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Posttransplant lymphoproliferative disorders following liver transplantation: Where are we now?

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Abstract

Liver transplantation has emerged as a life-saving treatment for several patients with acute liver failure, end stage liver disease and primary hepatic malignancies. However, long term immunosuppressive therapy aiming to reduce the risk of transplant rejection increases the incidence of several com-

plications including malignancies. This is illustrated by the observation of a high ratio between observed and expected cases of lymphoproliferative disorders following liver transplantation. Despite a huge heterogeneity in morphological appearance of these disorders ranging from reactive-like lesions to real lymphomas, they are collectively termed posttransplant lymphoproliferative disorders. In this review we will provide an overview of this rare but challenging disorder as a complication of liver transplantation.

Key words: Epstein Barr virus; Liver transplantation; Posttransplant lymphoproliferative disorders

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Core tip: Prevention of organ rejection following solid organ transplantation requires long term immunosuppressive therapy, leading to an increased risk of infections and malignancies. Posttransplant lymphoproliferative disorder (PTLD) comprises one of the most serious complications following transplantation with high morbidity and mortality rates. In this article we will review the different aspects on PTLD following liver transplantation.

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INTRODUCTION

Posttransplant lymphoproliferative disorder (PTLD) is serious complication of both solid organ (SOT)

and hematopoietic stem cell transplantation (HSCT). From a pathological point of view PTLD can vary from an infection-like appearance to a frank lymphoma. In about 70% of the cases Epstein Barr virus (EBV) is involved, whereas pathogenesis in the remaining cases is less clear. The most important risk factors for PTLD are EBV status at time of transplantation, type of transplanted organ and duration and type of immunosuppressive regimen. Reconstitution of the immune system, by reduction or withdrawal of immunosuppressive therapy, is considered the mainstay of therapy, although additional treatment is mandatory in a large proportion of patients. In this article we will review incidence, risk factors, diagnosis, treatment and prognosis of PTLD, focusing in particular on patients with liver transplantation.

INCIDENCE

Incidence data on PTLD in a transplant population may be underestimated given the lack of large prospective data, making retrospective single or rarely multicenter studies and large transplant registries the main information source. Population based cohort studies have shown that the standardized incidence ratio equals 10 for non-Hodgkin lymphoma and 3.5 for Hodgkin lymphoma following SOT^[1].

However, the incidence of PTLD largely depends on the type of organ transplanted. Initially liver transplantation was associated with a relatively high risk for PTLD development compared to other transplanted organs^[2]. However, in contrast to other solid organ transplantations, the risk seems to be decreasing due to a tendency to diminish and even discontinue all immunosuppressive therapy in a proportion of adult patients^[3,4]. Similar, in pediatric liver transplant recipients, the incidence of PTLD has decreased due to preventive and especially preemptive modulation of immune suppressive therapy based on systematic EBV viral load monitoring^[5,6].

RISK FACTORS

Several risk factors for development of PTLD have been described. The three most important are EBV mismatch, the type of transplanted organ and the use and duration of the immunosuppressive regimen.

EBV mismatch

Epidemiological studies in pediatric solid organ transplant recipients have shown that primary EBV infection from an EBV positive donor organ is the most important risk factor for development of PTLD, which was also confirmed in adult transplant populations. The major role of EBV in the development of PTLD is due to the dramatic decrease of EBV specific cytotoxic T lymphocytes caused by immune suppressive medication. This loss of immune surveillance may

lead to uncontrolled proliferation of EBV-infected B cells. In a large Collaborative Transplant Study EBV negative serostatus at the time of transplantation was associated with a significant increased PTLD risk in kidney and heart transplant recipients. However, this was not the case following liver transplantation in which the risk was unaffected by the EBV serostatus^[7]. This unexpected finding was challenged by a more recent analysis of a United States Scientific Registry of Transplant Recipients study, showing that recipient EBV seronegativity is significantly associated with risk for PTLD in heart, kidney but also liver transplantation with unadjusted hazard ratios (HR) of 6.528, 5.005 and 2.615 respectively. This lower HR in liver transplantation seems to be attributed to the higher baseline risk in EBV seropositive liver transplant patients^[8]. The reason for this finding is not known, but may be related to the higher lymphoid mass of the transplanted liver, increasing the risk for EBV reactivation and subsequently development of PTLD^[7].

Type of organ transplantation

The risk for PTLD development clearly varies according to the transplanted organ. Opelz *et al*^[9] conducted a large retrospective study analyzing data from the Collaborative Transplant Study database. In this study the authors observed a 5 year relative risk (RR) for non-Hodgkin lymphoma of 29.9 following liver transplantation. RR was highest in lung-heart transplantation, followed by lung, heart, liver, pancreas and deceased donor kidney transplantation. This increased risk -for all types of transplantation- was most pronounced in the pediatric population, reflecting the higher percentage of EBV negative serostatus in children. In our own center we performed a retrospective analysis on 140 biopsy-proven PTLD cases collected during a 20-year period (1989-2010), confirming the organ-dependent differences in PTLD risk. Highest risk was observed in heart (5.0%), followed by lung (3.2%), liver (2.8%), hematopoietic stem cell (1.7%) and kidney (1.5%) transplant recipients, with an overall incidence in the whole transplant population of 2.12%. For statistical reasons heart-lung transplant patients were classified as lung transplant recipients, whereas no PTLD was seen following multivisceral transplantation, but this is probably due to the small ($n = 9$) number of this type of transplantation in our center during the studied period^[10]. Other studies have shown incidence rates of 20% in both multivisceral and heart-lung transplantation. One of the largest series including 4000 consecutive liver transplant patients during the period 1981-1998 has been reported by the Pittsburgh group, who observed a PTLD incidence of 4.3% following liver transplantation, with clear difference between children (9.7%) and adults (2.9%)^[11]. Possible reasons for the large differences in incidences between different organs include the fact that more

intensive immune suppressive therapy is required in high risk patients and that a larger burden of lymphoid tissue may increase the risk for EBV infection^[12].

Immunosuppressive regimen

The often lifelong required intake of immunosuppressive medication is another important risk factor of PTLD development. Given the fact that most transplant protocols use combination regimens including induction and maintenance therapy, it is very difficult to determine the impact of each drug separately. However, although often controversial, some agents seem to be associated with development of PTLD, whereas others can even be considered protective.

Early studies have shown that the use of calcineurin inhibitors, both cyclosporine and tacrolimus, is associated with an increased risk for development of PTLD. Due to the stronger immunosuppressive properties of tacrolimus, this agent seems to be associated with a higher risk compared to cyclosporine in different organ types, including liver transplantation^[13]. In contrast to the use of calcineurin inhibitors in liver transplantation the antimetabolite mycophenolate mofetil does not seem to increase the risk for PTLD, which is also observed in other organ transplantations^[14]. Mammalian target of rapamycin (mTOR) inhibitors, often also referred to as proliferation signaling inhibitors, are very attractive agents given their combination of both immunosuppressive and antiproliferative characteristics. Currently two of these agents are used in organ transplantation, namely sirolimus and everolimus. In 2013 everolimus was approved in the United States and in Europe to prevent organ rejection in adult liver transplant patients. In a small study of 50 pediatric transplant patients, including 26 liver transplant recipients, the use of sirolimus combined with reduced dose tacrolimus was not associated with an increased risk for PTLD^[15]. On the other hand, trials incorporating mTOR inhibitors in other organ transplantation have shown conflicting results with respect to the risk for PTLD development^[16-18]. In liver transplantation, the use of combining everolimus with low dose tacrolimus may be a promising approach with acceptable tolerability, preserved renal function and decreased PTLD risk^[19].

Most organ transplantation registry studies have shown a clear association between the use of polyclonal T cell depleting antibodies, in particular anti-thymocyte globulins, and the occurrence of PTLD^[9]. Similar, the use of the monoclonal anti-CD3 antibody muromonab CD3 (= OKT3) was associated with an increased risk for PTLD development in a monocentric study including 1206 adult liver transplant recipients^[20]. Given the depletion of both B- and T-cells when using the anti-CD52 monoclonal antibody alemtuzumab, this agent offers the theoretical advantage of

protection against B cell proliferation. However, no clear data confirming this hypothesis do exist in liver transplantation^[21]. Recently selective depletion of activated T cells with anti-interleukin-2 receptor (CD25) monoclonal antibodies (basiliximab and daclizumab) have been used extensively as induction therapy in liver transplantation, without increasing the incidence of PTLD^[9,22,23].

In a recently published Cochrane systematic review all different types of polyclonal and monoclonal depleting and non-depleting antibodies used as induction therapy in liver transplantation were evaluated in order to assess their benefits and disadvantages. In this analysis 19 randomized clinical trials with a total of 2067 liver transplant recipients were included. No specific harm in general (PTLD in particular) was found when comparing each antibody with no induction therapy. However the authors concluded that more well designed clinical trials are needed because of the high risk of bias in the studied trials, the small numbers of randomized trials and the limited numbers of participants and examined outcomes in these trials^[24].

Other risk factors

Many other risk factors for development of PTLD in general have been described and proposed, although their relationship remains controversial. In liver transplant patients the underlying disorder and non-EBV viruses also have been proposed as risk factors for development of PTLD.

In a German monocentric retrospective analysis the authors observed a significant relation between pretransplant steroid treatment due to immunological disorders and liver transplantation for autoimmune hepatitis and the occurrence of PTLD^[25].

About one third of the PTLD cases is not EBV-associated^[12]. In these cases other infectious agents may be involved or the malignant cells may have lost EBV expression^[26]. Different viruses have been proposed as important contributors in the pathogenesis of PTLD, but as will be discussed in the next paragraph, no conclusions can be made on their exact role.

Hézode *et al*^[27] reported on an increased risk for PTLD development in liver transplant patients with underlying hepatitis C cirrhosis. However, a large cohort study in SOT recipients failed to confirm this observation^[28]. This apparent lack of association between hepatitis C and development of PTLD clearly contrasts to its role in lymphomagenesis in immune competent patients. Recently a large population-based Swedish study including 135 PTLD cases following solid organ transplantation suggested hepatitis C virus to be associated with late onset PTLD, which also needs confirmation in larger studies^[29]. Although less well studied, Zhang *et al*^[30] observed an increased incidence of PTLD in liver transplant recipients transplanted

Table 1 World Health Organization classification posttransplant lymphoproliferative disorder

	Early lesions	Polymorphic PTLD	Monomorphic PTLD
Underlying architecture	(Partially) preserved	Destructed	Destructed
Cells	Plasma cells, small lymphocytes and immunoblasts	Complete spectrum of B cell maturation	Fulfill criteria for lymphoma
Immunohistochemistry	No diagnostic value	Mixture of B and T cells	Most cases CD20 positive
EBV	100%	> 90%	+/- 70%
Clonality	In most cases polyclonal	Variable	Monoclonal
Oncogenic mutations	No	Variable (BCL6)	Oncogenes (N-Ras, c-MYC,...) and tumor suppressor genes (p53,...)

PTLD: Posttransplant lymphoproliferative disorder; EBV: Epstein Barr virus.

for benign liver diseases with hepatitis B virus (HBV) compared to HBV-negative patients. Available data on the impact of Cytomegalovirus (CMV) both in liver and other organ transplantations are very controversial, so currently no conclusions can be drawn regarding the role of CMV in PTLD development^[31-33].

In summary we can conclude that EBV mismatch, type of transplanted organ and immunosuppressive regimens are major determinant factors in the risk for PTLD development following solid organ (and liver) transplantation. The impact of other factors, including underlying disorder and non-EBV viruses remains controversial.

CLINICAL PRESENTATION

The clinical presentation of patients with PTLD is very heterogeneous. Whereas some patients have no symptoms or a mononucleosis-like presentation, other present with very aggressive disease including rapid evolution to multi-organ failure. Large mono- and multicentric case series following solid organ transplantation reveal a high incidence of extranodal invasion (62%-79%), including bone marrow (15%-17%), gastrointestinal tract (23%-56%) and central nervous system involvement (5%-13%). The majority of patients present with advanced disease (Ann Arbor stage III-IV in 66%-72%). In accordance with the increased survival of patients following organ transplantation, most recent series show that the majority of PTLD cases are late onset cases, developing more than one year following transplantation (61%-72%), with up to 21% occurring more than 10 years post transplantation^[10,11,29,34]. A minority of cases are characterized by early onset (first six months) presentation and are often limited to the allograft^[35].

DIAGNOSIS

Once diagnosis of PTLD is suspected prompt diagnostic investigations are essential in order to confirm or exclude the diagnosis and to initiate treatment as soon as possible. Although diagnosis can be assumed based on clinical presentation and EBV

monitoring in peripheral blood, the gold standard for diagnosis remains biopsy with histopathological and immunohistochemical examination. Based on morphological and immunohistochemical findings and on the structure of the underlying lymph node/organ, the World Health Organization distinguishes four major categories of PTLD (Table 1)^[36]: (1) early lesions (plasmacytic hyperplasia and infectious mononucleosis-like lesions); (2) polymorphic PTLD; (3) monomorphic PTLD; and (4) hodgkin lymphoma/Hodgkin-like lymphoma.

STAGING

Adequate staging examinations are needed aiming to define the extent of the disorder. Staging tools include: CT scan abdomen/thorax/pelvis, bone marrow examination and in case of suspicion of central nervous system invasion magnetic resonance imaging of the brain and/or analysis of cerebrospinal fluid. Based on these findings all cases can be categorized in stages according to the Ann Arbor classification, classifying patients based on the number of involved lymph node regions, the localization of nodal involvement and the presence of organ invasion. Stage I and II are considered limited disease, whereas stage III and IV point to a more advanced or disseminated disease (Table 2)^[37].

The high frequency of extranodal involvement in PTLD and the relative contra-indication for the use of intravenous contrast in patients with compromised calcineurin inhibitor-induced renal dysfunction have led to a particular interest in the use of ¹⁸F-fluorodeoxyglucose- positron emission tomography (FDG-PET) scan in diagnosis and staging of PTLD. We evaluated the use of FDG-PET in 170 cases with suspected or biopsy-confirmed PTLD following solid organ or hematopoietic stem cell transplantation, confirming its high sensitivity and specificity and showing an excellent ability to differentiate PTLD from non-malignant disorders. Potential pitfalls include central nervous system involvement and -isolated-allograft localization in heart and kidney transplant recipients, for which PET scan is not the ideal imaging modality^[38]. Similar results were observed in two

Table 2 Ann Arbor staging system for lymphoproliferative disorders

Stage I	Involvement of a single lymph node region (I) or one extralymphatic site (IE)
Stage II	Involvement of two or more lymph node regions, at the same side of the diaphragm (II) or local extralymphatic extension plus one or more lymph node regions at the same side of the diaphragm (IIE)
Stage III	Involvement of lymph node regions on both sides of diaphragm (III) which may include the spleen (IIIS) or accompanied by local extralymphatic extension (IIIE) or both (IIIES)
Stage IV	Diffuse or disseminated involvement of one or more extralymphatic organs or sites, with or without associated lymphatic involvement

Each stage number is followed by either A (absence of B-symptoms) or B (presence of B-symptoms: unexplained weight loss > 10% baseline during 6 mo before, unexplained fever > 38 °C, night sweats).

other studies in which the authors also compared PET findings with those obtained with more conventional imaging modalities^[39,40].

PREVENTION

Improved knowledge on the important contribution of EBV in the pathogenesis of PTLD and ongoing concerns regarding poor prognosis of the disorder with significant morbidity and mortality, has moved the attention to prevention of the disorder.

Prophylactic therapy

The use of antiviral agents, especially the nucleoside analogues acyclovir and ganciclovir, in prophylaxis and treatment was already explored more than thirty years ago, with limited benefit^[41]. Information on the effect of prophylactic use of viral agents with regard to the development of PTLD is limited. In a randomized controlled trial in 48 pediatric liver transplant recipients prophylactic treatment with two weeks of intravenous ganciclovir alone (10 mg/kg per day) was compared to two weeks of ganciclovir followed by 50 wk of high-dose oral acyclovir (4 × 800 mg/m² per day). Patients who were treated with prolonged use of acyclovir did not show an increased frequency of PTLD in this study^[42]. In a recent multicenter case-control study Funch *et al.*^[43] examined the impact of acyclovir and ganciclovir on the development of PTLD following kidney transplantation. This analysis showed that prophylactic anti-viral therapy, especially when using ganciclovir, provides a significant protection against early onset (< 1 year following transplantation) EBV-driven PTLD. However, these findings were not confirmed in a large retrospective registry study including 44,828 deceased-donor kidney transplant recipients, showing that prophylactic treatment with antiviral drugs did not reduce the risk of PTLD^[44].

The use of intravenous immune globulins (IVIG)

might be another promising therapy in PTLD. However, efficacy of this approach is not very clear as often similar therapies are given^[45]. As the results of two trials (one in kidney and one in pediatric liver transplant recipients) examining the effect of anti-CMV IVIG showed controversial, the use of IVIG early in transplant programs remains questionable^[44,46].

Preemptive therapy

With the availability of quantitative polymerase chain reaction, monitoring of EBV viral load has become common practice in many centers taking care of transplant patients. Potential preemptive strategies based on EBV viral load monitoring include reduction of immune suppressive medication, antiviral medication and/or administration of rituximab, a monoclonal anti-CD20 antibody. McDiarmid *et al.*^[47] reported on their experience using a protocol incorporating serial peripheral blood EBV viral load monitoring following pediatric liver transplantation. In patients with increasing viral copy number, tacrolimus was decreased and ganciclovir was re-initiated or continued. In a similar single center study Lee *et al.*^[5] proposed a similar approach with reduction of immune suppression in case of high EBV load in 43 pediatric liver transplant patients and compared them with a historical control group. In both studies the authors concluded a significant decrease in PTLD incidence was observed with the introduction of this preemptive strategy.

TREATMENT

Given the rarity of the disorder and due to the lack of randomized phase III trials, optimal treatment of PTLD is currently not clearly defined. This is illustrated by the recently published guidelines from the British Committee for Standards in Haematology and the British Transplantation Society, showing low levels of evidence and weak recommendations grades for the different therapeutic options^[48].

The development of PTLD always implies a high degree of overimmunosuppression. This observation explains why reduction of immunosuppression is the main therapeutic intervention which should be initiated promptly, leading to restoration of the EBV-specific T cell response.

Restoration of the immune system

Reduction of immunosuppression: As soon as the diagnosis of PTLD is made, prompt initiation of RIS is recommended. In most cases antimetabolites are discontinued, calcineurin inhibitor dose is reduced with 50% and steroids or continued^[48,49]. If the clinical situation of the patients allows, the effect should be re-evaluated after two to four weeks. Response rates to RIS alone in PTLD have a very wide variation, reflecting the lack of standardization

with respect to duration of RIS before re-evaluation, response criteria and reduction regimen. The impact of RIS on PTLD following liver transplantation is difficult to assess as most large series contain cases following different kinds of organ transplantation. In a large monocentric analysis from the University of Pennsylvania, including 67 SOT recipients (16 liver transplant patients) with PTLD, RIS alone was associated with an overall response rate of 45% and a complete response rate of 37%. The most important factors predictive for response to RIS alone were the absence of bulky disease (> 7 cm), early stage (Ann Arbor I - II) and lower age (< 50 years)^[50,51]. In a large Swedish study 135 PTLD cases following solid organ transplantation (SOT) were analyzed, including 19 (14%) liver transplant recipients. Twenty-one patients were treated with RIS alone, of which 57% had a complete remission (CR)^[29]. However, in a prospective trial from Baltimore including 16 SOT recipients, only 6% responded to RIS alone with no CR, but no liver transplant recipients were included^[52]. In a small retrospective analysis focusing on liver transplant recipients ($n = 17$) RIS alone was associated with a CR rate of 46%^[53].

In conclusion, RIS should be initiated in all patients presenting with PTLD following liver transplantation. If the condition of the patient doesn't require urgent additional therapy, a re-evaluation should be performed after 2 to 4 wk. During RIS, regular monitoring of transplant function is essential, as RIS is associated with an increased risk of organ rejection.

As already discussed before mTOR inhibitors may be a promising approach in the treatment of malignancies in transplant recipients, given their immunosuppressive and antiproliferative capacities. Recently, Ashrafi *et al.*^[54] published their experience with 13 kidney transplant recipients who were treated with everolimus following diagnosis of PTLD, indicating promising results regarding both disease control and graft survival. This may be in particular a very attractive approach in liver transplant patients, given the beneficial effect of everolimus in prevention of transplant rejection^[19].

Adoptive immunotherapy: The use of EBV specific cytotoxic lymphocytes has shown impressive results in refractory PTLD cases with a very good toxicity profile, as reviewed by Merlo *et al.*^[55]. However, we will not discuss this therapy in detail as wide applicability has been limited so far.

Anti- B cell therapy

Surgery and radiotherapy: Surgery and radiotherapy should only be used in localized disease, especially in early lesion PTLD^[48,50]. Other indications for radiotherapy include palliative symptom control and treatment of isolated central nervous system-PTLD^[56].

Chemotherapy: Although chemotherapy (mostly CHOP) was initially considered standard therapy, especially after failure of RIS, treatment related mortality seemed to be very high compared to immune competent patients^[57-59]. However, as will be discussed in the next part, the use of rituximab has substantially changed the treatment of patients presenting with CD20-positive B-cell PTLD, making omission of chemotherapy possible in a substantial proportion of patients. However, in case of aggressive CD20 negative PTLDs, upfront chemotherapy is mandatory in most cases^[48].

Monoclonal anti-B cell therapy: Several prospective phase II trials have assessed the role of rituximab, a chimeric monoclonal anti-CD20 antibody, in PTLD. Based on the results of these trials, showing overall response rates ranging between 44% and 64% combined with a favorable toxicity profile, rituximab has emerged as standard therapy for CD20-positive PTLD with inadequate response to RIS^[60-64].

Recently Trappe *et al.*^[65] reported on the results of the large prospective phase II PTLD-1 trial examining the sequential use of rituximab and CHOP chemotherapy in 70 patients presenting with CD20-positive PTLD following SOT, including liver transplantation. This trial demonstrated the efficacy (90% ORR with 67% CRR) and safety of sequential treatment. As the response to rituximab predicted overall survival, the trial was amended in 2007 introducing risk stratification (risk stratified sequential treatment) according to the response to rituximab. The final analysis of this approach needs to be awaited before final conclusions can be made.

Anti- EBV therapy

Antiviral therapy: The use of antiviral treatment has not been assessed in prospective trials. In addition, as already mentioned before, nucleoside analogues don't seem to be efficient as most EBV positive tumors do not express viral TK.

Arginine butyrate: Recently very promising results have been described with the short-chain fatty acid arginine butyrate, a selective activator of viral TK making the tumor sensitive to treatment with nucleoside analogues. Combining arginine butyrate with ganciclovir in the treatment of 6 refractory PTLDs was feasible and showed an impressive response rate of 83%^[66].

PROGNOSIS

In general the prognosis of PTLD following SOT is poor with 3-year and 5-year overall survival of approximately 50%-60% and 40% respectively^[10,29,34], although sequential therapy with rituximab and CHOP

chemotherapy shows improved overall survival (61% at 3 year)^[65]. Kremers *et al*^[20] observed a 5-year OS of 40.8% in 37 patients with PTLD following liver transplantation. Importantly, a significant percentage of deaths (42% in our retrospective analysis) are not PTLD-related, but are due to other causes, in particular infections^[10].

In our opinion and experience the International Prognostic Index score^[67] - a risk score initially defined for immune competent patients with aggressive non-Hodgkin lymphoma, based on 5 independent risk factors: age > 60 year, elevated LDH, poor performance state, advanced Ann Arbor stage and presence of extranodal localizations- is also a reliable and predictive factor in patients presenting with PTLD, which was also confirmed in the PTLD-1 trial^[10,68,69]. An additional risk factor for poor prognosis in the PTLD-1 trial was the presence of a thoracic organ transplantation not responding to rituximab monotherapy^[69].

CONCLUSION

Posttransplantation lymphoproliferative disorders remain an important cause of morbidity and mortality following solid organ transplantation in general and liver transplantation in particular. Although the overall PTLD incidence has increased during the last years, liver transplantation seems to be an exception to this general rule, probably due the tendency to diminish and even discontinue all immunosuppressive therapy in a proportion of adult patients and to the use of preemptive strategies, especially in the pediatric setting. Classical risk factors for PTLD include the EBV serostatus of the patient, the organ transplanted and the immunosuppressive regimen. Once PTLD is suspected, diagnostic evaluation and staging should be done as soon as possible, as pathological identification of the subtype and evaluation of the involved nodes and organs are critical factor for optimal treatment and prognostic stratification. As soon as the diagnosis is made, treatment should be initiated promptly by reducing immune suppressive therapy. In most cases this will be followed by systemic treatment with rituximab and/or chemotherapy.

REFERENCES

- 1 **Grulich AE**, van Leeuwen MT, Falster MO, Vajdic CM. Incidence of cancers in people with HIV/AIDS compared with immunosuppressed transplant recipients: a meta-analysis. *Lancet* 2007; **370**: 59-67 [PMID: 17617273]
- 2 **Jiang Y**, Villeneuve PJ, Fenton SS, Schaubel DE, Lilly L, Mao Y. Liver transplantation and subsequent risk of cancer: findings from a Canadian cohort study. *Liver Transpl* 2008; **14**: 1588-1597 [PMID: 18975293 DOI: 10.1002/lt.21554]
- 3 **Benítez C**, Londoño MC, Miquel R, Manzia TM, Abrales JG, Lozano JJ, Martínez-Llordella M, López M, Angelico R, Bohne F, Sese P, Daoud F, Larcier P, Roelen DL, Claas F, Whitehouse

- G, Lerut J, Pirenne J, Rimola A, Tisone G, Sánchez-Fueyo A. Prospective multicenter clinical trial of immunosuppressive drug withdrawal in stable adult liver transplant recipients. *Hepatology* 2013; **58**: 1824-1835 [PMID: 23532679 DOI: 10.1002/hep.26426]
- 4 **de la Garza RG**, Sarobe P, Merino J, Lasarte JJ, D'Avola D, Belsue V, Delgado JA, Silva L, Iñarrairaegui M, Sangro B, Sola JJ, Pardo F, Quiroga J, Herrero JI. Trial of complete weaning from immunosuppression for liver transplant recipients: factors predictive of tolerance. *Liver Transpl* 2013; **19**: 937-944 [PMID: 23784747 DOI: 10.1002/lt.23686]
- 5 **Lee TC**, Savoldo B, Rooney CM, Heslop HE, Gee AP, Caldwell Y, Barshes NR, Scott JD, Bristow LJ, O'Mahony CA, Goss JA. Quantitative EBV viral loads and immunosuppression alterations can decrease PTLD incidence in pediatric liver transplant recipients. *Am J Transplant* 2005; **5**: 2222-2228 [PMID: 16095501]
- 6 **Lu BR**, Park KT, Hurwitz M, Cox KL, Berquist WE. Impact of immunosuppression on the development of Epstein-Barr virus (EBV) viremia after pediatric liver transplantation. *Transplant Proc* 2013; **45**: 301-304 [PMID: 23267800 DOI: 10.1016/j.transproceed.2012.04.035]
- 7 **Opelz G**, Daniel V, Naujokat C, Döhler B. Epidemiology of pretransplant EBV and CMV serostatus in relation to posttransplant non-Hodgkin lymphoma. *Transplantation* 2009; **88**: 962-967 [PMID: 19855238 DOI: 10.1097/TP.0b013e3181b9692d]
- 8 **Dharnidharka VR**, Lamb KE, Gregg JA, Meier-Kriesche HU. Associations between EBV serostatus and organ transplant type in PTLD risk: an analysis of the SRTR National Registry Data in the United States. *Am J Transplant* 2012; **12**: 976-983 [PMID: 22226225 DOI: 10.1111/j.1600-6143.2011.03893.x]
- 9 **Opelz G**, Döhler B. Lymphomas after solid organ transplantation: a collaborative transplant study report. *Am J Transplant* 2004; **4**: 222-230 [PMID: 14974943]
- 10 **Dierickx D**, Tousseyn T, Sagaert X, Fieueus S, Wlodarska I, Morscio J, Brepoels L, Kuypers D, Vanhaecke J, Nevens F, Verleden G, Van Damme-Lombaerts R, Renard M, Pirenne J, De Wolf-Peeters C, Verhoef G. Single-center analysis of biopsy-confirmed posttransplant lymphoproliferative disorder: incidence, clinicopathological characteristics and prognostic factors. *Leuk Lymphoma* 2013; **54**: 2433-2440 [PMID: 23442063 DOI: 10.3109/10428194.2013.780655]
- 11 **Jain A**, Nalesnik M, Reyes J, Pokharna R, Mazariegos G, Green M, Eghtesad B, Marsh W, Cacciarelli T, Fontes P, Abu-Elmagd K, Sindhi R, Demetris J, Fung J. Posttransplant lymphoproliferative disorders in liver transplantation: a 20-year experience. *Ann Surg* 2002; **236**: 429-436; discussion 436-437 [PMID: 12368671]
- 12 **Tsao L**, Hsi ED. The clinicopathologic spectrum of post-transplantation lymphoproliferative disorders. *Arch Pathol Lab Med* 2007; **131**: 1209-1218 [PMID: 17683183]
- 13 **Younes BS**, McDiarmid SV, Martin MG, Vargas JH, Goss JA, Busuttill RW, Ament ME. The effect of immunosuppression on posttransplant lymphoproliferative disease in pediatric liver transplant patients. *Transplantation* 2000; **70**: 94-99 [PMID: 10919581]
- 14 **Chardot C**, Nicoluzzi JE, Janssen M, Sokal E, Lerut J, Otte JB, Reding R. Use of mycophenolate mofetil as rescue therapy after pediatric liver transplantation. *Transplantation* 2001; **71**: 224-229 [PMID: 11213063]
- 15 **Sindhi R**, Webber S, Venkataramanan R, McGhee W, Phillips S, Smith A, Baird C, Iurlano K, Mazariegos G, Cooperstone B, Holt DW, Zeevi A, Fung JJ, Reyes J. Sirolimus for rescue and primary immunosuppression in transplanted children receiving tacrolimus. *Transplantation* 2001; **72**: 851-855 [PMID: 11571449]
- 16 **Kirk AD**, Cherikh WS, Ring M, Burke G, Kaufman D, Knechtel SJ, Potdar S, Shapiro R, Dharnidharka VR, Kauffman HM. Dissociation of depletion induction and posttransplant lymphoproliferative disease in kidney recipients treated with alemtuzumab. *Am J Transplant* 2007; **7**: 2619-2625 [PMID: 17868060]

- 17 **Mathew T**, Kreis H, Friend P. Two-year incidence of malignancy in sirolimus-treated renal transplant recipients: results from five multicenter studies. *Clin Transplant* 2004; **18**: 446-449 [PMID: 15233824]
- 18 **Nassif S**, Kaufman S, Vahdat S, Yazigi N, Kallakury B, Island E, Ozdemirli M. Clinicopathologic features of post-transplant lymphoproliferative disorders arising after pediatric small bowel transplant. *Pediatr Transplant* 2013; **17**: 765-773 [PMID: 24118781 DOI: 10.1111/ptr.12150]
- 19 **Kwong AJ**, Fix OK. Update on the management of the liver transplant patient. *Curr Opin Gastroenterol* 2015; **31**: 224-232 [PMID: 25774445 DOI: 10.1097/MOG.000000000000173]
- 20 **Kremers WK**, Devarbhavi HC, Wiesner RH, Krom RA, Macon WR, Habermann TM. Post-transplant lymphoproliferative disorders following liver transplantation: incidence, risk factors and survival. *Am J Transplant* 2006; **6**: 1017-1024 [PMID: 16611339]
- 21 **Marcos A**, Eghtesad B, Fung JJ, Fontes P, Patel K, Devera M, Marsh W, Gayowski T, Demetris AJ, Gray EA, Flynn B, Zeevi A, Murase N, Starzl TE. Use of alemtuzumab and tacrolimus monotherapy for cadaveric liver transplantation: with particular reference to hepatitis C virus. *Transplantation* 2004; **78**: 966-971 [PMID: 15480160]
- 22 **Ganschow R**, Grabhorn E, Schulz A, Von Hugo A, Rogiers X, Burdelski M. Long-term results of basiliximab induction immunosuppression in pediatric liver transplant recipients. *Pediatr Transplant* 2005; **9**: 741-745 [PMID: 16269045]
- 23 **Ramirez CB**, Doria C, di Francesco F, Iaria M, Kang Y, Marino IR. Basiliximab induction in adult liver transplant recipients with 93% rejection-free patient and graft survival at 24 months. *Transplant Proc* 2006; **38**: 3633-3635 [PMID: 17175352]
- 24 **Penninga L**, Wettergren A, Wilson CH, Chan AW, Steinbrüchel DA, Gluud C. Antibody induction versus placebo, no induction, or another type of antibody induction for liver transplant recipients. *Cochrane Database Syst Rev* 2014; **6**: CD010253 [PMID: 24901467 DOI: 10.1002/14651858.CD010253.pub2]
- 25 **Zimmermann T**, Hoppe-Lotichius M, Tripkovic V, Barreiros AP, Wehler TC, Zimmermann A, Schattenberg JM, Heise M, Biesterfeld S, Galle PR, Otto G, Schuchmann M. Liver transplanted patients with preoperative autoimmune hepatitis and immunological disorders are at increased risk for Post-Transplant Lymphoproliferative Disease (PTLD). *Eur J Intern Med* 2010; **21**: 208-215 [PMID: 20493424 DOI: 10.1016/j.ejim.2010.02.009]
- 26 **Gao Y**, Lu YJ, Xue SA, Chen H, Wedderburn N, Griffin BE. Hypothesis: a novel route for immortalization of epithelial cells by Epstein-Barr virus. *Oncogene* 2002; **21**: 825-835 [PMID: 11850810]
- 27 **Hézode C**, Duvoux C, Germanidis G, Roudot-Thoraval F, Vincens AL, Gaulard P, Cherqui D, Pawlotsky JM, Dhumeaux D. Role of hepatitis C virus in lymphoproliferative disorders after liver transplantation. *Hepatology* 1999; **30**: 775-778 [PMID: 10462385]
- 28 **Morton LM**, Landgren O, Chatterjee N, Castenson D, Parsons R, Hoover RN, Engels EA. Hepatitis C virus infection and risk of posttransplantation lymphoproliferative disorder among solid organ transplant recipients. *Blood* 2007; **110**: 4599-4605 [PMID: 17855632]
- 29 **Kinch A**, Baecklund E, Backlin C, Ekman T, Molin D, Tufveson G, Fernberg P, Sundström C, Pauksens K, Enblad G. A population-based study of 135 lymphomas after solid organ transplantation: The role of Epstein-Barr virus, hepatitis C and diffuse large B-cell lymphoma subtype in clinical presentation and survival. *Acta Oncol* 2014; **53**: 669-679 [PMID: 24164103 DOI: 10.3109/0284186X.2013.844853]
- 30 **Zhang A**, Zhang M, Shen Y, Wang W, Zheng S. Hepatitis B virus reactivation is a risk factor for development of post-transplant lymphoproliferative disease after liver transplantation. *Clin Transplant* 2009; **23**: 756-760 [PMID: 19664018 DOI: 10.1111/j.1399-0012.2009.01049.x]
- 31 **Walker RC**, Marshall WF, Strickler JG, Wiesner RH, Velosa JA, Habermann TM, McGregor CG, Paya CV. Pretransplantation assessment of the risk of lymphoproliferative disorder. *Clin Infect Dis* 1995; **20**: 1346-1353 [PMID: 7620022]
- 32 **Mañez R**, Breinig MC, Linden P, Wilson J, Torre-Cisneros J, Kusne S, Dummer S, Ho M. Posttransplant lymphoproliferative disease in primary Epstein-Barr virus infection after liver transplantation: the role of cytomegalovirus disease. *J Infect Dis* 1997; **176**: 1462-1467 [PMID: 9395355]
- 33 **Kim JM**, Lee SK, Kim SJ, Joh JW, Kwon CH, Choe YH, Shin M, Kim EY, Moon JI, Jung GO, Choi GS. Risk factors for posttransplant lymphoproliferative disorder in pediatric liver transplant recipients with cytomegalovirus antigenemia. *Transplant Proc* 2010; **42**: 895-899 [PMID: 20430199 DOI: 10.1016/j.transproceed.2010.02.042]
- 34 **Evans AM**, David KA, Helenowski I, Nelson B, Kaufman D, Kircher SM, Gimelfarb A, Hattersley E, Mauro LA, Jovanovic B, Chadburn A, Stiff P, Winter JN, Mehta J, Van Besien K, Gregory S, Gordon LI, Shammo JM, Smith SE, Smith SM. Multicenter analysis of 80 solid organ transplantation recipients with post-transplantation lymphoproliferative disease: outcomes and prognostic factors in the modern era. *J Clin Oncol* 2010; **28**: 1038-1046 [PMID: 20085936 DOI: 10.1200/JCO.2009.25.4961]
- 35 **Leblond V**, Choquet S. Lymphoproliferative disorders after liver transplantation. *J Hepatol* 2004; **40**: 728-735 [PMID: 15094218]
- 36 **Swerdlow SH**, Webber SA, Chadburn A, Ferry JA. Post-transplant lymphoproliferative disorders. In: Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, Thiele J, Vardiman JW (eds). WHO classification of Tumours of Haematopoietic and Lymphoid Tissues. Lyon, France: IARC Press, 2008: 343-349
- 37 **Moormeier JA**, Williams SF, Golomb HM. The staging of non-Hodgkin's lymphomas. *Semin Oncol* 1990; **17**: 43-50 [PMID: 2406917]
- 38 **Dierickx D**, Tousseyn T, Requilé A, Verscuren R, Sagaert X, Morscio J, Wlodarska I, Herreman A, Kuypers D, Van Cleemput J, Nevens F, Dupont L, Uyttebroeck A, Pirenne J, De Wolf-Peeters C, Verhoef G, Brepoels L, Gheysens O. The accuracy of positron emission tomography in the detection of posttransplant lymphoproliferative disorder. *Haematologica* 2013; **98**: 771-775 [PMID: 23065524 DOI: 10.3324/haematol.2012.074500]
- 39 **Panagiotidis E**, Quigley AM, Pencharz D, Ardeshtna K, Syed R, Sajjan R, Bomanji J. (18)F-fluorodeoxyglucose positron emission tomography/computed tomography in diagnosis of post-transplant lymphoproliferative disorder. *Leuk Lymphoma* 2014; **55**: 515-519 [PMID: 23772644 DOI: 10.3109/10428194.2013.813501]
- 40 **Takehana CS**, Twist CJ, Mosci C, Quon A, Mittra E, Iagaru A. (18)F-FDG PET/CT in the management of patients with post-transplant lymphoproliferative disorder. *Nucl Med Commun* 2014; **35**: 276-281 [PMID: 24296883 DOI: 10.1097/MNM.000000000000050]
- 41 **Hanto DW**, Frizzera G, Gajl-Peczalska KJ, Sakamoto K, Purtilo DT, Balfour HH, Simmons RL, Najarian JS. Epstein-Barr virus-induced B-cell lymphoma after renal transplantation: acyclovir therapy and transition from polyclonal to monoclonal B-cell proliferation. *N Engl J Med* 1982; **306**: 913-918 [PMID: 6278307]
- 42 **Green M**, Kaufmann M, Wilson J, Reyes J. Comparison of intravenous ganciclovir followed by oral acyclovir with intravenous ganciclovir alone for prevention of cytomegalovirus and Epstein-Barr virus disease after liver transplantation in children. *Clin Infect Dis* 1997; **25**: 1344-1349 [PMID: 9431375]
- 43 **Funch DP**, Walker AM, Schneider G, Ziyadeh NJ, Pescovitz MD. Ganciclovir and acyclovir reduce the risk of post-transplant lymphoproliferative disorder in renal transplant recipients. *Am J Transplant* 2005; **5**: 2894-2900 [PMID: 16303002]
- 44 **Opelz G**, Daniel V, Naujokat C, Fickenscher H, Döhler B. Effect of cytomegalovirus prophylaxis with immunoglobulin or with antiviral drugs on post-transplant non-Hodgkin lymphoma: a multicentre retrospective analysis. *Lancet Oncol* 2007; **8**: 212-218 [PMID: 17329191]
- 45 **Trappe R**, Riess H, Anagnostopoulos I, Neuhaus R, Gärtner BC,

- Pohl H, Müller HP, Jonas S, Papp-Vary M, Oertel S. Efficiency of antiviral therapy plus IVIG in a case of primary EBV infection associated PTLD refractory to rituximab, chemotherapy, and antiviral therapy alone. *Ann Hematol* 2009; **88**: 167-172 [PMID: 18636261 DOI: 10.1007/s00277-008-0538-0]
- 46 **Green M**, Michaels MG, Katz BZ, Burroughs M, Gerber D, Shneider BL, Newell K, Rowe D, Reyes J. CMV-IVIG for prevention of Epstein Barr virus disease and posttransplant lymphoproliferative disease in pediatric liver transplant recipients. *Am J Transplant* 2006; **6**: 1906-1912 [PMID: 16889546]
- 47 **McDiarmid SV**, Jordan S, Kim GS, Toyoda M, Goss JA, Vargas JH, Martín MG, Bahar R, Maxfield AL, Ament ME, Busuttill RW. Prevention and preemptive therapy of posttransplant lymphoproliferative disease in pediatric liver recipients. *Transplantation* 1998; **66**: 1604-1611 [PMID: 9884246]
- 48 **Parker A**, Bowles K, Bradley JA, Emery V, Featherstone C, Gupte G, Marcus R, Parameshwar J, Ramsay A, Newstead C. Management of post-transplant lymphoproliferative disorder in adult solid organ transplant recipients - BCSH and BTS Guidelines. *Br J Haematol* 2010; **149**: 693-705 [PMID: 20408848 DOI: 10.1111/j.1365-2141.2010.08160.x]
- 49 **Tsai DE**, Hardy CL, Tomaszewski JE, Kotloff RM, Oltoff KM, Somer BG, Schuster SJ, Porter DL, Montone KT, Stadtmayer EA. Reduction in immunosuppression as initial therapy for posttransplant lymphoproliferative disorder: analysis of prognostic variables and long-term follow-up of 42 adult patients. *Transplantation* 2001; **71**: 1076-1088 [PMID: 11374406]
- 50 **Reshef R**, Luskin MR, Kamoun M, Vardhanabhuti S, Tomaszewski JE, Stadtmayer EA, Porter DL, Heitjan DF, Tsai de E. Association of HLA polymorphisms with post-transplant lymphoproliferative disorder in solid-organ transplant recipients. *Am J Transplant* 2011; **11**: 817-825 [PMID: 21401872 DOI: 10.1111/j.1600-6143.2011.03454.x]
- 51 **Meij P**, van Esser JW, Niesters HG, van Baarle D, Miedema F, Blake N, Rickinson AB, Leiner I, Pamer E, Lowenberg B, Cornelissen JJ, Gratama JW. Impaired recovery of Epstein-Barr virus (EBV)--specific CD8+ T lymphocytes after partially T-depleted allogeneic stem cell transplantation may identify patients at very high risk for progressive EBV reactivation and lymphoproliferative disease. *Blood* 2003; **101**: 4290-4297 [PMID: 12576337]
- 52 **Swinnen LJ**, LeBlanc M, Grogan TM, Gordon LI, Stiff PJ, Miller AM, Kasamon Y, Miller TP, Fisher RI. Prospective study of sequential reduction in immunosuppression, interferon alpha-2B, and chemotherapy for posttransplantation lymphoproliferative disorder. *Transplantation* 2008; **86**: 215-222 [PMID: 18645482 DOI: 10.1097/TP.0b013e3181761659]
- 53 **Patel H**, Vogl DT, Aquí N, Shaked A, Olthoff K, Markmann J, Reddy R, Stadtmayer EA, Schuster S, Tsai DE. Posttransplant lymphoproliferative disorder in adult liver transplant recipients: a report of seventeen cases. *Leuk Lymphoma* 2007; **48**: 885-891 [PMID: 17487731]
- 54 **Ashrafi F**, Shahidi S, Ebrahimi Z, Mortazavi M. Outcome of rapamycin therapy for post-transplant-lymphoproliferative disorder after kidney transplantation: case series. *Int J Hematol Oncol Stem Cell Res* 2015; **9**: 26-32 [PMID: 25802698]
- 55 **Merlo A**, Turrini R, Dolcetti R, Martorelli D, Muraro E, Comoli P, Rosato A. The interplay between Epstein-Barr virus and the immune system: a rationale for adoptive cell therapy of EBV-related disorders. *Haematologica* 2010; **95**: 1769-1777 [PMID: 20421267 DOI: 10.3324/haematol.2010.023689]
- 56 **Buell JF**, Gross TG, Hanaway MJ, Trofe J, Roy-Chaudhury P, First MR, Woodle ES. Posttransplant lymphoproliferative disorder: significance of central nervous system involvement. *Transplant Proc* 2005; **37**: 954-955 [PMID: 15848587]
- 57 **Buell JF**, Gross TG, Hanaway MJ, Trofe J, Muthiak C, First MR, Alloway RR, Woodle ES. Chemotherapy for posttransplant lymphoproliferative disorder: the Israel Penn International Transplant Tumor Registry experience. *Transplant Proc* 2005; **37**: 956-957 [PMID: 15848588]
- 58 **Choquet S**, Trappe R, Leblond V, Jäger U, Davi F, Oertel S. CHOP-21 for the treatment of post-transplant lymphoproliferative disorders (PTLD) following solid organ transplantation. *Haematologica* 2007; **92**: 273-274 [PMID: 17296588]
- 59 **Lee JJ**, Lam MS, Rosenberg A. Role of chemotherapy and rituximab for treatment of posttransplant lymphoproliferative disorder in solid organ transplantation. *Ann Pharmacother* 2007; **41**: 1648-1659 [PMID: 17848421]
- 60 **Oertel SH**, Verschuuren E, Reinke P, Zeidler K, Papp-Vary M, Babel N, Trappe RU, Jonas S, Hummel M, Anagnostopoulos I, Dörken B, Riess HB. Effect of anti-CD 20 antibody rituximab in patients with post-transplant lymphoproliferative disorder (PTLD). *Am J Transplant* 2005; **5**: 2901-2906 [PMID: 16303003]
- 61 **Blaes AH**, Peterson BA, Bartlett N, Dunn DL, Morrison VA. Rituximab therapy is effective for posttransplant lymphoproliferative disorders after solid organ transplantation: results of a phase II trial. *Cancer* 2005; **104**: 1661-1667 [PMID: 16149091]
- 62 **Choquet S**, Leblond V, Herbrecht R, Socié G, Stoppa AM, Vandenberghe P, Fischer A, Morschhauser F, Salles G, Feremans W, Vilmer E, Peraldi MN, Lang P, Lebranchu Y, Oksenhendler E, Garnier JL, Lamy T, Jaccard A, Ferrant A, Offner F, Hermine O, Moreau A, Fafi-Kremer S, Morand P, Chatenoud L, Berriot-Varoqueaux N, Bergougnoux L, Milpied N. Efficacy and safety of rituximab in B-cell post-transplantation lymphoproliferative disorders: results of a prospective multicenter phase 2 study. *Blood* 2006; **107**: 3053-3057 [PMID: 16254143]
- 63 **González-Barca E**, Domingo-Domenech E, Capote FJ, Gómez-Codina J, Salar A, Bailen A, Ribera JM, López A, Briones J, Muñoz A, Encuentra M, de Sevilla AF. Prospective phase II trial of extended treatment with rituximab in patients with B-cell post-transplant lymphoproliferative disease. *Haematologica* 2007; **92**: 1489-1494 [PMID: 18024397]
- 64 **Choquet S**, Oertel S, LeBlond V, Riess H, Varoqueaux N, Dörken B, Trappe R. Rituximab in the management of post-transplantation lymphoproliferative disorder after solid organ transplantation: proceed with caution. *Ann Hematol* 2007; **86**: 599-607 [PMID: 17522862]
- 65 **Trappe R**, Oertel S, Leblond V, Mollee P, Sender M, Reinke P, Neuhaus R, Lehmkuhl H, Horst HA, Salles G, Morschhauser F, Jaccard A, Lamy T, Leithäuser M, Zimmermann H, Anagnostopoulos I, Raphael M, Riess H, Choquet S. Sequential treatment with rituximab followed by CHOP chemotherapy in adult B-cell post-transplant lymphoproliferative disorder (PTLD): the prospective international multicentre phase 2 PTLT-1 trial. *Lancet Oncol* 2012; **13**: 196-206 [PMID: 22173060 DOI: 10.1016/S1470-2045(11)70300-X]
- 66 **Perrine SP**, Hermine O, Small T, Suarez F, O'Reilly R, Boulad F, Fingerth J, Askin M, Levy A, Mentzer SJ, Di Nicola M, Gianni AM, Klein C, Horwitz S, Faller DV. A phase 1/2 trial of arginine butyrate and ganciclovir in patients with Epstein-Barr virus-associated lymphoid malignancies. *Blood* 2007; **109**: 2571-2578 [PMID: 17119113]
- 67 A predictive model for aggressive non-Hodgkin's lymphoma. The International Non-Hodgkin's Lymphoma Prognostic Factors Project. *N Engl J Med* 1993; **329**: 987-994 [PMID: 8141877]
- 68 **Dierickx D**, Tousseyn T, Morscio J, Fieuews S, Verhoef G. Validation of prognostic scores in post-transplantation lymphoproliferative disorders. *J Clin Oncol* 2013; **31**: 3443-3444 [PMID: 23960181 DOI: 10.1200/JCO.2013.50.3326]
- 69 **Trappe RU**, Choquet S, Dierickx D, Mollee P, Zaucha JM, Dreyling MH, Dührsen U, Tarella C, Shpilberg O, Sender M, Salles G, Morschhauser F, Jaccard A, Lamy T, Reinke P, Neuhaus R, Lehmkuhl H, Horst HA, Leithäuser M, Schlattmann P, Anagnostopoulos I, Raphael M, Riess H, Leblond V, Oertel S. International prognostic index, type of transplant and response

to rituximab are key parameters to tailor treatment in adults with CD20-positive B cell PTLD: clues from the PTLD-1 trial. *Am J*

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