12

Malignancy Following Renal Transplantation

A. Vanacker and B. Maes
Heilig-Hartziekenhuis Roeselare-Menen
Belgium

1. Introduction

After transplantation, there is an increase in the incidence of a wide variety of malignancies compared to the general population, due to the chronic use of immunosuppressive agents. They appear to have a more aggressive behavior and a worse outcome. As a result, among recipients of renal transplantation, malignancy is the third most common cause of patient death with graft function, after cardiovascular diseases and infections. Since management and outcomes of the cardiovascular and infectious complications are improving, malignancy after transplantation will probably become more important (Briggs, 2001).
In this chapter, we will focus on the increased cancer incidence in solid organ transplant recipients, in order to emphasize the clinical importance of this topic in renal transplant patients. Since skin cancer and post-transplantation lymphoproliferative disorder PTLD are most strikingly increased after renal transplantation, we will study them in detail. There is some evidence that individual immunosuppressive agents have a different role in the development of post-transplantation malignancy. The available data on this will be discussed. Finally, based on the currently available international guidelines, we will propose an appropriate prevention and early detection program for patients undergoing renal transplantation.

2. Epidemiology and risk factors

Cancer risk is a major problem after renal transplantation. There is much data on the incidence of cancer after renal transplantation, mostly derived from large transplant registries. One of the largest is an American report (by the United States Renal Data System USRDS) on more than 35,000 patients who received a first renal transplantation (deceased or living donor). The incidence of malignancies during the first 3 years after transplantation was examined compared with the general US population. Three years after transplantation, a cumulative incidence of 7.5% for non-skin malignancy and 7.4% for skin cancer (excluding melanoma) was noted. Compared to the general population, there was especially an important increase in the incidence of Kaposi's sarcoma, non-Hodgkin's lymphoma and nonmelanoma skin cancers (more than 20-fold) and kidney cancer (approximately 15-fold). By contrast, the more common solid cancers in the general population (e. g. breast, lung, prostate, colorectal, uterine and ovarian cancer) were only slightly increased in incidence in transplant recipients (roughly twofold higher). Since cancer appears to be more common among haemodialysis patients (because of the correlation between uremia and abnormalities in the immune system), an additional comparison between the population of

transplant recipients and haemodialysis patients on the waiting list was performed, in order to assess whether this increased incidence was attributed to the presence of end-stage renal disease (ESRD) or could really be related to the post-transplantation setting. For some malignancies, the risk was similar between both groups; however, several cancers (in particular for non-melanoma skin cancers, melanoma, Kaposi's sarcoma, non-Hodgkin's and Hodgkin's lymphoma, cancer of the mouth, cancer of the kidney, oesophageal cancers and leukaemia) are clearly more common after transplantation compared to patients on the waiting list (Kasiske et al., 2004).

A cohort study using data of 28,855 patients from an Australia and New Zealand Dialysis and Transplant Registry (ANZDATA) found similar results. When excluding non-melanoma skin cancer, they reported a slightly increased incidence of malignancy in patients with ESRD receiving dialysis compared to the general population (standardised incidence ratio SIR 1.35), which increased significantly after renal transplantation (SIR 3.27) (Vajdic CM et al., 2006). A Danish retrospective cohort study also showed that the major increase in incidence of malignancy occurs after transplantation and not during dialysis: SIR after transplantation 3.6 versus 1.4 during dialysis, both compared with the general population (Birkeland et al., 2000). In general, we can conclude that the risk of *de novo* malignancies is increased in transplant recipients, with a relative risk 3-5 times that of the general population. In table 1, we summarize the relative risk of certain malignancies compared to the general population and patients with ESRD on the waiting list.

The increased risk of developing malignancy after renal transplantation can in the first place be attributed to the use of immunosuppressive medication, which may damage DNA, lead to malignant transformation of cells and may interfere with normal immunosurveillance to neoplastic cells (allowing uncontrolled growth). It is clear that the intensity and duration of immunosuppressive therapy impacts cancer risk. Whether the type of immunosuppressive agent used also plays an important role in the development of secondary malignancy is a controversial issue. We will focus on this issue in more detail further in this chapter.

Moreover, some common viral infections after transplantation are linked to the development of certain malignancies: Kaposi's sarcoma (associated with human herpes virus 8, HHV8), non Hodgkin's lymphoma NHL and Hodgkin's lymphoma (Epstein-Barr virus, EBV), hepatocellular carcinoma (hepatitis B and C virus, HBV and HCV), cancer of cervix, vulva/vagina, penis, anus and oral cavity and pharynx (human papilloma virus, HPV). Some of those malignancies occur with the highest incidence in transplant recipients, compared to the general population. It is suggested that this could be explained by the impaired immune control of viral oncogenes.

Besides the etiological role of the intensity and duration of immunosuppression and infection by oncogenic viruses, also the genetic background of the host, chronic pretransplantation dialysis treatment, the patient's age at the time of transplantation, pre-transplant malignancy and established carcinogenic exposures (such as exposure to ultraviolet UV light, total sun burden, analgesic abuse and tobacco smoking) play an important role in the occurrence of malignancy after renal transplantation (Dantal & Pohanka, 2007; Morath et al., 2004).

The average time to presentation differs for other type of malignancies. Post-transplantation lymphoproliferative disorder PTLD can occur more early after transplantation, with 20% of PTLD occurring in the first year after renal transplantation. In contrast, skin cancer becomes more common with time.

	Vs. general population	Vs. patients on the waiting list
More common tumours:	2	Similar
Colon		"
Lung		"
Prostate		"
Stomach		"
Oesophagus		2.7
Pancreas		Similar
Ovary		"
Breast		"
Testicular cancer	3	Similar
Bladder cancer		
Melanoma	5	2.2
Leukemia		1.6
Hepatobiliary tumours		Similar
Cervical tumours		"
Vulvovaginal tumours		"
Renal cell cancer	15	1.4
Kaposi's sarcoma	> 20	9
Non-Hodgkin's lymphoma		3.3
Non-melanoma skin cancer		2.6

Table 1. Standardised incidence ratio (SIR) of cancer after transplantation, compared with the general US population and with patients with end-stage renal disease ESRD (adapted from Kasiske et al., 2004)

3. Skin cancer

Skin cancer is the most common cancer type following renal transplantation in Caucasian transplant recipients, occurring in more than 50% of patients in high incidence areas (such as Australia) after 20 years of renal transplantation. The incidence increases with the duration of immunosuppressive therapy. They occur at younger age (10 to 15 years younger than in the general population) and in multiple sites. Moreover, they are more aggressive and more likely to recur after resection. For that reason, they can cause serious morbidity and may have a life-threatening course.

As in the immunocompetent population, sun exposure (UV radiation, causing genetic mutations in epidermal keratinocytes that affect cell cycle regulation) is the major risk factor of developing skin cancer. In transplant patients, an additional important risk factor is the duration and intensity of immunosuppression. For that reason, skin cancer is 2 to 3 times more common after heart transplantation (requiring higher levels of immunosuppression), compared to kidney transplantation. It has been suggested that certain immunosuppressive medications (like azathioprine AZA and cyclosporine CsA) are associated with greater risk of skin cancer due to photosensitizing and mutagenic effects and that others (like mTOR inhibitors) may have antiproliferative effects (Kovach & Stasko, 2009). We will discuss this in detail in below (see '5. Immunosuppressive drugs and the risk of malignancy after transplantation').

3.1 Types of skin cancer

Skin cancer includes squamous cell carcinoma SCC, basal cell carcinoma BCC, malignant melanomas, Merkel cell carcinoma and Kaposi's sarcoma. In contrast to the general population, there is a predominance of SCC over BCC in renal transplant recipients, with a ratio of SCC to BCC of 4:1.

3.1.1 Squamous cell carcinoma SCC

Squamous cell carcinoma SCC arises from atypical keratinocytes of the epidermis. It occurs most commonly in sun exposed areas and is usually associated with precursor lesions like actinic keratoses, Bowen's disease (SCC in situ), viral warts and/or keratoacanthomas. The risk of SCC is 60 to 100 times greater than in the general population. The lesions appear as small red, keratotic, hard nodules that occasionally ulcerate. The pathogenesis is multifactorial, with cumulative sun exposure as most important factor. Also infection with human papillomavirus (HPV, particularly oncogenic HPV 5 and 8 strains) plays an important role in the development of SCC, with HPV being detected in 65 to 90% of SCC of transplant recipients. Other risk factors are fair skin, age, the level of immunosuppression, duration of pretransplantion dialysis, ionizing radiation, chronic inflamed skin (like scars or chronic ulcers) and possibly smoking. SCC is more aggressive in transplant recipients than in the general populations, resulting in higher risk of local recurrence (14% of patients), regional and distant metastasis (6-9% of patients) and mortality. In patients with metastases, disease-specific survival is approximately 50%. Treatment consists of complete local excision and lymphadenectomy if necessary. In immunocompromised patients with the initial presentation of aggressive SCCs, Mohs micrographic surgery should be administered in order to minimize the risk of recurrence and tissue loss. Mohs micrographic surgery includes removal of the tumour followed by immediate frozen section histopathologic examination of margins with subsequent re-excision of tumour-positive areas and final closure of the defect. When more than one lymph node is affected or when there is extracapsular spread, adjuvant radiotherapy should be considered. Systemic chemotherapy can be used for metastatic SCC (Kovach & Stasko, 2009).

3.1.2 Basal cell carcinoma BCC

Basal cell carcinoma BCC arises from the basal layer of the epidermis and its appendages. It occurs on sun-exposed skin, most commonly on the face or head (up to 70%). Common sites are eyelid margins, nose folds, lips and around and behind the ears. The incidence of BCC is increased by a factor 10 to 16 in transplant recipients, compared to the general population. Intense intermittent sun exposure is important in the pathogenesis of BCC, in contrast with SCC were the cumulative sun exposure plays an important role. Other risk factors for developing BCC are similar as for SCC. According to the clinical presentation, BCC can be divided in three sub-groups: nodular BCC (a pink or flesh-colored papule, often with a translucent, 'pearly' appearance and a teleangiectatic vessel, sometimes with central erosion), superficial BCC (a slightly scaly, light red papule or plaque) and morpheaform BCC (smooth, flesh-colored, or very lightly erythematous papules or plaques, frequently atrophic). As for SCC, treatment of BCC consists of local excision (Mohs surgery) with or without lymphadenectomy. Metastases of BCC are very rare even in immunosuppressed patients. However, BCC can cause serious local destruction, necessitating surgery and resulting in significant cosmetic deformity (Kovach & Stasko, 2009).

3.1.3 Malignant melanoma

Malignant melanomas arise from melanocytes. To detect a malignant melanoma, new or changing pigmented lesions should be examined with special attention for A, assymmetry; B, border irregularity; C, color variation/dark black color; D, diameter more than 6 mm; and E, evolution or change. Malignant melanomas can be classified into lentigo malignant melanomas (arising on sun-exposed skin of older individuals), superficial spreading malignant melanomas (most common, occurring in 70%, especially in Caucasian people), nodular malignant melanomas, acral lentiginous melanomas (arising on palms, soles and nail beds, commonly in more darkly pigmented persons), malignant melanomas on mucous membranes and miscellaneous forms. The risk of developing melanoma is 3.6 times greater in renal transplant recipients than in the general population. Risk factors for the development of post-transplant malignant melanomas are the presence of atypical nevi, history of blistering sunburns, immunosuppression, fair skin, a personal or family history of malignant melanomas, older age at the time of transplantation and the use of depleting anti-lymphocyte antibodies.

While SCC and BCC are rarely lethal, melanoma is a potentially fatal malignancy. The most prognostic factor is tumour thickness (Breslow depth). Patients diagnosed with malignant melanoma with a tumour thickness of less than 1 mm have an excellent outcome. However, if there is lymph node involvement or distant metastasis, survival rate is low with a 5-year survival of respectively 30% and less than 10% in immunocompetent persons. Outcome for posttransplant lesions with < 2 mm thickness is similar to the general population, while for lesions > 2 mm thickness prognosis is significantly worse (Matin et al., 2008). Treatment of melanoma consists of surgical excision, with reexcision of margins according to the thickness of the tumour. Sentinel node biopsy is recommended for patients with clinically negative nodes if Breslow depth is more than 1 mm. Reduction or change of the immunosuppressive regimen should be considered, balancing the prognosis of the tumour and the risk of graft rejection (Zwald FO et al., 2010).

3.1.4 Kaposi's sarcoma

Kaposi's sarcoma KS is a vascular neoplasm, characterized by reddish-brown or purple-blue plaques or nodules on cutaneous or mucosal surfaces, including the skin, lungs, gastrointestinal tract and lymphoid tissue. KS has been associated with the reactivation of latent human herpes virus 8 (HHV-8) infection or donor-to-recipient transfer of HHV-8-infected progenitor cells. The incidence of KS is 20 times increased in renal transplant recipients. It occurs frequently early after renal transplantation, with an average time to development after transplantation of 13 to 21 months. It is more common in male transplant recipients, with a male to female ratio ranging from 2:1 to 4:1. Most cases occurs in patients from Mediterranean, Jewish, Arabic, Caribbean or African ethnic groups. The treatment of Kaposi's sarcoma in renal transplant patients primarily consists of a reduction or discontinuation of the immunosuppressive medication, and possibly a conversion to alternative immunosuppressive agents like mTOR inhibitors (as will be discussed below) (Antman & Chuang, 2000; Campistol & Schena, 2007).

3.2 Prevention

As for immunocompetent individuals, prior exposure to solar ultraviolet radiation (UVR) is the predominant risk factor for development of cutaneous malignancies. In patients at high-risk, primary prevention including the avoidance of sun exposure (especially during peak

hours of radiation), use of protective clothing and use of an effective sunscreen (protection factor >15) for unclothed body parts (head, neck, hands and arms) is very important. Early detection of skin cancer is essential to reduce disfiguring surgery and to prevent mortality from advanced or metastatic lesions. For this reason, patients should be aware of the increased risk of skin cancer and perform regular self-screening. Annual skin examination by a dermatologist is recommended, especially in high-risk patients (e.g. patients with a history of skin cancer, fair-skin, living in high sun-exposure climates, having occupations with sun exposure or having had significant sun exposure as a child). Treatment of premalignant lesions (actinic keratoses, viral warts) is advised in order to prevent progression to SCC. This can be done with liquid nitrogen cryosurgery, excision, and curettage or with topical therapies such as 5-fluorouracil (which interferes with DNA synthesis and cell proliferation) or imiquimod 5% cream (a topical imidazoquinolone immunomodulator stimulating local cell-mediated immune response directed against tumoral and viral antigens). When actinic keratoses or viral warts persist with these therapies, biopsy is required to rule out progression to SCC (Kovach & Stasko, 2009).

There are several studies suggesting that retinoids (vitamin A derivates, available in topical and oral preparations) may be beneficial to the treatment and/or prevention of non-melanoma skin tumours after solid organ transplantation. They are said to influence a broad spectrum of cellular functions through interactions with nuclear receptors. Topical retinoids are used to control actinic keratoses and to diminish SCC recurrence. Oral retinoids (most common acitretin) has been advised for patients with multiple and/or recurrent skin cancers. Chen et al. reviewed three small randomized controlled clinical trials on the use of oral retinoids as preventive agents in the development of skin cancer. The first trial was a cross-over trial with 23 high-risk patients. Compared to the acitretin period (25 mg daily), a 42% increase in the incidence of SCC was seen in the drug-free period. In the second trial, 44 high-risk patients were randomized to receive acitretin 30 mg daily or placebo. After 6 months of follow-up, 18 new skin cancers developed in the placebo group, whereas only 2 new skin cancers developed in the acitretin group. The last trial compared two different dose regimens (0.2 mg/kg/day versus 0.4 mg/kg/day) in 26 renal transplant recipients and did not find a significant difference in development of skin cancers between the two groups. While the first two trials included only high-risk patients, the last included any stable renal transplant recipient, which could explain the lack of benefit (Chen et al., 2005). After cessation of therapy, rebound phenomena with development of large numbers of cutaneous malignancies are reported. For that reason, oral retinoids should always be given as long-term maintenance therapy.

The major factor, however, limiting the use of oral retinoids in the prevention of skin cancer is the poor tolerance associated with it. Adverse effects include headaches, mucocutaneous side effects, musculoskeletal symptoms and hyperlipidaemia. Cheilitis has been reported in 70 to 100% of patients. In conclusion, in recipients with multiple and/or recurrent skin cancers, the use of systemic retinoids, such as low-dose acitretin (dose between 0.2 and 0.4 mg/kg/day), could be advised for months/years, if well tolerated. Gradual dose escalation to an effective dose in combination with monitoring of symptoms and laboratory findings and proactive management of adverse effects rather than discontinuation of therapy is recommended (Kovach et al, 2006; Otley et al., 2006).

4. Post-transplantation lymphoproliferative disorder PTLD

Post-transplantation lymphoproliferative disorder PTLD is a heterogeneous group of diseases characterized by abnormal lymphoid proliferation, that develop in a recipient of a

solid-organ transplantation or bone marrow allograft. It is the second most frequent cancer after transplantation after skin cancer, with an overall incidence of 1 to 2% after kidney transplantation (30 to 50 times higher than in the general population). PTLD frequently arises from B lymphocytes, but can rarely also originate from T-cell proliferation. It is the most frequent malignancy during the first post-transplantation year, when the level of immunosuppression is the highest. There is a strong association with Epstein-Barr virus (EBV) infection, with 98% of cases associated with latent EBV infection. An increase in the EBV viral load in peripheral blood is often detected before development of PTLD. This EBV infection leads to B cell proliferation in the setting of decreased T-cell immune surveillance due to immunosuppressive treatment. Only 10 of almost 100 viral genes in the EBV DNA are expressed in latently infected B cells, including two oncogenes latent membrane protein type 1 LMP-1 and type 2 LMP-2. The number of expressed viral genes is reduced to diminish the recognition of cytotoxic T cells.

PTLD can be divided in three distinct morphologic groups, according to the World Health Organization classification, each containing some subtypes:

- Early disease (55% of cases), characterized by diffuse B cell hyperplasia of polyclonal nature, with no signs of malignant transformation. This has a good prognosis after reduction of immunosuppression.
- Polymorphic PTLD (30%), usually polyclonal B cell proliferation with evidence of early malignant transformation, such as clonal cytogenetic abnormalities and immunoglobulin gene rearrangements.
- Monomorphic PTLD (15%), characterized by monoclonal B cell proliferation with malignant cytogenetic abnormalities and immunoglobulin rearrangements. This includes high-grade invasive lymphoma of B or T lymphocyte centroblasts. It is associated with the worst outcome.

In table 2, the clinical and pathological features and the management of the different groups is summarized (Magee et al., 2008).

The clinical manifestations from PTLD are extremely variable and it often presents in a nonspecific way. Early PTLD (first year after transplantation) presents often with an infectious mononucleosis-like presentation, with prominent B-cell symptoms (fever, night sweats and weight loss) and rapid enlargement of the tonsils and cervical nodes. Late PTLD (more than 1 year after transplantation) has often a more gradual clinical course and fewer systemic symptoms. In half of the patients, extra-nodal disease is present, with involvement of gastrointestinal tract (stomach, intestine), lungs, skin, liver, central nervous system or frequently the allograft itself. It is of major importance to recognize early clinical signs and symptoms of PTLD. PTLD is often associated with elevated serum markers such as lactate dehydrogenase LDH. For an accurate diagnosis of PTLD, tissue biopsy is required. Fluorodeoxyglucose (FDG)-positron emission tomography (PET/CT) is an important tool in the diagnosis, staging and post-treatment evaluation.

Prognosis of PTLD varies according to clonality and extent of disease. However, in general, PTLD has a poor prognosis with a 1-year mortality of approximately 40%. The most important risk factors for PTLD are the type, length and intensity of immunosuppressive drug therapies. There is an increased risk of PTLD in patients who received potent T-cell depleting antibodies (like OTK3 or anti-thymocyte globulin ATG) for induction therapy or for treatment of rejection. There would be a twofold higher risk for development of PTLD in patients receiving tacrolimus in comparison to cyclosporine. A special category of patients at particular risk for PTLD development are seronegative patients at the time of

transplantation, receiving an organ from an EBV-seropositive donor (inducing a primary EBV infection after transplantation). An age effect on the development of PTLD is present, with the incidence highest among children < 10 years of age and adults > 60 years of age (Opelz & Henderson, 1993; Opelz & Döhler, 2003).

	Early disease (55%)	**Polymorphic PTLD (30%)**	**Monomorphic PTLD (20%)**
Clinical features	Infectious mononucleosis-like disease	Infectious mononucleosis-like disease, +/- weight loss, localizing symptoms	More gradual Fever, weight loss, localizing symptoms
Pathology	Preserved architecture, atypical cells infrequent	Signs of early malignant transformation	High-grade lymphoma with confluent transformed cells and marked atypia
Clonality	Polyclonal	Usually polyclonal	Monoclonal
Treatment	Reduce immunosuppression, acyclovir	Reduce immunosuppression, acyclovir, rituximab.	Reduce immunosuppression to low-dose steroids only, combination surgery, chemotherapy, radiotherapy, immunotherapy, rituximab
Prognosis	Good	Intermediate	Poor

Table 2. Summary of clinical and pathological features and management of the different types of post-transplant lymphoproliferative disorder (PTLD) (adapted from Magee CC, 2008).

In the prevention of PTLD, monitoring of EBV viral load in high-risk patients (who received large dose of immunosuppressive drugs for induction or allograft rejection) is recommended since reduction of immunosuppressive treatment can be considered if high viral loads are detected. Use of antiviral therapy as profylaxis for PTLD in high-risk patients is controversial.

Treatment of PTLD consists in the first place of reduction or discontinuation of the immunosuppressive therapy (especially cyclosporine CsA, tacrolimus and mycophenolate mofetil MMF) to reestablish host defense mechanisms. Concomitantly, prednisone can be increased to prevent allograft rejection. This can lead to complete and durable resolution of some lymphomas, especially of early and polymorphic PTLD (sometimes in combination with antiviral therapy such as acyclovir and ganciclovir). Evidence for the treatment of PTLD with antiviral therapy is lacking and it is not used in monomorphic PTLD. For monomorphic PTLD, besides reduction or discontinuation of immunosuppressive therapy, other therapeutic strategies must be considered. In localized disease, surgical resection can be an option, for example transplant nephrectomy when PTLD is restricted to the renal

graft. The use of rituximab RTX as first-line therapy is increasing, because of its low toxicity and high specificity. RTX is a chimeric monoclonal antibody against the B-cell-specific CD 20 antigen (widely expressed on B lymphocytes). Treatment consists of doses of 375 mg/m^2 intravenously weekly for a total of 4 weeks. In case of diffuse lymphomas, lack of response to RTX or CD20 negative lymphoma, chemotherapy (e.g. CHOP cyclophosphamide, doxorubicin, vincristine and prednisone) can be considered (Andreone et al., 2003; Bakker et al., 2007).

5. Immunosuppressive drugs and the risk of malignancy after transplantation

The principal factor influencing the risk of posttransplant malignancy is the overall level of immunosuppressive treatment. Indeed, in a prospective, randomised trial comparing low-dose cyclosporine CsA (trough blood concentrations 75-125 ng/mL) versus high-dose CsA (trough blood concentrations 150-250 ng/mL) both in combination with azathioprine AZA, a clear correlation between high-dose regimen and more secondary malignant disorders was demonstrated (Dantal et al., 1998). This may also explain why the incidence of post-transplantation malignancy is more frequent in heart transplant recipients (which usually receive more intense immunosuppression) than in renal transplant recipients. In transplant patients with cancer, a significant reduction or even cessation of the immunosuppressive therapy is advised.

There is some evidence that also the type of immunosuppressive agent would matter. However, since in most cases combinations of several immunosuppressive drugs are used, clear data concerning individual therapies are lacking and sometimes conflicting. The purine analogue a**zathioprine AZA** has been associated with increased risk of skin cancer, possibly as a result of increased photosensitivity to ultraviolet A light (Perrett et al., 2008).

In 1999, one study suggested that the **calcineurin inhibitor cyclosporine CsA** could promote cancer progression *in vitro* and *in vivo* in an immunodeficient mouse model by a direct cellular effect, independent of any effect on the host immune system. This would be mediated by stimulation of transforming growth factor β TGF-β production, which may lead to development of morphological transformation of cells from a non-invasive phenotype to an invasive phenotype and which may promote tumor invasiveness and metastasic spread (Hojo et al., 1999). Similar results were seen with **tacrolimus**, with increase in the number of pulmonary metastases and TGF-β overexpression in mouse renal cell carcinoma receiving tacrolimus (Maluccio et al., 2003).

In contrast, there is growing data suggesting that **inhibitors of the mammalian target of rapamycin mTOR** (**sirolimus** and **everolimus**) have antioncogenic properties and are therefore associated with a reduced risk for some malignancies and longer times for malignancies to develop. This can be explained by the fact that mTOR inhibitors repress several enzymes along the intracellular signaling pathways that play a role in the development and progression of different cancers (like p70 S6K, IL-10, and cyclins), resulting in deceleration or inhibition of cell-cycle progression, increased sensitivity to apoptosis and reduced angiogenesis.

There are several clinical trials linking the use of mTOR inhibitors to reduced incidence of malignancies. In 2004, Mathew et al. reviewed 5 multicenter studies, comparing the cancer risk for different immunosuppressive regimens. Two studies containing 1295 patients randomized to receive CsA in combination with sirolimus, AZA or placebo. After 2 years, they saw a significant lower incidence of skin cancer in the sirolimus-group (2% in a low-

dose group, 2.8% in a high-dose group) compared to the placebo-group (6.9%). Compared to the AZA-group (4.3%), the difference was not statistically significant. Two other trials (161 patients) compared maintenance therapy based on sirolimus or CsA (both in combination with steroids and AZA or mycophenolate mofetil MMF). In the CsA based-group, 5% of patients had some form of malignancy after 2 years, compared to 0% in the sirolimus-based group. In the fifth trial (525 patients), CsA withdrawal 3 months after renal transplantation in combination with steroids and increased sirolimus trough levels (20 to 30 ng/ml during year 1, 15 to 25 ng/ml thereafter) was compared with a continuous regimen of CsA, steroids and sirolimus (trough levels 5 to 15 ng/ml). After 2 years, the incidence of overall malignancies was significant lower in the CsA-elimination group (4.2% compared to 9.8%) (Mathew et al., 2004). The long-term results of this last trial are incorporated in the Rapamune Maintenance Trial (430 patients). Similarly, after 5 years follow-up, patients in the CsA withdrawal group had a reduced incidence of both skin and nonskin malignancies. What's more, the median time to first skin carcinoma was significantly shorter in the CsA group (491 days) compared to the withdrawal group (1,126 days) (Campistol et al., 2006).

A large registry (United Network for Organ Sharing database) reporting 33,249 renal transplant patients whose maintenance immunosuppression contained an mTOR-inhibitor, an mTOR-inhibitor in combination with a calcineurin inhibitor CNI or a CNI alone, showed reduction in the overall incidence of *de novo* malignancy in patients receiving an mTOR-inhibitor. After a mean follow-up of 2.3 years, an incidence of 0.6% was seen in the mTOR-inhibitor alone or the mTOR-inhibitor plus CNI group versus 1.8% in the CNI alone group (Kauffman et al., 2005). Similar results turned up in the Sirolimus Convert Trial where 830 renal allograft recipients receiving CNI-based immunosuppression were randomly assigned to convert to sirolimus or to continue CNI. The overall malignancy rates after 24 months were significantly lower in the sirolimus group (3.8%) versus the CNI group (11%). However, the number of adverse effects in the sirolimus group was higher than in the CNI group (Schena et al., 2009).

There is some evidence that sirolimus does not only prevent the occurrence of cancer, as described above, but is also promising in treating existing tumors. There would be some benefit of basing immunosuppression in patients with new-onset malignancy after transplantation on these drugs (especially for Kaposi's sarcoma). In 15 renal transplant recipients with biopsy-proven cutaneous Kaposi's sarcoma, cyclosporine and mycophenolate mofetil were stopped and sirolimus was started. After six months, all patients had complete clinical and histological regression of Kaposi's sarcoma lesions (Stallone et al., 2005). Gutierrez-Dalmau et al. reported similar results in 7 renal transplant patients after conversion of CNI to sirolimus (Gutierrez-Dalmau, 2005).

In patients with established malignancy after transplantation, some therapeutic options should be considered. It is clear that reduction of the total amount of immunosuppressive medication is very important. This should however be balanced against the risk of graft rejection and the quality of life with and without a functioning graft. The most serious effect of a reduction or cessation of therapy can be expected from malignancies with a greater increase in incidence after renal transplantation (like non-melanoma skin cancer, PTLD and Kaposi's sarcoma). Whether CNI should be converted into an mTOR-inhibitor is somewhat questionable. It is certainly advised for Kaposi's sarcoma. However, when considering switching CNI to mTOR inhibitors for other malignancies, it should be balanced against its frequent side effects, including increase in serum lipids, myelotoxicity, proteinuria, pneumopathy (hypersensitivity-like interstitial pneumonitis), dermatological

manifestations, some degree of oedema and aphtae. Up to one-third of patients starting sirolimus will stop because of side effects. When patients still need surgical intervention for the malignancy, potential wound healing complications attributed to mTOR-inhibitors should also be taken into account (Campistol et al., 2007; Cravedi P et al., 2009; Kidney Disease: Improving Global Outcomes (KDIGO) Transplant Work Group, 2009).

6. General recommendations for cancer screening after renal transplantation

Cancer should be a major focus in the long-term follow-up of renal transplant recipients. First and foremost, preventive measures should be taken, i.e. avoiding excessive immunosuppression (especially depleting anti-lymphocyte antibodies), screening transplant donors and recipients for cancer and avoiding carcinogenic factors (such as nicotin abuse, high sun exposure, etc.). Secondly, in order to detect malignancies in transplant patients at an early stage, periodic screening examinations are recommended. It is questioned whether guidelines for cancer screening for the general population are also applicable for renal transplant recipients, because the life expectancy of these patients is mostly less. Because of this, an individual approach for each patient is recommended, taking into account the individual prognosis and risk of developing malignancy (Webster et al., 2008). Based on the American (KDIGO Transplant Work Group, 2009) and European (European Best Practice Guidelines EBPG, 2002) transplantation professional guidelines, we can however suggest the following practical screening plan:

1. Annual examination of the skin and lip by a dermatologist (more frequently in high-risk patients, such as patients with a history of skin cancer).
2. Abdominal surveillance ultrasonography at least every three years to detect early stage renal cell carcinoma. Especially in high-risk patients including patients with a history of renal cell carcinoma or the presence of acquired cystic disease, analgesic nephropathy or tuberous sclerosis.
3. Standard cancer surveillance (appropriate for age) for neoplasms commonly seen in the general population:

- Colorectal cancer: colonoscopy every 5 years from the age of 50
- Breast cancer: breast exam and screening mammography every year from the age of 50 to 69 (from the age of 40 if mother or sister has had breast cancer)
- Cervical cancer: pap smear and pelvic exam every year for women within 3 years of onset of sexual activity or from the age of 21 (whichever comes first)
- Prostate cancer: digital rectal exam and PSA testing every year from the age of 50
- Hepatocellular cancer: abdominal ultrasound and alpha-feto protein testing every 6-12 months only in high-risk patients (cirrhosis or chronic viral hepatitis, especially HBV).

7. Conclusion

As short-term patient and graft survival have improved over the past few decades, long-term complications of kidney transplantation are becoming more important. The incidence of malignancies is considerably higher in renal transplant recipients than in the general population. In fact, malignancy is the third most common cause of patient death after renal transplantation (after cardiovascular events and infection). With longer graft survival and older donors (as well as recipients) and with the introduction of more potent immunosuppressive medication, malignancy is becoming even more common. Both

clinicians and patients should be aware of this risk, making primary prevention a major concern. In addition, they should consider a cancer screening plan adapted to the patient's individual risk profile and life expectancy.

8. References

Andreone P, Gramenzi A, Lorenzini S, Biselli M, Cursaro C, Pileri S & Bernardi M. (2003). Posttransplantation lymphoproliferative disorders. *Archives of Internal Medicine*, Vol. 163, No. 17, (September 2003), pp. (1997-2004).

Antman K, Chuang Y. (2000). Kaposi's sarcoma. *New England Journal of Medicine,* Vol. 342, No. 14, (April 2000), pp. (1027-1038).

Bakker NA, van Imhoff GW, Verschuuren EAM & van Son WJ. (2007). Presentation and early detection of post-transplant lymphoproliferative disorder after solid organ transplantation. *Transplantation International,* Vol. 20, No. 3, (March 2007), pp. (433-438).

Birkeland SA, Løkkegaard H & Storm HH. (2000). Cancer risk in patients on dialysis and after renal transplantation. *Lancet*, Vol. 355, No. 9218, (May 2000), pp. (1886-1887).

Briggs JD. (2001). Causes of death after renal transplantation. *Nephrology, Dialysis and Transplantation,* Vol. 16, No. 8, (August 2001), pp. (1545-1549).

Campistol JM, Eris J, Oberbauer R, Friend P, Hutchison B, Morales JM, Claesson K, Stallone G, Russ G, Rostaing L, Kreis H, Burke JT, Brault Y, Scarola JA & Neylan JF for the Rapamune Maintenance Regimen Study Group. (2006). Sirolimus therapy after early cyclosporine withdrawal reduces the risk for cancer in adult renal transplantation. *Journal of the American Society of Nephrology*, Vol. 17: No. 2, (February 2006), pp. (581-589).

Campistol JM, Albanell J, Arns W, Boletis I, Dantal J, de Fijter JW, Mortensen SA, Neumayer HH, Oyen O, Pascual J, Pohanka E, Schena FP, Seron D, Sparacino V & Chapman JR. (2007). Use of proliferation signal inhibitors in the management of post-transplant malignancies – clinical guidance. *Nephrology, Dialysis and Transplantation,* Vol. 22, Suppl. 1, (May 2007), pp. (i36-i41).

Campistol JM & Schena FP. (2007). Kaposi's sarcoma in renal transplant recipients – the impact of proliferation signal inhibitors. *Nephrology, Dialysis and Transplantation,* Vol. 22, Suppl. 1, (May 2007), pp. (i17-i22).

Chen K, Craig JC & Shumack S. (2005). Oral retinoids for the prevention of skin cancers in solid organ transplant recipients: a systemic review of randomized controlled trials. *British Journal of Dermatology*, Vol. 152, No. 3, (March 2005), pp. (518-23).

Cravedi P, Ruggenenti P & Remuzzi G. (2009). Sirolimus to replace calcineurin inhibitors? Too early yet. *Lancet*, Vol. 373, No. 9671, (April 2009), pp. (1235-1236).

Dantal J, Hourmant M, Cantarovich D, Giral M, Blancho G, Dreno B & Soulillou JP. (1998). Effect of long-term immunosuppression in kidney-graft recipients on cancer incidence: randomised comparison of two cyclosporin regimens. *Lancet,* Vol. 351, No. 9103, (February 1998), pp. (623-628).

Dantal J & Pohanka E. (2007) Malignancies in renal transplantation: an unmet medical need. *Nephrology, Dialysis and Transplantation*, Vol. 22, Suppl. 1, (May 2007), pp. (i4-i10).

European best practice guidelines for renal transplantation. (2002). Section IV: Long-term management of the transplant recipient. IV.6. Cancer risk after renal

transplantation. *Nephrology, Dialysis and Transplantation,* Vol. 17, Suppl. 4, (April 2002), pp. (31-36).

Euvrard S, Kanitakis J, Claudy A. (2003). Skin cancers after organ transplantation. *New England Journal of Medicine*, Vol. 348, No. 17, (April 2003), pp. (1681-1691).

Gutierrez-Dalmau A, Sanchez-Fructuoso A, Sanz-Guajardo A, Mazuecos A, Franco A, Rial MC, Iranzo P, Torregrosa JV, Oppenheimer F & Campistol JM. (2004). Efficacy of conversion to sirolimus in posttransplantation Kaposi's sarcoma. *Transplantation Proceedings,* Vol. 37, No. 9, (November 2005), pp. (3836-3838).

Hojo M, Morimoto T, Maluccio M, Asano T, Morimoto K, Lagman M, Shimbo T & Suthanthiran M. (1999). Cyclosporine induces cancer progression by a cell-autonomous mechanism. *Nature*, Vol. 397, No. 6719, (February 1999), pp. (530-534).

Kasiske, BL, Snyder, JJ, Gilbertson DT & Wang C. (2004). Cancer after kidney transplantation in the United States. *American Journal of Transplantation,* Vol. 4, No. 6, (June 2004), pp. (905-913).

Kauffman HM, Cherikh WS, Cheng Y, Hanto DW & Kahan BD. (2005). Maintenance immunosuppression with target-of-rapamycin inhibitors is associated with a reduced incidence of de novo malignancies. *Transplantation*, Vol. 80, No. 7, (October 2005), pp. (883-889).

Kidney Disease: Improving Global Outcomes (KDIGO) Transplant Work Group. (2009) KDIGO clinical practice guideline for the care of kidney transplant recipients. *American Journal of Transplantation,* Vol. 9, Suppl. 3, (October 2009), pp. (S1–S157).

Kovach BT, Murphy G, Otley CC, Shumack S, Ulrich C & Stasko T. (2006). Oral retinoids for chemoprevention of skin cancers in organ transplant recipients: results of a survey. *Transplantation Proceedings,* Vol. 38, No. 5, (June 2006), pp. (1366-1368).

Kovach BT & Stasko T. (2009). Skin cancer after transplantation. *Transplantation Reviews,* Vol. 23, No. 3, (July 2009), pp. (178-189).

Maluccio M, Sharma V, Lagman M, Vyas S, Yang H, Li B & Suthanthiran M. (2003). Tacrolimus enhances transforming growth factor-β1 expression and promotes tumor progression. *Transplantation*, Vol. 76, No. 3, (August 2003), pp. (597-602).

Magee CC, Javeed Ansari M & Milford EL. (2008). Renal transplantation : clinical managemant. In: *Brenner & Rector's The Kidney,* Brenner BM, pp. (2138-2167), Saunders Elsevier, ISBN 978-1-4160-3105-5, Philadephia.

Mathew T, Kreis H, Friend P. (2004). Two-year incidence of malignancy in sirolimus-treated renal transplant recipients: results from five multicenter studies. *Clinical Transplant*, Vol. 18, No. 4, (Augustus 2004), pp. (446-449).

Matin RN, Mesher D, Proby CM, Mc Gregor JM, Bouwes Bavinck JN, der Marmol V, Euvrard S, Ferrandiz C, Geusau A, Hacketal M, Ho WL, Hofbauer GFL, Imko-Walczuk B, Kanitakis J, Lally A, Lear JT, Lebbe C, Murphy GM, Piaserico S, Seckin D, Stockfleth E, Ulrich C, Wojnarowska FT, Lin HY, Balch C & Harwood CA, on behalf of the Skin Care in Organ Transplant Patients Europe (SCOPE) group. (2008). Melanoma in organ transplant recipients: clinicopathological features and outcome in 100 cases. *American Journal of Transplantation,* Vol. 8, No. 9, (September 2008), pp. (1891-1900).

Morath C, Mueller M, Goldschmidt H, Schwenger V, Opelz G & Zeier M. (2004). Malignancy in renal transplantation. *Journal of the American Society of Nephrology,* Vol. 15, No. 6, (June 2004), pp. (1582-1588).

Opelz G & Henderson R. (1993). Incidence of non-Hodkin lymphoma in kindey and heart transplant recipients. *Lancet,* Vol. 342, No. 8886-8887, (December 1993), pp. (1514-1516).

Opelz G & Döhler B. (2003). Lymphomas after solid organ transplantation: a collaborative transplant study report. *American Journal of Transplantation,* Vol. 4, No. 2, (February 2003), pp. (222-230).

Otley CC, Stasko T, Tope WD & Lebwohl M. (2006). Chemoprevention of nonmelanoma skin cancer with systemic retinoids: practical dosing and management of adverse effects. *Dermatologic surgery,* Vol. 32, No. 4, (April 2006), pp. (562-568).

Perrett CM, Walker SL, O'Donovan P, Warwick J, Harwood CA, Karran P & Mc Gregor JM. (2008). Azathioprine treatment photosensitizes human skin to ultraviolet A radiation. *British Journal of Dermatology*, Vol. 159, No. 1, (July 2008), pp. (198-201).

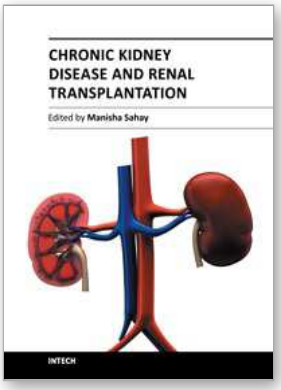
Schena FP, Dascoe MD, Alberu J, del Carmen Rial M, Oberbauer R, Brennan DC, Campistol JM, Racusen L, Polinsky MS, Goldberg-Alberts R, Li H, Scarola J & Neylan JF for the Sirolimus CONVERT Trial Study Group. (2009) Conversion from calcineurin inhibitors to sirolimus maintenance therapy in renal allograft recipients: 24-month efficacy and safety results from the CONVERT trial. *Transplantation*, Vol. 87, No. 2, (January 2009), pp. (233-242).

Stallone G, Schena A, Infante B, Di Paolo S, Loverre A, Maggio G, Ranieri E, Gesualdo L, Schena FP, Grandaliano G. (2005). Sirolimus for Kaposi's sarcoma in renal-transplant recipients. *New England Journal of Medicine,* Vol. 352, No. 13, (March 2005), pp. (1317-23).

Vajdic CM, Mc Donald SP, McCredie MRE, van Leeuwen MT, Stewart JH, Law M, Chapman JR, Webster AC, Kaldor JM & Grulich AE. (2006). *Journal of the American Medical Association,* Vol. 296, No. 23, (December 2006), pp. 2823-2831.

Webster AC, Wong G, Craig JC & Chapman JR. (2008). Managing cancer risk and decision making after renal transplantation. *American Journal of Transplantation,* Vol. 8, No. 11, (November 2008), pp. (2185-91).

Zwald FO, Christenson LJ, Billingsley EM, Zeitouni NC, Ratner D, Bordeaux J, Patel MJ, Brown MD, Proby CM, Euvrard S, Otley CC & Stasko T for the Melanoma Working Group of The International Transplant Skin Cancer Collaborative (ITSCC) and Skin Care in Organ Transplant Patients, Europe (SCOPE).(2010). Melanoma in solid organ transplant recipients. *American Journal of Transplantation,* Vol. 10, No. 5, (May 2010), pp. (1297-1304).



Chronic Kidney Disease and Renal Transplantation

Edited by Prof. Manisha Sahay

ISBN 978-953-51-0003-4
Hard cover, 226 pages
Publisher InTech
Published online 10, February, 2012
Published in print edition February, 2012

This valuable resource covers inpatient and outpatient approaches to chronic renal disease and renal transplant with clinical practicality. This first section of the book discusses chronic disease under distinct topics, each providing the readers with state-of-the-art information about the disease and its management. It discusses the fresh perspectives on the current state of chronic kidney disease. The text highlights not just the medical aspects but also the psychosocial issues associated with chronic kidney disease. The latest approaches are reviewed through line diagrams that clearly depict recent advances. The second section of the book deals with issues related to transplant. It provides effective and up-to-date insight into caring for your transplant patients.

InTech Europe
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821