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Post-transplant malignancy: focusing on virus-associated etiologies, pathogenesis, evidence-based management algorithms, the present status of adoptive immunotherapy and future directions

Post-transplant virus-associated malignancies

Abstract

Modern immunosuppression has led to a decrease in rejection rates and improved survival rates after solid organ transplantation (SOT). Increasing the potency of immunosuppression promotes post-transplant viral infections and associated cancers by impairing immune response against viruses and cancer immunoediting. This review reflects the magnitude, etiology, and immunological characteristics of various virus-related post-transplant malignancies, emphasizing the need for future research. A multidisciplinary and strategic approach may serve best but overall literature evidence targeting it is sparse. However, the authors attempted to provide a more detailed update of the literature consensus for the prevention, diagnosis, management, and surveillance of post-transplant viral infections and associated malignancies, with a focus on the current role of adoptive immunotherapy and the way forward. In order to achieve long-term patient and graft survival as well as superior post-transplant outcomes, collaborative research on holistic care of organ recipients is imperative.

Key Words: Post-transplant malignancy management; Post-transplant virus-associated malignancy; Cancer; Kidney transplantation; Solid organ transplantation; Virus

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Core Tip: Post-transplant malignancy poses a serious threat with increased risk in organ recipients, varying with the intensity of net immunosuppression. Various virus infections are either causative or associative or promote the development of post-transplant malignancies. It is crucial to be aware of different viral infections so as to pre-emptively screen viral infections and survey for post-transplant cancers, helping early diagnosis, thereby favouring improved outcomes and graft survival. Transplant clinicians must be up-to-date on current management strategies with the vital role of immunosuppression reduction and options like antivirals, rituximab, chemotherapy, adoptive immunotherapy, topical therapy and surgery based on individual case characteristics.

INTRODUCTION

Post-transplant infections and malignancies are on the rise with increasing efficacy of immunosuppression. Several population-based registries found a two- to five-fold rise in cancer risk after transplantation [1-7].

Though multifactorial, majority of these cancers were attributed to a viral cause (known or suspected) and immunosuppression plays most significant role as it suppresses the immune response to oncoviruses and impairs cancer immunosurveillance [3, 8]. Eight to ten percent of kidney transplant recipients' deaths are due to post-transplant cancers, the third leading cause of mortality after cardiovascular disease and infection in organ recipients [9, 10].

Diverse types of malignancies can develop after transplantation, with some incurring a significant increase in incidence (lymphoma, non-melanoma skin cancer, lung, colon and liver) and others are not (ovarian, brain, breast, prostate and cervical malignancy) as mentioned in table 1 [9, 11, 12]

Table 2 emphasizes burden of cancers especially related to viral infections during post-transplant period.

Currently, there is varied agreement regarding the prevention, diagnosis, treatment, and surveillance of post-transplant cancers, especially in relation to viral infections. Additionally, the introduction of adoptive immunotherapy(AI) has resulted in the dilemma of treatment management alternatives.

This article focuses on the up-to-date information of the various post-transplant virus-associated aetiologies and their pathogenetic differences compared to the general population with respect to post-transplant malignancy. It also mention in detail about comprehensive consensus regarding the management of post-transplant malignancy, pertaining to viral infections, in light of recent research findings, including the role of adoptive immunotherapy(AI). Furthermore, this article highlights the need of future research with the purpose of developing a tailored therapeutic strategy for each patient based on existing risk factors and diagnostic techniques.

VARIOUS VIRAL INFECTIONS THAT MAY INDUCE/PROMOTE/ASSOCIATED WITH POST-TRANSPLANT MALIGNANCY

Various viruses that have been associated with causing or promoting post-transplant malignancies as given in Table 3 [14-20].

Cancers of Skin (commonly found post-transplant and those related with viral infections)

Commonest cancer following kidney transplantation is skin cancer, which is more aggressive than the general population and nearly affects 50% of post-transplant patients [21]. Non-melanoma skin cancers (NMSC) are the most common type, reported in up to 82% of patients within 20 years of transplantation [22, 23]. 90% of all NMSCs are squamous cell carcinomas(SCC) and basal cell carcinomas(BCC) [24, 25]. Post-transplant recipients in comparison to the general population, have a 65- to 250-fold and 10-fold increased risk of developing SCC and BCC respectively [21]. Various studies, have reported that the ratio of BCC to SCC in the general population (5:1) is reversed in organ recipients (1:4 to 1:5)

[24, 25]. BCC, SCC, Kaposi sarcoma and malignant melanoma constitute up to 90%–95% of all skin cancers in transplant recipients [26, 27]. Rare skin cancers include cutaneous lymphoma, merkel cell carcinoma, vascular cutaneous tumours(angiosarcoma), mesenchymal cutaneous tumours and adnexal gland carcinoma.

Even though HPV is frequently detected in warts, hair follicles, and keratotic lesions, both in patients with and without skin tumors, there is no conclusive evidence linking HPV to skin tumor development in transplanted patients [28, 29]

Oncogenic (HPV types 16 and 18) and non-oncogenic (HPV types 6 and 11) HPV DNA is found in 65–90% of organ recipients' SCC, but its carcinogenic role is still unclear [28].

Novel polyoma virus has been identified in human Merkel cell carcinoma (hence the name Merkel cell virus or MCV) with possible causation [30].

The skin cancers of organ recipients tend to be more aggressive, present at a younger age, and involve multiple primary sites as opposed to those of the general population.

Multiple factors contribute to the aetiology of skin cancer, including immunosuppression, intensity of immunosuppression, ultraviolet radiation exposure, white race, older age, a history of skin cancer, human herpes virus 8 (HHV 8) and possibly HPV 16/18 and MCV [31].

Epstein-Barr virus(EBV)/Human herpes virus 4 (HHV 4)

EBV, is a member of gamma herpesvirus family, encapsulated single stranded DNA virus and ubiquitous.

There are two strains infecting humans, EBV-1 & 2 (previously called EBV A & B). In the United States (U.S.) and Europe, EBV-1 predominates, whereas in Africa and New Guinea, both EBV strains are equally prevalent [32].

It spreads *via* saliva (and possible transmission through sexual intercourse), before spreading to circulating B cells through infection of oropharyngeal epithelium [33]. EBV seroprevalence is 100% by age 4 and 89% by age 19 in developing and developed nations and varies with socioeconomic status [34, 35].

Kidney transplant recipients are susceptible to acute infection or reactivation of a latent virus, with clinical manifestations ranging from non-neoplastic viral replication

(asymptomatic viremia, infectious mononucleosis) to neoplastic viral proliferations, like post-transplant lymphoproliferative disorder (PTLD) and smooth muscle tumours [36, 37]. Asymptomatic low-level, high-level, or the absence of viremia may exhibit no distinguishable symptoms and usually detected through screening with EBV polymerase chain reaction (PCR) (37). In a few studies, renal dysfunction, patient and graft survival are not different between groups (absent, low or high viral loads), whereas others report a higher incidence of opportunistic infections with increasing viral loads [38, 39]. EBV seronegative at transplantation, prior history of PTLD and non-Caucasians are risk factors for EBV viremia [38].

Other manifestation of EBV includes EBV-associated Guillain-Barre syndrome [40], gastric carcinoma [41], smooth muscle tumours [42], hemophagocytic syndrome [43] and autoimmune haemolytic anaemia [44].

EBV-related PTLD, is the most serious sequel in organ recipients by the virus and cumulative incidence varies with 1–5%, 2–10% and 5-20% in kidney, heart and lung and intestinal & multi-visceral transplant recipients[45].

Other manifestations include an 11.8-fold increased risk of non-Hodgkin's lymphoma in kidney transplant recipient compared to the age-matched non-transplant group [46].

PTLDs, majorly (65-80%) present as extranodal masses and histologically varies from infectious mononucleosis-like, plasmacytic hyperplasia, florid follicular hyperplasia, polymorphic, monomorphic PTLD (B- and T-/NK-cell types) or classical Hodgkin's lymphoma PTLD [47]. Risk factors associated with PTLD in kidney transplantation are mentioned in table 4.

Early PTLD(< 1 year post transplant) likely in EBV-seronegative recipient, polymorphic, involves graft (in 57%) and respond to reduction in immunosuppression (RIS).

Late PTLD likely monomorphic, disseminated and extra-nodal (graft involvement-only 10%) and resistant to RIS [51-54].

The most common sites of PTLD involvement are the gastrointestinal (GI tract) (15–30%), lungs, skin (5–10%), liver, central nervous system (CNS) (20–25%, usually late PTLD) (54),

and the allograft (20–25%, often culminating in allograft loss) (54). CNS PTLD, often have poor prognosis, and has highest incidence in kidney transplant recipients [36, 49, 55].

Human papilloma virus (HPV)

HPV is a double-stranded DNA (dsDNA) virus that can infect the keratinized skin (basal epithelium), mucous membranes, and the cervical transformation zone and spread *via* direct contact transmission(person to person).

HPV types 6, 11, 16 and 18 are implicated in low and high grade neoplasia [29, 56-58].

HPV has been linked to precancerous lesions [cervical intraepithelial (CIN) and anal intraepithelial neoplasia (AIN)], lesions with low malignant potential like cutaneous, anogenital warts and certain cancers [(cervical, anal, vulvar/vaginal/penile squamous cell cancers, rarely oropharyngeal (head & neck) cancers)] [59].

There is higher risk of HPV-associated malignancies, extensive and treatment-refractory warts on the cutaneous and anogenital areas in transplanted patients (reactivation of old or new infection) compared to age matched non-transplant group[3, 60].

HPV rarely causes viremia (in immunocompetent as well as immunodeficiency states) but lack of cell mediated immunity at infected sites, especially in transplant recipients leads to its persistence, extensive warts which are non-responsive to treatment and increased probability of cancers [61, 62].

Persistent infection with HPV type 16 and 18 is associated with premalignant and malignant lesions of cervix, anus, vulva, penis or scrotum. Lesions are typically asymptomatic, may present with abnormal bleeding, ulcer/nodule/wart like, local pruritus, pelvic pain, and dyspareunia in some cases [63-65].

There has been links of HPV association with oropharyngeal and lung SCC but with conflicting results [3, 66, 67].

Human herpesvirus(HHV8) or Kaposi's sarcoma herpesvirus (KSHV)

HHV8, a DNA gamma-herpes virus, has four variants: sporadic or classic (first description by Kaposi), endemic (in sub-Saharan Africa), epidemic (associated with HIV), and iatrogenic (in immunosuppressed transplant recipients) [68].

Virus can be transmitted *via* saliva (primarily), sexually (semen/vaginal secretion), vertically (breast milk), intravenously (drug use or blood products) or through transplantation.

Like EBV[69], HHV8 invade B cells, macrophages, lymphoepithelial cells and epithelium, can persist as latent form lifelong or reactivates when immunosuppressed to enter lytic form leading to viremia [70, 71]. In organ transplant, lytic reactivation of virus due to immunosuppression (iatrogenic) may lead to uncontrolled monoclonal/oligoclonal proliferation of latently infected lymphoepithelial cells or B cell mature post-germinal centre [70, 71].

Lymphatic endothelium-derived cells infected with HHV8, form multicentric neoplasm classically known as Kaposi sarcoma(KS) [72, 73].

HHV8 induced neoplastic and non-neoplastic manifestation post-transplant can be derived from latent virus, seroconversion from positive donor to seronegative recipient[74], proliferation of seeded HHV8+ cells[75, 76] or KS tumour in transplanted organ[77] while in immunosuppressed state.

HHV8 is not ubiquitous like EBV, but seroprevalence is higher than 50% in some endemic regions (sub-Saharan Africa, Caribbean, Latin America, Mediterranean, and middle east regions) and matches post-transplant KSHV associated pathologies in such regions [78].

KS risk is low in transplant recipients but 200- to 500-fold more than in the general population [79, 80]. Besides key risk factor of HHV- 8 seropositivity, other includes ethnicity (more in seroprevalent geographic regions), receipt of lymphocyte depleting agents, HLA- B mismatch, older age and lung transplant [79, 81-85].

PT-KS (Post-transplant Kaposi sarcoma): higher incidence in kidney transplant compared to other SOTs(liver and heart) and rare in HSCT(haematopoietic stem cell transplant). This condition usually manifests early after transplantation (median 2.5 years) as cutaneous or mucosal lesions, but 25%–50% have visceral manifestations[85] with mortality ranging from 8 to 14%. Disseminated disease is associated with thrombocytopenia, anemia, and abnormalities of bone marrow progenitor cells and widespread involvement (cutaneous, mucosal and visceral). AA AI-Khader *et al* (86)

proposed clinical staging of PT-KS which assess extent of disease and guide treatment. Few studies have shown that CMV infection can reactivate HHV-8, initiate onset and/or recurrence of KS [86, 87].

Post-transplant, HHV-8 was also found to be cause other lymphoproliferative disease(LPDs) like primary effusion lymphoma (PEL), multicentric Castleman disease (MCD) [88, 89] and other non-malignant complications like plasmacytic B-cell proliferation, bone marrow failure and hepatitis [85, 90].

Human immunodeficiency virus(HIV)

Observations concerning the impact of HIV infection post-transplantation have been largely based on the experiences of recipients who previously had HIV infection and underwent transplantation. Transplant outcomes in HIV-positive recipients are almost similar to those in non-HIV-positive recipients with few differences [91, 92].

Kaposi sarcoma prevalence in HIV-positive patients on anti-retroviral therapy (ART) is 0.18%-0.46%, while it increases to 0.50%-0.66% in transplanted patients.[93]

People with HIV (SIR = 4.95%) and organ recipients (SIR = 3.28%) had a greater risk of developing new cancers compared to general population [94].

SOT in HIV-positive patients carries a low risk of recurrence or de novo cancer. HPV-associated neoplasia (cervical, anal and atypia) have slightly higher risk in few studies, however, this requires confirmation in future studies [95].

EBV associated PTLD/Lymphoma has similar prevalence in organ recipients with HIV [92].

Compared to non-HIV recipients, tuberculosis and fungal infections incidences appear to be more in HIV-infected recipients during the post-transplant period[96].

Hepatitis B Virus (HBV) and Hepatitis C Virus(HCV) related hepatocellular carcinoma(HCC)

In a U.S. registry data (223,660 recipients,1987–2005), de novo HCC post-transplant was evaluated among non-liver(kidney, heart, and lung) and liver transplant recipients [97].

In non-liver recipients, above study reported de novo post-transplant HCC incidence of 6.5 per 100,000 person-years. Hepatitis B surface antigenemia (hazard ratio [HR] 9.7),

HCV infection (HR 6.9), and diabetes mellitus (DM) (HR 2.8) are risk factors independently linked with HCC incidence. Incidence of HCC was greater in those with HCV (SIR = 3.4) or hepatitis B surface antigenemia (SIR = 6.5), but comparable with general population (SIR 0.8).

In liver recipients, de novo post-transplant HCC incidence was found to be 25 per 100,000 person-years. Advancing age, male sex (HR 4.6), HCV infection (HR 3.1), and DM (HR 2.7) was independently associated risk factors. Overall, the incidence of HCC was higher (SIR = 3.4), but particularly among individuals with HCV (SIR = 5.0) or diabetes mellitus (SIR 6.2).

Due to the high endemic prevalence of HBV infection in Taiwan, HCC is a major malignancy in general as well as post-transplant population, favouring hepatitis virus antigenemia as potential causative factor[98]. HCV infection is also related to post-transplant cirrhosis and thereby increasing the risk of post-transplant HCC [99].

Various other studies of different ethnicities also found HBV and HCV infection post kidney transplant, a significant risk factor for HCC even late [100, 101].

Polyomavirus(BKV)

The BKV is a ubiquitous polyoma virus that causes asymptomatic infection in childhood and has a seroprevalence of 70-80% in adults. It settles latency in organs like kidneys, ureters, spleen or brain [102].

Its non-oncological manifestations in kidney recipients are ureteral stenosis, vasculopathy, tubulopathy, haemorrhagic cystitis, and interstitial nephritis [103, 104].

BKV-related malignancies in kidney recipients include urothelial carcinoma of the renal pelvis, RCC, and collecting duct cancer [102, 105-108].

Cytomegalovirus(CMV)

Rarely, CMV has been associated with de novo gastrointestinal tumours and nephrogenic adenoma following renal transplantation. Its causal role is unclear[109, 110].

PATHOGENESIS OF POST-TRANSPLANT MALIGNANCIES

Pathogenesis and transplant specific risk factors for post-transplant malignancies are multifactorial but majorly includes immunosuppression and decreased immunosurveillance.

Cancer immune-editing involves three phases(Figure 1) [111-113]: Elimination phase(cancer immunosurveillance), equilibrium phase(cancer persistence/dormancy) and escape phase(cancer progression). Immunosuppression has an impact on all phases.

A post-transplant patient under the exposure of viral infections, UV radiation, carcinogens and chronic inflammation, cause some healthy cells to transform into highly immunogenic tumour/transformed cells. These tumour cells may revert to normal tissue by mechanism of intrinsic tumour suppression (repair, apoptosis or senescence) which may get weak due to effects of modern era immunosuppression.

As soon as these highly immunogenic transformed cells evade the intrinsic tumour suppression mechanism, they enter the elimination phase (cancer immunosurveillance). During the elimination phase, innate and adaptive immunity (NK and T cells) offer protection against the development of cancer (known as extrinsic tumour suppression). If the phase of elimination concludes successfully, the body restores healthy tissue but is weakened by immunosuppression.

When transformed cells escape elimination phase, they enter an equilibrium state (cancer persistence/dormancy), in which adaptive immunity (T cells, IL2, INF-gamma) works to maintain such cells in a dormant state. In the event that dormancy occurs efficiently, it prevents outgrowth of transformed cells or occult tumours/cancers for life time and represents the end stage of cancer immunoediting but is altered by immunosuppression. Tumour immunogenicity is edited during the elimination phase by constant immune selection. Antigen loss variants, flaws in antigen processing or presentation, immune effector cell resistance, and the generation of an immunosuppressive microenvironment within the tumour are some of the editing mechanisms. Genetic instability and tumour heterogeneity increase as editing proceeds, and highly immunogenic tumour cells become less immunogenic and immune-evasive tumour cells.

These less immunogenic and immune-evasive tumour cells escape immunosurveillance and progress to clinically apparent cancer. This phase is designated as escape phase(cancer progression).

Specific carcinogenic mechanisms of various viral infections post-transplant have been mentioned in Table 5. [114]

Multidrug immunosuppression in the transplant setting impacts cancer immune editing by a number of mechanisms, as shown in Table 6.

Multifactorial pathogenesis associated with post-transplant malignancy due to decrease immunosurveillance following exposure to viral infections, ultraviolet radiation (UV) and carcinogens including other related risk factors is summarized in figure 2.

DIFFERENCES BETWEEN MALIGNANCIES IN ORGAN RECIPIENTS COMPARED TO THE GENERAL POPULATION

Interaction with a healthy immune system(as in general population) selects tumours devoid of tumour-specific antigens, meaning poorly immunogenic or immune-evasive tumours.

Tumours formed in immunosuppressed host are more immunogenic than general population (immunocompetent host) as de novo malignancies arise due to permissive effect of immunosuppression by inhibiting cancer immunosurveillance and immune-editing [112, 113, 133]. RIS and immunotherapy (i.e., adoptive/ check- point inhibitors) may facilitate immune reconstitution, which can help by clearing immunogenic cancer cells but can raise risk of rejection [134].

SCREENING, DIAGNOSIS, AND TREATMENT OF POST-TRANSPLANT VIRAL INFECTIONS RELATED WITH THE POTENTIAL TO DEVELOP MALIGNANCY

In the literature, viral aetiology is well known and accepted as a probable association or causation (either promoting or inducing) of a wide variety of post-transplant malignancies. Table 7 highlights screening, diagnosis and treatment of Post-transplant viral infections.

DIAGNOSIS OF VARIOUS POST-TRANSPLANT VIRUS-ASSOCIATED MALIGNANCIES

Susceptibility of viral infections post-transplant is proportional to the degree of net immunosuppression and varies greatly due to inherent limitations in the available data. The availability of population registry data for specific viral infections related with the type of organ transplant is insufficient, differs with immunosuppression regimen and geographical distribution and is, in general, weak worldwide.

Upon conducting a thorough literature search, the authors could find EBV and HHV8 susceptibility with the type of organ transplanted.

Incidences of PTLD risk is highest for intestine and multi-organ transplants (12 to 17 percent), followed by lung (6 to 10 percent), heart (3 to 5 percent), liver (2 to 3 percent), and kidney (1.5 to 2.5 percent), being the least[140].

KS incidence varies with organ transplant and reported as per 100,000 person-years. It was reported as 95.79 (95%CI 42.81–214.31) in kidney, 44.25 (95%CI 4.78–409.20) in liver, 49.25 (95%CI 2.48–977.84) in heart and 10.97 (95%CI 4.12–29.23) in lung, respectively [141].

An in-depth detail to diagnose various post-transplant virus associated cancers is outlined in Table 8.

TREATMENT & PREVENTION OF POST-TRANSPLANT MALIGNANCIES

Literature lacks evidence on how many years of use of immunosuppression post-transplant increases the risk of cancer. Despite uncertainties, literature consistently indicates that the overall duration and intensity of immunosuppression, rather than individual drug in immunosuppression regimen, lead to an increased risk of cancer.

Table 9 describes treatment and prevention of post-transplant cancers.

SURVEILLANCE PROTOCOLS FOR POST-TRANSPLANT MALIGNANCY

Due to the rise in the risk of malignancy, monitoring organ recipients post-transplant is extremely vital.

Current data suggests that the liver is an immunologically favourable organ and immunosuppression withdrawal is reported in well selected patients who had underwent liver transplantation (i.e. up to 40% of adults and 60% of paediatric liver recipients)[171]. As data have not been specified in most clinical studies, usefulness of immunosuppression withdrawal in carefully selected liver transplant recipients has not demonstrated a significant clinical benefit on de novo malignancies post-transplant[171]. Hence, there is risk of carcinogenesis.

The surveillance protocol is provided in Table 10.

TREATMENT & PREVENTION OF POST-TRANSPLANT MALIGNANCIES

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ADOPTIVE IMMUNOTHERAPY

Principle

Immunosuppression increases the chance of opportunistic infections in the post-transplant period. Limitations of current pharmacological treatment of viral infections in organ recipients include cost, antiviral(s) toxicity, their variable efficacy and even resistance [178]. Most importantly, pharmacotherapies does not aid in pathogen-specific immune reconstitution, the repeated risk persists after successful cure or eradication of virus. Cytomegalovirus is one potential example of such a pattern[179].

Rosenberg and colleagues first described the efficacy of adoptive immunotherapy in murine tumours in 1987, and later demonstrating objective tumour response in metastatic melanoma patients[180, 181].

Adoptive immunotherapy (AI) uses pathogen/ virus-specific T cells (VSTs) to quickly restore immune responses to infectious pathogens/ virus in organ recipients. Apart from

eliciting virus-specific cytotoxic responses, AI has specific advantage over pharmacotherapy by establishing long-term T-cell memory and may help preventing recurrent infections and protects against the organ toxicity/ myelosuppression associated with some antivirals.

AI has been explored in post-HSCT, for CMV, EBV and adenovirus (AdV) and has weak evidence in SOT. Advancement in immunological techniques have further minimized alloreactivity and maximized cytotoxicity with AI, thereby, yielding a targeted approach with good safety profile [182-186].

Likely indications As inferred from partial/ complete response in certain subsets of patients post-transplant after AI therapy:

In EBV+ PTLD:

Failed standard therapy with RIS, rituximab, chemotherapy, and/or radiotherapy [187].

Children failed with RIS and rituximab therapy [188]. Delayed response is possible due to use of rituximab.

In CMV:

Refractory and resistant CMV [189-194].

Technique of Adoptive immunotherapy

Figure 3 illustrates the steps, isolation, and diverse forms of adoptive immunotherapy.

Outcomes of AI

AI is more explored in HSCT compared to SOT.

Most of data came from the variable success of AI in EBV+ PTLD disease.

Use of AI in CMV disease is sparse and limited only to few cases in SOT.

AI needs more evaluation in further controlled trials.

Particular facility & time to generate, cost, durability, long-term overall efficacy and safety, the potential for alloreactivity, and reduced ability to mount adequate response with ongoing immunosuppression are legitimate concerns for the widespread use of adoptive immunotherapy.

FACTORS INFLUENCING THE WAITING PERIOD FOR RE-TRANSPLANTATION AFTER SUCCESSFUL TREATMENT OF THESE MALIGNANCIES

Achievement of complete remission (clinically and radiologically).

Sustained disease free status for considerable period of time (at least 12 to 24 mo).

Presence of seroconversion (viral specific IgG antibodies).

Graft nephrectomy in cases of allograft PTLD.

Absent or undetectable viral loads after successful treatment of malignancy [54, 200, 201].

CONCLUSION

Post-transplant malignancy is a considerable risk and cause of significant morbidity and mortality in organ recipients. Strategically reducing immunosuppression is an important step in the management of post-transplant viral related cancers.

Literature evidence for prevention, treatment and surveillance in post-transplant viral infections and malignancy are extrapolated from the knowledge in general population.

Multi-disciplinary team is vital for successful outcome. An individualized approach is the most effective method and treatment to eradicate or cure might not be the ultimate goal in all cases.

Adoptive immunotherapy is currently in infancy and has inherent logistic problems. Wait time for re-transplantation following the successful treatment of cancer should be weighted on an individual case basis, taking due consideration of the risks associated with renal replacement therapies.

Collaborative efforts among all engaged in the care of post-transplant patients, observing more extensive care studies and multicentric interventional trials, can further enrich the evidence base, long-term, quality care of organ recipients.

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