REVIEW ARTICLE

POST RENAL TRANSPLANT MALIGNANCIES; A BASIC CONCEPT

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Background: Kidney transplantation remains the best possible solution for patients with chronic kidney disease, providing better long-term outcomes and drastically improving quality of life. However, it comes with its own set of risks. The use of immunosuppressives following renal transplants has been shown to increase the development of malignancies and infections, and the occurrence of post-transplant malignancies is now the third most common cause of death in transplant patients. This involves multiple mechanisms, including the carcinogenic tendency of some immunosuppressive drugs, along with the induction and promotion of post-transplant malignancies by certain viruses. The quantification of Cancer risk must be made an integral part of the overall management of transplant patients, and appropriate follow-up screening needs to be adopted. Kaposi's sarcoma, lymphoma, and non-melanoma skin cancers have a greater incidence. If a malignancy develops immediately after transplantation, it may have been transmitted from the donor; donor-transmitted and donor-derived tumours may be differentiated based on a two-year time limit. Immunosuppressive medications with carcinogenic tendencies, reduced immunological control of oncogenic viruses, and poor immunosurveillance remain the most important risk factors. The gravity of this situation is further exacerbated by the fact that not only is there an increased risk of developing these malignancies in the post-transplant period, but the prognosis is also worsened when compared to non-transplant patients. All transplant centers should therefore adopt a multidisciplinary approach including early detection and prompt treatment, to improve outcomes in transplanted patients.

Keywords: Chronic kidney disease; Immunosuppressives; Renal transplants

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INTRODUCTION

Kidney transplantation remains the best possible solution for patients of chronic kidney disease; not only does it provide a survival benefit, but also improves quality of life.[1,2] In countries like Pakistan, where dialysis survival is significantly lower than that of the Western world, these advantages of kidney transplantation also make it a cost-effective solution.

The increased risk of infections and malignancies due to the use of immunosuppressive medications following kidney transplants is considered to be one of the main causes of mortality and morbidity in transplanted patients.[3] With cardiovascular mortality being the number one cause of death in kidney transplanted patients, all such recipients are resultantly investigated for cardiovascular risks post-transplant. However, the occurrence of post-transplant malignancies is now the third most common cause of death, with some malignancies occurring more commonly in renal transplant patients than in the general population. One reason could be the carcinogenic tendency of some immunosuppressive drugs, irrespective of their immunosuppressive effect,[4,5] another being the induction and promotion of post-transplant malignancies by certain viruses.

The magnitude of this problem is probably far greater than what has been appreciated over the years. The quantification of Cancer risk must be made an integral part of the overall management of transplant patients, and appropriate follow-up screening and surveillance need to be adopted. All transplant programs should be cautious of the facts that the risk of developing a malignancy in the post-kidney transplant period is inversely related to age,[6,7] and further risk of developing a new cancer is 40% higher if there is a clinical history of a malignancy[8]. Kaposi's sarcoma, lymphoma, and non-melanoma skin cancers have a greater incidence, whereas the risk of multiple myeloma, prostate and ovarian cancers has not been seen to have increased.[9]

The gravity of this situation is further exacerbated by the fact that not only is there an increased risk of developing these malignancies in the post-transplant period, but the prognosis is also worsened when compared to non-transplant patients. The aggressive nature of these tumours in the transplant population leads to a lower mean survival rate, which was shown in the Israel Penn registry,[8] exemplified by the

mortality of breast cancer is 40% higher in kidney transplant patients as compared to the general population.[10]

The phenomenon of chimerism must not be neglected as it might help answer a few questions posed in evaluating the increased risk of developing malignancies in the post-transplant period. We can consider the transplant recipient a chimaera wherein two cellular populations exist. If a malignancy develops immediately after transplantation, it may have been transmitted from the donor; donor-transmitted and donor-derived tumours may be differentiated based on a two-year time limit. Donor-derived tumours do arise from donor cells but are not present at the time of transplant and are very rare.[11] There are a few reports where a tumour developed in the graft but originated from cells of the recipient; the process of metastasis cannot be confirmed but it still holds as an example of renal tumours of graft.[12]

The phenomenon of chimerism is quite interesting and studying it might help understand the development of malignancies in these patients, namely: how these chimeric cells transform into malignant cells, what the triggering factors could be, and what cells start the chimeric process. The fascinating concept that the migrated donor cells can give rise to a tumour of donor genotype in the recipient needs further elaboration.

Pathogenesis of post-transplant malignancy and potential role of viral infections

Long term management of kidney transplant patients involves the optimum maintenance of immunosuppression due to its role in reducing acute and chronic rejection along with being mandatory for allograft survival. The overall level of immunosuppression is the key factor leading to an increased risk of post-transplant malignancy.[13] This is confirmed by the fact that there is an increased risk of developing a secondary malignancy if the patient is treated for acute rejection during the first year of transplant, signifying an increased level of immunosuppression.[14] This increased level of immunosuppression allows for different pathways of cancer development to progress.

Moreover, there is an increase in virus-associated cancers due to the poor immunogenic control of such oncogenic viruses. Cancers in renal transplant patients caused commonly by viruses include Kaposi's Sarcoma (human herpes virus 8), lip, cervical, vulval, vaginal and anal cancers, Human Papilloma Virus (HPV) along with Post-transplant Lymphoproliferative Disorders (EBV), Human T-cell Lymphotropic Virus type 1 (HTLV1), and Merkel Cell Polyoma Virus (MCPyV) which causes Merkel Cell Skin Carcinomas.

Knowing the EBV serostatus of the donor and recipient before transplant is crucial, as 50% of PTLD are EBV-related. Furthermore, the risk of PTLD is increased 20-fold if the recipient is EBV- and the donor is EBV+.

Since the immune system of an individual is hampered post-transplant due to immunosuppression, there may be an accumulation of mutations that can no longer be repaired, resulting in the development of immunosuppression-related cancers. This is specifically true for skin cancers where cells lose their ability to repair ultraviolet radiation-induced DNA damage.

Although there is no concrete evidence to label a specific immunosuppressive agent to be more carcinogenic than others at present, experimental studies have shown Tacrolimus to increase the level of TGF-B, which promotes tumour progression and metastasis in cases of lung cancer, renal cell carcinoma and hepatocellular carcinoma.

CNIs can activate p53 which is attributed to cases of NMSCs, along with having a direct effect on tumour progression through TGF-b and IL 6 pathway overexpression.[15,16] The accumulation of mutations, inhibition of DNA repair, apoptosis of activated T cells, and apoptosis prevention of other cells by opening mitochondrial transition pores are all some of the proposed carcinogenic factors.[17] Mammalian targets of rapamycin (mTOR) are considered to have anti-tumour effects by causing cell cycle arrest and apoptosis.

The type of induction therapy given is another factor which can increase the risk of post-transplant cancers. T-cell depleting agents— both polyclonal and monoclonal—can also lead to an increased risk of post-transplant malignancies such as melanoma and PTLD.[18] The depletion of both T cells (CD4, CD8), which are crucial in adaptive antiviral immunity, can lead to an increased risk of virus-associated diseases. The concept of cancer development many years after the use of T cell depleting agents is not certain, however, it could be due to incomplete T cell recovery,[19] which leads to weakened immunosurveillance, and as a result, cancer development.[20,21]

Donor transmission

Several donor-transmitted malignancies have been reported in the literature which generally holds for deceased donor transplants. This is a very dreadful situation which can lead to metastatic disease in the recipient.[22] The most common cancers transmitted this way are, lymphomas, melanomas, renal and lung cancers. A donor history of melanoma, choriocarcinoma and lung cancer has a very high rate of transmission risk and should be avoided.[23]

Interestingly, it has also been observed that the greater the age of the patient and the period of dialysis, the greater the risk of post-kidney transplant malignancies.[24,25] Separately, recipients with a pre-transplant history of malignancy have an increased risk of developing de novo malignancies, along with a 30% increase in the possibility of death.[26]

The surveillance, diagnosis and treatment of post-transplant malignancies

The theory that early detection of any malignancy can lead to better outcomes holds in the transplant population as well. Unfortunately, there are no specific screening practices for solid organ transplants.[27] Most centers conduct age-appropriate screening in solid organ transplants as that in the general population. There is no consensus among the transplant community about the value of screening or the preferred modalities either. More frequent screening as compared to the general population has been advised for skin cancer, liver cancer, cervical cancer and anogenital cancer.

Skin cancers

The most common malignancy seen after kidney transplant is skin cancers, with Basal cell carcinoma and Squamous cell carcinoma making up 90% of these cases. The incidence of Kaposi's sarcoma also increases, especially in those who are at risk.[28] There are multiple risk factors involved in the pathogenesis of post-transplant skin cancers, such as exposure to ultraviolet radiation, older age, race, sex, HPV and certain carcinogenic immunosuppressive drugs like cyclosporin and azathioprine.

It is essential to educate all patients about self-assessment and encourage them to adopt general preventive measures like the use of sunscreen and hats, along with avoiding exposure to ultraviolet radiation during peak sun hours. As part of a surveillance program, these patients should be seen at least twice a year for up to five years, and then annually thereafter. A more intensive approach can be devised for patients with specific skin types and ethnicities.

Patients of Squamous cell carcinoma in situ get maximum benefit from topical fluorouracil, imiquimod cream, and surgical excision. Photodynamic therapy has also been used with promising results. Moh's micrographic surgery with clearance of margins cures 90–100% of patients with biopsy-proven Squamous cell carcinoma. Primary radiation therapy is reserved for inoperable cases. As for those who develop early onset or multiple squamous cell carcinomas, chemoprophylaxis with retinoids and nicotinamide can be considered.

Reduction of immunosuppression remains the cornerstone of treatment for Kaposi's sarcoma, along with switching a calcineurin inhibitor to an mTOR which can restore T cell immune activity against HHV8.

Malignant melanoma has the highest mortality rate if developed after transplantation, with white race, older age, and pre-transplant melanoma being the most prominent risk factors. According to the National Comprehensive Cancer Network guidelines, primary treatment is surgical excision ensuring adequate margin clearance.

Cervical cancers

The presence of precancerous lesions under the influence of immunosuppression in the post-transplant period can lead to an increased incidence of cervical cancer—two to threefold higher than in the age-matched general population.[29] Whether or not we need more intense screening for such patients is unclear, and current evidence does not support the need. International guidelines do not have consensus, with the American Society of Transplantation recommending annual pelvic exams and pap smears, and patients in the UK being screened like the general population. The human papillomavirus (HPV) vaccine, which is an inactivated vaccine, can be considered before and after transplantation as it has shown a reduction of dysplasia in the general population.[30,31]

Colorectal cancer

Screening guidelines still have no consensus, even though the risk of colorectal cancer is two to three times higher in kidney transplant patients. The recommendations are to treat patients like the general population, however, those above 55 can proceed with annual colonoscopy if feasible.

Renal cell cancers

Renal transplant recipients have an increased risk of developing renal cell carcinoma in native kidneys, especially those who have a family history of renal cell carcinoma, acquired cystic disease, prolonged duration of haemodialysis, or a history of analgesic nephropathy.[32] Transplant recipients with a primary disease of glomerular origin, hypertensive nephrosclerosis, or vascular disease have a greater risk than those with diabetes or autosomal polycystic kidney disease as the cause of ESRD. Management of these tumours is according to urological guidelines and depends upon staging and risk stratification. The outcome is comparable with the general population, with a 5-year patient survival rate of 68% to 88%. Renal cell carcinoma of graft is hardly seen, with an incidence of 0.1% and if possible, nephron-sparing surgery offers the best possible results. A patient-centred approach should be adopted to ensure optimum care. Screening is usually not recommended and the choice of modality for screening is also questionable, as ultrasounds are operator-dependent and can miss small lesions.

Post-transplant lymphoproliferative disorders (PTLD)

The presentation of PTLD is quite diverse–it can present as uncomplicated infectious mononucleosis or as haematological malignancies. EBV is a common virus and most patients acquire it during early childhood when it infects the B cells and remains dormant. After transplantation, the virus is reactivated due to depressed T cell function and can cause PTLD. The risk of PTLD is highest during the first 12 months and thereafter decreases until the fifth year of transplant. Pre-transplant

EBV seronegative status is the most important risk factor for early development of EBV-positive PTLD. It is recommended that high-risk patients (recipient negative/donor positive), should undergo EBV viral load measurement after transplantation, which should be done immediately after, monthly for six months, and then every three months for one year respectively. Overall immunosuppression should also be reduced if EBV tit ers rise significantly any time after transplant and should especially be monitored if the patient is treated for rejection.

The main objective of treatment is a complete cure, the first step for which is the reduction of immunosuppression. The overall survival (5-year survival of 60%) can be improved with standard management which includes Rituximab and other chemotherapeutic agents like cyclophosphamide, vincristine, doxorubicin and prednisolone.

Other malignancies

There are no definitive screening protocols for CA prostate, CA breast, or testicular tumours. Self-examination is advised for breast cancer and testicular tumours. Breast cancer screening should be done as in the general population, i.e., self-examination and mammography after every three years.[33]

Adoptive immunotherapy

One way of dealing with EBV-associated PTLD is the phenomenon of adoptive immunotherapy. EBV-infected B cells circulate in the blood and stimulate a complex host response, leading to the development of T cells specific for EBV-encoded nuclear antigens EBNA2, EBNA6 and latency membrane protein (LMP1 and LMP2). Post-transplant suppression of T cell immunity leads to the development of polyclonal, oligoclonal, or monoclonal EBV antigen-expressing lymphoproliferative disorders or B cell lymphomas. In such a scenario, adoptive transfer of peripheral mononuclear blood cells or EBV-specific T cells from a seropositive donor has shown regression of EBV-associated lymphoma in several cases.

These EBV-specific cytotoxic T cells or donor lymphocytes are used to kill dividing B cells. Most of this information is based on retrospective studies done on hematopoietic cell transplantation recipients. Remission and prevention have been achieved in 90% of patients suffering from an EBV-associated post-transplant lymphoproliferative disorder.[33,34] The most noted complication of adoptive immunotherapy is acute and chronic Graft Versus Host Disease (GVHD), which is primarily seen with donor lymphocyte infusion but is not associated with EBV-specific cytotoxic T lymphocytes.[35]

The use of adoptive immunotherapy is reserved for patients of EBV-associated PTLD who do not respond to initial therapy. Despite looking like an attractive approach, this facility is not available at most centers, a fact which minimizes its utility.

Waiting time for transplantation after successful treatment of primary malignancy

This is one of the most difficult decisions, as evidence is insufficient and every case needs to be individualized. Most guidelines advise a cancer-free waiting time of 2–5 years, depending upon the cancer type. However, it seems that the risk of tumour recurrence depends on the type of tumour, histological sub-classification, and genetic markers rather than any specific waiting time. Not to mention, staying on dialysis also increases the risk of cancer recurrence. In patients with a low risk of recurrence, a short waiting time is justified.

It has been suggested that for certain PTLDs, a waiting period of one year after treatment is appropriate for re-transplantation.[36] In the future, genetic profiles of patients will undoubtedly help in making such decisions, as has already been reported in a patient with ESRD and breast cancer who underwent transplantation long before the suggested waiting time, because the genomic profile confirmed her to be low risk.[37] It seems more reasonable that such patients should be discussed on a case-to-case basis with an oncologist, taking into account the following considerations: the potential for recurrence according to its type grade and staging, co-morbidities, and age of the patient.

CONCLUSION

Post kidney transplant malignancies have become one of the most common causes of death in kidney transplant recipients. Immunosuppressive medications with carcinogenic tendencies, reduced immunological control of oncogenic viruses, along with poor immunosurveillance remain the most important risk factors. All transplant centers should therefore adopt a multidisciplinary approach for cancer screening, early detection, and prompt treatment of these malignancies as doing so may improve outcomes in these patients.

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