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Post-Transplant Malignancy: Unveiling the Burden and Management Strategies

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Abstract

Post-transplant malignancy is a significant long-term complication following kidney transplantation. Although immunosuppressive therapy has led to a decrease in acute rejection rates and improved graft survival, it has also been associated with an increased risk of malignancy. While some post-transplant malignancies, such as lymphoma and skin cancer, are well-recognized, others remain less understood. Compared to malignancies affecting the general population, post-transplant malignancies often have distinct clinical features, treatment challenges, and outcomes. Additionally, the prognosis and survival rates of cancer in transplant recipients are lower than those in the general population. Careful screening of patients and donors before transplantation is recommended to detect any underlying, pre-existing malignancies.

Additionally, surveillance, diagnosis, and treatment of post-transplant oncogenic viral infections are critical for preventing and managing post-transplant malignancies. Unanswered questions surrounding post-kidney transplant malignancy include the role of pre-transplant screening, the optimal immunosuppressive regimen, the impact of viral infections such as Epstein-Barr virus and human papillomavirus, and the long-term outcomes of patients with malignancies. There is a need for further research to determine the most effective ways to monitor and prevent post-transplant malignancy, as well as to improve treatment options for those affected. In summary, post-kidney transplant malignancy is a complex and challenging issue that requires ongoing investigation to fully understand its mechanisms and to develop effective prevention and treatment strategies.

Keywords: Post-transplant malignancy (PTM); Kidney transplant recipient (KTR); Immunosuppression; Epstein-Barr virus; Human papillomavirus

Introduction

Post-transplant malignancy (PTM) is a significant and challenging complication of solid organ transplant (SOT) and hematopoietic stem cell transplant (HSCT) recipients. Generally, PTM accounts for 5-15% of all malignancies in transplant recipients, and the risk of having PTM is 2-4 folds higher than that of the general population. Additionally, PTM is the second leading cause of death after infection in transplant recipients [1]. Transplant recipients are at an increased risk of PTM due to lifelong immunosuppression for preventing rejection, which also increases their susceptibility to oncogenic viral infections [1]. The PTM incidence varies according to different risk factors such as age, sex, ethnicity, type of transplanted organ, immunosuppressive regimen, and the time since transplantation [2]. For example, the incidence of post-transplant lymphoproliferative disorder (PTLD) following solid organ transplantation ranges from 1% to 20%, while the incidence of post-transplant lymphoproliferative disorders (PTLD) following hematopoietic stem cell transplantation ranges from 2% to 15% [3]. Moreover, the pathogenesis, diagnosis, and management of PTM are complex and require a multidisciplinary approach. This article aims to review the current knowledge on PTM, focusing on the viral infections associated with its development, diagnosis of PTM, prevention, management, and the role of adoptive immunotherapy in the treatment of these malignancies.

The Magnitude of the Problem and Unanswered Questions

The most common de novo PTMs are non-melanoma skin cancers, followed by lymphoproliferative disorders (PTLDs),

which represent 40-60% of all PTMs [4-7]. The most common viruses associated with PTM are Epstein-Barr virus (EBV), human papillomavirus (HPV), human herpesvirus-8 (HHV-8), hepatitis B virus (HBV), and hepatitis C virus (HCV). However, the role of other viruses in PTM pathogenesis remains unclear [8]. Nevertheless, many questions remain unanswered regarding the mechanisms that lead to post-transplant malignancy, the optimal strategies for surveillance and management, the optimal immunosuppressive regimen that balances the risk of graft rejection with the development of PTM and the long-term consequences of recipients with post-transplant malignancy.

Epidemiology and Incidence of PTM

Solid organ transplant is associated with an increased risk of a varied range of malignancies [8-10]. Over 175,000 solid organ transplant recipients were examined in an extensive cohort study between 1987 and 2008 [9]. A total of 10,656 cases of malignancy were recognized, corresponding to a standardized incidence ratio (SIR) of 2.1 (95% CI 2.06-2.14) and an excess absolute risk of 719 cases per 100,000 person-years. There were more than 30 primary sites with a significantly increased malignancy risk. Compared with the general population, there was a fivefold or greater increase in the risk of tumors such as Kaposi sarcoma, skin tumors, lymphomas, liver, kidneys, melanoma, lung, pancreas, colon, and rectum [9]. In contrast, primary malignancies in the oral cavity, salivary glands, larynx, pharynx, esophagus, stomach, biliary tract, urinary bladder, thyroid, penis, testis, vulva, soft tissue sarcomas, myeloid leukemia, plasma cell neoplasms increased, but to a lesser degree [9].

Certain cancers can be linked to certain transplanted organs, such as lung malignancy is almost threefold higher among lung transplant recipients, whereas liver and kidney transplant recipients are more likely to develop liver and kidney cancers respectively [8-14]. Additionally, certain types of post-transplant skin cancers, such as Kaposi sarcoma occur commonly in the Mediterranean population, such as Jewish, Arabs, Caribbean, or African descents, probably because of the geographical distribution of HHV-8 [15,16]. Recently a standard incidence ratio (SIR) is used to illustrate the fold-increased risk of cancer among kidney transplant recipients (KTRs) compared to age-matched controls in the general population [17]. The Standard Incidence Ratio (SIR) for common malignancies post-kidney transplantation is illustrated in the following table and the epidemiology with a description of certain malignancies is illustrated in Table 2.

Table 1: The Standard Incidence Ratio of Selected Cancers After Kidney Transplantation.

SIR > 5	SIR 2-5	SIR < 2
Kaposi's sarcoma	Cervical	Breast
non-melanomatous skin	Thyroid	Ovarian
PTLD/NHL	Melanoma	Uterine
Kidney	Oesophageal	Pancreatic
Vulvar	Multiple myeloma	Brain
Penile	Leukaemia	Prostate
Anogenital	Oropharyngeal	Testicular
Liver	Bladder	Lung
Lip	Colon	

Abbreviations: NHL, Non-Hodgkin Lymphoma; PTLD, post-transplant lymphoproliferative disorder; SIR, standard incidence ratio. Retrieved from Asch WS. Advances in Chronic Kidney Disease. 2014 Jan 1;21(1): 106-113.[10]

Table 2: In the following table are examples of the most common malignancies encountered in transplant recipients, including risk factors, screening recommendations and general management [1,8,10,15-17,36-44].

Type of cancer	Incidence	Description	Average period post-transplant	Screening	Treatment
Skin cancers	Following transplantation, the SIR for squamous cell carcinoma significantly exceeds that for basal cell carcinoma (i.e., the ratio reverses compared to the general population)	Commonly are squamous cell (SCCs) and basal cell carcinomas. Other skin cancers can occur and include melanoma, Merkel cell carcinoma, and Kaposi sarcoma (KS).	Within 10 years of transplant.	Regular self-examination. Dermatology referral for a full-body skin examination every 1- 2 year.	Surgery For SCCs (Mohs surgery, if not available then conventional surgical excision). Organ transplant recipients and immunocompetent patients are treated similarly for basal cell carcinoma (BCC), melanoma, and Merkel cell carcinoma.

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Kaposi sarcoma (KS)	People of Mediterranean, Jewish, Arab, Caribbean, or African descent are most likely to develop posttransplant KS. The geographic distribution of human herpesvirus 8 (HHV-8/ KS-associated herpesvirus) contributes to this. Male to female ratio is 3.3:1, and the average age of diagnosis is 43 years.	Angiomatous lesions predominantly affect the legs, causing lymphedema.	13- 21 months post-transplantation		KS may respond to immunosuppression reductions or discontinuations. Converting CNI to sirolimus is useful. Additional treatment options are similar to those available for the general population.
Lymphoproliferative disorders (PTLD)	The rate of PTLD in KTRs is nearly 1% to 4%.	Is a spectrum of diseases that range from benign lymphoproliferation to metastatic neoplastic lymphocyte growths. Non-Hodgkin lymphoma is the most common type.	>80% of PTLDs occur during the first-year post-transplantation.	Testing of serum EBV PCR once during the first week post-transplant, then at least monthly for the initial 3-6 months, then every 3 months until the end of the first post-transplant year.	Treatment options for PTLD range from immunosuppression reduction to aggressive chemotherapy with rituximab-CHOP.
Anogenital cancers (involving i.e., anus, perianal region, vulva, scrotum, penis, or perineum)	2-3% of total malignancies in transplant recipients	Multiple Pigmented papular lesions or extensive lesions, with concurrent cervical cancer in one-third of whom. may resemble genital warts.	Commonly within 84-112 months	Ob/Gyn examination for anal, vulvar, and vaginal lesions. Additionally, Pap smears are performed every 1-3 years. post-transplantation	In situ, malignancies can be managed with laser therapy, electrocautery, or topical fluorouracil. Reducing the immunosuppressive regimen is useful. Invasive tumours require wide local excision (e.g., radical vulvectomy), with inguinal lymphadenectomy for tumours >1 mm thick and adjuvant therapy in selected patients.
Lung cancer	The incidence is high among recipients of heart and lung transplants, probably related to the high incidence of cigarette smoking leading to heart and lung disease.	Cancer occurs mainly in the residual native lung		A low-dose helical CT (Grade 2B) is recommended for adults aged 50-80 years old who smoke or quit smoking within 15 years and are at risk of lung cancer due to smoking. Otherwise, screening is not recommended in other patients by many guidelines.	Generally, lung cancer patients undergoing heart or lung transplants are treated similarly to those without transplants. However, Immune checkpoint inhibitors should be avoided as they may cause rejection.
Liver cancer	The risk is higher among liver transplant		Commonly occurs within the first 6 months post-transplantation.	Those with recurrent viral hepatitis and who progress to bridging fibrosis or cirrhosis should undergo abdominal ultrasound + alpha-fetoprotein (AFP) measurement every six months and/or annual magnetic resonance imaging (MRI).	There is a need for a multidisciplinary management algorithm. A combination of a reduced CNI and a mammalian target of rapamycin inhibitor can be considered with the staging of tumours. Sorafenib may confer survival benefits but is associated with significant toxicity in patients with disseminated recurrence. Surgical resection, ablation, or regional treatments are available for intra- and extra-hepatic oligo-recurrences.
Kidney cancer	Those who have undergone prolonged periods of dialysis are more likely to develop carcinoma of the native kidneys. The incidence is approximately 100 times higher than expected. Rarely, kidney tumours can develop in transplanted kidneys.			Generally, screening is not recommended by most guidelines, however, Ultrasound imaging is accurate but operator-dependent	RCC that develops from a transplanted kidney can be managed in several ways. A total transplant nephrectomy can be curative in patients without metastatic disease, although dialysis must be resumed. In cases of nonmetastatic RCC< 4 cm in size and located peripherally, nephron-sparing surgery may be considered. Patients with metastatic disease should stop immunosuppression, undergo transplant nephrectomy, and receive immune therapy.

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Colorectal	There is no clear evidence that transplant recipients are at a higher risk for colorectal cancer after transplant, compared to public. However, a cohort of Korean transplant recipients showed an increased risk for advanced neoplasia by 12-fold.			Screening colonoscopy and fecal occult blood test (FOBT) as suggested for the general population. The screening process should begin at a younger age than recommended for the general population.	The treatment of early-stage colorectal cancer is well-established in the general population, such as surgical resection of localized tubular adenomas, or endoscopic mucosal resection of high-grade tubular adenomas. Adjuvant agents, however, are nephrotoxic and should be avoided or dose adjusted.
Breast cancer	It is estimated that the SIR for breast cancer in KTRs increases modestly after transplantation, despite being so common in the general population.			Regular self-examination. Mammography for KTR females > 50 years of age every 1- 3 year.	Solid organ transplant recipients are generally treated in a similar way as the general population when dealing with breast cancer. This includes Surgery, Chemotherapy, Radiotherapy, and Hormonal therapy, however, there is no data on Targeted therapy such as Tyrosine kinase inhibitors of HER2 anti-VEGF therapy. Additionally, dosage reduction and/or changing immunosuppressant is required.
Prostate cancer	An increased incidence of prostate cancer occurs in KTRs and is diagnosed at an earlier age.	84% are diagnosed with localized disease. KTRs, however, seem to progress more rapidly after diagnosis and their disease-specific survival is significantly shorter than the general population at stage II, III, or IV.	The average stage at diagnosis among KTRs is the same as in the general population	To date, there are no standard screening regimens or established guidelines, however, The AST and the European Expert Group on Renal Transplantation do encourage annual screening with PSA measurement and digital rectal exam in all-male KTRs > 50 years old	Almost similar to the general population. Most surgical approaches have been described in RTRs, including open radical retropubic prostatectomy, perineal radical prostatectomy, minimally Invasive Radical Prostatectomy, including Laparoscopic and Robotic-assisted laparoscopic radical prostatectomy. Radiation therapy has been used to treat prostatic cancer in KTRs, however, is often avoided due to risks of allograft injury, ureteral injury, and urethral strictures. In KTRs, a paucity of data exists regarding the use of other treatment modalities (proton beam therapy, cryotherapy, high-intensity focused ultrasound, hormonal therapy, and stereotactic guided radiation therapy). Prostate brachytherapy can also be performed safely and effectively in patients who are poor surgical candidates.

Risk Factors for PTM

The higher incidence of malignancies in transplant recipients has been linked to several factors, including the type and duration of immunosuppressive drugs, sun exposure, concomitant viral infections, environmental factors, and genetic susceptibility. Moreover, there have been rare cases in which malignancies have been transmitted from donors.

Immunosuppression

Immunosuppression appears to be the primary risk factor for posttransplant malignancy. [18] Based on a study of over 50,000 kidney and heart transplants, the PTLD rates were mostly in the first year, with the maximum intense immunosuppression, and fell by approximately 80% thereafter [19]. Similarly, Caforio AL et al. found in another analysis that the episodes of graft rejection during the first-year post-transplantation may raise the risk of developing secondary malignancies, possibly because of the higher level of immunosuppression required to treat rejections [20].

Immunosuppressive Agents Seem to Influence the Risk of Malignancy Differently, As Follows:

Antibody therapy: OKT3 and anti-lymphocyte agents, which target T lymphocytes, specifically predispose patients to PTLD induced by Epstein-Barr virus (EBV). Alternatively, Antibody

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therapy targeting B lymphocytes (such as rituximab) may reduce the incidence of lymphoproliferative disorders and is used as first-line therapy for PTLD [8].

Calcineurin inhibitors: It appears that cyclosporine promotes cancer progression in animal models, primarily by producing transforming growth factor-beta (TGF-beta), promoting tumour growth in immunodeficient animals [21]. Additionally, cyclosporine has been reported to increase proangiogenic effects by stimulating vascular endothelial growth factor expression. [22]. There is also an increase in interleukin-6, which may facilitate B-cell growth in response to EBV [22]. Similarly, TGF-beta levels appear to rise with tacrolimus, which has been linked as well to tumour growth [23,24].

Azathioprine: In particular, azathioprine has related to an increased risk of cutaneous squamous cell carcinoma after transplantation.18 Through DNA intercalation, the mechanism of action is postulated to be an inhibition of repair splicing and induced codon misreading [8].

Mycophenolate Mofetil: Through inhibition of inosine monophosphate dehydrogenase, mycophenolate mofetil impairs lymphocyte function by blocking purine biosynthesis.[18,25] However, based on data from two large registries, mycophenolate-versus non-mycophenolate-based therapy was accompanied by a non-significant decrease in the risk of malignancies in some populations [26], probably as a consequence of reducing acute rejection with mycophenolate mofetil, the need for higher doses of immunosuppressive agents is reduced, which, in turn, results in a lower malignancy risk.

Viral Infection

At least four viruses might be cocarcinogenic in the transplant population.

Epstein-Barr virus (EBV): Lymphomas are among the most common complications in patients infected with EBV infection [3,4,8].

Human herpesvirus 8 (HHV-8) and Kaposi sarcoma: almost all forms of Kaposi sarcoma (KS) are infected with HHV-8, including classic KS, AIDS KS, endemic KS, and post-transplant KS, with serological evidence of HHV-8 infection [8,16,18]. HHV-8 can be transmitted from a donor to recipients of kidneys and cardiac transplants.[13,27] Infection with HHV-8 is essential but is not sufficient for KS to develop. Cofactors such as transplant-related immune dysfunction play a crucial role. Identifying high-risk patients before transplantation with antibodies might be useful, especially in high-seroprevalence areas [28].

The Merkel cell polyomavirus (MCV) is believed to contribute to Merkel cell carcinoma [8].

The human papillomavirus infection (HPV) has a potential role in the pathogenesis of head and neck squamous cell carcinomas as well as cervical and anogenital cancer [8].

Additionally, viruses such as HBV and HCV are associated with hepatocellular carcinoma (HCC) in transplant recipients [17].

Donor Transmission

The transmission of malignant cells from donors is rare but might result in metastatic cancer in immunosuppressed transplant recipients [29,30]. The risks of having an undetected malignancy in a donor and the risk of transmitting cancer were 1.3% and 0.2%, respectively, in a single kidney transplant centre survey [30]. Cancer type and extent are important factors to consider in determining the risk of inadvertent transplantation of malignant cells. There have been documented cases of melanoma, KS, cancer of the breast, lung, kidney, rectum, colon, and glioblastoma multiforme being transmitted to recipients [30]. Comparatively, the transmission of non-melanoma skin cancers and some CNS tumors (excluding a medulloblastoma) appears to be rare, and the risk appears low among donors with a history of cancer but without signs of current disease [31]. Conversely, melanoma and choriocarcinoma are associated with high transmission rates, with early and almost universal deaths [8].

Pathogenesis of Post-Transplant Malignancies

Post-transplant malignancies (PTMs) are biologically distinct from malignancies that occur in the general population, with differences in their incidence, clinical behavior, and pathogenesis. The pathogenesis of PTMs is multifactorial and involves both traditional risk factors for cancer and the unique immunological milieu of the transplant recipient, such as viral infections, genetic susceptibility, environmental factors, and the use of immunosuppressive drugs [32]. The immune system plays a critical part in the development and progression of cancer. In most cases, as mentioned earlier, post-transplant malignancy is related to viral infection.

These viruses can induce/promote the development of post-transplant malignancy by various mechanisms, including direct oncogenic effects, immune dysregulation, and chronic inflammation. [8,32] EBV is the most common virus associated with post-transplant malignancy. It is implicated in the development of PTLD, Hodgkin's lymphoma, and nasopharyngeal carcinoma among transplant recipients. [3-5] EBV infects B cells, transforming them into lymphoblastoid cells, leading to uncontrolled proliferation and malignant transformation. In addition, EBV can evade hosting immune surveillance by downregulating the major histocompatibility complex (MHC) molecules and inhibiting T-cell function, leading to immune dysregulation and increased risk of post-transplant malignancy [32,33].

HPV is another virus associated with post-transplant malignancy, particularly cervical and anogenital cancer. HPV infects epithelial cells and can cause persistent infection, leading to dysplasia and malignant transformation. In transplant recipients, the risk of HPV-related malignancy is increased due to the use of

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immunosuppressive drugs, which impair cell-mediated immunity and promote viral persistence [34]. HBV and HCV are viruses associated with hepatocellular carcinoma (HCC) in transplant recipients. Chronic viral infection can cause chronic inflammation and cirrhosis, leading to an increased risk of HCC [17]. In addition, Immunosuppressive therapy post-transplantation causes a state of chronic immune suppression, which impairs immune surveillance against tumor cells. This leads to a reactivation of latent viruses and the development of PTMs [35].

The incidence of PTMs varies based on the type of transplanted organ, with the highest rates observed among lung, heart, and kidney transplant recipients [36]. PTMs also tend to occur earlier in the post-transplant period compared to malignancies in the general population. This is likely due to the immunosuppressive therapy required to prevent rejection of the transplanted organ, which creates a permissive environment for tumor growth [36]. The surveillance, diagnosis, and management of post-transplant viral infections is associated with the potential to develop malignancy. Effective surveillance, diagnosis, and treatment of post-transplant viral infections are critical in preventing the development of PTMs. Transplant recipients are at increased risk of viral infections due to the use of immunosuppressive therapy, which impairs their ability to mount an effective immune response to viral pathogens. The risk of viral infections is highest in the early post-transplant period when immunosuppression is most intense [32-36]. Thus, surveillance for viral infections in transplant recipients should begin pre-transplantation and continue throughout the post-transplant period. Pre-transplant screening for viral infections is important to identify seropositive recipients who may require prophylactic antiviral therapy after transplantation. Post-transplant surveillance should include regular monitoring of viral load and serology for viruses associated with PTMs. Solid organ transplant recipients should undergo more frequent screenings than the general population for certain malignancies, such as skin cancers, cervical, anogenital cancer, and liver cancer. There is, however, a lack of direct evidence to support specific screening practices for solid organ transplant recipients [37].

The Diagnosis of Various Post-Transplant Viral-Associated Malignancies

The diagnosis of post-transplant malignancies requires a high index of suspicion in the context of the patient's medical history, clinical presentation, and imaging studies. Furthermore, the diagnosis of viral infection in transplant recipients can be challenging because of the atypical presentation of viral illness in immunocompromised patients. Diagnostic tests such as polymerase chain reaction (PCR) and serology could be used to recognize viral infections. Imaging studies such as computed tomography (CT) and magnetic resonance imaging (MRI) may also be done to evaluate the extent of viral-associated disease [1,2,10].

EBV-associated post-transplant lymphoproliferative disorder (PTLD) can present with a wide range of symptoms, including fever, lymphadenopathy, and organ dysfunction. The diagnosis of PTLD is based on histologic inspection of tissue samples obtained by biopsy or cytologic examination of fine-needle aspirates. The histologic subtypes of PTLD include early lesions, polymorphic PTLD, and monomorphic PTLD. In addition to histologic analysis, serologic testing for EBV viral load and DNA can aid in the diagnosis of PTLD. [3-5,45] On the cancer and, HPV-associated post-transplant malignancies, including cervical, anal, and oropharyngeal cancers, are diagnosed using various screening methods, including Papanicolaou (Pap) tests, human papillomavirus DNA testing, and colposcopy.

Table 3: Preventing Post-Transplant malignancies begins with general preventive measures such as [8,36].

Carefully screen the patient and donor for preexisting malignancies before transplantation.
Avoid excess immunosuppression.
Uses of sunscreens (SPF 15^{+}), protective clothing and avoid the sun during sun-peak hours.
HPV vaccination for high-risk patients, HPV vaccine is preferably to be given pre-transplantation, however its safe if given post-transplant though immunogenicity and safety profile lacking
Prophylactis antiviral therapy for EBVseronegative recipients receiving organs from seropositive donors.
Treating HBV and HCV infections can reduce the risk of post-transplant malignancies

In addition to screening, HPV-associated malignancies are diagnosed using tissue biopsies for histologic analysis. Enrolment in the HPV vaccination program should be encouraged [10,34,36,46]. Hepatitis B and C virus-associated post-transplant malignancies are diagnosed using serologic testing for viral markers, including hepatitis B surface antigen (HBsAg) and hepatitis C virus PCR. Imaging studies, including computed tomography (CT) and magnetic resonance imaging (MRI), can assist in the diagnosis of HCC.[17] Antiviral therapy is the cornerstone of treatment for viral infections in transplant recipients. Antiviral therapy can prevent the development of PTMs by suppressing viral replication and reducing the viral burden. Antiviral therapy is highly effective when initiated early in the course of the infection before the development of significant organ damage.

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Preventive Therapy and Treatment of Post-Transplant Malignancies

The prevention of post-transplant malignancies involves minimizing the patient's exposure to risk factors, including viral infections through optimizing immunosuppressive therapy, general preventive measures and screening for malignancies (Table 3).

Management of PTMs

Reduction/ Cessation or Modification in Immunosuppression

Immunosuppressive therapy can be reduced in kidney transplant patients diagnosed with PTM since the rejection of the graft is not a fatal event. This approach may result in the regression of a few tumors, such as some forms of lymphoma, skin cancer and Kaposi sarcoma (KS), where reducing exposure to CNI may be particularly important [6,8,47]. It is unclear how to reduce immunosuppression in this setting, and strategies may vary based on the type of cancer and organ transplantation. The majority of data evaluating the effectiveness and safety of reducing immunosuppression in transplant recipients with de novo cancer comes from observational studies.

Generally, several approaches can be used: [8, 48-50]**.**

For transplant recipients with de novo cancers (other than KS/PTLD), it is recommended to discontinue the antimetabolite rather than discontinuing CNI or switch to mTOR inhibitors. Double therapy with prednisone and a CNI is less likely to cause rejection than combining prednisone with an antimetabolite.

In well-matched transplant recipients, such as 0-HLA or 0-B, 0-DR mismatched recipients discontinue the CNI instead of the antimetabolite. The combination of antimetabolites and prednisone minimizes the risk of rejection and avoids the nephrotoxicity and malignancy potential associated with CNI.

Post-transplant KS patients should switch from a CNI to an mTOR inhibitor, rather than discontinuing their antimetabolite.

Clinical Advantages of Mtor-Inhibitors Therapy Over Other Immunosuppressants

Multiple studies have linked sirolimus to reduced malignancies, including the CONVERT study in which individuals who received sirolimus at 12 and 24 months were significantly less likely to develop malignancies than those on CNI [51-53]. Furthermore, Campistol JM et al. reported effective regression of Kaposi's sarcoma and PTLD after replacing CNI with mTOR inhibitors with no changes in renal function.[50] Upregulation of adhesion molecules and alteration of tumour cell phenotype are believed to be responsible for this anti-tumor effect [54]. Additionally, mTORI can inhibit tumor cell growth in preclinical studies. These activities may be mediated through inhibiting p70 S6K (which decreases the proliferation of tumor cells), cyclins-d1 (which arrests the cell cycle) and interleukin-10 (which decreases Jak/STAT stimulation in tumor cells) [55,56].

Furthermore, it inhibits the proliferation of T and B cells affected by HTLV-1 and EBV [51,56]. Based on a meta-analysis of kidney and kidney-pancreas transplant recipients, Sirolimus reduced the risk of malignancy by 40% and non-melanoma skin cancers by 56%.57 However, sirolimus was associated with a higher mortality risk, driven primarily by cardiovascular and infection-related events.

Cancer Specific Treatment

The treatment of post-transplant malignancies depends on various factors, including the type of malignancy, the severity of the disease, and the recipient's overall health. Treatment selections include surgical resection, radiation, chemotherapy, and immunotherapy (Table 2). Solid organ transplant recipients who develop a de novo cancer post-transplant can generally be treated with the same therapies as non-transplant patients without fear of organ rejection. One exception is checkpoint inhibitor immunotherapy (cytotoxic T-lymphocyte antigen 4 and programmed cell death 1 antibodies), which should be avoided by solid organ transplant recipients because of the high risk of rejection [8, 58-60].

Adoptive immunotherapy (principle, indications, techniques, and outcomes)

Adoptive immunotherapy (Figure 1) implicates obtaining tumor-infiltrating lymphocytes (TILs) from the patient's tumour, isolated, modified, and expanded ex vivo, to express a receptor that recognizes a specific antigen on the cancer cell, and then infused back into the patient to recognize, target and eradicate cancer cells.[61]. The use of adoptive immunotherapy for the treatment of post-transplant malignancies is promising. Adoptive immunotherapy is indicated for patients with refractory cancer who have failed standard treatments, such as surgery, chemotherapy, and radiation therapy. [62] Adoptive immunotherapy has also shown promising results in inducing remission and improving survival rates in treating resistant PTLD cases associated with EBV. During the phase II multicenter clinical trial, Haque T et al. reported a clinical achievement response rate of 64% and 52% at five weeks and six months in 33 PTLD cases who failed to respond to conventional treatment [63]. As a major side effect of adoptive immunotherapy, graft-versus-host disease (GVHD) can develop acutely or chronically [64]. Also, they are not available at many centers. Considering the risk of GVHD, adoptive immunotherapy should only be used in patients with resistant EBV-associated PTLD [65].

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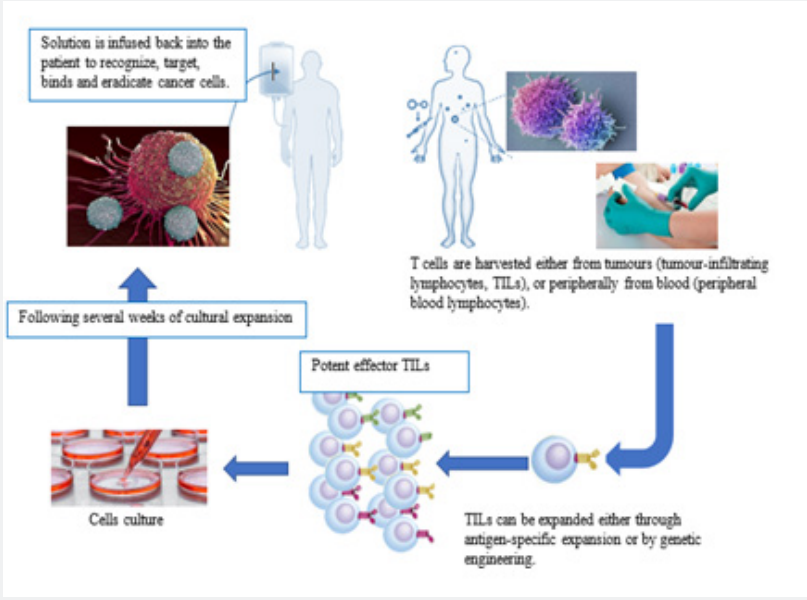

Figure 1: Diagrammatic scene showing the process of Adoptive T cell therapy (ACT).

Factors affecting the waiting period for re-transplantation following successfully treating malignancies:

After successful treatment of post-transplant malignancies, patients may require re-transplantation. Nevertheless, for post-transplant malignancies, a suitable period of disease-free status is required [66]. Defining a 'suitable disease-free period' before they can safely be transplanted is an important issue in this situation. The longer the waiting period between treatment and listing for kidney transplantation, the less expected recurrence is, however, some patients may not be able to wait for several years [41]. An analysis of pre-existing neoplastic diseases in kidney allograft recipients found recurrence rates differed by tumour type, where a low recurrence rate (<10%) is found in cancers of the thyroid, uterine cervix, testis, and lymphoma. Conversely, malignancies with intermediate recurrence risks (11–25%) include carcinomas of the breast, colon, and prostate, whereas those with high recurrence risks (>25%) include melanoma, invasive urothelial carcinoma, sarcomas, and multiple myeloma [67].

Recurrences of neoplastic diseases occurred in 53% of patients treated within 2 years of transplantation but dropped to 34% in those treated between 2 to 5 years before transplantation and 13% in those treated more than 5 years pre-transplantation [67]. Accordingly, many clinical guidelines recommend patients wait for at least 2 years after successfully undergoing cancer treatment, and in some cases up to 5 years. A few exceptions to this rule are non-invasive malignancies of the cervix (in situ) and non-melanoma skin cancers. It is important to note, however, that these recommendations come from old reports, which ignore the dramatic improvement in cancer treatment over the past decade [41]. Tumour type, grade, and response to treatment are likely to affect the chance of recurrence and time to recurrence. Thus, the latest EDTA guidelines recommend that these factors must be cautiously considered with the assistance of an oncologist, balancing the risks of recurrence with the general benefits of organ transplantation for each patient [68].

Patient and kidney graft outcomes in KTRs with different malignancies:

Compared to dialysis patients and the general population, cancer incidence was significantly higher at 25 sites following transplantation. At 18 sites, the risk exceeded 3-fold [11]. The prognosis of kidney recipients diagnosed with cancer is much worse compared to cancer patients in the general population. Additionally, cancers of transplant recipients were more aggressive and diagnosed at a later stage than those without transplants [69]. According to the Israel Penn International Transplant Tumour Registry, stage-specific survival rates for cancer types like colon, lungs, breast, prostate, and bladder were significantly lower in patients with transplants compared to those in the general population regardless of their histological stage at diagnosis [70]. Specific cancers such as lung cancer have very poor outcomes and the lowest graft survival as compared to PTLD, colorectal, and renal malignancies among KTRs [71,72]. The 1-year adjusted survival rates of recipients with advanced-stage colorectal, prostate, and non-small-cell lung cancers were 10%, 40%, and 20% respectively, compared to 40%, 80%, and 30% in

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the general population.

In addition, patients with early-stage disease have much worse prognoses than those without kidney transplants [70]. A poor prognosis was also associated with other malignancies in transplant recipients. Compared to women with breast cancer in the general population, transplant recipients with breast cancer have an excess mortality of at least 40% according to the Australian and New Zealand Dialysis and Transplant Registry [73]. Similarly, the overall 5-year survival rate for kidney-transplanted men with colorectal cancers is 27%, compared with 75% for those without transplants. The median survival of a Dutch kidney transplant cohort after cancer diagnosis was only 2.7 years, compared with an average survival of 8.3 years for recipients without cancer [74]. Also, patients with PTLD had a >6-fold higher risk of kidney allograft loss [75], and at least a tenfold increase in the overall risk of cancer death post-transplantation in comparison with the age- and sex-matched population [76]. Recipients with a previous pre-transplant cancer have an additional risk of dying from cancer by almost 15-fold.

Conclusion

Post-transplant malignancy is a serious and common complication of solid organ transplantation. In most cases, post-transplant malignancy is related to viral infection, particularly with Epstein-Barr virus and human papillomavirus. Compared to malignancies affecting the general population, post-transplant malignancies often have distinct clinical features, treatment challenges, and outcomes. Moreover, cancers in transplant recipients are very aggressive with worse prognoses and lower survival rates compared to those in the general population regardless of their histological stage at diagnosis. Careful screening of patients and donors before transplantation is recommended to detect any underlying, pre-existing malignancies. Additionally, surveillance, diagnosis, and treatment of post-transplant oncogenic viral infections are critical for preventing and managing post-transplant malignancies. A de novo cancer after transplant can generally be treated with the same therapeutic approaches used to treat non-transplant patients with cancer, without concern that such therapies will result in organ rejection. Emerging therapies, such as adoptive immunotherapy, hold promise in the treatment of post-transplant malignancies associated with viral infections.

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