

Hematological malignancies post-transplant - what's new?

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Acute rejection and infection were the most common side effects in the early days of transplantation. Nowadays, cardiovascular issues and malignancies are the major complications in the transplanted population due to improved graft and patient survival, older recipient age, and the availability of more potent immunosuppressive treatments. The pathogenesis of cancer is extremely complex and multifaceted. Besides DNA damage caused by smoking, exposure to UV radiation, and compromised immune surveillance, oncogenic viral infections, such as Epstein-Barr virus (EBV) and human papillomavirus (HPV), can also transform cells and trigger uncontrolled proliferation. Immunosuppressive and T-cell depletion therapies further contribute to cancerogenesis in transplanted patients. The standardized cancer incidence ratios from different registries worldwide show that kidney transplant recipients have at least a twofold higher risk of developing cancer than the general population. Kidney cancer, lip cancer, non-Hodgkin lymphoma, and nonmelanoma skin cancer exhibit especially high rates in this population.

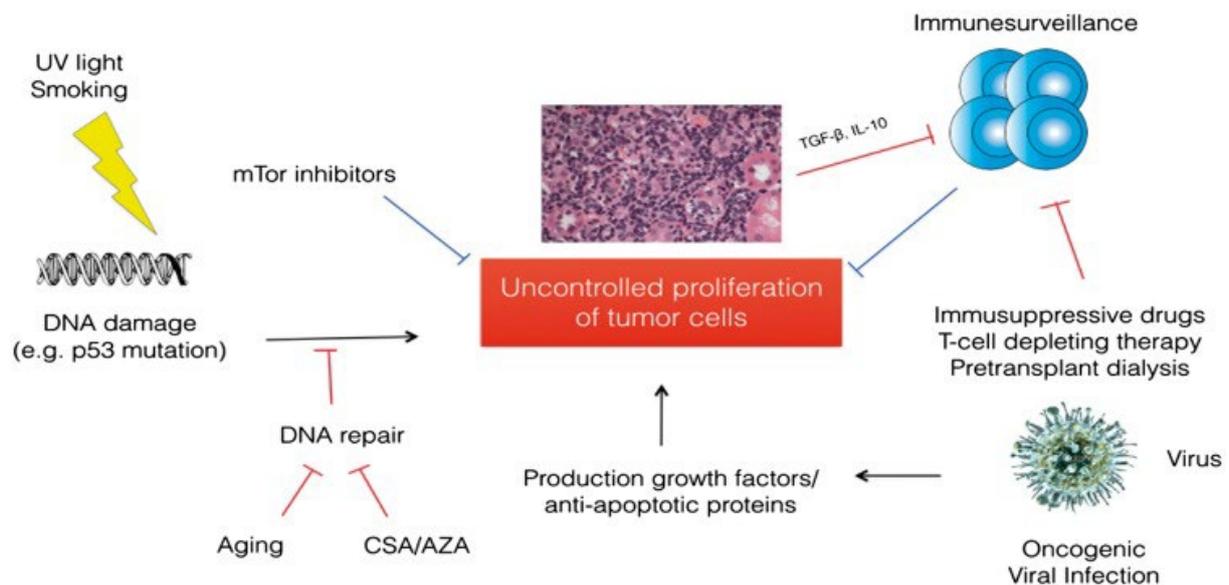


Figure 1. Cancerogenesis mechanisms following kidney transplantation

Post-transplant lymphoproliferative disorders (PTLD) are the major cause of death in transplant recipients. The incidence of PTLD is estimated to be around 2 - 2.5%, with an early rise in the first year post-transplantation, followed by a late disease wave. The three main risk factors associated with PTLD are the type of the transplanted organ, EBV status at the time of transplantation, and immunosuppression. Heart transplant recipients have the highest PTLD incidence (4.2%), whereas the occurrence in kidney transplant recipients is slightly lower (1.6%). The risk of developing PTLD is also increased if the recipient is EBV-negative and the donor is EBV-positive. Also, certain induction therapies, such as anti-thymocyte globulin (ATG) and Muromonab-CD3 (OKT3), and maintenance immunosuppressive agents, such as azathioprine and tacrolimus, have been associated with an

increased incidence of PTLD, whether used conventionally or for the episodes of acute rejection. Other risk factors for PTLD include underlying disorder, donor and recipient age, number and severity of rejection episodes, cytokine and cytokine receptor gene polymorphism, and HLA status.

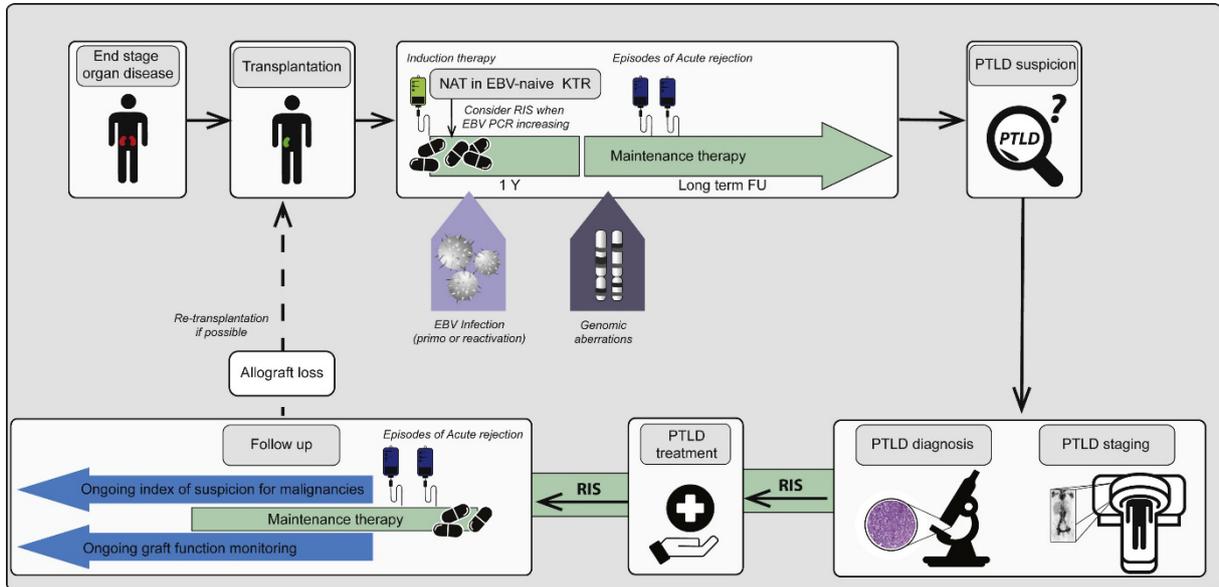


Figure 2. Natural history of post-transplant lymphoproliferative disorder

World Health Organization classifies PTLT into non-destructive PTLT, polymorphic PTLT, monomorphic PTLT, and classic Hodgkin lymphoma PTLT. The non-destructive PTLT and polymorphic PTLT are considered precursors of PTLT and are 100 % EBV-driven. In contrast, the monomorphic PTLT and the classic Hodgkin lymphoma patients can be either EBV-positive or EBV-negative.

The EBV attacks resident B cells in the oropharyngeal mucosa, which then undergo proliferation and differentiation in the germinal centers or the lymph nodes and progress through the stage of resting memory B cells. The resting memory B cells can be reactivated again, followed by EBV proliferation and release from lysed B cells to infect naive B cells in the oropharyngeal mucosa. During this proliferation and differentiation, the B cells express several EBV-associated proteins at different levels, which can be targeted by the immune response. Based on the expression of EBV-associated proteins, different latency types are defined, which are associated with particular malignancies. Post-transplantation EBV can be derived from the graft or the recipient. The donor is the sole source of EBV following hematopoietic stem cell transplantation, whereas in 85% of solid organ transplants with PTLT, EBV originates from the recipient.

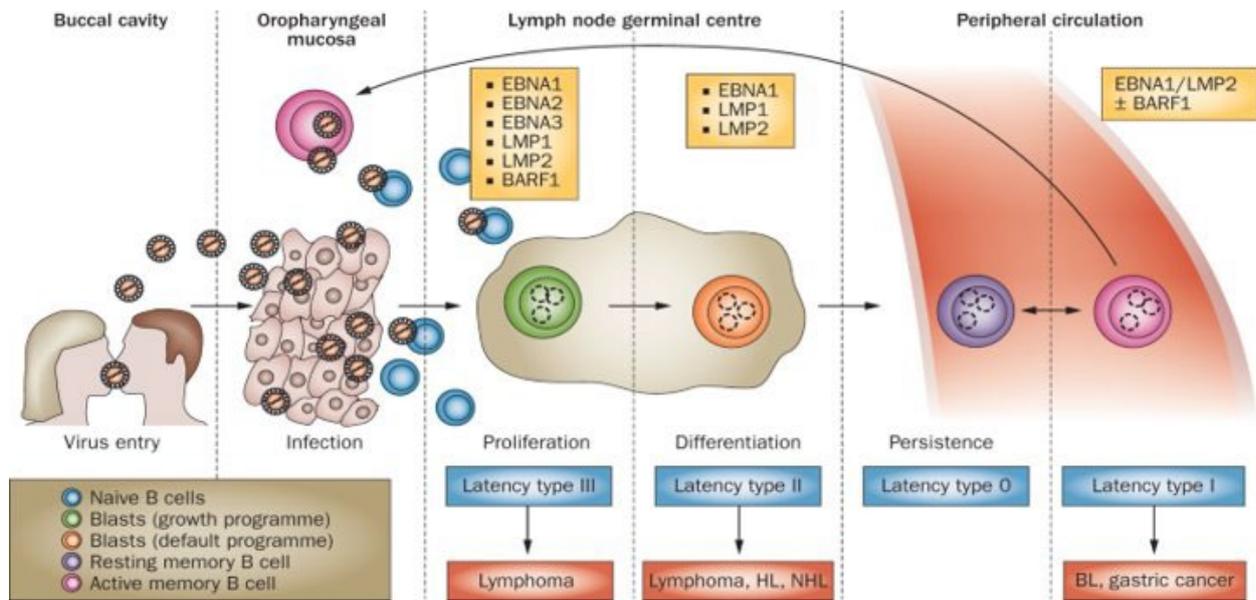


Figure 3. EBV-associated PTLD pathogenesis

Whether EBV-positive and EBV-negative PTLD are the same disease types has been a matter of debate for some time. The use of newer immunosuppressants, the prolonged survival rate of transplant recipients, and the possibility that initially EBV-positive patients eventually become EBV-negative have been discussed as the possible causes for the rising prevalence of EBV-negative PTLD. Despite evidence that EBV-negative and EBV-positive PTLD may share some common features, such as a similar survival rate, it is clear that there is a significant difference between the two diseases upon reviewing the genetic aberrations and the composition of the tumor microenvironment.

Restoring T cell function is a crucial goal in PTLD. Over the last two decades, several studies demonstrated the effectiveness of antigen-specific T cells to treat hematologic malignancies. The use of specific cytotoxic T lymphocytes (CTLs) to treat or prevent PTLD identified the absence of graft-versus-host disease as the key benefit over donor lymphocyte infusion. The group led by Helen Heslop studied patients who had received infusions of EBV-negative CTLs to prevent or treat EBV-positive lymphoproliferative disease arising after hematopoietic stem cell transplantation. This work paved the way for future investigation on the use of third-party derived and autologous EBV-specific CTLs to treat PTLD following solid organ transplantation which confirmed that there is commercial interest to develop independent EBV-specific CTLs. A broad range of EBV-specific DTL lines can be isolated from EBV-positive donors and HLA typed to be administered to patients with PTLD.

The treatment of PTLD is controversial as there have been no randomized control trials so far. The therapeutic approach has mainly focused on restoring T cell function, reducing B cell mass, and targeting EBV by inducers of the lytic cycle as an emerging treatment option. Since the lytic cycle is very susceptible to an immune response, the treatment strategy is to induce it, thus rendering the cells more susceptible to various treatments. Other treatments, such as ibrutinib, have also been suggested, but it is still unresolved whether they would be adequate in PTLD. Only small phase 2 trials are currently ongoing evaluating these treatment options for PTLD.

Research into autologous stem cell transplant after the development of PTLD focused on whether it can prevent the recurrence of the illness. Although good progression-free survival rates and overall survival rates have been reported, there was a high one-year treatment-related non-relapse mortality (24%) observed. Also, studies on anti-CD19 CAR-T cells in the treatment of PTLD showed conflicting results.

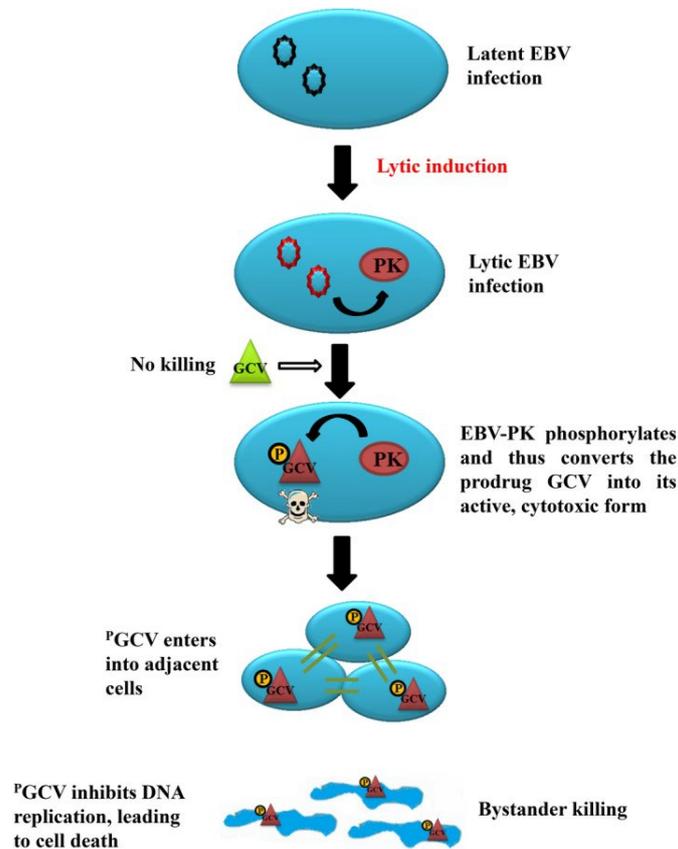


Figure 4. Inducing lytic cycle for EBV-positive tumors

Re-transplantation after the onset of PTLD has been explored as a therapeutic option in two recent trials, which used the Organ Procurement and Transplantation Network - OPTN and United Network for Organ Sharing (UNOS) databases. The results showed that in post-PTLD re-transplanted patients, the death-censored graft survival and patient survival rates were similar compared to other re-transplanted patients. Also, the study by Caillard et al, which reviewed the data from all patients who underwent kidney retransplantation after PTLD in all adult kidney transplantation centers in France between 1998 and 2015, concluded that re-transplantation is an option only in selected patients after the development of PTLD and graft loss.

Key points

1. Post-transplant lymphoproliferative disorders (PTLD) are the major cause of death in transplant recipients.
2. EBV-positive and EBV-negative PTLD are different diseases, where EBV-negative PTLD is most likely classic non-Hodgkin lymphoma occurring after kidney transplantation.
3. Novel PTLD treatments are focusing on cellular therapies. The most promising are third-party CTLs and lytic cycle-inducing agents.

4. Re-transplantation is a beneficial option for PTLD treatment, but only in selected patients.

Further reading

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