Post-transplant lymphoproliferative disorders: from treatment to early detection and prevention?

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Post-transplant lymphoproliferative disorder (PTLD) encompasses a heterogeneous group of lymphoproliferative diseases, ranging from polyclonal proliferations resembling infectious mononucleosis, to monomorphic proliferations indistinguishable from aggressive types of lymphoma such as diffuse large B-cell lymphoma.[1] The relation between PTLD and Epstein-Barr virus (EBV) is well recognized. The immunosuppressive drugs administered to suppress rejection of the transplanted organ, and/or T-cell depletion to suppress graft-versus-host disease in the case of allogeneic hematopoietic stem cell transplantation, can lead to a profound decrease in EBV-specific T-cell surveillance.[2] In this situation, latently EBV-infected B cells may escape immune surveillance and expand to a polyclonal proliferation, ultimately leading to PTLD. However, according to the international classification,[3] any lymphoma arising in the post-transplant patient is considered to be (a variant of) PTLD,[1] while the presence of EBV in tumor cells is not required for the diagnosis.[1] In addition, although most PTLD are of B-cell origin, also T- or natural killer (NK)-cell lymphomas arising in the transplant recipient are classified as PTLD.[1] The role of EBV in the pathogenesis of T-cell PTLD, of which only a minority is EBV-positive,[4] is less clear. This heterogeneity emphasizes the fact that, besides EBV, also other pathways must be involved in the pathogenesis of PTLD. This perspective will focus on early detection, staging, treatment and pre-emptive treatment of PTLD after solid organ transplantation.

In keeping with its pathogenesis, the most important risk factors for PTLD are primary EBV infection after transplantation, and the amount and intensity of immunosuppressive drugs used after transplantation.[5]

The incidence of PTLD after solid organ transplantation varies, with the highest incidence (5-20%) found after heart, lung and small bowel transplants.[6] In contrast, the incidence in kidney transplant recipients is much lower (1-3%). This difference is most likely related to the less intensive immunosuppressive protocols used in kidney transplantation.[6]

The primary presentation is often extranodal, with the transplanted organ and digestive tract being the most frequently involved sites. Interestingly, involvement of the graft is associated with PTLD arising early (<1 year) after transplantation, which suggests a possible permissive role of the graft microenvironment in the pathogenesis of these early PTLD.[7] Although some PTLD may derive from donor lymphocytes transplanted with the graft, this does not explain the tendency of early PTLD to be localized in or near the graft, as the vast majority of PTLD in solid organ transplantation are host-derived.[8,9]

EBV-DNA load monitoring

Much effort has been put into devising methods that can identify patients at risk of PTLD. After the first studies reporting a quantitative difference in circulating EBV-DNA load and EBNA antibodies between transplant recipients with and without PTLD,[10,11] the clinical relevance of the amount of circulating EBV-DNA in the peripheral blood has been extensively investigated. It is unclear, however, which threshold values are predictive of the development of PTLD.[12] A rising trend in the individual patient probably more accurately defines the patient at risk than a set EBV-DNA load threshold.[12]

Strategies to prevent PTLD guided by EBV-DNA load include reduction of immunosuppression[13,14] and, based on the successful approach of donor lymphocyte infusion in PTLD arising in patients after allogeneic stem cell transplantation,[15] the infusion of autologous EBV-specific cytotoxic T-lymphocytes (CTL) in solid organ transplantation.[16] A study performed at our center showed that immunosuppression can be safely reduced in lung transplant recipients with high EBV-DNA loads, suggesting that even in patients at high risk of allograft rejection (i.e. lung transplant recipients), this approach is feasible.[17] Results of pre-emptive reduction of immunosuppression in pediatric liver transplant recipients suggest that this strategy may indeed lead to a lower incidence of PTLD.[13,14]

Treatment

The optimal treatment of PTLD, when the diagnosis has been established, is still a matter of debate. As the development of PTLD is generally considered to be the result of decreased T-cell surveillance, the logical first step of treatment is reduction of immunosuppression.[18] Especially early, polyclonal, lesions may respond well to the reconstitution of EBV-specific T-cell control.[1]

Although some reports show a beneficial result of antiviral agents, the value of these agents in the treatment of PTLD remains at least doubtful. Agents such as acyclovir and ganciclovir only limit productive viral replication, and do not affect the latent cycle of EBV infection associated with PTLD, in which B-cell prolif-

eration is independent of spontaneous viral replication.[19] Before the introduction of monoclonal antibody therapy, polychemotherapy (usually CHOP-like) was considered first-line treatment for PTLD. Only results from retrospective, non-randomized and small groups of heterogeneous patients treated with polychemotherapy have been published, reporting wide ranges of complete remission (CR) from 30% up to 80%, and overall long-term survival rates from 20% up to 60%. Because the immunocompromised transplant patient is much more vulnerable to infections than the non-immunocompromised patient, infection-related complications during treatment have profound effects on feasibility and outcome of polychemotherapy in PTLD.[20]

During the last years, monoclonal antibody therapy (especially rituximab, directed against the B-cell receptor CD20) has been introduced for the treatment of B-cell PTLD.[21-23] Rituximab is especially attractive in PTLD, because of its low toxicity profile. The first report on monoclonal antibody therapy in PTLD evaluated the use of two murine monoclonal antibodies against B-cell antigens (CD21 and CD24).[21,24] Since the introduction of rituximab, more evidence has become available of its efficacy in PTLD,[22,23,25] including that from the Spanish multicenter trial on extended treatment with rituximab reported by Gonzalez-Barca *et al.* in this issue of the journal.[26]

Although rituximab undoubtedly has become the most important first-line treatment modality in B-cell PTLD, several questions about its use in the management of PTLD remain to be answered. In the Spanish multicenter trial reported by Gonzalez-Barca *et al.*, CD20 expression in biopsy specimens was a prerequisite for inclusion. Whether the expression of CD20 should always be a prerequisite for initiation of rituximab therapy in B-cell PTLD has not been well established. Although it seems obvious that T-cell PTLD will not respond to rituximab administration, this is less clear for B-cell PTLD without expression of CD20. In these cases, sampling errors, especially when only a small amount of tissue is available for analysis, might be responsible for the absence of CD20 expression. Moreover, PTLD may present with discordant lesions,[1] in which different levels of CD20 expression might be present in the same patient.

Another issue is when to start rituximab therapy. Should treatment only be initiated in the absence of response after discontinuation or reduction of immunosuppressive treatment, as was done in the Spanish multicenter trial? In monomorphic PTLD, the chance of complete response after reduction of immunosuppression only is low. Moreover, early treatment of PTLD probably leads to a better prognosis.[27] Given its low toxicity, starting rituximab at the same time as immunosuppression is reduced does, therefore, seem a justified approach.

Extended treatment of B-cell lymphoma with rituximab (i.e. maintenance therapy) has gained much interest over the last years. Recent results from prospective controlled trials indicate that maintenance treatment increases freedom from lymphoma progression, especially in recurring follicular lymphoma and mantle cell lymphoma.[28,29] Maintenance studies in diffuse large B-cell lymphoma are ongoing.[30] The data presented by Gonzalez-Barca *et al.* suggest a possible beneficial effect of extended rituximab treatment in PTLD as well.[26] However, which particular group of patients might truly benefit from this approach needs further clarification.

Staging of and treatment evaluation

Besides conventional diagnostic methods to visualize malignant lymphoma, fluorodeoxyglucose (FDG)-positron emission tomography (PET) scanning is increasingly recognized as an important tool in the visualization of malignant lymphoma, especially for the detection of extranodal sites of disease.[31] Because PTLD frequently presents at extranodal sites,[7] FDG-PET is very useful for the visualization of this disease.[32-34] In addition, FDG-PET performed after treatment provides a more accurate classification of response and prediction of prognosis when compared with computed tomography (CT)-based assessment in lymphoma.[35]

Probably, this is also true for the assessment of response in PTLD.[34] In the absence of FDG-PET scanning, the implications for clinical practice of the data presented by Gonzalez-Barca *et al.* must be interpreted with caution. Patients with FDG-PET-negative mass lesions on CT-scans might not need additional treatment. More importantly, whether patients with persisting FDG-PET-positive PTLD lesions after rituximab would truly benefit from extended treatment is questionable, given the high predictive value for therapy failure of FDG-PET-positive lesions during treatment in aggressive lymphoma.[36-38]

Conclusions and perspectives

The emerging data on the efficacy of rituximab treatment in PTLD have established its use, along with reduction of immunosuppression, as first-line treatment in PTLD. FDG-PET is an important tool for staging and response evaluation in PTLD, and its incorporation in future clinical trials is mandatory. In those cases refractory to first-line treatment with rituximab, as confirmed by FDG-PET scanning, it is as yet unclear whether extended treatment with rituximab alone is appropriate, or whether polychemotherapy should be initiated.

Although the introduction of rituximab has undoubtedly led to an improvement of outcome, 20-50% of patients with PTLD will fail to respond to treatment. Therefore, better early detection and development of strategies to prevent PTLD in high risk patients will remain important challenges in the coming years. A promising and safe first step to prevent PTLD in solid organ transplant patients is EBV-DNA load-guided reduction of immunosuppression. Further prospective clinical studies exploring this strategy are eagerly awaited.

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