A. Introduction

In the last 30 years, the development of new immunosuppressant treatments has been a major therapeutic advance that has facilitated the success of organ transplantation. The number of transplants performed has constantly grown, even in developing countries, and has resulted in an increase in the number of tumors observed in the transplanted population. This increase is 3 to 5 times greater than that observed in the general population. It has been
known for many years that there is a greater incidence of lymphoproliferative processes in people with congenital, acquired, or pharmacologically induced immunodeficiencies.\textsuperscript{1} Those that present in this way after immunosuppressive therapy for organ transplant represent a heterogeneous group of mono- or polyclonal proliferations, ranging from plasma hyperplasia to non-Hodgkin lymphoma. These lymphoproliferative processes are clinically and morphologically heterogeneous, and are known as posttransplant lymphoproliferative disorders (PTLDs), which occasionally evolve into clinical lymphoma.\textsuperscript{2} Lymphomas (50\%) occur more frequently than cutaneous tumors (20\%) among pediatric transplant recipients, and the tumorsthe are more common in adult patients.\textsuperscript{3}

A. 1 Pathogenesis

A clear relationship exists between PTLDs and infection with Epstein–Barr virus (EBV).\textsuperscript{2,4} It has been postulated that infection with this lymphotropic herpes virus, whether primary infection or reactivation, could initially produce the polyclonal expansion of B cells. Due to the suppression of T-cell immunovigilance, which is caused by immunosuppression treatments, mutations in oncogenes and tumor suppressor genes accumulate over time, leading to the selection of malignant clones that continue to present episomal EBV DNA.

Primary EBV infection can be asymptomatic, producing a clinical picture of nonspecific or infectious mononucleosis. The infected individual maintains anti-EBV IgG antibodies and the virus resides in the nasopharynx. The EBV genome (DNA) encodes a number of proteins and molecules, each of which possesses a specific function. Among the most important of these, from an oncology point of view, are 3 latent membrane proteins (LMPs), 2 nuclear RNAs (EBER1/2), and 6 transcription factors (EBNAs). EBNA1 is essential for viral
maintenance, whilst LMP1 possesses oncogenic potential.\textsuperscript{4} The function of the EBERs is only partially understood.

The expression of each of these proteins in normal and neoplastic cells is different. Three types of expression or latency have been described that permit the evasion of immune control mediated by cytotoxic lymphocytes. In all EBV-infected individuals, with or without tumors, EBNA1 is expressed. Latency type I is typical of Burkitt lymphoma, and is characterized by the sole expression of EBER1/2. Type II demonstrates the expression of EBNA1, the EBERs, and the LMPs1, 2A & 2B, and is characteristic of nasopharyngeal carcinoma, Hodgkin lymphoma, and nasal lymphomas. Type III, which is typically observed in the lymphoid processes of immunodeficient individuals, shows a pattern in which all of the proteins are expressed.

\textbf{A. Table 1}

\textbf{EBV-associated pathology}

\begin{tabular}{|l|}
\hline
\textbf{B-lymphoid origin:} \\
- Burkitt lymphoma  \\
- B lymphomas in immunosuppressed individuals (HIV+ and/or post-transplant) \\
\hline
\textbf{T/NK-lymphoid origin:} \\
- T/NK lymphomas  \\
- Hydroa vacciniforme-like lymphoma \\
\hline
\textbf{Others:} \\
- Nasopharyngeal carcinoma  \\
- Hodgkin lymphoma (Hodgkin disease) \\
\hline
\end{tabular}

At the histological level, EBV can be detected by \textit{in situ} hybridization (ISH), essentially applied for the detection of EBERs, but can also be detected with immunohistochemistry using anti-LMP1/2 and anti-EBNA1 antibodies, or by southern blot, which allows the detection of clonality.\textsuperscript{4} In addition, one use real-
time PCR to establish the correlation between EBV load and the risk of developing a PTLD, although this correlation is not precise in patients with profound immunodeficiency.\textsuperscript{5,6}

Another important factor in the development of PTLD in transplant recipients is the state of immunodeficiency that these patients present after immunosuppressant treatment has been administered to them to prevent the rejection of transplanted organs.\textsuperscript{7} The incidence of PTLD varies depending on the type of transplanted organ, the age of the recipient, and the type of immunosuppressant regimen. The incidence of PTLDs is around 1\% in renal transplant patients,\textsuperscript{8} up to 5\% in hepatic transplant recipients,\textsuperscript{9,10} and approximately 20\% in cardiac or intestinal transplant recipients.\textsuperscript{11} The frequency of PTLD in bone marrow transplant recipients varies depending on whether the bone marrow is unmanipulated, in which case the risk is less than 1\%, or manipulated through T–lymphocyte depletion, when it can reach 7.5\%.\textsuperscript{12} The use of therapy against graft-versus-host disease (GVHD), especially with anti-T-cell agents, advanced donor age, the use of total body irradiation (TBI) and the involvement of non-HLA identical recipients/donors\textsuperscript{13} are risk factors for PTLD. Of note, the recipients of non-HLA identical transplants with grafts depleted of T cells have a higher risk of developing PTLDs, up to 15\%,\textsuperscript{14} which is reduced when umbilical cord blood is used instead.

Another important factor influencing the development of a PTLD is the presence of an underlying disease. For example, patients who receive a bone marrow transplant (BMT) for the treatment of congenital immunodeficiency have an increased risk of developing PTLD compared to those who receive BMT for other reasons. Shpilberg \textit{et al} suggested that patients who receive liver transplants because of underlying autoimmune disorders, such as autoimmune hepatitis or primary biliary cirrhosis, may also have an increased risk of developing PTLD.\textsuperscript{15}

The frequency of PTLD occurrence also depends on the immunosuppressive regimen administered to patients. For example, patients
given combined treatments with anti-lymphocytic globulin, steroids, and azathiopurine, with or without cyclosporine, are considered a low risk group, provided that the levels are monitored. On the other hand, initial studies have suggested that patients treated with tacrolimus may have an increased risk of developing PTLDs, although this could not be completely confirmed.\textsuperscript{16-18}

Other risk factors for immunocompromised transplant recipients developing PTLDs include episodes of rejection warranting intensification of immunosuppression, especially the therapeutic use of cellular antibodies against T cells,\textsuperscript{19} negative EBV serology at the time of transplantation;\textsuperscript{20,21} pulmonary or small intestinal transplant; and young age at the time of transplant (particularly less than 5 years of age). The incidence of PTLD is greatest in the first year after transplant, when T-cell immunity against EBV is at its lowest.\textsuperscript{22} Pediatric patients have a higher incidence of PTLD than adult patients receiving similar grafts.

A. References

\textsuperscript{7}Aucejo F, Roafael G, Miller C. Who is at risk for post-transplant lymphoproliferative disorders (PTLD) after liver transplantation? \textit{J Hepatol} 2006;44:19-23.


Buyck HC, Ball S, Junagade P, Marsh J, Chakrabarti S. Prior immunosuppressive therapy with antithymocyte globulin increases the risk of EBV-related lymphoproliferative disorder following allo-SCT for acquired aplastic anaemia. *Bone Marrow Transplant* 2009;43:813-816.


B. Classification

The great majority of PTLDs are of the B phenotype (86%), although cases of T-cell lineage (14%) and a small percentage of null phenotypes (1%) also exist. PTLDs are subclassified on the basis of their phenotypic, histological, and molecular peculiarities, as well as their clinical progression. The current system for classification is that of the WHO. Currently used is the classification of the World Health Organization (WHO), which is an evolution of the classification system used by the American and Canadian Society of Hematopathology, which was developed by consensus at a workshop meeting.

The initial signs of PTLD include a series of events that have reactive processes in common and occur preferentially during the first 3 months post-transplant. Such events include reactive follicular hyperplasia, plasma cell hyperplasia, certain cases that have been labeled polyclonal lymphomas, and cases of infectious mononucleosis-like disease. These events usually affect young patients who are not infected with EBV, and they present with preferential involvement of the adenoids, tonsils, spleen, and less commonly the lymph nodes. Furthermore, these events are histologically characterized by structural preservation of the affected organ, presentation of a polymorphous lymphoid infiltrate with interspersed cells of both B and T phenotypes that are polyclonal in most cases, molecular rearrangements of both immunoglobulins, and EBV detectable by PCR or southern blot. Mutations of c-myc, ras, and p53 are usually not present. These are the typical cases of PTLDs described in the literature, and are usually resolved upon reduction of immunosuppression.
B. Figure 1
Typical plasma cells (black arrow) and isolated immunoblasts (dotted red line) interspersed with normal lymphocytes (H-E, 40×).

B. Figure 2
The same characteristics are observed in tonsil tissue where the normal epithelium appears narrowed by plasmacytoid proliferation (H-E, 10×).
B. Figure 3
The same characteristics are observed in tonsil tissue where the normal epithelium appears narrowed by plasmacytoid proliferation (H-E, 40×).

B. Figure 4
The same characteristics are observed in tonsil tissue where the normal epithelium appears narrowed by plasmacytoid proliferation (H-E, 40×).
B. 1 *Polymorphic Post-transplant Lymphoproliferative Disease*

The polymorphic PTLD classification encompasses vague terms used previously such as polymorphic B-cell hyperplasia and polymorphic B-cell lymphoma. These conditions usually appear at a later point in time that varies between 4 months and 8 years after transplant. These conditions typically involve an extranodal location, and histologically the architecture of the affected organ is lost. The cellular spectrum that makes up the lesions is extremely varied, with the possible presence of plasmacytoid lymphocytes, plasma cells, and immunoblasts being very typical. B lymphocytes usually predominate although there are usually an important number of T lymphocytes interspersed. In many cases, it is difficult to demonstrate restriction to light or heavy chain immunoglobulins by histochemistry, but it is generally possible to demonstrate monoclonality for IgH or EBV with molecular techniques. Mutations in oncogenes such as *c-myc*, *ras* and *p53* are not commonly observed. This type of neoplasia usually regresses with the reduction of immunosuppression, although in some cases, the disease progresses and requires a more active intervention such as the use of monoclonal antibodies.
B. Figure 5
Lymphatic node (H-E, 10×). Distortion of the lymphatic node architecture is visible with infiltration of the surrounding adipose tissue (arrow).

B. Figure 6
Polymorphic nodal infiltration including normal lymphocytes, immunoblasts, isolated plasma cells, and some mitotic forms of cells. Immunoblasts can show bizarre characteristics, mimicking Reed–Sternberg cells (H-E, 20×).
B. Figure 7

B. Figure 8
B. Figure 9
Polymorphic nodal infiltration including normal lymphocytes, immunoblasts, isolated plasma cells, and some mitotic forms of cells. Immunoblasts can show bizarre characteristics, mimicking Reed–Sternberg cells (100× immersion).

B. Figure 10
EBER staining.
Monomorphic PTLDs include B-cell lymphomas, such as certain cases of Burkitt lymphoma, and these PTLDs are frequently extranodal. Histologically, these cases cannot be distinguished from those that occur in non-immunosuppressed patients. They are typically associated with a clear loss of tissue architecture and large zones of necrosis. Cytological appearance need not necessarily be monomorphic, although generally they have a blastic appearance, may be multilobular, and appear more like centroblasts or immunoblasts.

Monomorphic PTLDs have a mature B phenotype. In these cases, it is usually possible to demonstrate restriction for light or heavy chain surface immunoglobulins by reaction with immunoperoxidase. In addition, molecular techniques show most cases to be monoclonal for IgH and EBV. Mutations in the oncogenes ras and p53 are frequently observed. These cases rarely resolve upon the reduction of immunosuppression, and it is necessary to treat them with chemotherapy.
B. Figure 12
Monomorphic proliferation indistinguishable from Burkitt lymphoma showing medium-sized cells with multiple cytoplasmic basophil nucleoli and significant mitosis.

B. Figure 13
CD20-positive staining.
 Approximately 10% of non-Hodgkin lymphomas observed in post-transplant patients are T-cell lymphomas. In general, the prognosis of these patients is poor, particularly because they commonly show no response to treatment. The existence of classical Hodgkin lymphoma is extremely rare in transplanted patients.

Other PTLDs that are not associated with EBV also exist. These cases amount to approximately 8–14% of lymphomas that develop in post-transplant patients, and represent a distinct clinical entity. A characteristic feature of these PTLDs is that they occur during the later post-transplantation phase, and they most often affect the lymph nodes. Lastly, the reduction of immunosuppression in these patients does not influence the progression of the disease.

B. 2 Classification

B. Table 1
Classification of post-transplant lymphoproliferative disorders

<table>
<thead>
<tr>
<th>Category</th>
<th>Subcategories</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial PTLD</td>
<td>Reactive plasma hyperplasia</td>
</tr>
<tr>
<td></td>
<td>Infectious mononucleosis-like</td>
</tr>
<tr>
<td>Polymorphic PTLD</td>
<td>Polymorphic B-cell hyperplasia</td>
</tr>
<tr>
<td></td>
<td>Polymorphic B-cell lymphoma</td>
</tr>
<tr>
<td>Monomorph PTL</td>
<td>Large diffuse B-cell lymphoma</td>
</tr>
<tr>
<td></td>
<td>Burkitt lymphoma</td>
</tr>
<tr>
<td></td>
<td>T-cell lymphoma</td>
</tr>
<tr>
<td>Others</td>
<td>Hodgkin disease</td>
</tr>
<tr>
<td></td>
<td>Hodgkin-like disease</td>
</tr>
<tr>
<td></td>
<td>EBV PTLD</td>
</tr>
</tbody>
</table>
B. 3 Staging

In general, it is difficult to adapt staging systems for PTLDs, especially in the polymorphic cases. The PTLD stage reflects the extent of the disease; local vs. disseminated, and nodal vs. organ involvement. In approximately 50% of cases, involvement of multiple organs or various nodes is found at the time of presentation. The 2 sites that are most commonly involved are the lymph nodes and the gastrointestinal tract. There is no formal stratification system for PTLD; the standard classification of Ann Arbor is suggested, although no staging system has yet been adapted for this approach.

B. References


C. Clinical Manifestations

The clinical presentations of PTLDs are highly varied and include asymptomatic lymphadenopathy, similar to atypical or severe infectious mononucleosis, and one or more nodal and/or extranodal tumors.1,2 In contrast to that which occurs in immunocompetent individuals, PTLDs are usually extranodal. Clinical manifestations of PTLDs include (1) a syndrome similar to infectious mononucleosis with or without generalized lymphadenopathy, (2) one or more extranodal tumors, and (3) fulminant disseminated presentation with sepsis.

Mononucleosis syndrome can occur soon after transplantation, especially in cases with primary EBV infection. This presentation is particularly common in the pediatric population. Moreover, otolaryngological signs and symptoms are
frequently the first manifestations of PTLDs in children. Patients can present with symptoms that mimic tonsilar hypertrophy, pharyngitis, necrotizing pharyngitis, lymphadenitis, sinusitis, and otitis media. There is a tendency for severe forms of PTLD tend to show symptoms of area obstruction. When PTLD occurs at a later stage after transplant, it is more anatomically circumscribed and can be associated with a more gradual clinical course. In this situation, extranodal disease with visceral involvement is common, which is associated with gastrointestinal; pulmonary; or, less frequently, central nervous system (CNS) symptoms. However, the associated lymphadenopathy is not painful.

The majority of PTLD patients present with at least a dominant tumor. The graft may also be involved with the disease; in such cases, the frequency of involvement varies according to the specific graft site. In pulmonary or intestinal transplant recipients, PTLDs demonstrate graft involvement in a significant proportion of cases. In PTLDs that arise in patients receiving other types of grafts, such as liver or kidney transplants, demonstrate graft involvement in up to one-third of the cases. In contrast, heart transplants rarely develop PTLDs associated with this condition.

The symptoms of PTLDs are related to the site of tumor growth. Gastrointestinal tumors can cause abdominal pain with bleeding, and can give rise to perforation with acute surgical abdominal symptoms. CNS tumors can cause symptoms related to local necrosis or the effects of the tumor bulk.

PTLDs can occur at any site, and isolated skin involvement has also been reported. Cases arising in the pleura have occasionally been described. Similarly, fulminant presentation is rare, occurring in approximately 1% of cases, but must be diagnosed early due to the high risk of mortality.
C. 1 Diagnosis

Diagnosis of PTLD requires knowledge of the diverse forms of presentation of this heterogeneous syndrome, and an awareness of the high probability of its development. The localization of organ dysfunction should direct clinicians toward the appropriate diagnostic evaluation. For example, an abrupt appearance of lymphadenopathy, whether isolated or systemic, means that PTLD must be considered among the list of alternative diagnoses. Abdominal pain, particularly in the context of intestinal bleeding, may indicate the possibility of PTLD in the gastrointestinal tract. Persistent headache or CNS symptoms may suggest localization of PTLD in the brain. Upper respiratory tract infections that do not respond to antibiotic therapy and are associated with lymphadenopathy should raise the suspicion of PTLD.

Endoscopic evaluation may lead to the discovery of nodular ulcers that can reflect PTLD in that organ. In the case of pulmonary involvement, multiple nodular densities can be seen with a simple chest X-ray.

Clinicians must keep in mind that PTLD may involve the graft itself. Serological tests for EBV can be used to evaluate the presence of a recent or remote infection. However, the diagnosis of EBV infection, whether active or passive, is not synonymous with PTLD. For example, one study showed that pediatric liver transplant recipients who were initially EBV-seronegative exhibited an 80% rate of conversion to seropositivity within 3 months of transplant. Of these patients, 85% were asymptomatic and only 15% developed PTLD.

Of the various tests used to detect EBV, IgM against viral capsid antigen (VCA-IgM) is particularly useful for detection of active EBV infection. However, the immune response in these immunocompromised patients can be inconsistent. A quantitative PCR estimate of the number of copies of the EBV genome in the peripheral blood has proven to be the most useful tool for determining the type of EBV infection, and the most likely association with
PTLD. Patients with PTLDs demonstrate an elevated number of circulating viral genome copies. Normal EBV-positive patients were found to have less than 2,000 copies of the viral genome per microgram of blood cell DNA, but this increased 10–100 times in patients with PTLD. Furthermore, a regression in the PTLD was associated with a reduced number of circulating copies, indicating that this approach could be useful for monitoring the effect of institutional therapy.

Biopsy specimens obtained from the graft or transplanted organ must be examined carefully to exclude PTLD before starting treatment for a possible rejection of the transplanted graft, because the increased immunosuppression is contraindicated in PTLD patients. Biopsy is the definitive diagnostic tool. Biopsied samples should be analyzed to detect infiltration by B cells and subjected to in situ hybridization to detect EBV.

C. Figure 1
CT of abdomen. A 5-year-old patient with who received a hepatic transplant for biliary duct atresia. Hypodense image in the right flank with necrotic images in the interior region corresponding to Burkitt lymphoma.
C. Figure 2
CT of the abdomen. A 5-year-old patient who received a hepatic transplant for biliary duct atresia. Hypodense image in the right flank with necrotic images in the interior region corresponding to Burkitt lymphoma.

C. References

8 Traum AZ, Rodig NM, Pilichowska ME, Somers MJ. Central nervous system lymphoproliferative


**D. Treatment**

The majority of centers follow a scale as to the overall treatment approach of PTLDs, with an initial intervention influenced by the extent of the disease and the degree of aggressiveness with which it presents in the patient. The initial treatment always consists of a reduction of immunosuppression whenever possible.1,2 Another measure that can be adopted as a first-line therapy is surgical excision, when the disease is limited and the location permits.3 Acyclovir, ganciclovir, and more recently cidofovir, are used for prevention but their effectiveness as treatments has not been proven.4 It is important to highlight that even though complete surgical resection can, upon removal of all tumor manifestations, obviate the need for future treatments such as in the case of tonsil resection, it is not adequate to attempt extensive
resections with the same aim in other locations such as the abdomen. In these cases, the management is similar to that for pediatric patients with non-Hodgkin lymphoma, where the initial surgery should be limited to biopsy.

Second-line treatment modalities for PTLDs include interferon-alpha, which currently is rarely used,\(^5\) or monoclonal antibodies; chemotherapy is reserved for select cases.

### D. 1 Immunosuppression Reduction

The most immediate measure for treating patients with PTLDs is to reduce the level of immunosuppression. This by itself is sufficient for only about one-third of the cases, and its efficacy varies according to the type of PTLD and the type of transplant.\(^2,4\) One obvious disadvantage of this therapeutic approach is the possibility of graft rejection that would later require a greater increase in immunosuppression and possibly cause organ damage that sometimes prevents adequate administration of chemotherapy. Reduction of immunosuppression does not normally control lymphomas that are already established. For this reason, other therapies, both immunological and non-immunological have been tested to identify a cure for this disease entity.

### D. 2 Systemic Antiviral Therapy

Acyclovir has been used as an inhibitor of EBV DNA replication with marginal success in eliminating polyclonal EBV lesions of the oropharynx (lesions that have not progressed to the proliferative phase). However, latent infected lymphocytes are not affected by this treatment. To date, the efficiency of this antiviral therapy for treating PTLD has not been definitively demonstrated. The results for ganciclovir and cidofovir are similar.
D. 3 Cytokine Therapy

Cytokine therapy is a logical extension of the therapeutic approach for PTLDs. The intention of this strategy is to stimulate a host's immune response to eliminate or reject the PTLD. The cytokine that has been most commonly used for this purpose is interferon-alpha. This treatment modality can be successful when immunosuppression reduction fails to control the disease, although the possibility of graft rejection also exists when this agent is used. However, with the introduction of rituximab, this treatment is rarely used today.

D. 4 Radiotherapy and Chemotherapy

The role of radiation therapy and the required doses for treating PTLDs have yet to be established, but it may be useful for the treatment of CNS tumors and controlling localized PTLD processes. However, it is likely that radiation treatment would only be useful in cases of primary cerebral lymphoma or in those cases where a tumor may be compressing a vital structure. Therefore, this approach is not commonly used today.

The reported results of using conventional chemotherapy to treat PTLDs are controversial. Clinicians must be careful in prescribing high-dose regimens for patients with organ dysfunction. Cyclophosphamide alone or together with rituximab, as well as chemotherapy regimens such as CHOP (cyclophosphamide, Adriamycin, vincristine, and prednisone), have been used in PTLD patients. Despite the high rate of complete remission in PTLD patients (up to 70%) after chemotherapy, the associated toxicity is significant and includes treatment-related mortality and significant co-morbidity in this population. The high mortality associated with standard chemotherapy regimens in the PTLD population may be due to various factors, including
pharmacological immunosuppression, graft dysfunction, and colonization with hospital-acquired resistant microorganisms.

Chemotherapeutic treatment cycles are typically repeated every 21–28 days or until hematological recovery. Patients who experience complete remission after 4 cycles are treated with 2 additional cycles. These patients are maintained without immunosuppression during treatment with this scheme and later receive the least possible dose of immunosuppression that allows adequate organ function. Patients with mature B-cell lymphomas must receive prophylactic intrathecal chemotherapy.

Chemotherapy is cytotoxic for proliferative B cells, and is also useful for treating or preventing GVHD and graft rejection. For patients with concurrent graft rejection and PTLD, chemotherapy offers the best control for these 2 processes. However, the conventional drug doses used for treating non-Hodgkin lymphoma patients appear to result in greater organ toxicity and susceptibility to infection in patients with primary immunodeficiency and in post-transplant patients.

D. 5 Cellular Therapy

Cellular therapy represents a recent innovation in the treatment of malignant diseases related to EBV, although it is only available in specialized treatment centers. The therapeutic use of immune effector cells against EBV arises from the effect of graft-versus-leukemia responses in patients with bone marrow transplant.\textsuperscript{11,12} However, this approach is not normally used in lymphoproliferative processes after solid organ transplant.
D. 6 Monoclonal Antibodies

Given that the majority of PTLDs are of B-lineage, the use of anti-B-cell monoclonal antibodies appears to be an attractive approach for treating these disorders,\textsuperscript{13,14} and is currently one of the pillars of treatment. In the first report describing the use of monoclonal antibodies for treating PTLD, patients were treated with both anti-CD21 and anti-CD24 antibodies, and 61\% of the patients responded to these treatments, whereas 46\% of the patients achieved long-term survival with acceptable toxicities.\textsuperscript{15} Treatment of PTLD patients with anti-CD19 monoclonal antibodies has also shown good results.\textsuperscript{15} However, these antibodies have not been commercialized on a large scale, and they have been replaced by rituximab.

Rituximab, an anti-CD20 monoclonal antibody, has already demonstrated its utility in treating both indolent and aggressive non-Hodgkin lymphoma, even in pediatric patients.\textsuperscript{16} This antibody is readily available commercially, and has recently been used in PTLD patients, with very promising results; in one study, more than 60\% of patients showed complete remission without significant toxicity.\textsuperscript{17} Rituximab should be considered part of the necessary multimodal strategies for treating PTLDs.

Rituximab is a chimeric monoclonal anti-CD20 IgG antibody that consists of human constant regions ligated to murine variable domains. The murine Fab domain of rituximab binds the CD20 antigen, a transmembrane protein situated on the surface of mature B cells, but not on plasma cells or on hematopoietic stem cells. The murine Fab domain confers specificity, while the human large constant region (Fc) binds to complement proteins. Rituximab has 3 potential mechanisms of action; apoptosis, complement activation, and antibody-dependent cellular cytotoxicity.

Rituximab was first approved for the treatment of CD20-positive low-grade non-Hodgkin lymphoma relapse, and later, in combination with CHOP, for large-cell lymphomas.\textsuperscript{16} Since its initial approval, it has been widely used both
as a single agent, and together with chemotherapy regimens for treating various CD20-positive hematological neoplasias. Rituximab also has an important role in the treatment of various non-malignant diseases, especially autoimmune diseases, such as rheumatoid arthritis, Sjögren syndrome, systemic lupus erythematosus, myasthenia gravis, autoimmune hemolytic anemia, and idiopathic thrombocytopenia purpura.

In each of these diseases, it is assumed that B cells play a critical role in the autoimmune process. Rituximab is generally administered weekly by slow intravenous infusion over 4 doses. In contrast to many other chemotherapeutic regimens, rituximab does not require dose adjustment for treatment of the lungs, kidneys, liver, or heart. Premedication with paracetamol and diphenhydramine is recommended before each infusion in order to prevent reactions related to the infusion. Adverse reactions related to rituximab treatment generally occur during the first administration. The reactions are usually milder upon subsequent infusions. Reactions observed during the infusion (flu-like syndrome, fever, shivering, nausea, headache, and rashes) can be treated symptomatically. Rarely, more serious reactions can appear, such as angioedema, hypotension, and bronchospasm, can appear around 20–120 minutes after the commencement of the first infusion. At this point, rituximab administration must be halted, but can be reinitiated at a slower infusion rate after all symptoms have resolved. The standard dose of rituximab is 375 mg/m² once per week for 4 consecutive weeks, although some patients require larger doses.

Previous results have confirmed that only rituximab and chemotherapy are highly effective in patients that fail immunosuppression reduction, even as a second-line therapy.¹⁸,¹⁹ Both of these therapies give rise to prolonged survival and cure in a large number of PTLD patients. The combination of rituximab and a chemotherapy like CHOP has proven efficacious in PTLD patients, even in those with monomorphic forms.²⁰ Rituximab has also been used intrathecally in
patients with primary cerebral lymphoma associated with a solid organ transplant.\textsuperscript{21}

\section*{D. References}

\textsuperscript{1}Mazariegos GV. Withdrawal of immunosuppression in liver transplantation: lessons learned from PTLD. \textit{Pediatr Transplant} 2004;8:210-213.


\textsuperscript{12}Lynch BA, Vasef MA, Comito M, Gilman AL, Lee N, Ritchie J, Rumelhart S, Holida M, Goldman F. Effect of in vivo lymphocyte-depleting strategies on development of lymphoproliferative


