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Supplement Article

II. Challenges in the management of post-transplant lymphoproliferative disorder

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Introduction

Post-transplant lymphoproliferative disorders (PTLDs) represent a heterogeneous group of lymphoid proliferations arising as a consequence of immunosuppression (IS) in subjects who received solid organ transplant (SOT) or allogeneic stem cell transplant (aSCT). Despite their low incidence, PTLDs are always a concerning problem in a patient who has previously undergone a complex transplant procedure, with the necessity of a multidisciplinary management between the hematology team and the transplant team.

The risk of PTLD depends on the type of transplant, with a probable direct relationship with the intensity and the duration of the IS. The incidence of PTLD after aSCT is about 1% but increases in patients undergoing HLA-mismatched aSCT, receiving T-cell depletion or developing graft versus host disease (GvHD) [1]. Overall, SOT recipients have a higher risk of PTLD compared with aSCT patients, but the incidence is different according to the type of transplant (renal < liver < heart < multi-organ transplant such as heart–lung or liver–bowel) and according to Epstein–Barr virus (EBV) serological status of patients, with a higher risk in EBV-negative recipients [2].

Pathology

Post-transplant lymphoproliferative disorders are not represented by a single type of proliferation, and the World Health Organization classification defines four categories of PTLD: (i) early lesions (reactive plasmacytic hyperplasia and infectious mononucleosis-like); (ii) polymorphic PTLD; (iii) monomorphic B-cell and T-cell PTLD; and (iv) Hodgkin's lymphoma (HL) and HL-like PTLD [3].

Early lesions are lymphoid proliferations characterized by a preservation of tissutal architecture. They are usually polyclonal, EBV-positive and are more frequent in younger patients and in EBV-negative transplant recipients. Polymorphic and monomorphic PTLDs represent the most frequent lesions. Polymorphic PTLDs are composed of B-cells with different maturation and may be either monoclonal or polyclonal. In contrast, monomorphic PTLDs are consistently monoclonal and should be classified as separate B-cell or T-cell lymphomas according to their morphological and immunohistochemical features. HL and HL-like PTLDs are the less frequent subtypes of PTLD. Rare subtypes of PTLD are represented by plasmablastic lymphoma, plasmocytoma-like PTLD and primary central nervous system (CNS) PTLD.

Considering the cellular origin, the large majority of PTLD in SOT recipients are of host origin, while a donor origin characterizes the majority of PTLD arising in aSCT recipients, whose post-transplant immune system is in fact of donor origin.

Epstein–Barr virus has a crucial role in the development of PTLD in the majority of patients, particularly in those with early lesions and polymorphic PTLD. EBV, a γ-herpesvirus, can be found in more than 90% of adult population after a primary infection, frequently asymptomatic, occurring usually during childhood. After the primary infection, which determines a T-cell response in the immunocompetent host, a latent infection occurs, persisting for life under the control of EBV-specific T-cells. Different types of latency are distinguishable according to the expression of viral antigens; type 3 latency, which is associated with the expression of all latency proteins, is the one associated with PTLD. In the setting of SOT and aSCT, iatrogenic IS is necessary to reduce the risk of graft rejection in SOT and GvHD in aSCT. IS leads to an imbalance between latent EBV-infected B-cells and EBV-directed T-cells, which are down-regulated, thus determining a progressive EBV-mediated lymphoid proliferation. EBV-negative PTLD (about 20% of cases)

tends to arise later after transplantation; their etiology is largely unknown, but some patients do respond to IS reduction [4].

Clinical presentation

There is no specific feature of PTLD, which is frequently a multiorgan disease that could involve both nodal and extranodal sites. B-symptoms are frequent, but when extranodal sites are involved, symptoms specific to the involved organ are possible and in most cases lead the clinicians to further investigations. As well as in non-transplant associated lymphomas, a biopsy is mandatory in order to establish a correct diagnosis. Besides basic techniques (morphology and immunohistochemistry), the pathological assessment of lymphoid proliferations in SOT or aSCT recipients should include the evaluation of EBV-associated antigens [EBV latent membrane protein 1 (LMP1) and EBV nuclear antigen 2 (EBNA-2)] and EBER *in situ* hybridization, which may not be available in all pathology units.

Once a PTLD diagnosis is confirmed, a thorough staging with whole body CT and bone marrow biopsy is necessary to evaluate the correct extent of disease [5]. The precise role of ^{18}FDG-positron emission tomography in the context of PTLD has not been well clarified yet, but it is increasingly used in association with CT scan for staging and restaging of PTLD. Lumbar puncture with analysis of cerebrospinal fluid (cytology and flow citometry) should be restricted to patients with a suspicion of CNS or meningeal involvement.

Epstein–Barr virus monitoring and pre-emptive therapy

Because of the relation between EBV and PTLD, it has been speculated that the identification of an EBV viral load increase might be a precocious sign of PTLD triggering a pre-emptive approach possibly reducing the actual development of PTLD. However, even if EBV DNAemia could be easily monitored with real time polymerase chain reaction techniques, there is no consensus regarding the frequency of controls and whether it should be evaluated on plasma, serum, whole blood or mononucleated cells [6]. Recently, an International Standard has been developed by the World Health Organization for EBV amplification techniques in order to allow an inter-laboratory comparison. However, each laboratory should develop its own optimal test and then determine a threshold having the best sensitivity, specificity, negative and positive predictive values. In high-risk aSCT recipients, monitoring should be performed at least weekly in the first 3 months, then every 2 weeks in the second 3 months, then according to clinical conditions and presence of cGvHD. In the SOT setting, the frequency of testing may vary according to the type of transplant, IS regimen, recipient's age and EBV serologic status.

In addition to EBV DNAemia, the number of EBV-specific CD8+ T-cells may be evaluated in order to estimate the capacity of the immune system to respond to an EBV-driven proliferation. The combination of the two methods may increase the predictive value of a high EBV DNAemia, permitting then a more calibrated pre-emptive treatment. This is based on IS reduction and, mainly in aSCT recipients, on the administration of rituximab, a chimeric murine-human antiCD20 antibody, so as to deplete the B-cell population and reduce the EBV proliferation capability [7].

Therapy

As previously anticipated, a multidisciplinary team should evaluate the possible therapies for PTLD patients, considering all the aspects of the disease and the patient. These include the timing of PTLD onset (early versus late), the recipient serological status, the current IS regimen, the histologic type of PTLD and the extent of disease.

As soon as the diagnosis is established, and possibly even at suspicion of PTLD, a reduction of IS treatment is mandatory, starting with the interruption of myelotoxic agents such as mycophenolate mophetil or azathioprine. The entity of the reduction should be decided according to the clinical characteristics of PTLD and to the risk of graft rejections or GvHD. Early lesions and polymorphic PTLD tend to respond better than other lesions. A strict follow-up is useful to assess a response to IS reduction.

Apart from the necessity of diagnostic biopsies, surgery is seldom the treatment of choice in PTLD. However, in the case of gastrointestinal PTLD, a surgical resection may be advised considering the high risk of local complications (perforation, occlusion and bleeding) [8].

Because of the frequent multifocal nature of the disease, radiation therapy (RT) has a limited role in PTLD, but it should be considered in particular cases such as primary CNS PTLD (alone or in association with chemotherapy, particularly cytarabine or methotrexate) [9], and in the rare plasmocytoma-like PTLD. The technical aspects of RT (doses, fractioning and fields) should not be different from lymphomas arising outside the transplant setting. An irradiation of the transplanted organ should obviously be avoided.

Systemic treatments such as immunotherapy with rituximab and chemotherapy represent the gold standard for treatment of advanced PTLD failing IS reduction. Rituximab may be administered in CD20+ PTLD as a single agent, determining a response in up to 60% of patients in different phase 2 studies [10,11]. The association of rituximab with chemotherapy, mainly cyclophosphamide,

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vincristine, doxorubicine and prednisone (R-CHOP), could increase the response rate in PTLD, but higher toxicity rates should be taken into account, as well as the higher risk of infections (opportunistic and non). Recently, the sequential administration of rituximab followed by CHOP has been investigated in a European multicentre trial, with an overall response rate of 90% and a 3-year progression-free survival of 54% [12]. As expected, toxicity was high, with 11% of treatment-related mortality; this protocol was amended in 2007 with a risk stratified sequential treatment approach, in which patients obtaining a complete response (CR) after an induction of four weekly doses of rituximab did not proceed to CHOP but received four 3-weekly doses of rituximab, while patients without CR received four cycles of R-CHOP21. This approach seems to be very promising, sparing the toxicity of chemotherapy in patients responding to rituximab alone.

The functionality of the transplanted organ is fundamental to the risk of toxicity. The cardiotoxicity of anthracyclines is of particular concern in cardiac transplants recipients, who may then receive anthracycline-free chemotherapy regimen; the use of liposomal anthracyclines should be evaluated in these patients.

In the rare setting of Burkitt PTLD, the use of standard, multidrug regimens such as CODOX-M/IVAC is associated with high, almost unacceptable, toxicity rates. R-CHOP is more tolerated, even if the response rate is quite lower than in Burkitt lymphoma occurring outside the PTLD setting.

CD20 negative PTLDs, such as HL, HL-like, T-cell, plasmablastic lymphoma and plasmocytoma-like PTLD, are treated differently according to the diagnosis, without rituximab. HL and HL-like PTLD could be treated with HL-directed treatments, such as the combination of doxorubicine, bleomycin, vinblastine and dacarbazine (ABVD), while RT may be an option in stage I patients. Plasmablastic and T-cell PTLD are characterized by a worse prognosis, and CHOP chemotherapy is the treatment of choice. Plasmocytoma-like PTLD may be treated with RT and a myeloma-like systemic treatment. CD30-positive PTLD may benefit from brentuximab vedotin, an antibody drug conjugate with monomethyl auristatin E directed against CD30, which may be associated with lesser toxicity compared with conventional chemotherapy. Prospective data are necessary to comprehensively evaluate this drug in the context of PTLD.

While the use of antiviral drugs and intravenous immunoglobulins could be useful in PTLD associated with primary EBV infections, there is scant data to recommend its use in PTLD occurring in EBV-positive recipients.

During the last years, there have been promising data about the role of adoptive immunotherapy for the treatment of PTLD, particularly in the context of aSCT. The use of HLA-matched donor lymphocyte infusions (DLI) has proved successful in treating PTLD patients after aSCT, determining, however, an increased risk of GvHD. DLIs were recently confronted with donor origin or third-party EBV-specific T-cells [13], observing comparable results in the absence of acute GvHD in patients receiving EBV-specific T-cells. The evident drawback is that of the long time necessary to obtain an adequate number of EBV-specific T-cells, which could not be acceptable in patients with a rapid need of treatment. Recently, a rapid protocol (30 h) has been developed to isolate EBNA-1 specific T-cells from the aSCT donor peripheral blood, and after the infusion of these cells, a clinical and virological response was observed in 7 out of 10 patients, with an increase of EBNA-1 specific T-cell response [14].

These approaches are less likely to function in SOT recipients, in which IS could be reduced but not suspended. Although limited to a pre-clinical setting, in a xenogenic mouse model regression of PTLD has been observed despite the contemporaneous administration of IS drugs after infusion of autologous EBV-specific cytotoxic T-cells genetically engineered and rendered resistant to tacrolimus [15]. This approach, although complex, expensive and unavailable to most patients, may represent an interesting option in order to treat PTLD in SOT recipients without increasing the risk of graft rejection.

Conclusions

Diagnosis and treatment of PTLD are a complex issue, and multidisciplinary teams are needed to correctly evaluate the many aspects of the patient and the disease. Despite the newly adoptive immunotherapy approaches, the large majority of patients with PTLD is still treated with IS reduction and chemo-immunotherapy. Toxicity sparing approaches are mandatory in order to reduce the adverse effects induced by chemotherapy, which are presently the main reason of failure of treatment in this group of patients frequently characterized by frailty and poor performance status.

Conflict of interest

The authors have no competing interest.

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