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Review Article

Post-transplant Malignancy: An Overview and Review of Literatures

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Abstract

Post-transplant malignancy is one of the contentious and feared consequences of Solid Organ Transplantation (SOT), which might detrimentally alter the outcome of transplantation. Risk factors are manifold, principally related to a suppressed immune system with intercurrent immunosuppressant medications commonly used in the context of SOT. Opportunistic viral infections encountered in SOT are crucial promoters of mitogenic proliferation in several common tumors. Lastly, immune suppressant therapy might trigger mitogenic changes directly.

In this paper, we are discussing post-SOT malignancies, elaborating on the different phases of its pathogenesis, and elucidating on the different aspects that linger in its risk factors, preventive strategies, and management.

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Introduction

The most feared complication post-SOT is the development of malignancy. Its incidence varied according to type and organ involved; 50 percent of SOT recipients in one series studied, developed post-transplant skin malignancies, representing a 100-fold higher risk compared to the general population [1]. Similarly, Post-Transplant Lymphoproliferative Disease (PTLD) incidence amounts to between 2 and 20 percent of SOT recipients [2]. Mortality secondary to post-transplant malignancy among kidney transplant recipients was notably higher at around 2.5% in comparison to the general population [1]. This exceedingly higher incidence of post-transplantation malignancy was influenced by several factors (Figure 1) stemming from donors' and recipients' distinctive backgrounds [2]. Different types of malignancies will be specifically addressed in this article, highlighting the common risk factors, and discussing the proposed strategies to tackle their provocative oncogenesis, with special emphasis on the post-transplant management and immune suppressant therapy implications. Concludingly, we will be deliberating the common suggestions and opinions and sharing our thoughts and experiences in this yet-to-be-further-explored field.

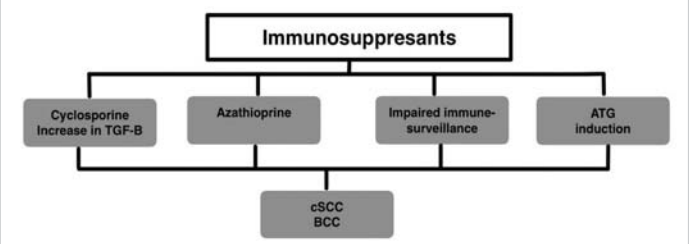

Figure 1: Immunosuppressants are the main trigger for the oncogenic process. By impairing immune surveillance, azathioprine, ATG and cyclosporin predispose to skin malignancy. Potentially, immunosuppressants portend higher risk via particular oncogenic mechanisms. TGF-B transforming growth factor beta, ATG: Anti-thymocytes Globulins; cSCC: Cutaneous Squamous Cell Carcinoma; BCC: Basal Cell Carcinoma. Created by the author.

Common pathogenetic factors

Immune suppressant medications (Figure 1): Immune suppressant medications are the most common predisposing factor for increasing incidence of malignancy post-transplantation [3]. Relevant mechanisms might comprise inactivation of the immune system and failure of immune surveillance. The direct link of malignancy development to immune suppression status was indicated by the higher incidence of PTLD in the first year post-transplantation, during which the immune suppression is at its maximum level with induction therapy and maintenance protocols maintaining increasingly higher doses of immune suppressants. Hence, the risk of PTLD is diminished by 80% after the first year [4]. Furthermore, owing to the higher incidence of acute rejection in the first year post-transplantation that is treated with increasing doses of anti-rejection therapy, excessive suppression of the immune system prevails with an escalating risk of PTLD [4]. The higher dose of maintenance immune suppressants was related to the soaring incidence of malignancy. Distinctively, calcineurin inhibitor cyclosporin is pertinent to increasing malignancy

incidence and propagation, particularly non-melanoma skin cancer. The major underlying mechanism is increased production of the cytokine Transforming Growth Factor Beta (TGF-B) [5] which promotes mutagenic proliferation and metastasis. The level of TGF-B is directly proportional to the dosage of cyclosporin. Similarly, cyclosporin stimulates the production of Vascular Endothelial Growth Factor (VEGF) with enhancement of angiogenesis, which is another risk factor. Moreover, IL-6 production is provoked by cyclosporin administration. IL-6 stimulates Epstein-Barr (EBV)-induced B-lymphocyte proliferation and risk of PTLD [6]. Tacrolimus exhibits a similar risk profile for the development of PTLD stemming from increasing production of TGF-B [6].

On the other hand, anti-proliferative medication mycophenolic acid (MMF) features a lower malignancy incidence rate, which is attributed to its mechanism of action that confers inhibition of the enzyme inosine monophosphate dehydrogenase. This enzyme is quite prevalent in malignant cells; thus, MMF administration is directly inhibiting the proliferation of malignant cell clones [7]. However, an increased incidence of skin basal cell carcinoma was encountered post-transplantation secondary to MMF administration [7]. Furthermore, its function of inhibiting the proliferation of lymphocytes via a similar mechanism reduces the mutagenic transformation of EBV-infected lymphocytes. Owing to its potent immune suppression, a lesser incidence of acute rejection episodes is reported with a consequent lower burden of immune suppression status that is usually created by anti-rejection therapy, lending a lower risk for invoking mutagenesis [7].

Induction therapy with T-lymphocyte depleting agents such as Anti-thymocyte Globulin (ATG) is predisposing to PTLD formation, secondary to profound immune suppression and the flourishing of EBV infection of B lymphocytes. On the contrary, anti-CD20 monoclonal antibody therapy with rituximab is associated with a lower incidence of PTLD as it depletes B-lymphocytes, which are the culprits for the development of PTLD [7].

Recipients related factors [8]

Altered immune surveillance for detection of tumoral cells.

Defective immune response against oncogenic viruses.

Oncogenic cellular alteration induced by immuno-suppressants.

Older age, as is associated with excessive immune suppression.

Viral infection and oncogenic propensity post-transplantation (Figure 2): Reactivation of dormant viruses or de novo infection with oncogenic viruses are essential predisposing factors for the development of malignancy post-transplantation [9]. EBV, Human Herpesvirus 8 (HHV8), Cytomegalovirus (CMV), Human Papillomavirus (HPV) and Merkle cell polyomaviruses are the commonest culprit viruses.

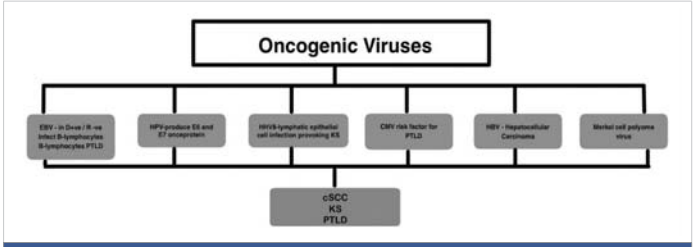

Figure 2: Oncogenic viruses (EBV, HPV, HHV8, CMV, HBV, MCPV) are reactivated post-transplantation and cause different types of malignancies. Oncogenic viruses, immunosuppressants, and other factors are the main culprits predisposing to malignancy development. The main malignancies are PTLD and skin tumors. EBV: Epstein-Barr Virus; HPV: Human Papillomavirus, HHV8: Human Herpesvirus 8; CMV: Cytomegalovirus; PTLD: Post-transplant Lymphoproliferative Disease; HBV: Hepatitis B Virus; cSCC: Cutaneous Squamous Cell Carcinoma; KS: Kaposi Sarcoma. Created by the author

EBV

Is a double-stranded DNA virus, it is the main culprit for the initiation and propagation of PTLD, as it infects B-lymphocytes, integrating its DNA into B-lymphocytes nucleic acid, resulting in alteration of the cell cycle and uncontrolled proliferation of EBV-infected B-lymphocytes population.

Primarily, EBV-infected B-lymphocytes with explicit viral antigen on their surface would abrogate the selective maturation of B-lymphocytes in the germinal center and drive it to a memory cell phenotype where the virus resides in a latent phase with trace expression of viral protein, coined as latency 0 status. Upon reactivation of EBV-infected B-lymphocytes, 3 latency phases can be recognized contingent on the number of viral antigens expressed by infected cells. 9 antigens are detected in this context, 6 nuclear and 3 membrane-associated antigens, Hence, when 9 antigens are expressed, the genetically mutated B-lymphocytes are recognized as growing programs with latency III, which is the common pattern in PTLD status. On the contrary, with the expression of minimal antigens number, EBV-infected B-lymphocytes adopt latency I pattern, which is advantageous in evading immune surveillance. Latency I pattern is recognized in Burkitt lymphoma. The different latency patterns reflect immune deficiency status and impairment of immune surveillance extent [10].

It is frequently encountered in the first-year post-transplantation with high risk in those who are EBV-negative recipients of an SOT from EBV-positive donors. T-lymphocyte lymphomas are negative for EBV. T-lymphocyte depleting agents are reportedly associated with an increasing risk of developing PTLD [11] owing to the resultant imbalance of T-lymphocyte cell-mediated immunity and EBV-infected B-Lymphocyte mutation and proliferation.

HHV8

Is commonly associated with Kaposi sarcoma KS: KS is the most prevalent tumor post-transplantation with a reported incidence of 200 times higher than in non-transplant people [12]. It occurs months to years post-transplantation. Arise from lymphatic epithelial cells infected with HH8, which triggers cell cycle alteration and mutagenic transformation via integrating its genomic material into cellular nucleic acid material. Categorized into cutaneous, mucocutaneous, and visceral types. Visceral KS is rarely reported in the context of kidney transplantation, hence, mortality related to KS post-transplantation is increasingly recognized with non-kidney SOT [13]. Risk of contracting KS includes prior infection with HH8 virus, transmitted over saliva and persists dormant under intact immune system conditions. Therefore, immune suppression status post-transplantation is the essential trigger for its development.

Melanocytic cutaneous malignancy

It's not known to be provoked by oncoviruses, however, its incidence is reported to be exceedingly higher in comparison to immune-competent patients with relatively aggressive course of tumor with higher mortality. Stage of melanoma, presence of residual disease, and duration since diagnosis and treatment before transplantation are the major risk factors for recurrence post-transplantation. It is associated with poor prognosis when developed post-transplantation, commonly represents recurrence, or is rarely transmitted via SOT.

Human Papilloma Virus (HPV)

HPV is a common inhabitant of human skin.

A certain HPV genotype was a proven etiologic factor for specific types of head, neck, and oropharyngeal squamous cell carcinoma [14]. Similarly, cervical carcinoma and anogenital cancer are commonly reported with HPV as an essential etiological factor, as its DNA was anecdotally recovered from the tumor cells with Polymerase Chain Reaction (PCR) assay. Potentially cutaneous squamous cell carcinoma cSCC post-transplantation {which is 100 times more prevalent post transplantation} linked to HPV infection. The underlying mechanism of HPV-induced oncogenesis might comprise the production of oncoproteins E6 and E7 which influence cell cycle transit and apoptosis function. Therefore, the first hit in initiation of cSCC is cutaneous cellular DNA injury inflicted by UV light exposure, and the second hit results from failure of repair or removal of the damaged cells owing to HPV infection related oncoprotein release and faltered immune surveillance provoked by immune suppressants, particularly azathioprine, and cyclosporin. This hypothesis was heavily investigated in more than one meta-analysis study, with conflicting results [15].

Cytomegalovirus CMV

CMV was not reported to induce or propagate any kind of malignancy post-transplantation. However, a debatable role for CMV in PTLD was indicated by other studies and it is considered as a potential risk factor for the development of PTLD [16].

Merkle cell polyoma virus

Merkle cell polyomavirus might induce and propagate Merkle cell carcinoma, which is a neuroendocrine cutaneous tumor. It is more common in immunocompromised patients, where it is 66-182-fold more prevalent than in the general population. Furthermore, it is more aggressive and malignant in immune-compromised patients than in their counterparts' patients with an intact immune system. Immune suppression status post-transplantation is considered the most potent predictive factor for a poor prognosis, regardless of the grade of differentiation or stage of the tumor. This finding was confirmed in several observational studies. The discrepant prognosis and tumor behavior between the immune deficient and immune intact groups might be attributed to impaired immune surveillance. Similarly, an impaired immune system predisposes to overwhelming viral replication with overproduction of oncoproteins, provoking oncogenesis [17].

Recurrence of primary malignancies (Figure 3): Posttransplant recurrence of pretransplant malignancy was initially reported to be increasingly prevalent, with predisposition instigated by immune-compromised status. Hence, the general recommendation was to wait 5 years before embarking on kidney transplantation. However, a recent meta-analysis revealed a comparable outcome of cancer recurrence in transplanted patients and non-transplant patients with prior malignancies [18].

Lifestyle: The magnitude of sun exposure:

UV sun rays exposure influences the incidence and propagation of skin cancer.

This increased risk of skin cancer is attributed to impaired immune surveillance induced by immune suppressants, particularly azathioprine and CNIs, in which case damaged skin cells by UV light are not removed by the suppressed

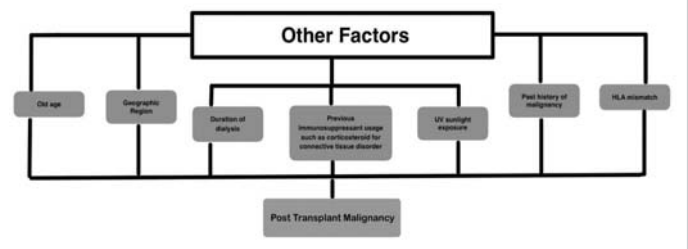

Figure 3: Different other risk factors predispose to variable oncogenic processes. Created by the author.

immune system. Comparably, UV light exposure suppresses the immune system in the cutaneous tissues. The effect of UV light is accumulative and increases steadily in proportion to its duration post-transplantation. Therefore, 32% of kidney transplant recipients were diagnosed with non-melanotic skin cancer after 10 years. The most common skin tumors reported in kidney transplant recipients are KS and squamous cell carcinoma [19].

Duration of dialysis therapy pre-transplantation

Duration of dialysis therapy reflects the duration of immune suppression status entailed by chronic kidney disease, which is commonly predisposing to increasing risk of malignancy, regardless of the subsequent SOT [20].

Level of HLA incompatibility and DSAs magnitude

As it influences the level of immune suppression required to mitigate the high risk of rejection triggered by HLA incompatibility and preformed and de novo emerging DSAs.

Allograft rejection: Episodes of allograft rejection prompted an intensified anti-rejection therapy protocol to overcome the rejection process. This procedure confers excessive immune suppression, resulting in the potentiation of oncogenic viral proliferation and the escalation of cancerous mutation risk. On the contrary, HLA mismatch was reported in other studies to confer a lesser risk of skin cancer, attributed to the potential activation of malignancy surveillance by the immune system [21].

Geographical factors: Variable types of post-transplantation malignancies were distinctively reported in different parts of the world, reflecting local geographical and environmental factors potentially influencing the incidence of variable malignancies. Hence, non-melanotic skin cancer, lip, and PTLD are commonly reported in Australia, New Zealand, and North America. On the other hand, an increasing prevalence of urothelial transitional cell carcinoma, gastrointestinal cancer, and renal cell carcinoma was purported in other parts of the world. An incidence contrast might be attributed to the variable prevalence of oncogenic viruses, the burden of sun exposure, and dietary habits. Therefore, higher consumption of aristolochic acid was linked to transitional cell carcinoma in the general population and even higher incidence in immune-suppressed patients with SOT [22].

Aggressiveness and mortality rate of Post-transplant malignancies

The prognosis of post-transplant malignancies is dreadful in comparison to the outcome of the same malignancies in non-SOT patients [23]. This observation might be attributed to several factors, including:

I. Altered cancer cells' mitogenic cycle in favor of extended life span and uncontrolled malignant behavior, influenced by a lack of immune surveillance and escalated provocative stimulatory cytokines.

II. The immune suppressive status flourishes the cancerous process, leading to advanced growth and metastasis of the tumor.

III. Multiple comorbidities post-transplantation.

IV. Non-adherence of the transplant patients to general precautionary measures advocated by the transplant team, such as the avoidance of excessive sun exposure, as most patients are driven by their focus on the transplanted kidneys rather than other medical issues [23].

Donors-related risk factors

Transfer of HBV, as HBV is a predisposing factor for hepatocellular carcinoma.

Transplanted organ transmission of EBV in donor EBV-positive / EBV-negative recipients

Transmission of malignant cells via transplanted organs represents a lethal, yet preventable, portal for acquiring cancerous processes in the recipient's post-transplantation. In one study, it was shown that the risk of having a potential donor with an undetected malignancy amounted to 1.3% and the hazard of transmitting the cancer was up to 0.2% [24].

Prevention and treatment of post-transplant malignancies (Figure 4): Prevention of post-transplant malignancy must be planned properly and commenced in an early stage of pre-transplant preparation.

Approach to managing post-transplant malignancy (Figure 4)

Malignancy screening: Meticulous screening of both potential donors and recipients for covert malignancies is crucial, however, identifying the high-risk patients for developing malignancy and the criteria for selecting them must be prioritized and addressed thoroughly (Figure 3).

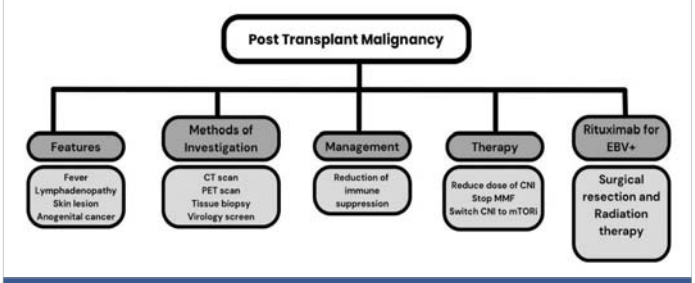

Figure 4: Features suggestive of post-transplant malignancy include fever, lymphadenopathy, skin, and anorectal lesions. Radiology screening and tissue biopsy are mandatory. Virology screening for relevant viruses is crucial. Management generally entails the reduction of immune suppression to boost the immune system. Switching to mTORi is pivotal in certain conditions. Monoclonal antibodies and cytotoxic therapy with or without surgical therapy.
Abbreviations: CT scan: Computerized Tomography scan; PET scan: Positron Emission Tomography; MMF: Mycophenolate Mofetil; CNI: Calcineurin Inhibitors; mTORi: Mammalian Target of Rapa inhibitor. Created by the author

High risk patients [24,25] (Figure 3)

1. Patients with a previous malignancy
2. Long duration of dialysis
3. Patients with connective tissue diseases, such as systemic lupus erythematosus
4. Prior administration of immune suppressants
5. Elderly recipients
6. Co-morbidities, such as chronic liver disease
7. Patients with known immune deficiencies,

Screening for viral infections

The virology status of the donors and recipients is crucial to identifying the potential recipients at risk of developing post-transplant malignancy. Hence, the infective status of EBV, HH8, HPV, CMV, HBV, and Merkle polyoma viruses must be uncovered and closely observed.

Human Leukocyte Antigen (HLA) matching

The degree of HLA mismatch and donor-specific antibody T titer is pivotal for predicting the outcome of transplantation. However, it is similarly important for planning the immune suppressant protocol. Hence, the higher the mismatch found, the more potent, the anti-rejection protocol would be.

Post-transplant management

Anti-rejection protocol: Selecting HLA matched donor would obviate the need for aggressive induction and maintenance anti-rejection protocol, particularly the induction with T-lymphocyte-depleting agents. Comparably, HLA-compatible donor transplantation is associated with a lesser risk of rejection and consequently less immune suppression pertinent to evading anti-rejection therapy, such as high-dose pulse steroid and T-lymphocyte depleting agents, with a subsequent lower risk of malignancy development. Furthermore, in case of perfect HLA 0 mismatch immune suppression minimization protocol might be implemented with great success which entails lowering doses of CNIs by 50 to 25 %, dual antirejection with CNIs, and prednisolone avoiding anti-metabolites and switching CNIs to mTORi such as sirolimus or everolimus with its favored anti-proliferative profile. Owing to less immune suppression status, these modifications of immunosuppression protocol minimize the risk of developing post-transplant malignancy Figure 1 [26].

Regular inspection and follow-up

For skin cancer, anogenital cancer, and PTLD, it's indicative to follow the patients at risk, proper vaccination, and a standard protocol for regular screening to detect earlier cancer.

EBV naïve potential recipients

Patients who are EBV negative and their potential donor is EBV positive are at great risk of developing EBV infection; similarly, in seropositive patients and seropositive donor status, the risk of transmitting and/or reactivating the EBV is mounting. Hence, selecting a seronegative donor for an EBV-nave patient is a protective strategy.

Ganciclovir and valganciclovir prophylaxis were considered by some centers for high-risk patients, with debatable results.

Reducing the level of immune suppression is another effective strategy, particularly for CNIs, by maintaining the tacrolimus trough level between 2 and 5 ng/ml.

Regular screening for EBV with PCR testing was adopted by some centers, a cut-off DNAemia value of 1000 copies/mL is considered positive for EBV infection. The risk of developing PTLD is increasing with EBV DNAemia of 10000 copies/ml which is pondered as clinically significant. Moreover, DNAemia of more than 40000 copies/ml is specifically related to a higher risk of developing PTLD. The strategy of management is generally based on the follow-up of EBV DNA copies trend. The occurrence of symptoms consistent with PTLD and planned radiology screening for symptomatic and asymptomatic patients with progressively overwhelming EBV DNAemia is the common practice. Reduction of CNI's dose to the lowest therapeutic trough level or switching to mTORi is advocated. Subsequently, the next step would be the administration of a single dose of rituximab to deplete the emerging abnormal B lymphocytes. The risk of rejection must be balanced and cautiously evaluated [27]. Adopted immune therapy is promising to control PTLD.

Approaching recipient with PTLD (Figure 5)

Depending on the onset of the disease, 4 phenotypes are recognized, and the burden of disease is verified via LDH, organ involvement, organ dysfunction, the transplanted organ, and CD20 positive vs. CD20 negative B lymphocytes. As a rule of thumb, minimization of immune suppression is the initial strategy to treat PTLD. However, the risk of rejection is mounting, and loss of organs is detrimental with an exceedingly elevated mortality rate in liver, lung, and heart transplantation. Immunotherapy with Rituximab for CD20-positive monomorphic or polymorphic PTLD is indicated for those patients at higher risk of rejection and intolerant of immunotherapy minimization. Chemotherapy and surgical resection are other modalities for advanced metastasized disease versus localized disease [28].

Adoptive immunotherapy [29,30]

Adoptive immunotherapy is a promising horizon for proper treatment.

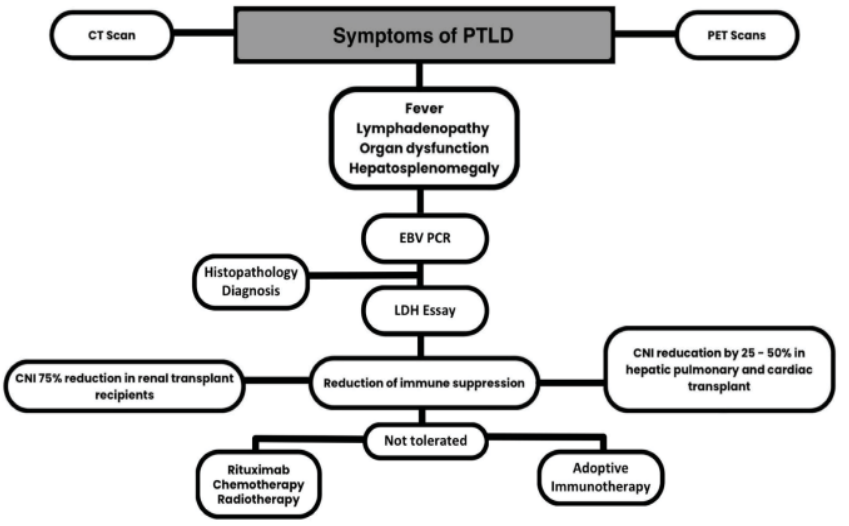

Figure 5: Post-transplant lymphoproliferative disease PTLD management.
The first step in the diagnosis is a PET scan and CT scan for those suspected patients. EBV status is pivotal to differentiate between EBV-positive and EBV-negative PTLD patients.
LDH measurement is indicated to assess the burden of the tumor. Diagnosis is confirmed by tissue biopsy. Management involves the reduction of immune suppression in a proper manner, which is usually more moderate in liver, lung, and cardiac than it is with kidney transplantation due to higher mortality with a rejection rate of those organs.
Abbreviations: PTLD: Post-transplant Lymphoproliferative Disease; EBV: Epstein-barr Virus; PET scan: Positron Emission Tomogram. Created by the author

Adopted immunotherapy is the utilization of autologous or allogenic lymphocytes to boost cell-mediated anti-cancerous activity.

Three modalities are available

1. **Tumour infiltrating lymphocytes TILs:** Specific lymphocytes activated against malignant cells expressing HLA-related abnormal proteins. Those TILs are commonly isolated from tumor biopsy tissues, then the colony is expanded in the laboratory via treatment with colony-stimulating cytokine IL2, subsequently, the expanded population of TILs is infused back into the patient. The activated TILs are supposed to be home to the tumor tissues mounting cell-mediated necrosis of malignant cells. This procedure might be augmented via systemic administration of IL2 and cyclophosphamide to increase the expression of tumor cells' antigenic protein. TILs used commonly in malignant melanoma with a success rate of more than 60%. The drawback is the high cost and difficult technique of harvesting and growing TILs.

2. **Chimeric antigen receptor T-lymphocytes CAR T-cells:** This modality includes the genetically created receptor for identified tumor cell membrane antigens. These receptors attached in the laboratory to peripherally isolated and expanded T-lymphocyte population from patients' blood. When transfused back to the patient, those CAR-T cells are recruited to the tumor site where they exert cell-mediated tumoral cell necrosis. This technique is mainly used in certain resistant leukemia. The main drawbacks are cytokines release syndrome, tumor lysis syndrome, neurological toxicity, and on-target off-target effects. The complete remission is more than 90 % in treating B-lymphocytes stemmed malignancies, with anti CD19 CAR T-cells adopted immune therapy.

3. **EBV-specific T lymphocytes:** It's a promising mode of therapy, reserved for PTLD patients who failed to respond to immunotherapy or chemotherapy. It's designed to utilize the patient's T-lymphocytes to fight against the malignant cells. Principally, owing to the expression of EBV antigens in PTLD tumor cells {type 3 latency}, EBV-sensitive cytotoxic T-lymphocytes might be used to fight against tumoral cells. Similarly, donor lymphocyte infusion DLI is used for the same purpose. The response to this modality of therapy was reported to linger at around 84%, with clinical improvement within 15 days and radiological reversal of the findings in 6 months. The main limitation is its selectivity for EBV-positive PTLD. Acute and chronic graft versus host disease GVHD were reported in the context of this therapy.

Approach to reduce Post-transplant risk of malignancy

1. Proper selection of a patient for potential transplantation, considering the history of past medical illnesses, therapies received, history of malignancy, its treatment, and duration post-recovery.

2. Selection of potential donor: meticulous screening

for underlying malignancy, history of previous malignancy, its treatment, and duration post-therapy.

3. Screening of the donors and recipients for oncogenic viruses. Treatment pre-transplantation when applicable.
4. Avoid EBV-positive donor / EBV-negative recipient transplantation.
5. Consider prophylactic protocol with valganciclovir for EBV for risky patients.
6. Regular follow-up of EBV copies post-transplantation and its trend in high-risk patients with lower thresholds for pre-emptive management.
7. Avoidance of HLA mismatch transplantation as it portends a higher risk of acute rejection.
8. Avoid induction with ATG
9. Steroid minimization or avoidance protocol is recommended in high-risk patients.
10. CNI minimization or avoidance protocol is advocated.
11. Early switching of CNI to mTORi protocol.
12. Maintenance anti-rejection with MMF and mTORi than CNI-based protocol.

Conclusion

Kidney transplantation is the best modality for renal failure replacement. However, post-transplant malignancy is the most serious drawback that is associated with increasing morbidity and mortality. The key to successful transplantation is proper donor selection and stratification of potential risk factors with a long-term plan to overcome the drastic consequences.

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