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Epstein-Barr virus-related post-transplant lymphoproliferative disorder in solid organ transplant recipients

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Abstract

Epstein-Barr virus (EBV) contributes to the pathogenesis of post-transplant lymphoproliferative disease (PTLD) in more than 70% of cases. EBV DNAemia surveillance has been reported to assist in the prevention and treatment of PTLD in hematopoietic stem-cell transplantation (HSCT) recipients. Derived from experience in HSCT and taking into account that PCR-based EBV monitoring techniques are currently available in most solid organ transplant (SOT) centres, there is a great interest in EBV surveillance and prevention of PTLD in SOT recipients. In the present document we have tried to address from a practical perspective different important topics regarding the prevention and management of EBV-related PTLD in SOT. To this end, available information on SOT was analysed and combined with potentially useful data from HSCT and expert observations. The document is therefore structured according to different specific questions, each of them culminating in a consensus opinion of the panel of European experts, grading the answers according to internationally recognized levels of evidence. The addressed issues were grouped under the following topics. (i) Timing and epidemiological data of PTLD. Prophylaxis guided by clinical risk factors of early and late PTLD in SOT. (ii) Relationship of EBV DNAemia load monitoring and the development of PTLD in solid organ transplant recipients. (iii) Monitoring of EBV DNAemia after SOT. Which population should be monitored? What is the optimal timing of the monitoring? (iv) Management of SOT recipients with persistent and/or increasing EBV DNAemia.

Keywords: Epstein Barr virus, post-transplant lymphoproliferative disease, recommendations, risk factors, viral kinetics
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Hot Topics

- EBV serostatus should be determined for all SOT donors and recipients because an EBV-seronegative recipient with an EBV-seropositive donor is the most high-risk situation for development of PTLD *(A-II)*.
- For EBV-negative recipients, the use of T-cell depleting agents should be avoided if possible *(B-II)*. Anti-CD25 or no induction should be preferred *(B-III)*.
- Prophylaxis using intravenous immunoglobulins and (Val)-Ganciclovir should be considered in EBV-seronegative recipients of EBV-seropositive donor organs *(B-II)*.
- Chronic or persistent high EBV load SOT carriers are more frequent in primary infections but are not clearly related to a higher risk of the development of EBV-positive PTLD. A rise in EBV load could be more informative regarding the risk of developing PTLD *(C-III)*.
- Universal monitoring of EBV DNAemia is not recommended in SOT recipients *(C-III)*.

- Monitoring of EBV DNAemia should be useful for EBV D+/R- SOT recipients *(AII)* and should be considered in EBV-seropositive recipients of lung and intestinal transplants *(B-III)*.
- For asymptomatic EBV-seropositive SOT recipients undergoing acute rejection therapy, EBV load monitoring should be initiated *(B-III)*.
- For SOT patients with significantly increasing EBV loads (usually more than 10-fold or >1 log10 cp/mL), regardless of the EBV-serostatus, a careful clinical and radiological examination using computer tomography and/or PET-CT should be performed to search for lymphadenopathy, mass lesions and other signs of PTLD *(B-III)*.
- For asymptomatic EBV-seropositive SOT recipients without clinical or radiological evidence of PTLD, but significantly increasing EBV loads, reducing immunosuppression should be considered *(B-III)*. A change in immunosuppressive therapy towards a regimen based on a mammalian target of rapamycin (mTOR) inhibitor may be beneficial, although data supporting the rationale for this approach in the preemptive setting are insufficient *(C-III)*.
- There are currently insufficient data to determine the efficacy of anti-CD20 antibody as a preemptive agent in SOT recipients with persistent and/or increasing EBV DNAemia, although in the case of explosive EBV dynamics, many experts would consider this as preemptive treatment and follow the EBV loads *(C-III)*.

Introduction

Post-transplant lymphoproliferative disorders (PTLDs) occur on average in 1 to 16% of solid organ transplantation (SOT) recipients. The risk depends on the type of transplanted organ, being higher for the heart and liver as compared with the kidney, exposure to lymphocyte-depleting antibody therapies, the presence of some specific risk factors and Epstein-Barr virus (EBV) infection and the immunity status of the donor and recipient, being highest in EBV-seronegative recipients of EBV-seropositive donor organs [1,2]. Accordingly, PTLD occurs at higher rates in paediatric recipients compared with adult recipients [3,4]. In kidney transplant patients, early PTLD occurring within the first year post-transplantation has been reported in 0.46 per 100 person years [5]. PTLD represents a spectrum of diseases that range from an indolent (polyclonal) lymphoproliferation, which can resolve following reduction of immunosuppression, to malignant aggressive lymphoma, which has a high mortality despite intensive chemotherapy [6].

Epstein-Barr virus contributes to the pathogenesis of PTLD in more than 70% of cases [7,8]. EBV DNAemia surveillance has been reported to assist in prevention and treatment of PTLD in hematopoietic stem-cell transplantation recipients (HSCT) [9]. Derived from experience in HSCT and taking into account that PCR-based EBV monitoring techniques are currently available in most SOT centres (unpublished data from the European Survey of PTLD in SOT, personal communication, San Juan *et al.*), there is a great interest in EBV surveillance and prevention of PTLD in SOT recipients. Unfortunately, the first recommendation documents [10,11] are limited in their applicability to clinical practice and based on only limited evidence.

In the present document we have tried to address from a more practical perspective different important topics regarding the prevention and management of EBV-related PTLD in SOT. To this end, available information in SOT was analysed and combined with potentially useful data from HSCT and expert observations. The document is therefore structured according to different specific questions, each of them culminating in a consensus opinion of the panel of experts, grading the answers according to internationally recognized levels of evidence [12].

Timing and Epidemiological Data of PTLD. Prophylaxis Guided by Clinical Risk Factors of Early and Late PTLD in SOT

The incidence of post-transplant lymphoproliferative disorder varies according to the type of transplanted organ and age of the recipient at time of transplantation. The incidence of PTLD is higher after intestinal, lung and heart lung transplantation, ranging from 2 to 10% [13–15], whereas lower rates are reported after liver and kidney transplantation, ranging from 0.2 to 2.5% [15–17]. Recent registry data, however, suggest that liver transplant recipients have a higher risk of PTLD compared with kidney transplant recipients. Hypothetically, the presence of lymphoid tissues in the hepatic graft might be a contributing factor [2]. Reports of the UK Transplant Registry showed that standardized incidence ratios matched for age, gender and timing of non-Hodgkin lymphoma compared with the general population in SOT recipients are 12.5 for kidney recipients, 13.3 for liver recipients, 19.8 for heart recipients and 30 for lung recipients [18]. In the French Registry, where all PTLDs in adult kidney transplant patients were recorded over a 10-year period (1998–2007), PTLD cumulative incidence was 0.35% patient-years at 1 year, 1.2% patient-years at 5 years and 2.1% patient-years at 10 years post-transplantation [16]. The incidence of PTLD is higher in paediatric (from 1