Cancer in patients on dialysis and after renal transplantation

Michael Fischereder

Nephrologisches Zentrum, Medizinische Poliklinik Innenstadt, Klinikum der Ludwig-Maximilians-Universität München, Pettenkoferstr. 8a, 80336 München, Germany

Keywords: dialysis; immunosuppressive therapy; malignancy; renal transplantation; screening examination

Introduction

During the past few years, it has become evident that standardized mortality rates for patients on dialysis and for renal transplant recipients are greatly increased not only due to excess cardiovascular disease and infection but also from mortality related to malignancies, i.e. solid organ cancers and lymphomas [1]. However, relative risks vary between dialysis and transplant patients and with ongoing efforts to further reduce cardiovascular morbidity, malignancy-related morbidity and mortality are of increasing importance. Due to different clinical implications one may differentiate between

- Malignancy in dialysis patients
- Donor-derived malignancy
- De novo malignancy after renal transplantation

Malignancy in dialysis patients

Almost 10 years ago, a large international registry analysis demonstrated a significant increase in cancer mortality for dialysis patients. Among European patients, the most frequent malignancies were located in the genitourinary and haematopoietic system and 73.9–16.7 deaths per 10 000 patient-years respectively were attributed to these malignancies [1]. As curative treatment allows transplantation after a waiting period to minimize recurrence, it is not surprising that 13% of patients evaluated for a transplant and 10% of patients on waiting list carry the diagnosis of a malignancy [2]. Thus, the increased prevalence of malignancy of the dialysis population persists in patients on the transplant waiting list despite cancer screening [3].

Donor-derived malignancy

Transmission of malignancy with the transplanted organ is an old yet very infrequent and does not substantially contribute to post-transplant cancer incidence [4]. This is illustrated by a review of the UNOS database with 35 503 deceased donors free from malignant melanoma or high-grade CNS tumour. Only nine of these donors transmitted tumours to 12 of 109 749 recipients during a median follow-up period of 30 months [5]. Nevertheless, under certain
circumstances such donor-derived cancers may prove fatal, i.e. for transmission of malignant melanoma [5–7].

Somewhat more frequent, but less problematic, are renal cell cancers within the transplant, of which a total of 43 cases had been compiled by 2002 [5]. These tumours are usually easily detected on routine ultrasound and are often amenable to curative radical or even nephron-sparing resection.

Although colorectal, breast and prostate and lung cancers are far more common in the general population, these are hardly ever transmitted to the recipient. This may be due to the current guidelines that recommend a careful history and careful examination of the abdominal and thoracic cavity during organ retrieval along with procedural standards of the organ procurement organizations which often also include a skin, rectal and breast examination, chest X-ray and abdominal ultrasound of the donor [8]. The utility of PSA testing is highly questionable, as no case of transmission of a prostate cancer has been reported so far.

De novo malignancy

The overall increase in incidence of malignancy after transplantation is mainly due to de novo cancers and lymphomas [9]. If studied in more detail, this phenomenon is not affecting all types of tumours equally but rather shows a predominance of certain malignancies.

Colon, prostate and breast cancer exhibit a modest two- to threefold increase during the first year after transplantation and thus affect overall lifetime expectancy of transplant recipients only modestly [10].

On the other hand, non-melanoma cancer of the skin (84-fold), kidney cancer (42-fold), uterine cancer (74-fold) and non-Hodgkin lymphomas (40-fold) are substantially more frequent during the first year after renal transplantation compared to the general population [11]. When the Australian and New Zealand transplant registry was analysed by age groups, skin cancer incidence among renal transplant recipients age below 35 years was found in ∼2% of transplant recipients (10-fold increased compared to the general population) and was thus as frequent as in patients aged 45–54 without a transplant [12]. Likewise, renal cell cancer of the native kidneys is found in ∼5% of transplant recipients at or some time after transplantation [13,14].

Risk factors and tumour development

Given this high incidence of malignancies, strategies are warranted to identify patients at risk, diagnose tumours early and optimise immunosuppressive treatment during and after tumour therapy to maintain graft function while maintaining remission free survival. So one may ask what are risk factors for the development of malignancy after transplantation. Beyond gender, age, genetic risk, conventional risk factors, pre-existing cancer, previous use of cytotoxic agents and viral infection, immunosuppressive therapy constitutes a substantial risk for tumour growth, development of metastasis or even induction of malignancies [15,16]. Immunosuppressive therapy prior to transplantation may as well contribute to the post-transplant development of malignancies. Although the analysis of representative cohorts does not usually detail immunosuppressive therapy prior to dialysis, it is interesting to note that e.g. patients with glomerulonephritits are more likely to develop any cancer while on dialysis than patients with diabetic nephropathy [1]. On the other hand, patients with polycystic kidney disease experience more non-melanoma skin cancer [11]. Beyond association of cancer development with the underlying renal disease, a number of mechanisms have been postulated by which this may occur. First, all immunosuppressive protocols are designed to decrease lymphocyte reactivity that results in both reduced alloreactivity towards the transplant as desired and less immunosurveillance. In that respect e.g. the use of lymphocyte depleting antibody therapy has been proposed to increase late mortality from malignancy [16,17]. Furthermore, direct effects of individual immunosuppressants on tumour growth have been reported (Figure 1). Azathioprine e.g. has been shown to induce DNA mutations when combined with UVA radiation [18]. Enhanced angiogenesis, tumour invasion, metastasis and EBV-induced B-cell expansion have been described with the use of calcineurin inhibitors [19].

Screening examinations with special reference to renal patients

All transplant recipients have to be considered a high-risk cohort and thus should undergo screening examinations. However, unlike for cohorts of the general population, no validated studies are available in transplant recipients to truly address the benefit for a given procedure. Therefore recommendations published on this topic are rather adapted from the general population.

As the utility of any screening test has to be viewed in the context of mortality from non-malignant causes,
extrapolation of benefits from screening examinations for the general population, for renal transplant recipients and for patienton dialysis may be misleading [10]. This is illustrated e.g. by the numbers needed to screen to save one life. Calculated for breast and colon cancer in transplant recipients, between 338 and 429 for non-diabetic transplant recipients below the age of 50 years and well into the thousands for diabetic recipients above 65 years would have to be screened [10]. Otherwise, for the more frequent tumours of the kidney, skin and lymphatic tissue a net benefit may still be expected.

Urinalysis represents a simple and non-invasive test; however, the utility of this examination to identify patients at risk is suboptimal. Eighty-five of 640 patients after renal transplantation were repeatedly dip-stick positive for haeme but only 1 of 85 was found to have renal cell CA, while for the majority no cause could be identified [20]. Likewise, urine cytology is of limited benefit to detect urothelial carcinoma in transplant recipients with analgesic nephropathy. Although routine urine cytology in these patients indeed detected urothelial carcinoma of the native kidneys and /or bladder in 11/78 patients (14.1%) 5–77 months after transplantation, neoplasms were detected rather late resulting in a fatal course in 8 of these 11 patients [21]. At present the most prudent screening test of the native kidneys is a renal ultrasound for the presence of acquired cystic disease, of- ten associated with renal cell cancer [13,14]. Appearance of the acquired cysts should be graded according to the Bosniak classification which also aids in the further decision whether to observe or recommend nephrectomy [14].

In summary, most current recommendations include an annual skin examination, PAP smear and ultrasound of the native kidneys beyond routine screening examinations [14,22–24].

**Immunosuppressive management**

Minimization of the immunosuppressive therapy nowadays is widely practiced and certainly may also reduce growth as well as the likelihood of de novo cancer after renal transplantation. The reduction of CSA exposure form trough levels of ~200 ng/ml to 100 ng/ml reduces cancer incidence while maintaining adequate immunosuppression [25]. Furthermore, registry data suggest a trend towards the reduced cancer development when azathioprine is substituted by mycophenolate [26].

Is there additional evidence that beyond a general reduction in the immunosuppressive potency the use of some immunosuppressants may favourably affect cancer progression? When discussing such questions, one has to clearly differentiate between

- **de novo** cancer incidence under certain regimens
- Immunosuppressive management after curative cancer treatment and
- Immunosuppressive treatment in patients with active tumours

Indeed, with **de novo** cancer in experimental animals subjected to UV-B irradiation and various immunosuppressants, treatment with sirolimus correlated with smaller tumours due to decreased angiogenesis while mycophenolate reduced tumour number [27]. In human transplantation, registry data from 33 249 deceased donor transplant recipients also indicate fewer tumours in patients treated with mTOR inhibitors during first 963 days [28]. Furthermore, a reduced incidence of skin cancer and non-skin cancer has been reported in a post hoc analysis of randomised transplantation trials comparing sirolimus with cyclosporine [29].

From this perspective, it appears reasonable to consider mTOR inhibitors also in recipients having undergone curative tumour therapy and randomised trials addressing this question are currently under way.

**Progressive tumours**

Experimental animals treated with sirolimus even demonstrated regression of transplanted tumours [30]. Human data on this problem are scant and available e.g. as case series in certain clinical situations such as post-transplant Kaposi’s sarcoma. Indeed, conversion of the immunosuppressive reg-imen to sirolimus resulted in complete or partial regression of Kaposi sarcoma post-transplant in 41 of 48 reported cases between 2005 and 2006 [31].

In summary, malignancies appear as increasing medical problem in patients on dialysis and transplant recipients. With reduced cardiovascular mortality tumour screening, minimization of immunosuppressive therapy and possibly the use of mTOR inhibitors may convey additional benefits.

**Conflict of interest statement.** The author receives grant support from Wyeth, Novartis, Astellas and Roche.

**References**


Received for publication: 13.12.07
Accepted in revised form: 7.3.08