

Malignancies after renal transplantation

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■ ABSTRACT

Post-transplantation malignancies represent a highly relevant diagnostic and therapeutic challenge. The relative frequency of skin tumours, lymphomas and urogenital neoplasias is especially high, while the course of these neoplasias, as of malignancies in general in this patient group, is particularly severe and aggressive. While immunosuppression is necessary to prevent transplant rejection, it contributes to the incidence of tumour transformation. The effects are dose-dependent and differ among the available immunosuppressive substances. Appropriate screening and early tumour detection are mainstays of successful transplant patient surveillance.

Key-Words:

Post-transplantation malignancies; PTLD; immunosuppression; skin tumours; tumour registry.

■ INTRODUCTION

Less than 10 years after the first renal transplantation in 1954, an increased incidence of tumour manifestations was already noted. Data from transplant registries and from prospective clinical trials have since confirmed these early observations. Skin tumours and post-transplant lymphoproliferative disease (PTLD) are the most dominant manifestations among renal transplant recipients followed by urogenital tumours. Different causes appear to be responsible for this scenario, including viral infections, but differential choice and intensity of immunosuppressive

therapies play key roles in the development of post-transplant malignancies.

■ EPIDEMIOLOGY

The risk of malignancies increases dramatically after renal transplantation when compared to a normal population. The cumulative tumour frequency rises proportionally with time following transplantation and, taking all tumour entities as a whole, is estimated to be 10 to 15 times higher after 10 years than in the general population¹⁻³. The incidence of individual tumours must, however, be regarded in a more differentiated manner. For example, quite relevant geographical differences exist. Gastrointestinal tumours are significantly more frequent in the Asian region, while Kaposi sarcoma is a typical tumour manifestation in Mediterranean and Arabian regions. In general, skin tumours and lymphomas represent by far the most prevalent tumour entities after transplantation, while the rate of common tumours, such as breast and prostate cancer, is not higher than that in the general population. Nevertheless, these latter tumours still deserve special attention, because they are generally frequent and, thus, must be detected at an early stage. Early tumour identification is of major importance, since most malignancies have a more rapid and aggressive disease courses than in patients with an intact immune system. Moreover, malignancies increasingly contribute to mortality in the transplant population. In the early days of transplantation medicine, infections were the major threat to patients, however, in the last decade,

Table I

Mortality documentation in renal transplant recipients at the University of Florida from 1970 to 1999¹⁹

Cause of death	1970-79	1980-89	1990-99
Infections	42%	42%	28%
Cardiovascular	9.6%	23.8%	30.2%
Neurological	2.4%	5.2%	8.5%
Malignancies	1.2%	5.2%	13.2%

cardiovascular events but also malignancies play major roles in compromising overall patient survival (Table I).

■ PATHOGENESIS

Generally, there are three distinct modes of malignancy development following renal transplantation: a) *de novo* development of neoplasia; b) transmission of an (occult) neoplasia from the donor, and c) recurrence of a tumour in the recipient. The first scenario clearly dominates clinically, while transmission from the donor, theoretically via micrometastases, is rare, and recurrence of a known malignancy is usually minimised by carefully respecting staging measures and safety margins with documented freedom of tumour manifestations. Currently, a two-year tumour-free safety margin is recommended for most neoplasias before patients can be actively placed on a waiting list. Exceptions are breast cancer, colorectal carcinomas and melanoma, for which longer margins may be more appropriate. This view, however, is debatable, since it must be weighed against the 2- to 3-fold increased mortality risk associated with prolonging dialysis treatment as compared to transplantation.

Which factors have a key influence on tumour development after transplantation? First, intensity and specificity of immunosuppression plays a crucial role. For example, lymphoma incidence is highly increased in association with induction therapies using monoclonal (OKT-3) or polyclonal antilymphocyte antibodies¹⁻³. The importance of individual immunosuppressants will be detailed at the end of this overview. Second, viral infections are serious factors for development of specific malignancies including Epstein-Barr virus (EBV) for PTLN, Herpesvirus-8 (HHV-8) for Kaposi sarcoma and some human papilloma viruses

(HPV) for cutaneous and genital malignancies¹⁻⁵. Finally, analogous to the normal population, environmental factors (UV light, smoking), genetic predispositions and general risk factors (such as age) are also of relevance to the transplant population.

■ TUMOUR MANIFESTATIONS AFTER KIDNEY TRANSPLANTATION

As pointed out above, incidences of tumour manifestation vary significantly after transplantation. Table II lists the most *versus* least common relative incidences of malignancies in transplant recipients, based on the Australian-New Zealand transplant registry and compared to the general population. Current data concerning the most prevalent malignancies, i.e. skin tumours, lymphomas and urogenital tumours will be presented below.

Table II

Standardised relative incidences for tumour risk – comparisons of patients after renal transplantation with the Australian/New Zealand normal population²⁰

Neoplasia	Observed	Expected	Relative risk
Lymphoma	231	22.74	10.16
Urogenital	125	14.73	8.49
Kaposi sarcoma	28	1.06	26.44
Cervix	46	6.97	6.6
Colorectal	141	72.76	1.94
Prostate	53	54.72	0.97
Breast	87	69.52	1.25

■ Skin tumours

Skin tumours represent the most frequent tumour entity after transplantation. Melanomas must be regarded separately from nonmelanomatous tumours such as spinaliomas and basal cell carcinomas. While melanomas are relatively rare regarding both relative and absolute numbers, nonmelanomatous tumours are extremely frequent. Data on incidence and prevalence is somewhat heterogeneous, but it can be estimated that spinaliomas are 60 – 250 times and basal cell carcinomas are 10 times more frequent in transplant recipients than in the general population¹⁻⁵. This relation emphasises the fact that there is a shift

towards an overrepresentation of spinaliomas, contrary to the normal population. This shift, however, also means an increased threat to affected patients, since spinaliomas are usually much more aggressive, cause metastases and, thus, contribute significantly to patient mortality. The cumulative 10-year incidence for skin tumours is calculated at 10% (45% in Australia), and the 20-year incidence at 40% (70% in Australia) after renal transplantation. The Australian observations emphasise the causal role of UV irradiation, but infections, especially with HPV types 2, 5/8, 31/35 and 16/18, are also associated with the induction of spinaliomas and basal cell carcinomas. Central aspects in post-transplantation surveillance are instructions concerning appropriate prevention of unsheltered sunlight exposure and preventive removal of skin warts – the current recommendations for prevention and early detection of skin tumours after renal transplantation are summarised in Table III.

Early surgical removal with appropriate safety margins is of key importance in the treatment of skin tumours. Retinoids can be helpful and effective in some precanceroses such as actinic keratosis. Suspicion of lymph node metastases may necessitate extensive and invasive surgical treatment (e.g., neck dissection in case of spinaliomas of the head region), alternatively or supportively radiation therapy may be of value. Furthermore, it must always be considered that these tumours develop at multiple sites in many patients. Additionally, reduction or modification of immunosuppressive therapy must be considered.

HHV-8-associated Kaposi sarcoma represents a special entity quite frequently encountered in

Mediterranean and Arabian regions, in contrast to the north-western hemisphere. The characteristic clinical picture is the development of blue-livid skin nodes. The disease course, however, is determined by the magnitude of visceral manifestations, which is associated with a poor prognosis. Therapy is limited and not well established, but again withdrawal, reduction or modification of the immunosuppressive treatment combination are options to improve outcome, and recently especially switching therapy from calcineurin inhibitors to rapamycin showed promising results, which is outlined in more detail below.

■ Post-transplant lymphoproliferative disease – PTLD

PTLDs are second among the most typical tumours after renal transplantation. The risk of developing PTLD after transplantation is estimated to be 10 to 30 times higher than in the general population, and PTLD is the most frequent tumour manifestation in transplanted children¹⁻³. Up to 11% of transplant recipients may suffer from PTLD during their lifetime, while prognosis remains quite poor with an average mortality of around 50%. PTLDs occur with two peaks, one within the first year after transplantation, the other late with cumulative frequency proportional to the time after transplantation. Lymphoproliferation after transplantation may manifest in four different ways: a) as a mononucleosis-like clinical disease picture, b) as a benign polyclonal B-cell hyperplasia, c) as an early malignant transformation, and d) as a monoclonal polymorphic B-cell lymphoma (highly malignant Non-Hodgkin lymphoma).

Early PTLDs are nearly always associated with EBV replication. The highest risk for PTLD development exists in the constellation of an EBV-seropositive donor and an EBV-seronegative recipient. Unfortunately, measurement of EBV replication is not helpful for PTLD screening, because replication is generally very frequently observed after transplantation and, thus, only possesses a low predictive value. In children with this high-risk constellation, however, an antiviral prophylaxis (e.g., aciclovir) is recommended. In late PTLD manifestation, EBV-association is less prominent.

There are several therapeutic options how to tackle PTLD. The first step still must be reduction

Table III

Recommendations for prevention and treatment of skin tumours after transplantation⁵

- Avoidance of and/or protection from unsheltered UV-irradiation, use of sunscreens with high photoprotection factor (“daylong actinica”)
- Cessation of smoking (co-carcinogen)
- Yearly skin inspections (more frequent in association with additional risk factors: age, history of skin tumours, high UV exposure)
- Explicit recommendations for self-inspection
- Suspicion = Biopsy
- In selected cases: topical retinoids (+interferon- α)
- Surgical treatment: excision with appropriate safety margin, cryotherapy, electrodissection
- In selected cases: photodynamic therapy, chemotherapy (5-FU, Cisplatin etc.)

or modification of immunosuppressive therapy, under close surveillance of transplant function. Reports on the usefulness of antiviral therapies based on the close association with EBV replication have given heterogeneous results. This option, however, is questionable, since EBV within the tumour tissue is usually not in a replicative state. The anti-CD20-antibody rituximab and/or the CHOP protocol (cyclophosphamide, doxorubicine, vincristine and prednisone) currently represent the ‘gold standard’ of PTLD treatment, while ongoing clinical trials evaluate separate and combined treatment modalities⁶. Both approaches have the additional advantage of enabling effective immunosuppression against transplant rejection and, thus, maintain rejection-free transplant function during therapy – in fact, a number of reports document the efficacy of rituximab in the treatment of therapy resistant acute rejections, independent of its use in PTLD treatment. Likewise, CHOP offers 3- to 4-weekly prednisone “pulse” therapy. The worst cases of PTLD regarding prognosis are CNS manifestations, presumably since these tumours are not reached by sufficient concentrations of rituximab or chemotherapeutics even if applied intrathecally.

■ Urogenital tumours

Urogenital tumours are ranked third among post-transplantation malignancies (1-3). The risk of developing tumours of the kidneys, ureters or bladder is estimated to be 5 to 10 times higher than in the general population and is highest in the failing or failed kidneys as well as in any urothel tissue in particular, but not exclusively, in patients with analgesic-induced chronic interstitial nephritis and in areas of cystic degeneration. Therefore, yearly ultrasound examinations of the urogenital system are currently recommended in post-transplantation surveillance. The occurrence of micro- or macrohaematurias should be perceived as an immediate warning signal and followed up with urine cytology and appropriate imaging techniques. In high-risk patients (chronic interstitial nephritis, cyclophosphamide exposure, cystic degeneration), urine cytology should also be monitored in the yearly post-transplantation routine surveillance.

The risk of cervical carcinoma is increased approximately 6-fold. The risk of developing vaginal, vulva or penis carcinomas is even increased by a factor of

16 to 40 over the general population¹⁻³. However, the latter tumours are generally rare, so the absolute numbers remain relatively low. In all of these tumour entities, the association with “unleashed” HPV infections is highly prevalent. Thus, women require particularly careful and intense gynaecological supervision following kidney transplantation.

■ Further malignancies

Breast, prostate and lung cancer rates are not or only marginally more frequent than in the general population. However, these are generally frequent tumours, so they also occur in transplant recipients in relevant absolute numbers, comparable to those observed with PTLDs or urogenital tumors. Similarly, colorectal malignancies additionally show a relative cumulative increase in time after transplantation and tend to metastasise aggressively. Therefore, it appears of eminent importance that state-of-the-art strategies of cancer screening are meticulously performed in transplant recipients as recommended for the general population – although it must be noted that this recommendation is extrapolated from experience in the general population lacking, at present, specific data on the efficacy of these screening approaches in the transplant population.

■ ROLE OF IMMUNOSUPPRESSANTS

Immunosuppressants serve to prevent and protect from acute transplant rejection. A high-dose immunosuppression more effectively reaches this goal than a moderate- or low-dose approach at the potential cost of an “oversuppression state” of the immune system. On the one hand, overimmunosuppression permits viral replication and impairs recognition and attacking of malignant cell transformations. On the other hand, in a Ying-and-Yang scenario, an immunosuppression which is dosed too low may cause a higher rate of rejections subsequently leading to a greater exposure to high-dose antirejection therapies and finally to even higher total immunosuppressant exposure. A balanced and individualised choice of treatment, between “overkill” and “*laissez-faire*”, seems to be a golden path to guide transplant recipients, while prediction of individual therapeutic requirements is generally quite difficult.

■ Azathioprine

Together with glucocorticoids, the antimetabolites azathioprine and 6-mercaptopurine were the first immunosuppressants used in patients after renal transplantation. These combinations were associated with acute rejection rates of more than 50% and significant rates of tumour incidences (especially skin tumours and myelodysplastic syndromes). Azathioprine therapy cannot be guided by trough level, which may be a particular problem, since we currently know that there are polymorphisms of the metabolizing enzyme causing quite dramatic differences in effective substance exposure and, thus, incalculable states of under- or over-immunosuppression in individual patients⁷.

■ Ciclosporine A

The introduction of the calcineurin inhibitor (CNI) ciclosporine A (CsA) in the early eighties represented a milestone in transplantation medicine, since acute rejection rates dropped to 30 to 40% in combination with glucocorticoids and azathioprine, with less severe rejections and allowing lower doses of the latter compounds. A publication by the Cincinnati Transplant Tumor Registry from 1988 compared tumour incidences between azathioprine- versus CsA-based immunosuppressive protocols demonstrating a 2-fold higher rate of skin tumours with the older protocols, but a significantly higher occurrence of other tumours (lymphoma, Kaposi sarcoma, urogenital tumours) with the CNI (Table IV)⁸. In multivariate analyses of general tumour incidences under both protocols, CsA showed a two-fold increase in risk when compared to azathioprine^{9,10}. However, more recent observations in this context need considering and may change this picture, since the average doses and trough levels of CsA were far higher 10 years ago when compared to current protocols.

Table IV

Comparison of tumour incidences between azathioprine and ciclosporine A – Data from the Cincinnati Transplant Tumor Registry (1988)

	Azathioprine		Ciclosporine A	
	n	%*	n	%*
Neoplasia				
Skin tumours	1255	40	90	22
Lymphomas	362	12	119	29
Kaposi sarcoma	106	3	44	11
Urogenital	89	3	23	6

* Percent of tumour morbidity

■ Tacrolimus

Tacrolimus (TAC) is currently regarded as a slightly more potent CNI than CsA. Therefore, a potentially increased risk of tumour development in association with TAC based immunosuppression was expected which, however, has not been confirmed by most registry analyses³. The general association between TAC use and post-transplantation neoplasias appears to be comparable or even more favourable to CsA use, as recently demonstrated by the UNOS registry (Table V). However, data from the European CTS registry showed a 2-fold higher incidence of PTLD manifestations associated with TAC¹¹. Definite conclusions on the relative safety of one versus the other CNI should be avoided at this time, since the clinical experience with CsA is 10 years longer than with TAC, now about 15 years on the market. This may be a considerably confounding factor when judging long-term tumour development³.

Table V

Comparison of tumour incidences between ciclosporine A and tacrolimus – Data from the UNOS registry – Period 1998-2003

	Ciclosporine A		Tacrolimus		p value
	n	%*	n	%*	
Neoplasia					
Malignancies (total)	1275	4.9	1046	3.4	<0.001
Solid tumours	537	2.0	432	1.4	<0.001
Skin tumours	576	2.2	382	1.2	<
PTLD	174	0.7	224	0.7	ns

* Percent of transplanted patients

■ Mycophenolate Mofetil / Mycophenolic acid

Mycophenolate Mofetil (MMF) was introduced in 1996 as an antiproliferative agent (inhibitor of inosinmonophosphate dehydrogenase, IMPDH) in anti-rejection treatment following renal transplantation. In pivotal studies, significant superiority in prevention of acute rejection episodes was demonstrated compared to the previous standard azathioprine. Despite obviously higher immunosuppressive potency, a greater risk for malignancies has not been demonstrated *versus* azathioprine so far. Recently, data from the UNOS registry on tumour morbidity and data from the CTS registry on PTLD incidence showed favourable outcomes for MMF *versus* non-MMF treatment

after renal transplantation^{3,12}. There are two potential explanations for this phenomenon:

1. Several forms of lymphoma or leukaemia are characterised by a massive endogenous upregulation of IMPDH, which is potentially involved in malignant cell transformation and proliferation – this step may be specifically blocked by MMF;
2. MMF (as well as TAC) reduce the incidence of acute rejection episodes and, thus, may consecutively facilitate a reduction in cumulative immunosuppressant exposure compared to those individuals requiring high-dose antirejection protocols.

However, there is currently no proof from prospective trials supporting one or both of the two concepts, and data on associations between MMF and malignancy risk are still young, covering approximately 10 years of clinical practice experience. Nevertheless, they are promising and should be continuously recorded and evaluated in registries and current study protocols.

■ Sirolimus (Rapamycin) / Everolimus

Sirolimus is a so-called mTOR-Inhibitor and as such a highly potent antiproliferative substance mostly used as a less nephrotoxic immunosuppressive alternative to CNIs since 2001. Sirolimus was originally developed as a chemotherapeutic agent; its later use in transplant medicine is a step in a different indication. In experimental animal models, sirolimus prevents tumour growth by blocking neoangiogenesis and by inducing thromboses in tumour vessels¹³. The proliferative effect of CsA can be antagonised by sirolimus in neoplasia models in the rat, and *in vitro* proliferation of EBV-transformed lymphoma cell lines can be effectively blocked by the sister compound everolimus^{14,15}. A recent study showed that switching immunosuppression from CNI to sirolimus was associated with clinically significant regression of Kaposi sarcoma¹⁶. In most of the published prospective trials the general tumour incidence was found to be reduced by approximately 50% in mTOR inhibitor-based protocols, at least during the first 3 to 5 years after transplantation³. In Europe, there are currently a number of observational studies underway evaluating the potential of mTOR inhibitors to beneficially influence development and progression of malignant

skin tumours. A switch from CNIs to mTOR inhibitors may indeed represent a relevant option in many transplant recipients who develop tumours. However, caution is advised in patients in whom chemotherapy and radiation protocols are planned, because it is unclear how the potent antiproliferative effects of these compounds may interfere with the immediate antitumour strategies.

■ Antilymphocyte antibodies / anti-CD25 antibodies

Epidemiological data clearly point to a highly increased and dose-dependent malignancy risk in transplant recipients with exposure to monoclonal OKT3 or polyclonal antilymphocyte antibodies. The novel humanised anti-CD25 antibodies (basiliximab, daclizumab) were proven to be effective in preventing acute rejections, with a surprisingly low incidence of side effects. Despite some limitations regarding length of retrospective observation periods, there is now data from the CTS registry demonstrating similar antirejection success of all antibodies used in induction therapies after transplantation, but no increases in lymphoma incidence with anti-CD25 antibodies in contrast to antilymphocyte preparations¹⁷. Should these results be confirmed in long-term observations, anti-CD25 antibody induction will probably become rated as the superior strategy for moderate- to high-risk recipients – with the potential added value of enabling reduction of oral immunosuppression with similar benefits for rejection prevention, as was recently demonstrated in the Symphony study¹⁸.

■ CONCLUSIONS

Post-transplantation malignancies are frequent and aggressive. Prevention is much more efficacious than treatment. In routine surveillance of renal transplant recipients, skin inspection, regular (at least yearly) ultrasound and x-ray controls (urogenital tumours, lymphomas) and general employment of good clinical cancer screening practice must all play a key role. With regard to immunosuppression, combinations of appropriately dosed MMF and mTOR inhibitors or of MMF and TAC (with relatively low TAC trough levels) seem to be associated with decreased tumour risk, however, definite judgement should be avoided at this

time due to limited observation periods. In selected transplant recipients who have developed tumours, a switch from CNIs to mTOR inhibitors may be the best option to maintain an effective immunosuppression with reduced risk of tumour progression.

Conflict of interest statement. None declared.

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