Clinical Kidney Journal

ckj

OXFORD

Leading European Nephrology

Clinical Kidney Journal, 2015, vol. 8, no. 5, 637–644

doi: 10.1093/ckj/sfv054
Advance Access Publication Date: 23 July 2015
CKJ Review

CKJ REVIEW

Management and prevention of post-transplant malignancies in kidney transplant recipients

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Abstract

The central issue in organ transplantation remains suppression of allograft rejection. Thus, the development of immunosuppressive drugs has been the key to successful allograft function. The increased immunosuppressive efficiency obtained in the last two decades in kidney transplantation dramatically reduced the incidence of acute rejection. However, the inevitable trade-off was an increased rate of post-transplant infections and malignancies. Since the incidence of cancer in immunosuppressed transplant recipients becomes greater over time, and the introduction of new immunosuppressive strategies are expected to extend significantly allograft survival, the problem might grow exponentially in the near future. Thus, cancer is becoming a major cause of morbidity and mortality in patients otherwise successfully treated by organ transplantation. There are at least four distinct areas requiring consideration, which have a potentially serious impact on recipient outcome after transplantation: (i) the risk of transmitting a malignancy to the recipient within the donor organ; (ii) the problems of previously diagnosed and treated malignancy in the recipient; (iii) the prevention of *de novo* post-transplant malignant diseases and (iv) the management of these complex and often life-threatening clinical problems. In this scenario, the direct and indirect oncogenic potential of immunosuppressive therapy should be always carefully considered.

Key words: immunosuppression, kidney transplantation, onconephrology, post-transplant malignancies

Introduction

The key issue in organ transplantation is the prevention of allograft rejection. Thus, development of immunosuppressive drugs is crucial to assure successful allograft function. Several immunosuppressive drugs were introduced in the 1980s and 1990s on the basis of their ability to reduce the incidence of acute rejection and to demonstrate better short-term outcomes than those achieved with established immunosuppressive therapy. The improved immunosuppressive efficiency obtained in the last three decades in kidney transplantation dramatically reduced the incidence of acute rejection and its influence on graft outcome. Indeed, to date, the two main causes of kidney transplant failure are represented by chronic rejection and death of the patients with a functioning graft. Thus, today we are playing in a completely different ballpark and in this setting it is essential to understand the causes of post-transplant mortality and to realize whether they are preventable.

Malignancies represent one of the main causes of death in kidney transplant recipients worldwide. The development of post-transplant malignancies represents a key issue and there is a strong need to have a clear understanding of the challenges that malignancies represent for kidney graft recipients. There are at least four distinct areas requiring consideration, which have a potentially serious impact on recipient outcome after transplantation: (i) the risk of transmitting a malignancy to the recipient

Received: January 18, 2015. **Accepted:** June 11, 2015

within the donor organ; (ii) the problems of previously diagnosed and treated malignancy in the recipient; (iii) the prevention of *de novo* post-transplant malignant diseases and (iv) the management of these complex and often life-threatening clinical problems.

Donor-derived malignancies

It is well known that donor malignancies might be transmitted through solid-organ transplantation and, in the presence of immunosuppressive therapy, might progress rapidly with devastating consequences. Accidental transmission of several types of malignancy has been reported. Consequently, it is currently a standard practice to avoid transplantation of organs from donors with known malignant disease. The exceptions to this well-established rule are donors with low-grade non-melanoma skin cancer and carcinoma *in situ* of the uterine cervix, which have a negligible risk of transmission. Although there is a risk that malignancy can be transmitted by transplantation, the evidence for accurately quantifying this risk is still lacking. The risk of transmission is largely dependent on the nature and extent of the malignancy. The potential transmission of metastatic cancer is very high. Indeed, the analysis of 29 deceased organ donors with metastatic central nervous system (CNS) cancer, erroneously diagnosed as primary intracranial haemorrhage or primary brain malignancy [1] demonstrated that 64% of recipients suffered diffuse metastatic disease and overall 5-year survival rate was 32% [1]. However, donors with localized or low-grade malignancy present an undoubtedly lower risk of cancer transmission.

To reduce the possible transmission of neoplastic disease, the clinical history of each donor should be carefully analysed and a comprehensive clinical examination should be undertaken. At the time of organ harvesting from deceased donors, the main intra-thoracic and intra-abdominal organs should be carefully examined to exclude evidence of hidden neoplastic diseases, and any suspicious lesions should be biopsied. This procedure is particularly important in older donors where the risk of cancer is significantly higher.

In consideration of the likely incidence of occult malignancy in the potential donor population, it is conceivable that a small, although difficult to quantify, number of active malignancies, particularly breast and prostate cancer, might never be recognized in deceased organ donors. Interestingly, the rate of donor cancer transmission observed in transplant recipients is particularly low (only 0.012% in one report). This observation suggests that early stage unrecognized tumours in organ donors might not lead to cancer transmission [2]. In consideration of the serious shortage of organs for transplantation, the issue is, then, to balance the risk of tumour transmission with the benefit associated with organ transplantation. Since the risks and outcomes of tumour transmission are still unclear for a large number of cancer types, the decision can be very challenging. An analysis of the OPTN/UNOS database revealed that 1% of deceased-donor organ transplants were performed using organs from donors with a previous history of cancer and only one case of cancer transmission was recorded in this patient population [3]. It is noteworthy that the cancer-free interval in organ donors varied significantly from <5 years for 40% of donors with uterus, kidney or prostate cancer to >10 years in the majority of donors. Melanoma, irrespective of the length of disease-free survival, should always be considered as an absolute contraindication to donation. Also the use of organs from donors with a previous history of breast cancer or lymphoma should always be considered with great caution.

Donor-transmitted malignancy usually becomes evident within 2 years of transplantation, and generally involves the graft. Thus, in selected cases, post-transplant graft surveillance using ultrasound or computed tomography is mandatory. Donor-transmitted malignancy usually leads to recipient death, especially if it occurs in life-saving transplants, where graft removal and immunosuppression withdrawal is not an option. Liver resection or even re-transplantation is a possibility for malignancy localized within the liver graft. In renal transplantation, donor nephrectomy and immunosuppression withdrawal may result in a complete resolution of the neoplastic disease, even after it has spread outside the graft. In these cases, re-transplantation should be considered only after an appropriate period of time, to ensure that the recipient remains free of disease recurrence.

Recipients with pre-transplant malignancies

It is widely accepted that patients with active neoplastic disease should not be considered as suitable candidates for organ transplantation. There are at least two reasons to implement this recommendation. First, the shortage of organs available for transplantation is such that their use cannot be justified in patients who might, in a relatively short period of time, die for a neoplastic disease, or become so unwell because of it that they would not fully appreciate the benefits of transplantation. Second, the immunosuppression needed to ensure an acceptable graft survival might accelerate the progression of a pre-existing malignancy leading to an increased cancer-related morbidity and mortality. Convincing evidence that immunosuppression might cause the progression of neoplastic disease was provided by the early experience of liver transplantation in patients with primary/secondary liver cancers. Half of these patients presented with an early recurrence of the pre-existing neoplastic disease, leading to death in most of the cases within 2 years of transplantation [4]. Although it might be argued that disease recurrence in these patients might solely represent the natural history of their malignancy, the time of recurrence and the rate of progression were inconsistent with the natural evolution of their neoplastic disease and suggest a role for the immunosuppressive therapy.

Clinical evaluation of transplant candidates should always include a thorough examination of any symptom or sign suggestive of a possible malignancy. This evaluation is of particular relevance in older recipients in whom hidden neoplastic disease is more likely to be present. If a malignancy is identified, transplantation should not be contemplated until the disease has been successfully treated, and a suitable disease-free interval achieved [5]. A key issue in this setting is, indeed, the definition of a 'suitable disease-free period of time' before they can be safely considered for transplantation. Although the longer the waiting period from treatment to listing for kidney transplantation the less likely recurrent disease becomes, waiting for several years might be unfeasible in many cases, especially for older patients. A retrospective analysis of pre-existing neoplastic disease in kidney graft recipients reported that recurrence rate varied according to tumour type [6]. Cancers with a low recurrence rate (below 10%) include carcinoma of testis, thyroid, uterine cervix and lymphoma. Cancers with an intermediate recurrence risk (11–25%) include carcinoma of colon, breast and prostate and those with a high risk (>25%) included melanoma, invasive urothelial carcinoma, multiple myeloma and sarcoma. Overall, 53% of neoplastic disease recurrences occurred in graft recipients treated within 2 years before transplantation, falling to 34% for patients transplanted between 2 and 5 years after cancer

treatment and 13% for those treated for more than 5 years before transplantation [6]. On the basis of this, most clinical guidelines recommend that patients should wait for at least 2 years and in some cases up to 5 years after successful cancer treatment. Exemptions to these suggestions are non-invasive malignancies (*in situ*) of the cervix and non-melanoma skin cancer. However, these recommendations are based on old reports and do not take into consideration the dramatic improvement in the treatment of several cancers observed in the last decade. Since the recurrence rate and the time to recurrence are likely to vary depending on tumour type and grade as well as type of treatment and response to treatment, the latest EDTA guidelines suggest that for each patient these factors should be carefully considered with the help of an oncologist, balancing the risks of recurrence with the overall benefits of organ transplantation [7].

De novo malignancies after transplantation

All transplant patients should be considered at high risk for the development of *de novo* post-transplant neoplasia. Several studies demonstrate a significant increase in cancer incidence rate after transplantation, although with a wide variability. Kasiske *et al.* [8] and the Australian and New Zealand Data Registry (ANZDATA) [9] reported a 3-year cumulative incidence of 14.9 and 13%, respectively, whereas previous analyses of the Collaborative Transplant Registry (CTS) and the Organ Procurement and Transplantation Network/United Network for Organ Sharing (OPTN/UNOS), observed an incidence of 4.7 and 3.9%, respectively [10]. Some of the differences observed in these incidence rates might be explained by different follow-up times, since the duration of immunosuppression is an independent risk factor for the development of post-transplant neoplasia [11]. The overall standardized incidence rate (SIR) of post-transplant malignancies compared with that of the general population in most of the studies is over 2 means that transplant recipients have a risk of malignancies at least doubled when compared with subjects of their age and gender in the general population. This SIR is not equal for all tumour types. Indeed, the neoplastic diseases most frequently observed in the general population have an almost identical incidence in transplant recipients. On the other hand, the highest SIR for kidney graft recipients is reported for neoplastic diseases classically associated with virus infection, including Kaposi sarcoma, non-Hodgkin lymphoma and cervix carcinoma [12]. The high incidence of neoplasia in transplant recipients has a significant clinical impact. Post-transplant malignancies represent a significant cause of mortality after transplantation, causing between 10 and 47% of deaths. The variability in this setting mainly depends on the length of post-transplant follow-up [13–15]. In most studies, the main cause of mortality remains cardiovascular disease, although the role of neoplasia is progressively growing as long-term survival is achieved in a greater number of transplant recipients. Indeed, neoplastic disease represents the first cause of mortality in the ANZDATA registry [9], and is among the top causes of death in most of the other registries [11, 13–15]. Thus, malignancy is currently one of the major factors limiting life expectancy in kidney allograft recipients.

The overall mortality associated with *de novo* post-transplant malignancies is high and gradually rises with time. The ANZDATA study on 6596 deceased donor kidney recipients reported 420 post-transplant malignancies other than skin cancer with a 26% cancer-related mortality at 10 years [9]. Data on 760 kidney graft recipients from North America observed for a mean time of 13.4 years, reported an all-cause mortality of 54%, with a majority represented by cancer-related deaths [16]. Howard *et al.* demonstrated that malignancies represented the cause of death for 1.2% of patients receiving a kidney graft between 1970 and 1979. This percentage rose to 5.2 between 1980 and 1989, and to 13.3 in the 1990s [17]. The dramatic increase in cancer-related deaths was due to a combination of increased patient age, longer survival and heavier immunosuppression. The OPTN/UNOS data on patient mortality between 5 and 10 years after transplantation demonstrate that malignancies were the cause of death in 14.5% of kidney, 18.7% of liver and 21.5% of heart recipients [18].

Non-immune-related risk factors

Several reports suggested numerous immunosuppression-independent factors associated with the development of post-transplant malignancy. All reports indicated that increasing age and male gender are associated with an increased risk of any *de novo* cancer [19–24] and, in particular, of non-melanoma skin cancer [19]. The pre-transplant dialysis vintage represents an independent risk factor in three studies, although the weight of this factor varied significantly [19, 20, 22]. Kasiske *et al.* [19] suggested that a pre-transplant dialysis duration of >3 years is associated with a significantly increased neoplastic risk. Several studies recognized diabetes mellitus as a protective factor [19, 25]. The USRDS study reported a significantly lower risk for both non-skin malignancies and non-melanoma skin cancers in recipients with diabetes [19]. The USRDS report further suggested cystic kidney diseases as an independent risk factor for non-melanoma skin cancer [19]. Two registry studies indicated that a previous history of neoplastic disease was significantly associated with the development of a *de novo* post-transplant malignancy [23, 25]. This observation was further confirmed by a UNOS study including kidney and heart graft recipients [26]. Kasiske *et al.* [19], finally, identified an increased body mass index as a negative risk factor for the development of post-transplant non-melanoma skin cancer.

Post-transplant malignancy and immunosuppression

The pathogenesis of *de novo* post-transplant malignancies is difficult to investigate because of the mixture of potential pathogenic factors present in transplant recipients. The presence of environmental/genetic factors along with a complex interaction between a reduced tumour immunosurveillance, the activation of pro-oncogenic viruses and the direct carcinogenic effects of immunosuppressive drugs, converge in this particular patient population. In this scenario, however, the direct or indirect effect of immunosuppressive drugs is definitely overwhelming. This hypothesis was first suggested by a prospective, open-labelled, randomized trial evaluating two cyclosporine A (CsA) regimens (low versus normal-dose) in renal graft recipients. In this study, the incidence of malignancies, over a 66-month follow-up, was significantly more frequent in the normal-dose group [15]. Several retrospective studies confirmed this observation, demonstrating that an increased malignancy rate was associated with a more intense immunosuppression [27–29] or with the use of a stronger immunosuppressive regimen [29]. It is well known that intensification of immunosuppression is commonly implemented in patients with one or more episodes of acute graft rejection [30, 31] and, indeed, this event is correlated with a significant growth in malignancy rates in solid organ transplantation and translates also into an accelerated tumour progression and a significantly lower patient survival [30, 31].

Although overall immunosuppression plays a key role in the development of post-transplant malignancies, each immunosuppressive drug presents a distinct safety profile in this setting due to the inhibition of specific mechanisms in the immune response potentially important for immunosurveillance or for anti-viral defence or in some cases to a direct oncogenic potential. Thus, it is worth considering the potential role of the main immunosuppressive drug in the scenario of post-transplant malignancy.

Biologic agents

The use of lymphocyte-depleting antibodies has been associated with a clear increase in the incidence of malignancies, mainly related to viral infection. The pro-neoplastic effect, of this class of drug has been mainly associated with a significant increase in EBV infection often observed in patients treated with these therapeutic agents whose relationship with the pathogenesis of non-Hodgkin lymphomas is clearly established [32–34]. Most studies do not analyse the risk for each specific agent. However, a report showed a significant difference in the incidence of post-transplant lymphoproliferative diseases (PTLD) between two different preparations of anti-thymocyte globulins (ATG). Thymoglobulin carried a higher relative risk (RR: 2.16) than Fresenius ATG [34]. This observation was supported by a retrospective study analysing the incidence of non-Hodgkin lymphoma according to the type of induction therapy in 112.122 renal graft recipients [35]. The underlying mechanism of this difference is unknown, although the variable oncogenic activity might be explained by differences in the extent of activity of the two formulations. Opelz *et al.* [35] suggested that the increased risk of PTLD could be linked to the activity against CD3, present in thymoglobulin and in other monoclonal/polyclonal depleting antibodies, which is virtually absent in Fresenius ATG. A possible alternative to depleting T-cell antibodies in the induction therapy of kidney transplantation is represented by anti-CD25 monoclonal antibodies, whose therapeutic effects are due to the inhibition of IL-2 binding to its cognate receptor, that are characterized by a similar efficacy in reducing acute rejection rates [36, 37] compared to depleting biologic agents, without any consistent evidence to increase malignancy risk [36, 37]. The last biologic agent introduced in clinical transplantation, belatacept, exerts its immunosuppressive effect through the inhibition of the co-stimulation signal. Phase III clinical trials demonstrated that the use of this drug was associated with an increased risk of PTLD with a prevalent localization within the CNS. Interestingly, the development of PTLD was significantly associated with donor's and recipient's EBV status. Indeed, PTLDs were observed more frequently in EBV– recipients receiving their kidneys from EBV+ donors [38].

Corticosteroids

Glucocorticoids have been an essential part of most immunosuppressive regimens since the dawn of clinical organ transplantation, but there are very few epidemiologic data on their effect on the development of post-transplant malignancy, although in non-transplant patients, corticosteroids were shown to significantly influence cancer cell phenotype [39]. Glucocorticoids have been, indeed, proposed to play a dual role in oncogenesis: a direct pro-oncogenic effect in lymphoid cells and an indirect effect on the ability of cancer cells to escape immunosurveillance. Indeed, glucocorticoids can enhance tumour cell resistance to immune response, inactivate B and T lymphocytes, reduce major histocompatibility class I antigen expression, leading to a reduction in the tumour immunosurveillance even at very low doses [40–43].

Anti-proliferative drugs

Azathioprine is an immunosuppressive drug that has been used in clinical transplantation for >30 years. Azathioprine might directly influence the development of melanoma and non-melanoma skin cancer through a direct synergism with UV light [44] in causing chronic oxidative stress and mutagenic DNA lesions. The *in vitro* data on the oncogenic potential of this drug were indirectly confirmed by registry data, reporting a decrease in skin cancer incidence after the introduction of cyclosporine and the subsequent reduction in azathioprine use in the face of a significant increase in the incidence of any other neoplastic disease [20].

Mycophenolic acid (MA) is a selective and reversible non-competitive inhibitor of inosine monophosphate dehydrogenase, a key enzyme in T- and B-lymphocyte proliferation. MA has been demonstrated *in vitro* to exert an anti-proliferative effect also in several cancer cell lines [45, 46], potentially suggesting an anti-neoplastic activity. This hypothesis was further confirmed by the observation of the prevention of adhesion-receptor-dependent tumour dissemination [47]. However, there are *in vitro* reports suggesting a potential mutagenic effect [48] and the induction of tumour cell invasiveness [49, 50]. Data from CTS registry and the Scientific Registry of Transplant Recipients (SRTR), however, suggest that MA use in kidney graft recipients is associated with a reduced risk of any cancer and, in particular, of PTLD [10].

Calcineurin inhibitors

The introduction of calcineurin inhibitor (CNI) deeply changed the world of transplantation and this class of drugs has been the cornerstone of immunosuppression for the last three decades. Several studies demonstrated that, apart from the effect on IL-2 expression, CNI exerts an array of effects potentially promoting the development and progression of neoplastic diseases including transforming growth factor β1 production and suppression of anti-tumour-specific immune responses [51, 52]. In addition, CNIs induce the expression of vascular endothelial growth factor (VEGF), leading to an increased tumour angiogenesis [53] and inhibit cancer cell apoptosis, through a calcineurin-dependent pathway [54, 55].

In this scenario, the two CNIs, cyclosporine and tacrolimus do not differ significantly [56, 57], although *in vitro* the tacrolimus oncogenic effects require higher doses than those currently needed to promote allograft acceptance [58]. Indeed, in patients without induction therapy, the cumulative PTLD incidence was lower in CsA- than in tacrolimus-treated patients [31]. On the other hand, in solid tumours there are no differences in the incidence rate between CsA- and tacrolimus-based immunosuppressive regimens [58]. It is conceivable that the higher rate of PTLD, a class of malignancies closely related to virus infection and, thus, highly dependent on the overall immunosuppression level, might be explained by the higher immunosuppressive efficacy of tacrolimus.

Mammalian target of rapamycin inhibitors

The development of an oncogenic state is a complex process involving the synergistic effects of multiple genetic mutations and external inputs, leading to the deregulation of cell signalling pathways involved in the control of cell growth and fate [59]. Mammalian target of rapamycin (mTOR) is a serine/threonine

kinase that plays a role as a key cell switch at the crossroads of multiple signalling pathways, influencing several cell metabolism- and growth-related processes [60] including protein translation, ribosome biogenesis, autophagy, transcription of many genes controlling the main biosynthetic pathways, and mitochondrial functions. The activity or expression of many signalling elements located upstream or downstream of mTOR is frequently altered in a large number of human neoplastic diseases. Indeed, a growing body of evidence suggests that the sensitivity of an array of human tumours to mTOR inhibition is, indeed, associated with the abnormal activation of the PI3K-Akt-mTOR pathway and/or with an altered expression of cell cycle regulatory or anti-apoptotic proteins [61–63]. On the basis of these observations, mTOR inhibitors have received growing attention over the last decade as the potential treatment of different types of cancer. The results of several clinical trials demonstrated that mTOR inhibition might induce a significant stabilization of progressive neoplastic diseases and even tumour regressions in a subset of patients [64–69].

The immunosuppressive effects of these drugs are directly dependent on the inhibition of mTOR complex 1 (mTORC1) kinase activity. mTORC1 inhibition can interfere with IL-2 effects and subsequently blunt alloantigen-induced activation of T- and B-cells. These drugs have been proved to effectively prevent acute rejection when included in different immunosuppressive regimens, in clinical solid organ transplantation [62, 64, 65]. After mTOR inhibitors' introduction in the clinical settings of solid organ transplantation, several studies investigated their dual role as immunosuppressive and anti-neoplastic drugs. Two studies demonstrated *in vivo* that sirolimus may inhibit tumour growth and its metastatic activity interfering with VEGF signalling in endothelial cells, thus suppressing tumour angiogenesis [61, 70]. Kohel *et al.* [62] reported that sirolimus can simultaneously protect allografts from rejection and inhibit tumour development and progression. It is noteworthy that the pro-neoplastic effects of CsA were counter-balanced by the simultaneous administration of sirolimus in different experimental models [61, 62]. In addition, a retrospective, registry-based study using the UNOS database demonstrated that maintenance of mTOR inhibitors-based immunosuppression is characterized by a significantly reduced risk to develop any *de novo* post-transplant malignancy or non-skin solid malignancy compared to CNI-based immunosuppressive regimen [71]. Interestingly, also the association of an mTOR inhibitor to a CNI was enough to significantly reduce the incidence rate of any *de novo* post-transplant neoplastic disease [71]. A particular interest has been dedicated on the effect of mTOR inhibition on the development and progression of post-transplant Kaposi's Sarcoma (KS), a rare malignancy with a close association with herpes virus 8 (HHV-8) infection. This indisputable link between the virus and the neoplastic disease led to a change in the virus name that is now known as KS-associated herpes virus. KS shows a dramatically higher incidence rate in transplant recipients compared with the general population with an SIR over 100. Also, after transplantation, the development of KS is related to HHV-8 infection [72]. This virus encodes a chemokine-like, G-protein-coupled receptor known to promote endothelial cell proliferation through the activation of the VEGF receptor Flk-1/KDR [72]. Since mTOR plays a key role in VEGF signalling pathways, leading to angiogenesis and VEGF is a key player in the pathogenesis of KS, this angiosarcoma was considered the best opportunity to confirm the anti-neoplastic effects of mTOR inhibitors [70, 73]. Several studies indeed suggested that mTOR inhibitors-based immunosuppression represents a valid option to prevent and treat post-transplant KS [74–79]. In addition, these human studies confirmed that the anti-neoplastic action of sirolimus was due to the inhibition of the Akt-S6K1 signalling pathway within the cancer cells, rather than to the reduction in the overall immunosuppression levels observed after CsA withdrawal and sirolimus or everolimus introduction [75, 79].

Screening of post-transplant malignancies

Primary prevention of post-transplant malignancies is a key goal in the follow-up of transplant recipients. From this perspective, screening is a strategic approach. However, screening for cancers has not been thoroughly evaluated in transplant recipients. Guidelines developed in the general population represent the reference, although they must be assessed for applicability to this population with their complex medical and social issues. Because of increased cancer risk, differences in diagnostic test performance, competing risks for deaths from causes such as cardiovascular disease and reduced overall life expectancies, validity of their recommendations is uncertain. It is, then, clear that, despite the difficulty of establishing primary studies in this population, good-quality trials are needed to address the issues of mortality benefits, harms, screening test accuracies and the cost-effectiveness of cancer screening in the transplant population. In the absence of such studies, an individualized approach to screening should be used and based on the individual's cancer risk, existing comorbidities and overall life expectancy.

Table 1 summarizes the suggestions for a standard approach to post-transplant screening of neoplastic disease, integrating the recommendations reported in the guidelines for screening of the general population and the epidemiologic information on the most frequent malignancies in this peculiar patient population.

Management of immunosuppressive therapy and post-transplant cancer

The risk of post-transplant neoplastic disease can be successfully reduced with a careful management of immunosuppressive

Table 1. Cancer screening in transplant recipients

Cancer type	Recommendations
Breast	Annual or biennial mammography for all women
Gastric and Colorectal	Annual FOBT and 3-yearly oesophagogastroduodenoscopy and flexible sigmoidoscopy for individuals older than 50 years and with a positive familial history
Cervical	Annual cytological cervical cancer screening and pelvic examination
Prostate	Annual digital rectal examination and PSA measurement in all male renal transplant recipients older than 40 years
Hepatocellular	α-Fetoprotein and ultrasound performed every 6 months in high-risk individuals
Skin	Monthly self-skin examination, total body skin examination every 12 months by expert physicians and dermatologists
Renal	Ultrasonography of the native kidneys every 6–12 months
PTLD-virus-related	Viral nucleic acid dosage every month until 6 months post-transplant, and every 6–12 months thereafter

therapy. The first consideration should regard the viral infection risk at transplantation, in particular, for those viruses known to be associated with post-transplant malignancies like EBV or Kaposi's Sarcoma Herpes Virus (KSHV). In patients at high risk for these infections, we should consider avoiding biologic agents, such as thymoglobulin or belatacept, that are well known to be associated with an increased risk of post-transplant neoplastic diseases directly linked with oncogenic viruses.

The second point to consider is that the experience with the different immunosuppressive regimens currently available clearly suggests that immunosuppressive therapies including mTOR inhibitors have a lower *de novo* malignancy risk, and that this risk further reduced if the regimen did not contain CNI. The final decision to include *ab initio* mTOR inhibition in a patient should be weighed mainly against the immunologic risk and, obviously, with the overall risk to develop a post-transplant neoplastic disease. Patients with an increased risk to develop malignancy-related morbidity and/or mortality after transplantation, including those with a clinical history of several non-melanoma skin cancers, a second transplant with a previous history of post-transplant PTLD or, in particular, KS, liver transplantation for hepatocellular carcinoma or a history of pre-transplant neoplastic disease might benefit from an immunosuppressive regimen characterized by a low malignancy risk. Since the use of mTOR inhibitors reduces overall rates of any post-transplant *de novo* malignancy and non-skin solid malignancy, these drugs should be seriously considered in the immunosuppressive regimen of these patients. In addition, since the association of mTOR inhibitors with CNI has been shown to achieve a significant reduction in the incidence of post-transplant malignancies, this immunosuppressive regimen may represent a valuable option to prevent neoplastic disease, in particular, for transplant recipients with a concomitant high immunologic risk.

Patients who develop post-transplant malignancies represent a serious challenge for transplant physicians. The management of immunosuppressive therapy in this setting is still debated. Although evidence-based guidelines are missing, the decision should consider the type and stage of malignancies along with actual graft function. Withdrawal of CNI and introduction of mTOR inhibitors is fully supported by the existing literature only for Kaposi sarcoma. Indeed, several studies report the regression of this neoplastic disease after CNI withdrawal and introduction of mTOR inhibitors. However, the use of mTOR inhibitors, instead of simply withdrawing immunosuppressive therapy, in patients with post-transplant malignancies can be considered as an option to preserve graft function and, at the same time, to reduce the effect of immunosuppressive therapy on neoplastic disease progression. Indeed, mTOR inhibitors allow a safe withdrawal of other immunosuppressive drugs with a demonstrated pro-oncogenic effect. In addition, mTOR inhibitors have been shown to present a synergistic effect with other anti-neoplastic agents. These findings may support the use of mTOR inhibitors as an adjuvant in the treatment of post-transplant solid tumours. However, the appropriate indication for the use of mTOR inhibitors in this setting should probably wait to be tested in clinical trials currently in development to investigate the efficacy of this type of drugs in different tumour types. In spite of recent advancement in the management of post-transplant malignancy management, including the modulation of immunosuppressive therapies and the use of mTOR inhibitors, further long-term clinical studies are warranted to establish an adequate balance prevention of graft rejection and progression of neoplastic diseases.

Conclusions

Currently, one of the unavoidable side effects of long-term immunosuppression is represented by post-transplant malignancy. In recent years, we realized that cancer might be considered as a major limitation in achieving optimal outcomes in organ transplantation. Thus, prevention of post-transplant malignancy-related morbidity and mortality must be considered a main end-point in solid organ transplant programmes. Thus, pre-existing donor- or recipient-associated neoplastic risk should be carefully examined and considered.

Epidemiologic data suggest that length of exposure to immunosuppression along with its intensity is clearly associated with the development of post-transplant malignancies, and that after cancer appearance, a more intense immunosuppressive therapy can induce an aggressive cancer progression in terms of accelerated growth and metastasis and subsequent lower patient survival. Several factors play a key pathogenic role in the association between immunosuppressive therapy and post-transplant malignancy development and progression. Two of these factors, and, probably, the most relevant, are that immunosuppression greatly increases the post-transplant risk by impairing immunosurveillance of cancer cells and facilitating viral infections closely related to the development of different neoplastic diseases. However, a direct and specific pro-oncogenic effect of immunosuppressive drugs might also play a pivotal role. The cancer promoting effect of CNI, independent of a reduced immunosurveillance, has been clearly shown in recent years, and currently mTOR inhibitors are the only class of immunosuppressive drugs that have been shown to exert simultaneously immunosuppressive and anti-neoplastic effects. Thus, to date, these drugs represent our best weapon to address the central issue of post-transplant malignancies although we still need long-term randomized, controlled clinical trial to definitively understand their true potential in this setting.

Conflict of interest statement

None declared.

(See related articles by Thakkar *et al*. Onconephrology abstracts and publication trends: time to collaborate. *Clin Kidney J* (2015) 8: 629–631 and by Lodhi *et al*. Thrombotic microangiopathy associated with proteasome inhibitors. *Clin Kidney J* (2015) 8: 632–636.)

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