Malignancies in renal transplantation: an unmet medical need

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Abstract
Registry data show that there is an overall 3–5-fold increase in cancer risk in transplant recipients compared with the general population, with skin cancers and lymphoma particularly prevalent. Cancers in transplant recipients are often more aggressive than those in the general population, with poor prognosis, particularly for gastrointestinal tumours and lymphomas. Risk factors for post-transplant malignancy include factors common to the general population, such as increasing age, cigarette smoking and sun exposure. In addition, immunosuppression is an important factor in the development of post-transplantation cancer, although data for individual agents are not definitive. A number of studies have demonstrated that ciclosporin is associated with an increased risk of malignancy, whereas a few studies report no increase in risk of cancer after the introduction of ciclosporin into treatment regimens. Similarly, studies have shown that the mycophenolic acid-based agent mycophenolate mofetil is associated with an increased risk of malignancy, whereas other studies have demonstrated that mycophenolate mofetil is in fact associated with a lower risk. Polyclonal anti-thymocyte antibodies used for induction therapy appear to be related to an increased incidence of post-transplant lymphoproliferative disorder, but this effect is not observed with monoclonal anti-interleukin 2 antibodies. Azathioprine has been implicated in the development of skin tumours, possibly as a result of increased photosensitivity to ultraviolet light. The proliferation signal inhibitors appear to be associated with a reduced risk of some malignancies. Further research will elucidate the role of these newer immunosuppressive agents in post-transplantation malignancies.

Keywords: cancer; epidemiology; immunosuppression; renal transplantation; risk factors

Introduction
Although improvements in transplantation technology and immunosuppressant medications which improve short-term graft survival continue to be made, long-term complications, such as malignancies, are becoming a limiting factor for graft and patient survival [1]. Indeed, the incidence of deaths as a result of malignancies is increasing (Figure 1) [2], although this is partly as a result of decreases in the incidence of deaths related to cardiovascular disease and infection [2]. Over the next 10–20 years, it is possible that deaths from malignancy in renal transplant recipients will exceed those related to cardiovascular disease.

Epidemiology
In published studies, the incidence of cancer in renal transplant recipients ranges from 2.3–31% [3], although this estimate is limited by the focus of individual studies on specific populations and a lack of long-term follow-up, thus potentially leading to an underestimate of the true cancer incidence. Using data from registries, the incidence of cancers can be compared with those in the age-matched general population and risk ratios or standardized incidence ratios calculated. Such analysis has confirmed that the risk of de novo malignancies is increased in transplant recipients, with a relative risk 3–5 times that of the general population [3]. For example, data from the Collaborative Transplant Study (CTS) show an increase of at least 3-fold in the incidence of cancer compared with the expected incidence (Figure 2) [4], while the Australia and New Zealand Dialysis and Transplant (ANZDATA) registry shows a standardized incidence ratio of 3.46 for all cancers reported in Australia and New Zealand between 1980 and 2005 in patients after a first transplant [5].

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Transplantation (ISHLT) show that 3.1% of surviving patients develop some form of malignancy after 1 year, which increases to 16.1% in 5-year survivors and 26.2% in 8-year survivors [6]. Data from lung transplant recipients in the ISHLT registry show a similar trend, with 4% of surviving patients developing a malignancy after 1 year, 18% after 7 years and 30% after 9 years [7]. In renal transplant recipients, data from the Medicare analysis of the US Renal Data Systems (USRDS) showed that the cumulative incidence of cancer [excluding non-melanoma skin cancer (NMSC)] was 3.3% at 1 year and 7.5% at 3 years, while the corresponding incidences of NMSC were 2.3 and 7.4%, respectively [8]. Overall, the risk of NMSC appears to be greatest in heart transplant recipients, with substantial increases between the 5th and 10th year post-transplantation reported in several studies [9]. Perhaps unsurprisingly, this effect was most pronounced in fair-skinned populations living in regions of high sun exposure, such as Australia or southern Europe. The highest risk of lymphoma occurs in heart–lung transplant recipients, with a 5-year relative risk of non-Hodgkin lymphoma (NHL) of 239.5 compared with 58.6 for lung transplant recipients, 27.6 for heart-only recipients and 12.6 for cadaveric kidney recipients [10].

Although all malignancies are represented in transplant populations, certain types of cancer appear at higher frequency than others. An analysis of the USRDS database using Medicare billing claims for cancer showed that, compared with an age-adjusted population, the incidence of common cancers, such as colon, lung, prostate or breast cancer, was approximately doubled in renal transplant recipients, while the increase in incidences of other cancer types ranged from 3-fold for bladder and testicular cancer to 15-fold for kidney malignancies, with an even higher incidence (>20%) of lymphomas and NMSC [8]. Similar results were obtained in patients enrolled in the ANZDATA registry, with the largest standardized incidence ratios observed for Kaposi’s sarcoma (40-fold), renal malignancies (10-fold) and lymphoma (9-fold) [5].

Not all malignancies observed in transplant recipients are, however, a consequence of transplantation or immunosuppressive agents, as some are related to the patients’ underlying conditions. When the incidence of different cancers in US renal transplant recipients was compared with that in patients on the waiting list for transplantation, most of the common malignancies occurred at similar rates. Significantly increased rates in transplant recipients were observed for leukaemia, renal cancer, mouth and oesophageal cancer, melanoma, NMSC, lymphoma and Kaposi’s sarcoma (Figure 3). Conversely, the incidences of ovarian cancer (relative risk, 0.34) and prostate cancer (relative risk, 0.79) were significantly reduced in transplant recipients compared with those on the waiting list (P < 0.05) [8].

Malignancies and long-term outcomes

Despite the high incidence of skin cancers in transplant recipients, these tumours are usually not fatal [1,11]. Solid organ cancers, although less common, are associated with a far worse prognosis in renal transplant recipients, with data from one centre in The Netherlands showing a median survival from time of diagnosis of <4 months [1]. A further database study of 1546 patients from The Netherlands, who received a total of 2075 renal transplantations, showed that skin malignancies developed in 53% of patients after renal transplantation, with 48% of those with one skin tumour subsequently developing a second malignant lesion of the same or different histological type [11]. The majority of these patients were treated successfully, with two deaths in the follow-up period; one from de-differentiated squamous cell carcinoma (SCC) and one from Merkel cell tumour with lung metastases. This mirrors the Australian experience,
where no deaths have been recorded from basal cell carcinoma (BCC) but increased mortality from SCC and Merkel cell tumours has been observed [2].

In The Netherlands study, post-transplant lymphoproliferative disorder (PTLD) developed in 11% of patients, of whom 65% presented with malignant lymphoma (with a median survival of 5 months). The poor prognosis of patients with PTLD has been confirmed by data from the CTS, with a 1-year mortality of ~40% and no relationship between time to development of lymphoma and survival [10]. When patients in the USRDS database with different types of lymphoid disease were compared, 10-year survival rates varied substantially with disease type: 26% for patients with myeloma, 39% for those with leukaemia, 42% for NHL and 55% for Hodgkin’s disease [12].

One notable finding of The Netherlands database study was that the prognosis of patients with malignancies of the gastrointestinal tract was particularly poor, often because the disease was at an advanced stage at the time of presentation [11]. Of 24 patients with such tumours, four had carcinoma in situ and survived for more than 1 year after curative resection. Median survival in the remaining patients was 1 month, with no patient surviving longer than 1 year [11]. An analysis of genitourinary cancer in 1804 patients who underwent 2068 renal transplantations included 34 patients with genitourinary tumours (15 of whom had renal cell carcinoma) [13]. Most tumours were diagnosed at an early stage and were therefore accessible to curative therapy, achieving good long-term results. One- and 5-year survival rates in these patients were 100 and 91%, respectively, which were significantly better than those obtained in patients with more advanced tumours (1- and 5-year survival rate, 38%; $P < 0.05$). Nine patients died as a result of tumour growth [13].

### Risk factors for malignancy

In transplant recipients, conventional risk factors for malignancy, such as age, sun exposure and cigarette smoking, contribute to the incidence of cancers, as well as factors such as immunosuppression that are specific to transplant patients (Table 1) [14,15]. For example, an analysis of cancer incidence in 1500 renal transplant recipients showed that age >45 years ($P = 0.007$) and cigarette smoking ($P = 0.016$) were significantly associated with an increased risk of cancer [16]. Exposure to carcinogens other than cigarette smoke, including cytotoxic drugs, and abuse of analgesics, can also play a role [17].

The pathogenesis of post-transplant malignancy can be directly related to the use of immunosuppressive therapy and its negative impact on immunosurveillance [15]. Crucial evidence for this concept was demonstrated in mice lacking natural killer T-cells, T-cells, and B-cells that were injected with a carcinogen. These mice developed sarcomas more rapidly and with greater frequency compared with genetically matched wild-type controls and also formed more spontaneous epithelial tumours compared with the wild-type mice [15].

A number of viruses predispose transplant recipients to specific malignancies, including Epstein–Barr virus (EBV) (which is linked with lymphomas), human herpes virus 8 (lymphomas and Kaposi's sarcoma), hepatitis viruses B and C (hepatocellular carcinoma) and human papillomaviruses (cervical, penile and
likely that this is related to the additional immunosuppressive effects of ultraviolet (UV) light in the skin [19]. Total sun exposure is an important risk factor for skin cancers, and studies have shown that Caucasian renal transplant recipients living in Queensland, Australia, have the highest global risk of NMSC [20]. In 361 Caucasian renal transplant recipients living in Queensland, the risks of SCC and BCC were found to be strongly associated with the time spent living in a hot climate [20]. Geographical factors also have an impact on other forms of post-transplant cancer, such as a high incidence of gastrointestinal tumours in Japan, a high incidence of urinary tract transitional cell carcinoma in Taiwan [21] and a high incidence of liver cancer in South-East Asia, where hepatitis B and C are endemic [14].

Genetic disposition and a history of pre-transplant malignancy are also key risk factors in transplant recipients. Patients with a history of invasive cancer before transplantation were found by one study to have more than double the risk of post-transplant cancer compared with patients with no history of malignancy (\(P = 0.015\)) [16]. Rare genetic conditions such as von Hippel–Lindau disease, Wiskott–Aldrich syndrome or Drash syndrome can also predispose transplant recipients to an increased risk of cancer [14]. An increased genetic disposition can also be manifested as multiple malignancies of different types. Indeed, reports exist of patients with four different types of post-transplant tumour, including carcinoma of the epiglottis, SCC of the lung, renal cell carcinoma and transitional cell carcinoma of the renal pelvis [22].

### Immunosuppressive therapies and post-transplant malignancy

Immune suppression remains the most important controllable risk factor for malignancy in transplant recipients. This is supported by the increased risk of malignancy seen in non-transplanted patients who require immunosuppressive therapy for other conditions. Data from population-based studies and smaller retrospective series indicate that the overall risks for developing malignancies such as BCC, NHL, Kaposi’s sarcoma and lymphoma were increased in patients receiving immunosuppressive agents, including corticosteroids, azathioprine and 6-mercaptopurine for conditions such as multiple sclerosis and inflammatory bowel disease [15]. Based on this evidence, patients prescribed immunosuppressive agents for conditions other than for organ transplantation are at a significant risk of malignancy, even when treated with single, low-dose therapies [15].

Organ transplant recipients often receive several combinations of immunosuppressive agents; therefore, it has been suggested that the duration and intensity of immunosuppressive treatment, as well as the type of agent, can affect cancer risk [15,23]. Perhaps the best evidence in this area relates to NMSC, in which the
duration of immunosuppressive therapy is a risk factor for the development of malignancy in kidney transplant recipients [14,24].

The use of combination therapies makes it difficult to assess the impact of individual immunosuppressive agents on cancer risk and thus there is a lack of robust evidence in this area. For example, a number of studies demonstrate that the incidence of post-transplant malignancy increases after the introduction of the calcineurin inhibitor (CNI) ciclosporin (CsA), whereas a few studies report no increase in risk of cancer after the introduction of CsA [10,25,26], although it has also been reported that triple therapy (CsA, azathioprine and corticosteroids) is associated with an increased cancer risk [14]. Overall, it is probable that cancer risk is related to immunosuppression in general, rather than to any particular agent.

In a study of PTLD in 667 renal transplant recipients, the results showed no significant differences in PTLD incidence when comparing patients from before and after the introduction of CsA and no effect of anti-lymphocyte globulins on PTLD risk; however, the occurrence time was shorter in patients treated with CsA and anti-lymphocyte globulins [26]. Overall, the authors concluded that the risk of PTLD results from a combination of graft antigenicity, immunosuppression and EBV infection. A variety of biological immunosuppressive agents have been shown to have an impact on the incidence of post-transplant malignancy. The use of lymphocyte-depleting antibodies has been shown to increase the risk of post-transplant malignancy, particularly virally induced cancers [15]. Furthermore, an induction regimen that contains lymphocyte-depleting antibodies (such as OKT3 and anti-thymocyte globulin) is a well-known risk factor for the development of PTLD [15]. For example, when the role of induction therapy in the risk of PTLD was evaluated in a large patient population as part of the CTS (n = 200 000), regimens involving OKT3 or anti-thymocyte globulins were associated with a substantially increased risk of lymphoma, particularly in the first post-transplant year (Figure 4) [10]. Conversely, anti-interleukin 2 receptor antibodies did not appear to be associated with an increased lymphoma risk within the 12 months immediately after transplantation (Figure 4).

The purine analogue azathioprine has been used in the transplantation setting for over three decades [15]. Azathioprine has long been known to cause chromosomal aberrations in human cells [27], and more recent work has shown that azathioprine treatment can lead to increased photosensitivity to UV [28]. In mice with UV-induced carcinogenesis, azathioprine reduced the period for tumour development and increased the number of skin cancers, compared with CsA [15]. Although this suggests a role for azathioprine in the development of skin cancer, there have also been reports of azathioprine-induced NHL, both in transplant recipients and in patients treated for immunological disorders such as Wegener’s granulomatosis or Crohn’s disease [29].

Data on the role of CNIs in cancer risk are conflicting. Some studies, such as the CTS, show no increase in the risk of lymphoma in patients receiving CsA [10], whereas a large number of studies show a substantial increase in risk with a CsA-based regimen or after the introduction of CsA [30,31]. A study of Medicare patients in the USA showed that CsA was associated with a significantly reduced risk of PTLD, compared with a tacrolimus-based regimen without induction therapy [32]. CsA may cause cancer progression through both direct cellular effects and increased expression of transforming growth factor β (TGF-β) [33]. Highly aggressive tumours have been shown to contain significantly higher levels of TGF-β compared with more differentiated tumours, highlighting the important relationship between TGF-β protein and TGF-β receptor dynamics in tumour progression [15]. In addition, a role for CsA in stimulating angiogenesis, mediated by vascular endothelial growth factor (VEGF), has also been demonstrated in vivo [34]. In vitro studies have suggested other possible mechanisms of CsA-induced malignancy, including a reduction in p53-induced apoptosis and suppression of UV-induced DNA repair [15]. Tacrolimus has also been reported to increase the incidence of post-transplant malignancy, with the CTS study indicating that renal transplant recipients treated with tacrolimus had a 2-fold higher risk of developing PTLD compared with those treated with CsA [10]. Furthermore, this increased risk of malignancy with tacrolimus was confirmed in the study of Medicare patients in the USA [32]. In contrast, several studies have shown no difference in non-PTLD malignancy between tacrolimus- and CsA-based regimens [15], whereas the USRDS database analysis of billing claims reported that tacrolimus was in fact associated with a reduction in overall malignancy and skin cancer risk [8,15].
Mycophenolate mofetil (MMF) is a selective and reversible inhibitor of inosine monophosphate dehydrogenase, which is essential for lymphocyte proliferation [15]. Data on the carcinogenic effects of MMF are conflicting. Studies demonstrate that MMF has a mutagenic effect in vitro and can enhance tumour invasiveness; however, MMF has also been associated with the prevention of in vitro tumour dissemination [15]. Although MMF was originally developed as an anti-neoplastic agent, some clinical trials suggested that it was associated with a non-significant trend towards an increased risk of PTLD in renal transplant recipients [35]. Analysis of two large databases—the Organ Procurement and Transplantation Network/United Network for Organ Sharing registry (n = 8246) and the CTS (n = 5266)—showed, however, that MMF was not associated with any increase in the risk of malignancy [35]. Indeed, there was a trend towards a lower risk of malignancy with MMF in both registries, and a significant increase in the time to first malignancy in the CTS database (P < 0.026). These data were further demonstrated in the US Medicare patient study [32] and were later reflected in a review of the incidence of PTLD in nearly 40,000 renal transplant recipients from the Scientific Registry of Transplant Recipients (SRTR), in which MMF was associated with a lower risk of PTLD when compared with azathioprine [15].

Proliferation signal inhibitors (PSIs; also known as mammalian target of rapamycin (mTOR) inhibitors) may also have a beneficial effect on the incidence of post-transplant malignancies [23,36,37]. In addition to their immunosuppressive properties, PSIs also exhibit anti-proliferative effects, as a result of their novel mode of action, by inhibiting vital regulators of cell growth, division and survival [38]. In vitro and in vivo studies have shown that PSIs can prevent the growth of transformed cells and tumour-derived cells, increase the rate of apoptosis in tumour cell lines and reverse the process of tumour progression and angiogenesis [34,39–42]. Clinical studies have reported a reduced incidence of post-transplant malignancy in patients receiving PSIs when compared with CNIs [43,44]. Furthermore, conversion to PSIs from CNIs can cause regression of Kaposi’s sarcoma in renal transplant recipients [45,46]. Therefore, the dual action of the PSIs indicate that they may be beneficial for the prevention of post-transplant malignancy [36] and further information is needed to ensure their optimal use in the clinical setting [37]. Furthermore, preliminary data from oncology studies suggest that PSIs may in fact be a viable treatment for patients with advanced solid tumours and further research in this area is ongoing [47,48].

Summary

The incidence of cancer is greatly increased in renal transplant recipients compared with the general population, with skin cancer and PTLD being the most common forms of malignancy in these patients. Importantly, the prognosis of transplant patients with cancer is worse than in the general population, with an aggressive course and short survival times. Many factors are implicated in the development of malignancy, including viruses, sun exposure, genetic predisposition and immunosuppressive therapy. Data on individual therapies are, however, conflicting and there is a lack of robust evidence for the role of specific agents in the development of cancer. Further research is necessary to define more clearly the role of immunosuppressive drugs in post-transplant malignancies and to develop new agents that are associated with fewer malignancies in this at-risk population.

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