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INVITED COMMENTARY

Post-transplant lymphoproliferative disorder prevention: new light on the horizon?

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Solid organ transplantation represents the ultimate therapeutic option for terminal organ failure and has experienced a tremendous success in the last decades. However, major problems, such as the risks associated with lifelong immunosuppression, have not been resolved so far. These risks are mainly threefold: (i) infections (usual and opportunistic ones), (ii) increased cancer incidence, and (iii) cardiovascular complications (newly induced or aggravated by chronic immunosuppression) [1]. There is also a close relation between infection and cancer, as certain viruses directly cause cancers such as post-transplant lymphoproliferative disorder (PTLD; mainly caused by Epstein–Barr virus, EBV), cervical cancer (papillomavirus) or Kaposi sarcoma (human herpesvirus 8) [2].

In this issue, Ville *et al.* [3] from the University Hospital in Nantes present a single-center retrospective cohort study on the occurrence of PTLD after kidney or kidney/pancreas transplantation. They found that in patients receiving an EBV high-risk (D+/R−) transplant, the incidence of late PTLD (beyond 1 year post-transplant) was significantly lower, when they received antiviral prophylaxis with either (val)acyclovir or (val)ganciclovir, whereas no difference was observed for early PTLD (within the first year post-transplant). This finding is an interesting observation, as it offers a potential intervention to prevent the feared complication of PTLD in this patient group.

The authors propose that anti-viral drugs might have an effect primarily on the lytic cycle of EBV replication and therefore reduce early EBV DNAemia, as shown previously in pediatric recipients [4]. This may further lead to a lesser number of B-cells eventually infected by EBV and therefore also to a reduced transformation potential [5]. However, these arguments do not well explain why there should be no effect on the occurrence of early PTLD. Histologically, early and late PTLDs were quite different in this study. Early PTLDs were all monomorphic diffuse large B-cell lymphomas (DLBCL), whereas late PTLDs presented with unusual histology and/or location: There was one polymorphic type, one monomorphic DLBCL, but with an anaplastic pattern and location to the CNS, one Burkitt lymphoma, one Hodgkin lymphoma, one non-Hodgkin lymphoma, and one with a smooth muscle tumor. This heterogeneity, therefore, suggests different mechanisms of tumor transformation in late PTLDs compared to early DLBCL, which merits further investigations.

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In addition to virological explanations for the observed phenomenon, also immunological differences may exist between the two retrospectively analyzed groups. Antiviral prophylaxis was not randomly distributed, but used only in patients, for which seropositivity against cytomegalovirus (CMV) was found either in the donor and/or in the recipient. Thus, in the prophylaxis group, there were 33/37 patients (89%) with CMV seropositivity either for the donor or the recipient, whereas in the no-prophylaxis group 32/36 patients (88%) were negative for both. CMV is well-known to induce chronic activation of the immune system [6], thereby potentially leading to a higher incidence of allograft rejection episodes (e.g., by cross-reactive $CD8^+$ T cells [7]) as well as leading to chronic inflammation associated with accelerated atherosclerosis [8]. This chronic immune activation may also lead to better control of other infections such as EBV. This author has not found any evidence in the literature of directly cross-reactive T cells between CMV and EBV. However, a low level and subclinical CMV replication with subsequent immune activation may help to induce EBV-reactive cells via bystander activation.

After reading the study of Ville *et al.*, what should we recommend for prevention of PTLD in EBV high-risk recipients (Table 1)? First, the most efficient approach on a systemic level might be to avoid an EBV D+R− situation already in the allocation process. As an example, EBV− kidney recipients have a general priority in the allocation algorithm of Swisstransplant when an EBV− negative organ is offered. This seems to lead to a particularly low rate of PTLD in this population (Steiner *et al.*, manuscript in preparation). Also, UNOS has adopted such a strategy with regard to pediatric recipients [9]. However, the community accepts, in this case, a slight inequity of allocation for the EBV+ recipients, which however is not critical, as the overall number of adult EBV− recipients is low. Second, guidelines recommend monitoring of EBV DNAemia with subsequent reduction in immunosuppression in case of primary infection [10]. However, limited data support this recommendation, and this approach might be difficult to follow in immunologically high-risk recipients. Third, the application of intravenous immunoglobulins might offer some protection against EBV replication and therefore the induction of PTLD. This has been suggested by a large retrospective study from the Collaborative Transplant Registry [11], in which particularly early PTLDs were reduced by intravenous immunoglobulins. However, the only randomized controlled trial in pediatric liver recipients yielded a negative result [12]. Fourth, the study by Ville *et al.* [3] suggests that anti-viral prophylaxis with valacyclovir or valganciclovir might be a good option to at least prevent a large percentage of the late PTLDs. However, the problem for early PTLDs is then still not resolved, and we still do not know whether this approach is equally effective in a CMV D−R− group, which normally will not receive any prophylaxis. Fifth, the preemptive application of rituximab, which is known as an effective treatment for at least some milder forms of PTLD, might also prevent EBV infection and the generation of PTLD. Encouraging results have been reported from kidney as well as hematopoietic stem cell transplantation [13,14]. However, further studies are needed to gain more evidence for this option.

Taken together, the high incidence of PTLD in EBV− recipients of an EBV+ solid organ is an important clinical problem. If possible, allocation algorithms should try to minimize the occurrence of such situations at the beginning. However, when caring for EBV high-risk solid organ recipients, EBV DNAemia should be monitored and immunosuppression reduced in cases of primary infection [15]. The prophylactic use of either antiviral drugs or rituximab might offer some benefit, although more detailed studies are needed to make evidence-based recommendations.

Table 1. Options for prevention of PTLD in EBV high-risk (D+R−) solid organ recipients (for references: see text).

Approach	Rationale	Effectiveness	Evidence
Allocation	Avoid EBV D+/R− constellation	+++	No studies, but practice in certain allocation algorithms (e.g., CH, UNOS)
EBV monitoring	Early detection of EBV replication and subsequent reduction in immunosuppression	+	Retrospective data
Immunoglobulins	Passive protection with antibody transfer	+	Retrospective studies positive, 1 RCT negative
Anti-viral prophylaxis	Prevention or reduction in viral replication	++	Several retrospective case series
Rituximab	Prevention of EBV infection and B-cell transformation	++	Few small studies in the solid organ and stem cell transplantation field

PTLD, post-transplant lymphoproliferative disorder; EBV, Epstein–Barr virus.

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