of herpes virus family including CMV and herpes simplex virus. Although theoretically these medications should be effective against EBV, in vivo they are not effective against EBV. These agents need intracellular phosphorylation by a viral-encoded thymidine kinase which is not expressed in infected latent B cells. One approach to overcome this limitation is to use these agents in combination with arginine butyrate which induces the lytic phase of EBV gene expression and thus can induce expression of thymidine kinase. This may enable gancyclovir to be phosphorylated into its active form. Several studies are investigating the efficacy of these 2 agents used in combination in both solid organ as well as bone marrow transplant patients with PTLD and have shown moderate success (Morgans et al, 2009 & Friedberg et al, 2011).

9.8.3 Local therapy

Localized PTLD involving skin or a single GI lesion can be managed by surgery or radiation without the use of systemic therapy. This will spare the patient side effects of systemic therapy and withdrawal of immunosuppression. Local treatment in conjunction with immunosuppression reduction has resulted in very low PTLD-related mortality. Rituximab in combination with surgery or radiation has shown some success. Patients requiring palliative and emergent therapy for advanced disease can benefit from local field radiation therapy (Morgans, 2009).

9.8.4 Anti-B-cell antibody

Since most PTLDs are of B-cell origin, the use of medications that target B-cell antigens is proven beneficial with a reasonable response rate of 50-80%. In earlier studies the use of antiCD21 and antiCD24 has achieved complete response rates of 63% and long-term survival of 46%. However, in the past 10 years, more and more emphasis is on the use of

antiCD20, the rituximab in the treatment of CD20 positive PTLDs. AntiCD20 binds to B cells, induces clearance of cells and destruction by antibody-dependant complement-mediated apoptosis. It may activate patient's immune system against EBV-infected B cells helping destruction of tumor and preventing its recurrence. These proposed mechanisms of action would explain the better efficacy of rituximab in patients with PTLD than the usual NHLs. Risk factors for poor response to anti B-cell therapy include late onset PTLD (onset > 1 years after transplantation), and involvement of CNS and multiple viscera. Rituximab has been reported to induce complete remission of PTLD in some patients with solid organ and bone marrow transplant. Early treatment with rituximab along with reduction of immunosuppression appears to be the evolving standard of care for CD20 positive PTLDs (Friedberg et al, 2011). Other anti-B-cell antibodies have not been fully evaluated systemically in PTLD. There are newer anti-CD20 antibodies such as tositumomab (anti-CD20 coupled with radioactive iodine-131), ibitumomab (anti-CD20 with yttrium-90), epratuzumab (anti-CD22), and galiximab (antiCD 80) that are currently being investigated (Morgans et al, 2009).

9.8.5 Cytotoxic chemotherapy

For patients in whom reduction of immunosuppression is ineffective and who have rapidly progressive or life-threatening disease, chemotherapy can be used as an alternative or additional treatment. Several chemotherapy regimens similar to those used in NHLs are offered for treating patients with monoclonal PTLD such as cyclophosphamide with prednisone, CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone), dose-adjusted ACVBP (doxorubicin, cyclophosphamide, vindesine, bleomycin, prednisone), and other new regimens. Unfortunately although these chemotherapy agents are highly effective, they are associated with serious side-effects that significantly affect patient morbidity and mortality. Studies show that using CHOP after reduction of immunosuppression is associated with a complete remission rate of 63% and median disease-free survival of 10.5 years. The overall response rate of patients to rituximab is 68%. Patient with EBV-positive disease are more likely to respond to rituximab and achieve a complete response rate than those with EBV-negative disease. Patients who received chemotherapy show an overall response rate of 74%. Several factors limit the use of chemotherapy in PTLD. These include suboptimal performance status, drug-to-drug interaction, high likelihood of infectious complications, and dose-limiting organ-dysfunction. Although the overall response rate is somewhat higher for chemotherapy, the associated toxic effects are significant. Approximately 50% of these patients get hospitalized for infections and about 6% eventually die of complications. The debate regarding when to use rituximab as opposed to chemotherapy and how to use them in combination is still ongoing with no consensus recommendations (Morgans et al, 2009 & Friedberg et al, 2011).

9.8.6 Cellular immunotherapy

Cellular immunotherapy of PTLD involves reinfusion of T-cells into a recipient targeting the EBV-related lymphoma. T-cell targeting is HLA specific and EBV-specific and therefore cytotoxic T lymphocytes (CTL) must be HLA-matched to the recipient. Autologous pre-transplant-harvested CTLs are shown to be effective in reducing the EBV viral loads. More recently several tissue banks have been storing EBV-specific CTLs for various HLA types.

The overall response rate after these infusions is close to 52% and the results are thought to have a better response at 6 months in patients receiving closest HLA-matched CTLs (Morgans et al, 2009).

9.8.7 Retransplant

Kidney transplant recipients can be treated with complete withdrawal of immunosuppression and even removal of transplanted organ as it is not a life-sustaining organ unlike heart and lung transplant. Successful treatment of PTLD can result in years of continuous transplant function. Patients with transplant failure due to PTLD may safely go through re-transplantation after 1-2 years. In addition, relapse of PTLD after re-transplantation only rarely occurs (Morgans et al, 2009).

10. Conclusion

Malignancy is a common cause of death after renal transplantation. Early detection and treatment of post-transplant malignancies is an important challenge. An even greater challenge is to prevent the development of these malignancies. Screening these patients for malignancies while they are on the waiting list for transplant and post-transplantation is crucial. It is also recommended to use the lowest planned doses of maintenance immunosuppressive medications by 2-4 months after transplantation, if there has been no acute rejection (Kasiske et al, 2010). The approach in these patients should start with preventive measures including minimizing immunosuppression, avoidance of carcinogenic factors such as ultraviolet radiation, avoidance of repeated exposure to depleting anti-lymphocyte antibodies, and screening of donors and recipients for cancer. There is also growing interest in the potential antioncogenic characteristics of the immunosuppressive agent - mTOR inhibitor. Once malignancy is detected, it should be managed with specific therapy. Reducing CNI dose is a good first approach in patients who develop lymphoma, skin cancer, or KS. Substitution of CNI for mTOR can lead to complete regression of early, small, or low grade KS in renal transplant recipients. Regression of PTLD has also been reported with conversion of CNI by mTOR. Long term studies are needed confirm the beneficial effects of mTOR in regression of cancer in transplant recipients.

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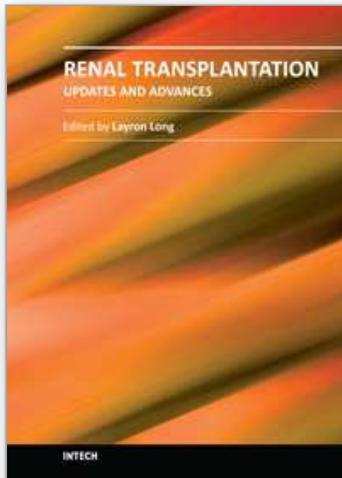
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This book presents a nice international compilation of scholarly papers and chapters which address the latest advances in renal transplant surgery. These works cover a variety of topics; the last advance and success of renal transplant science: biochemistry, immunology, molecular genetics, pharmacology - pharmacogenetics, pediatric transplant and a few rare uropathies that warrant organ replacement.

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