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Post-transplant lymphoproliferative diseases: Polish Lymphoma Research Group 2025 recommendations for diagnosis and treatment

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Abstract

Post-transplant lymphoproliferative disorders (PTLD) are a category of iatrogenic lymphoproliferative syndromes associated with immunodeficiencies. PTLD is defined as any lymphoproliferation (except lymphoproliferation from small B lymphocytes) occurring after organ transplantation or allogeneic hematopoietic stem cell transplantation, regardless of the time elapsed since transplantation. The diagnosis of PTLD is based on histopathological examination of the lymph node or suspicious lesion. The main treatment goal is eradication of PTLD, with a concomitant maintenance of graft function. This article presents the latest diagnosis and treatment recommendations of the Polish Lymphoma Research Group.

Keywords: treatment, lymphoma, transplantation, immunochemotherapy, immunosuppression, Epstein–Barr virus

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According to the authors and editors, this report contains the most justified principles of diagnostic and therapeutic procedures prepared, considering the scientific value of evidence and the category of recommendations. These principles should always be interpreted in the context of an individual clinical situation. The recommendations do not always correspond to the current reimbursement rules in Poland. In the case of doubt, the current possibilities

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for reimbursement of individual procedures should be determined.

1. The quality of scientific evidence:

I — Scientific evidence obtained from well-designed and properly conducted randomized clinical trials or meta-analyses of randomized clinical trials;

II — Scientific evidence obtained from well-designed and properly conducted prospective observational studies (non-randomized cohort studies);

III — Scientific evidence obtained from retrospective observational studies or case-control studies;

IV — Scientific evidence obtained from clinical experiences and/or experts' opinions.

2. Category of recommendations

A — Indications confirmed unambiguously and absolutely useful in clinical practice;

B — Indications probable and potentially useful in clinical practice;

C — Indications determined individually.

Epidemiology

Post-transplant lymphoproliferative disorders (PTLD) are one of the groups of iatrogenic lymphoproliferative syndromes that develop as a result of immunodeficiencies. They constitute a distinct group, different from both lymphomas and other iatrogenic lymphoproliferative diseases associated with immunodeficiencies/errors of immunity. This distinctiveness is emphasized by both the 2016/2017 World Health Organization (WHO) classification and the 2022 International Consensus Classification (ICC) [1]. According to the 2022 WHO recommendations, the term PTLD is no longer recommended, and these diseases should be referred to as:

1) hyperplasias arising from immune deficiency or dysregulation, or
2) polymorphic lymphoproliferative disorders, or
3) lymphomas arising from immune deficiency or dysregulation [2].

Despite these changes in nomenclature, the recent reclassification has not brought about any substantive changes.

Therefore, the term 'PTLD' will be used in these guidelines, in accordance with the ICC 2022 and WHO 2017 classifications.

By definition, PTLD is any lymphoproliferation (excluding small B-cell lymphoproliferation) (Table I.) occurring after solid organ transplantation (SOT; SOT-PTLD) or allogeneic hematopoietic cell transplantation (allo-HCT; HCT-PTLD) [1, 3]. The main risk factors include the type of transplantation, the degree of T-cell suppression, and the serological status of the recipient and donor regarding Epstein–Barr virus (EBV) infection. Although almost all cases of HCT-PTLD, and about 50% of SOT-PTLD, are EBV-positive, the number of EBV-negative cases, especially late ones, is increasing [4].

The risk of SOT-PTLD is much higher than that of HCT-PTLD, accounting for about 20% of cancers diagnosed after transplantation of vascularized organs (excluding skin cancers and cervical cancer in situ) [5]. In the case of allo-HCT, PTLD occurs much less frequently and accounts for a small percentage of cancers diagnosed in transplant recipients. However, the incidence of PTLD varies greatly, as a result of the heterogeneous patient population, the type of transplantation, and the immunosuppressive protocols used.

PTLD most often occurs after transplantation of multiple organs (12–33%), intestines (20–30%) and thoracic organs *i.e.* lungs (6–10%) and heart (3–5%). The lowest risk is observed after transplantation of liver (2–3%), kidney and pancreas (2–3%) and kidney alone (1.5–2.5%). The risk of developing HCT-PTLD (0.1–2.5%) is lower than SOT-PTLD, but it significantly depends on the type of transplantation and donor *i.e.* incompatible unrelated donor (11.2%), or compatible unrelated donor (4%), or haploidentical donor (2.8%), or compatible related donor (1.2%).

The rate of HCT-PTLD in recipients of cord blood-derived hematopoietic stem cells varies depending on the conditioning protocol. It has been shown to be lower after myeloablative conditioning (2.6–3.3%) and higher after reduced-intensity conditioning (7–13%). PTLD can occur at any time after transplantation, but is usually diagnosed within the first two years after SOT (90% of cases; median 6 months) [6–16]. In the case of HCT-PTLD, the corresponding period is even shorter, with a median of 2–3 months [17].

The degree of immunological competence of T lymphocytes is important for the control of latent EBV infection [18, 19]. The results of studies with belatacept (anti-CTLA4 antibody) and efalizumab (anti-LFA1) have confirmed the key role of increased immunosuppression of T lymphocytes, and thus an increased risk of developing PTLD, showing a relatively high risk of developing PTLD with a parallel low efficacy in preventing transplant rejection [20–22]. An increased risk of developing PTLD has also been demonstrated in the case of the use of muromomab (anti-CD3 antibody), alemtuzumab and anti-thymocyte globulin (ATG) [6, 23, 24]. However, mycophenolate mofetil (MMF) therapy is not associated with a significantly increased risk of developing SOT-PTLD [25, 26]. The risk of developing PTLD is significantly higher in EBV-seronegative recipients who received an organ from EBV-seropositive donors, an observation which has been confirmed in many observational and prospective studies [14, 27–29]. The significantly higher incidence of PTLD in children is most likely related to the much less frequent reports in pediatric cases of both previous and newly diagnosed EBV infection [27, 29].

The risk factors for developing HCT-PTLD differ from those for SOT-PTLD. In a retrospective analysis of 18,014 patients

Table I. Subtypes of post-transplant lymphoproliferative diseases according to WHO 2016/2017 classification and ICC 2022 classification

Category [4]	Incidence [%]	Association with EBV infection [%]	Morphology and immunophenotype
1. Non-destructive[a] — plasma cell hyperplasia — mononucleosis-like syndrome-nodular hyperplasia	5	100	Preserved structure of lymph node; mainly small lymphocytes and plasma cells; immunophenotypic examination shows polyclonal B lymphocytes and an admixture of T lymphocytes; EBV-positive; hyperplastic germinal centers
2. Polymorphic form of PTLD[b]	15–20	Nearly 100	Blurred structure of lymph node; morphologically, full spectrum of cells of maturing lymphatic system does not meet criteria of lymphoproliferative disease (lymphoma) diagnosis; immunophenotypically, polyclonal B lymphocytes, immunoblasts and T lymphocytes are found in the immunophenotyping test; often EBV-positive
3. Monomorphic form of PTLD[c] B-cell malignancies: — diffuse large B-cell lymphoma — Burkitt lymphoma — mantle cell lymphoma — multiple myeloma — solitary myeloma — other[c,d*]	>70 <5	50–80 10–60	Blurred structure of lymph node; it meets criteria for T-cell lymphoma, myeloma, and B-cell lymphoma (other than indolent subtypes); cell phenotype dependent on subtype; EBV-positive *While low-grade B-cell lymphomas such as follicular lymphoma, mantle cell lymphoma, chronic lymphocytic leukemia, and marginal zone lymphoma have historically been excluded from diagnosis of PTLD, 2017 update includes EBV-positive cases of extranodal marginal zone lymphoma of MALT type, which typically arises in skin or subcutaneous tissue, as PTLD.
T cell neoplasms: — peripheral T cell lymphoma, not otherwise specified — hepatosplenic T-cell lymphoma (HSCTL) — NK cell tumors	1	90	
4. Classical Hodgkin lymphoma type PTLD	<5	>80	Blurred structure of lymph node; it meets WHO criteria for classical Hodgkin lymphoma

[a]Non-destructive (early) are mostly polyclonal, although a small monoclonal population of B cells may be present and may show cytogenetic or molecular changes; [b]EBV-positive mucocutaneous ulcer, which may resemble polymorphic PTLD, should be considered a distinct disease entity; [c]Classification consistent with classification of lymphomas they resemble; [d]Small B-cell lymphomas are not classified as PTLD with exception of EBV-positive extranodal MALT type marginal zone lymphomas; EBV — Epstein-Barr virus; PTLD — post-transplant lymphoproliferative disorder; WHO — World Health Organization

from 235 centers, the 10-year cumulative risk of developing PTLD was 1%, with 82% of cases diagnosed within 12 months of transplantation [6]. Comparable results were reported in another retrospective analysis, in which PTLD was diagnosed in 127/26,901 allogeneic stem cell recipients [24].

In turn, an observational study showed that an increased risk of PTLD was associated with transplantation from an unrelated donor or a donor with HLA incompatibility, recipient age above 50 years, T-cell depletion, and the use of ATG and anti-CD3 antibodies in the prevention of graft-versus-host disease (GvHD), as well as the occurrence of chronic GvHD (risk of late PTLD) [6, 24]. It was also shown that risk factors are cumulative, increasing the probability of developing PTLD to 22% in the presence of three or more of the abovementioned factors.

Etiopathogenesis

Epstein–Barr virus-negative PTLD constitutes c.20–40% of SOT-PTLD, c.40% of PTLD diagnosed in the first year after transplantation, and the majority of late diagnosed PTLD, *i.e.* c.10 years after transplantation [30, 31]. In most cases, PTLD is associated with B-cell transformation due to EBV infection, resulting from immunosuppression and impaired T-cell immune surveillance. Serological evidence of previous EBV infection is present in 90–95% of adults,

depending on geographical region. In most adults, newly diagnosed infection is asymptomatic, although some patients develop infectious mononucleosis. EBV infection causes polyclonal expansion of B cells and activation of T cells, which eliminate most infected B cells. After the primary infection phase, the virus becomes latent, remaining mainly in B cells, from which it cannot be completely eliminated. Infected cells, however, are controlled by cytotoxic T lymphocytes. Loss of this control, caused for example by immunosuppression, leads to virus reactivation, excessive proliferation of infected B lymphocytes and, consequently, to the development of PTLD [32, 33].

Epstein–Barr virus induces B lymphocyte proliferation through a number of proteins such as LMP-1, LMP-2A, EBNA-2 and EBNA-LP, which can ultimately lead to their transformation into lymphoblasts. LMP-1 and LMP-2A membrane proteins activate B lymphocytes [34–36]. In turn, EBNA-2 and EBNA-LP proteins function as transcription factors, regulating the expression of host genes such as *MYC* and genes encoding transforming proteins, including LMP-1 and LMP-2A [37, 38]. Exceptionally rarely, PTLD can develop from T lymphocytes or NK cells. The role of T lymphocytes in the control of EBV-dependent transformation has been confirmed in an animal model *i.e.* in a study with mice with LMP-1 protein expression in B lymphocytes, lethal lymphoproliferative disease developed only in cases of T lymphocyte depletion [39].

In most cases, SOT-PTLD develops as a result of transformation of recipient lymphocytes, whereas in HCT-PTLD it usually arises from donor lymphocytes [33]. The association of PTLD with EBV infection is crucial in the development of PTLD early after transplantation. PTLD diagnosed later (even >10 years after transplantation) often shows no association with EBV and belongs to the monomorphic subtype. Most PTLD originating from NK lymphocytes shows an association with EBV infection, whereas in the case of PTLD developing from T lymphocytes, this association is found in 10–60% of cases [40]. It has been suggested that PTLD in which the association with EBV infection has not been confirmed should be treated as a second primary malignancy. However, this view is not currently reflected in international treatment guidelines [41].

Diagnostics

The PTLD diagnosis is based on histopathological examination of a surgically collected lymph node or a suspicious lesion. If this is impossible, a core needle biopsy can be performed in exceptional circumstances. This allows for the correct histopathological categorization of the PTLD subtype, which determines the appropriate clinical management. The 2017 WHO classification distinguishes four categories of PTLD (see Tab. I): non-destructive changes (referred to as 'early' in the 2007 WHO classification); and destructive changes, which are subdivided into three *i.e.* polymorphic, monomorphic, and classical Hodgkin lymphoma type PTLD (cHL-PTLD) [3]. A similar division has been maintained in the 2022 ICC classification. In the 2022 WHO classification, PTLDs have been classified in a broader category of immune deficiency and dysregulation (IDD), which currently includes: hyperplasia arising in IDD; polymorphic lymphoproliferative disorders arising in IDD; and lymphomas arising in IDD [2]. The recommended diagnostic tests for PTLD are set out in Table III.

The clinical course of PTLD can vary, and depends on the subtype and the transplanted organ. Early changes and the polymorphic form may be asymptomatic or oligosymptomatic. They develop mainly in children and adults after SOT, in whom EBV infection was not previously detected. Symptoms include fever and weakness. Physical examination reveals lymphadenopathy, enlarged tonsils, and clinical symptoms resembling infectious mononucleosis. These changes can regress spontaneously or as a result of reduced immunosuppression.

Monomorphic forms of PTLD often present typical features of lymphoproliferative malignancies with systemic symptoms. The most common manifestations of these PTLD subtypes are lymphadenopathy and fever. In contrast to lymphomas occurring in people without a previous organ transplant, PTLD can rarely be limited to the lymph nodes (approximately 10%). In late forms, extranodal locations predominate, primarily the gastrointestinal tract (up to 30%) and the central nervous system (5–20%). Organ involvement may be accompanied by symptoms of pneumonia, hepatitis, and gastrointestinal motility disorders. PTLD may also lead to the development of cytopenia due to bone marrow involvement (which may be the only site of the disease) or autoimmune complications. Rare symptoms of PTLD include encephalitis, myelitis, hemophagocytic lymphohistiocytosis (HLH), and a significant deterioration of the patient's general condition resembling septic shock.

Due to the nature of PTLD, diagnostics should include a histopathological examination of the affected organ or lymph node, as well as molecular and imaging diagnostics. Additionally, it is necessary to perform a peripheral blood count with a microscopic smear and biochemical tests to assess the function of the kidneys, liver, and lactate dehydrogenase (LDH) activity. Molecular diagnostics should include determining the number of copies of the EBV virus and cytomegalovirus (CMV). It is also recommended to perform serological tests for hepatitis B virus (HBV) and hepatitis C virus (HCV) as well as human immunodeficiency virus (HIV) infection [40, 42].

Pathomorphological diagnostics

Pathomorphological diagnostics form the basis for diagnosing PTLD and allow for determination of the four main categories of PTLD according to the WHO 2017 classification

(see Tab. I) [3]. Histopathological examination, in addition to morphological and immunohistochemical assessment, should include diagnostics for the presence of Epstein–Barr encoding RNA (EBER) using in situ hybridization (ISH), which allows for determining if the lesion is related to EBV infection. Immunohistochemical examination for Epstein–Barr virus latent membrane protein 1 (LMP1) is characterized by lower sensitivity, and therefore is not recommended [43].

The histopathological division, as indicated by international guidelines, does not take into account other important variables that may help to precisely define the category and subtype of PTLD and may influence the course of the disease [40, 44, 45]. These variables include:

- clonality of neoplastic cells (polyclonal *vs.* monoclonal lesions),
- molecular and cytogenetic characteristics of lesions,
- presence of the EBV genome or EBV infection status
- origin of lesions (*i.e.* donor *vs.* recipient).

Histopathologically, within the category of non-destructive lesions, three subtypes are distinguished: plasma cell hyperplasia; mononucleosis-like syndrome; and nodular hyperplasia.

Monomorphic lesions constitute the most diverse histopathological category within destructive changes, including B-cell lymphomas. The majority of these are diffuse large B-cell lymphoma (DLBCL). Less frequent are Burkitt lymphoma (BL) and plasma cell neoplasms [46–48]. Lymphomas derived from T lymphocytes and NK cells are observed much less frequently. These neoplasms most often occur in the form of peripheral T-cell lymphoma, type not otherwise specified (PTCL, NOS), or EBV-positive T/NK lymphoma (see Tab. II) [49–52].

The histopathological criteria for diagnosis of these lesions are the same as for similar neoplastic lesions in patients who are not recipients of organ or hematopoietic cell transplants. While low-grade B-cell lymphomas, such as follicular lymphoma, mantle cell lymphoma, chronic lymphocytic leukemia, and marginal zone lymphoma, were previously excluded from the PTLD category, the 2017 update includes EBV+ cases of extranodal marginal zone lymphoma of the MALT type, which typically occurs in the skin or subcutaneous tissue in PTLD [4].

Classical Hodgkin lymphoma type PTLD is characterized by the presence of an infiltrate of a small number of neoplastic cells expressing CD15 and CD30 antigens, surrounded by numerous inflammatory cells. Some cells may express CD20 antigen, but no expression of CD3 or CD45 antigens is observed.

Cytological diagnostics

Cytological diagnostics of solid lesions, bone marrow aspirate or body fluids have limited utility in the diagnosis of PTLD, but in specific clinical situations they may be helpful in differential diagnosis, assessment of organ involvement, or determination of disease severity.

Immunophenotyping

Immunophenotyping may complement diagnostic tests, supporting differential diagnosis or preliminary evaluation of solid, infiltrative or body fluid lesions before histopathological examination results become available.

Genetic diagnostics

Genetic testing currently does not play a significant role in the diagnosis of PTLD. Cytogenetic testing, on the other hand, may be helpful in differential diagnosis of individual types of PTLD and in determining the association with EBV infection, e.g. through EBER testing.

Molecular diagnostics

Real-time PCR enables the determination of the number of EBV copies/viremia in peripheral blood, and in some transplant centers it is an element of standard post-transplant surveillance. Currently, there are no clear recommendations regarding the frequency and duration of EBV viremia monitoring, the determination of the presence of the virus in peripheral blood cells or serum, or cut-off points for viremia in patients after SOT or allo-HCT [53].

Low EBV viremia in peripheral blood occurs in the vast majority of transplant recipients, but only in patients diagnosed with PTLD does its level increase significantly (median 740 copies/100 µL in patients undergoing immunosuppression *vs.* median 3,225 copies/100 µL in patients with PTLD) [54]. These observations suggest the possibility of using EBV copy number determination as an auxiliary tool in PTLD diagnostics, but histopathological examination is still necessary to make a final diagnosis.

Excluding the presence of EBV based on molecular tests does not eliminate the possibility of diagnosing PTLD, due to the possibility of only local EBV infection and local transformation, e.g. in the gastrointestinal tract or the central nervous system (CNS) [53, 55, 56]. Determining the number of EBV copies in peripheral blood or its morphological elements can also be useful for assessing the risk of developing PTLD or monitoring the response to treatment in cases of EBV-positive PTLD [57, 58].

Imaging diagnostics

The suggested imaging method in suspected PTLD is positron emission tomography-computed tomography (PET-CT), due to the possibility of identifying metabolically active sites [59, 60]. Examination using 18F-FDG (fluorodeoxyglucose) is characterized by higher sensitivity and specificity compared to CT, as confirmed by the results of three meta-analyses of more than 350 patients [61–63]. In these analyses, the diagnostic parameters for the detection of PTLD (mainly monomorphic form) showed sensitivity of

Table II. Histological subtypes of monomorphic PTLD category

	Histological subtype	
1	DLBCL	Constitutes vast majority of monomorphic forms and at same time most heterogeneous group of neoplasms. DLBCL cells are characterized by expression of pan-B markers, a diffuse type of infiltration and a high proliferative index, although there is no pathognomonic molecular or cytogenetic change in this type of lymphoma
2	BL type	Characterized by an infiltration of medium-sized monomorphic cells with a high proliferative index with expression of B-cell antigens, superficial expression of immunoglobulin M (IgM) and CD10 antigen, but with no expression of CD5 antigen and BCL2 protein. It is almost always EBV-positive
3	Plasmacytoma type	May occur as an infiltration of both mature and immature plasma cells characterized by light chain restriction (kappa or lambda) and expression of CD79a, CD138 and CD38 antigens, or in some cases CD56 antigen. Plasma cell tumors may take form of isolated plasma cell tumors or meet criteria for multiple myeloma. Both secreting and non-secreting monoclonal protein in the form of an immunoglobulin molecule or a light chain are encountered
4	Peripheral T-cell lymphoma, not otherwise specified (PTCL, NOS)	A heterogeneous group of lymphomas, characterized by expression of one of pan-T antigens. However, there are cases in which expression of CD5 and CD7 antigens is absent. Both histopathological and immunophenotypic characteristics are very diverse

BL — Burkitt lymphoma; DLBCL — diffuse large B-cell lymphoma; EBV — Epstein-Barr virus; PTCL, NOS — peripheral T-cell lymphoma, not otherwise specified; PTLD — post-transplant lymphoproliferative disorder

Table III. Suggested list of tests for PTLD staging

Complete blood count (CBC) with microscopic smear, reticulocyte count
Renal function (creatinine, urea, uric acid, sodium, potassium, calcium, phosphates)
Liver function (total bilirubin with fractions, ALT, AST, ALP, GGTP, total protein, albumin)
Hemostasis parameters (APTT, fibrinogen, PT)
CRP, LDH
Virological tests (HBsAg, anti-HBs, anti-HBc total, anti-HCV, anti-HIV, anti-EBV IgG and IgM, anti-CMV IgG and IgM, DNA-CMV, DNA-EBV)
Histopathological examination of tissue
Histological examination of bone marrow and myelogram assessment
Imaging tests (PET-CT or CT)
ECHO examination — if anthracycline treatment is necessary
MRI examination of central nervous system, sinuses, orbits in cases of suspected CNS involvement or PTLD of craniofacial region
Lumbar puncture with collection of cerebrospinal fluid for general and immunophenotypic examination — in cases of suspected CNS involvement and DLBCL and BL lymphomas

Ag — antigen; ALP — alkaline phosphatase; ALT — alanine transaminase; APPT — activated partial thromboplastin time; AST — aspartate transaminase; BL — Burkitt lymphoma; CMV — cytomegalovirus; CNS — central nervous system; CRP — C-reactive protein; CT — computed tomography; DLBCL — diffuse large B-cell lymphoma; EBV — Epstein-Barr virus; ECHO — echocardiography; GGTP — gamma glutamyl transpeptidase; HBV — hepatitis B virus; HCV — hepatitis C virus; HIV — human immunodeficiency virus; Ig — immunoglobulin; LDH — lactate dehydrogenase; MR — magnetic resonance imaging; PET — positron emission tomography

85–93%, specificity of 86–94%, positive predictive value (PPV) of 88–91%, and negative predictive value (NPV) of 87–91% [61–63].

The 18F-FDG PET-CT examination has been shown to allow for the identification of additional lesions not visible in CT or magnetic resonance imaging (MRI) in 28% of cases, and in 15% of cases led to an increase in the stage of the disease [64]. False positive results occur in about 5% of cases, and are most often associated with infections, inflammations of non-infectious etiology, or another neoplastic disease [64]. False negative results are noted in about 11% of cases, which is mainly due to high background activity or the presence of early, low-grade PTLD lesions [64]. The 18F-FDG PET-CT examination is also effective in the assessment of bone marrow infiltrations [65].

Standardized uptake value (SUV) to differentiate benign from malignant lesions is not currently used due to high rates of false positive and false negative results [60].

In the case of limited availability of PET-CT, computed tomography can be used, and, to a lesser extent, ultrasound examinations. Magnetic resonance imaging remains the

examination of choice in the assessment of brain and spinal cord structures [66].

Staging and prognostic factors

Lugano classification for staging of lymphomas (derived from Ann Arbor staging with Cotswolds modifications) [67–69] is used to assess the stage of monomorphic PTLD. The stage should be assessed using PET-CT, or in a case of limited availability of this test, CT. Histopathological examination of the bone marrow and an aspiration biopsy of the bone marrow are necessary in all cases of PTLD, except for cHL-PTLD. In cases of suspected involvement of the central nervous system (CNS), lumbar puncture and analysis of the cerebrospinal fluid should be performed, including immunophenotypic testing [70]. Currently, there are no clear recommendations regarding the prevention of CNS involvement.

The prognosis for early and polymorphic lesions that respond well to reduced immunosuppression is favorable. Monomorphic lesions respond less well to reduced immunosuppression. In patients with SOT-PTLD, the use of a combination of rituximab and classic chemotherapy (ChT) have contributed to improved treatment outcomes. In a phase II observational study, sequential treatment with rituximab, followed by intensification of the response with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) in patients who did not achieve CR after rituximab monotherapy, achieved a 3-year survival rate of 75%, with median overall survival (OS) of 6.6 years [71].

There are currently no validated prognostic indices for assessing the prognosis of PTLD, but most studies have used the International Prognostic Index (IPI), classifying patients into low-risk (0–2 risk factors) or high-risk (3–5 risk factors) groups [42, 72]. Previous studies indicate that lack of response to rituximab monotherapy is a significant prognostic factor, with an unfavorable impact on the course of the disease [73, 74]. CNS involvement, T-cell origin of PTLD, and late diagnosis of PTLD after SOT, are also factors that worsen the prognosis [75–78].

Recommendations

- PTLD diagnostics should include histopathological examination of the affected tissue or organ (IIA).
- PET-CT is the imaging modality of choice, which is used to assess the stage of advancement and response to treatment (IIA).
- MRI is preferred for the assessment of central nervous system structures (IIA).
- Monitoring EBV viral load after transplantation is a method that supports the diagnostic process (IVB)
- Analogous criteria to those used for the types of cancers diagnosed in the non-transplanted population should be used to assess response (IIB).

Treatment

General guidelines

The goal of therapy in patients with PTLD is to eradicate PTLD while maintaining graft function.

Antiviral prophylaxis and preemptive therapy

By definition, prophylactic antiviral therapy is used in asymptomatic patients at increased risk of developing EBV-positive PTLD. Preemptive therapy is used in patients with detectable EBV viremia, and its aim is to prevent the development of EBV disease [79, 80].

Prophylactic antiviral therapy with antiviral drugs (gancyclovir, acyclovir, foscarnet, cidofovir), immunoglobulins, anti-CMV immunoglobulin or rituximab is not recommended for the prevention of EBV-positive PTLD. Although antiviral drugs inhibit *in vitro* virus replication to some extent, they do not affect EBV infection in the latent phase [81, 82]. Data on the prevention of EBV-positive PTLD after vascularized organ transplantation comes from descriptions of small groups of patients [83–86]. A meta-analysis summarizing the efficacy of this strategy in preventing SOT-PTLD did not demonstrate a reduction in the incidence of PTLD in patients undergoing prophylactic treatment [RR (relative risk) = 0.95; 95%, CI (confidence interval) 0.58–1.54] [87].

In patients after allo-HCT, not only do doubts regarding the efficacy of antiviral treatment exist, but an additional problem is the toxicity of the drugs used, including the hematological toxicity of gancyclovir. The use of rituximab in this group of patients is also associated with side effects, such as prolonged cytopenias [88] or an increased risk of infection [89]. In a retrospective analysis by Dominietto et al. [90], a significantly lower frequency of EBV viremia (56% vs. 85%) was observed in patients who received prophylactic rituximab on the 5th day after allo-HCT. However, this procedure did not significantly reduce the frequency of PTLD or improve the prognosis compared to the preemptive therapy strategy.

Regarding preemptive therapy in patients after allo-HCT, the European Conference on Infections in Leukemia (ECIL) recommends the use of rituximab in combination with a reduction in immunosuppression, if possible. Rituximab is administered once a week at a dose of 375 mg/m^2 and treatment is continued until a negative EBV viral load is achieved [79]. The use of rituximab in this indication allows for negative EBV viral load in more than 90% of patients [91], and is also associated with a much reduced incidence of EBV-positive PTLD (1.4% *vs.* 21.7% in the control group) [92].

Recommendations

- Routine use of antiviral drugs (gancyclovir, acyclovir) is not recommended for the prevention of EBV-positive PTLD (IIIB).

- Immunoglobulins are not recommended for the prevention of EBV-positive PTLD (IIIC).
- In patients with EBV viremia after allo-HCT, preemptive therapy with rituximab at a dose of 375 mg/m^2 once a week is recommended until a negative EBV test result is obtained (IIB).

Reduction in immunosuppression

Reduction in immunosuppression (RIS) is essential in all PTLD patients, if this is possible considering graft function or GvHD severity. When deciding on RIS, the risk of loss of graft function should always be assessed individually, taking into account whether it concerns an organ crucial for the patient's survival (*e.g.* heart, lungs) or one whose function can potentially be replaced (*e.g.* kidney). Reduction in immunosuppression can be used as a stand-alone treatment method only in low-risk patients, in whom the changes are non-destructive, the disease is at a low stage of advancement, and the infiltrates are not massive [93].

Data on the efficacy of RIS comes mainly from retrospective studies with small patient groups. In the analysis by Tsai et al. [94], including 42 patients with SOT-PTLD, the use of RIS in combination with surgery allowed for complete remission (CR) in 73.8% of patients. For RIS alone, the overall response rate (ORR) was 63%. The median time to response was 3.6 weeks. In multivariate analysis, factors associated with a lower probability of response to RIS were increased LDH level, graft dysfunction, and multi-organ PTLD infiltration.

The study by Reshef et al. [95] included 148 patients with PTLD divided into three groups:

- 67 patients treated with RIS alone,
- 30 treated sequentially (surgery followed by RIS),
- 51 treated without RIS.

In the group treated with RIS alone, the response rate was 45% and the CR rate was 37%. In patients treated with RIS, a high rate of acute rejection (32%) was observed. Despite this, survival in the group with RIS was longer than in patients not treated with it (44 *vs.* 9.5 months). However, this difference did not reach statistical significance. The analysis identified predictors of lack of response to RIS, which included massive infiltrates (bulky disease), high stage of disease, and older patient age.

In a multicenter study of 104 patients with PTLD after kidney or combined kidney and pancreas transplantation, the probability of graft loss 10 years after PTLD diagnosis was 43.9% in patients who discontinued calcineurin inhibitor (CNI). The probability of the composite endpoint of graft loss or death with a functioning graft was 64.4% [96].

In the multivariate model, the risk of graft loss was increased by PTLD stage >II and CNI discontinuation. On the other hand, the composite endpoint of graft loss or death was influenced by factors such as PTLD stage >II, CNI discontinuation, and age >60 years. CNI discontinuation turned out to be the most significant risk factor for both graft loss (HR = 3.07; 95% CI 1.04–9.09) and death (HR = = 4.00; 95% CI 1.77–9.04). PTLD subtype and location, or type of ChT used, were not independent risk factors.

There is no unified definition of RIS, and the procedure should be individualized in consultation with the transplant center. The recommendations of the British Committee for Standards in Hematology (BCSH) and the British Transplantation Society (BTS) state [97]:

- in the case of limited disease (stages I–II according to Lugano classification) — reduction of immunosuppression by 25%;
- in the case of advanced disease (stages III–IV according to Lugano classification) — reduction of CNI dose by 50%, discontinuation of azathioprine or mycophenolate mofetil, and maintenance of prednisone at a dose of 7.5–10 mg;
- in the case of advanced disease and patient poor performance status — discontinuation of all immunosuppressive drugs except prednisone at a dose of 7.5–10 mg;
- in lung or heart transplant recipients, maximum reduction of immunosuppressive drug doses should not exceed 25–50% (*i.e.* a reduction to 50–75% of the initial dose).

The recommendations of the American Society of Transplantation Infectious Diseases Community of Practice additionally emphasize that there is no scientific evidence supporting the replacement of CNIs with mammalian target of rapamycin (mTOR) inhibitors [98]. Failure of RIS is defined as disease stabilization after 2–4 weeks or progression at any time [71]. Based on Reshef et al.'s study [95], it is permissible to extend this period to six weeks in patients with stable disease.

Recommendations

- After consultation with the transplant center, immunosuppression should be reduced to the lowest safe dose in all patients with PTLD (IIIB).
- The time to RIS response is 2–4 weeks, provided there is no disease progression; in selected cases, this may be extended to six weeks (IVB).

Radiotherapy

Data on the use of radiotherapy (RT) comes from retrospective analyses [99], and indications for its use should be individualized. This treatment may be effective in patients with polymorphic PTLD or early stage disease [100]. An alternative to classical RT is radioimmunotherapy (RIT) e.g. with the use of ibritumomab tiuxetan ([90Y]) which is not widely available [101].

Recommendation

RT may be indicated in the treatment of patients with limited PTLD (IIIC).

Rituximab in monotherapy and in combination with chemotherapy in CD20+ PTLD

In patients with CD20+ PTLD and ineffective RIS, treatment is initiated with rituximab monotherapy, administered at a dose of 375 mg/m^2 once weekly for four weeks. Rituximab treatment allows for a response rate of 44–79%, including 20–55% of CR [80].

In a phase II study, patients with SOT-PTLD received rituximab at a dose of 375 mg/m^2 every seven days for four weeks (*i.e.* on days 1, 8, 15, and 22) [102]. In patients who achieved CR, treatment was discontinued and no further therapy was required. Patients with partial remission (PR) received another four doses of rituximab in the same regimen (375 mg/m^2 every seven days). Extending rituximab therapy by an additional four doses almost doubled the CR rate in the intention-to-treat (ITT) population, from 34% to 60.5%. After 27.5 months, OS was 47%, and event-free survival (EFS) was 42%.

In 2020, González-Barca et al. [103] published the results of their long-term study, including an additional 21 patients receiving the same treatment regimen in the real world. Disease-specific survival (DSS) in patients treated in the clinical trial was 64.7% after 10 years, and among those who achieved CR it was 94.4% after five years and 88.1% after 10 years, respectively. In real-world patients, DSS after five years was 75.2%, while among patients with CR it was 87.5%.

The results of this study confirm the high long-term efficacy of rituximab in patients achieving CR. The efficacy of rituximab monotherapy, and the good tolerability of this treatment, became the basis for the risk-stratified sequential treatment (RSST) regimen developed in the PTLD-1 study (NCT01458548), with intensity adjusted to the response after treatment with rituximab monotherapy. In the first phase of the study, Trappe et al. assessed the efficacy of sequential treatment rituximab → CHOP [104], while in the second phase it was rituximab → R-CHOP [71].

In the first stage of RSST, patients received four intravenous doses of rituximab (375 mg/m^2) at weekly intervals, then four cycles of CHOP at 21-day intervals. The first cycle of CHOP was administered four weeks after the last dose of rituximab. In cases of progression during rituximab monotherapy, or in the period between completed rituximab monotherapy and CHOP, patients immediately started ChT according to the CHOP protocol. The primary prophylaxis of febrile neutropenia with granulocyte colony stimulating factor (G-CSF) was mandatory. Patients also received prophylactic antibiotic therapy and cotrimoxazole as part of *Pneumocystis jiroveci* prophylaxis. The first assessment of treatment efficacy was performed 2–4 weeks after the last dose of rituximab, and the assessment at the end of treatment was performed 1 month ± 7 days after the last CHOP cycle.

81% of the study group were DLBCL-PTLD patients. The response rate after rituximab monotherapy was 60%, and 90% after sequential treatment. CR rates were 20% and 68%, respectively. The median duration of response (DoR) was not reached, and the median OS was 6.6 years. Treatment-related mortality (TRM) was 11%.

In the second stage of the study, patients received rituximab according to the protocol used in the first phase, *i.e.* at a dose of 375 mg/m^2 on days 1, 8, 15, and 22. A control CT scan was performed between days 40 and 50. Patients who achieved complete remission in the interim CT study continued rituximab monotherapy for an additional four doses every 21 days, starting on day 50. Patients who did not achieve CR were given four cycles of the R-CHOP protocol, administered every 21 days, also starting on day 50.

Similarly to the first stage, patients who developed symptoms suggesting disease progression during rituximab monotherapy or before interim CT assessment were immediately examined to confirm or exclude progression. If progression was confirmed, R-CHOP immunochemotherapy was initiated. Patients were required to receive prophylaxis with G-CSF during treatment according to R-CHOP regimen.

Patients with DLBCL-PTLD comprised 73.7% of SOT--PTLD patients included in the study. The ORR after RSST was 88%, including CR in 70% of patients. The median duration of response was not achieved, and the median OS was 6.6 years. The most common infectious complication was febrile neutropenia (15.9%). Treatment-related mortality occurred in 8% of patients.

An attempt to modify PTLD treatment strategy was made in the PTLD-2 study (NCT02042391), introducing a treatment intensification in high-risk patients, and a de-escalation in low-risk CD20+ SOT-PTLD patients. In the initial phase, all patients received induction treatment with rituximab monotherapy, according to the PTLD-1 study protocol, but the drug was administered subcutaneously.

Patients who achieved CR or PR on CT, and were considered to be low risk according to IPI (0–2 points), continued to receive rituximab monotherapy. Patients with disease progression during or after induction therapy were given four cycles of R-CHOP. High-risk patients who underwent thoracic organ transplantation were classified as very high risk and were qualified for even more intensive treatment in the form of an alternating R-CHOP and R-DHAOx (rituximab, dexamethasone, cytarabine, oxaliplatin) regimen for six cycles.

The ORR in the entire study group was 94% (95% CI 83–98). The 2-year PFS and OS rates were comparable to those observed in the PTLD-1 study. Treatment-related mortality was 4/59 (7%, 95% CI 2–17). The 2-year survival rate in the low-risk group was 100%. In contrast,

the results of treatment in the very high-risk group were disappointing: no patient responded to rituximab monotherapy, and intensification of treatment with the alternating R-CHOP/R-DHAOx regimen was associated with a high mortality (25%) [72].

The PTLD-2 study confirmed previous observations from a multicenter, international retrospective analysis, which indicated that lack of response to rituximab (stable disease or progression) in the first stage of treatment is still a poor prognostic factor. Intensification of treatment to R-CHOP only improves the results to a limited extent (2-year OS of 45%; 59% in the PTLD-2 study) [72, 105].

Recommendations

- In cases of ineffective RIS in SOT-PTLD patients, sequential treatment should be used, with intensity adjusted to the response after initial treatment with rituximab (RSST), *i.e.*:
  - **Stage 1**: four doses of rituximab (days 1, 8, 15, and 22),
  - **Stage 2** (after assessment of treatment efficacy):
    - In patients who achieve CR in CT scan, or complete metabolic response (CMR) in PET/CT scan, continuation of rituximab treatment (four doses every 21 days starting from day 50), a total of eight administrations (IIB).
    - In patients who achieve PR in CT scan and with low IPI (<3), rituximab monotherapy can also be continued, as in patients who achieved CR or CMR. However, there is no data regarding whether such a treatment strategy can be adopted in patients with partial metabolic remission (PMR) in PET/CT scan.
    - In remaining patients: intensification of R-CHOP regimen (four cycles every 21 days starting from day 50) (IIB).
    - In patients with progressive disease (PD) during rituximab monotherapy: immediate initiation of chemoimmunotherapy according to R-CHOP regimen.

Adoptive immunotherapy with EBV-positive PTLD

The prognosis of patients who are refractory to sequential therapy is very poor. Median survival is only 0.7 months in patients after allo-HCT, and 4.1 months in patients after SOT [106, 107].

In patients with EBV-positive PTLD, the salvage therapy options include EBV-specific cytotoxic T-lymphocytes (EBV-CTLs) or donor lymphocyte infusion (DLI). Most data on these methods comes from studies with HCT-PTLD patients. In an analysis of 49 patients after allo-HCT with confirmed EBV-positive PTLD, 27 patients received DLI, 17 were treated with EBV-CTLs, and in the remaining five patients both methods were used [108].

Lymphocytes for DLI were collected from hematopoietic cell donors, while for CTLs from hematopoietic cell donors or other donors. The lymphocyte dose was 1×10^6 CD3+ +EBV-CTLs/kg of body weight (bw), administered intravenously once a week for three weeks. In the case of DLI, the dose was $0.2–1 \times 10^6$ unselected CD3+ lymphocytes/ /kg bw and was administered once.

The use of these methods allowed for response in 73% of patients treated with DLI and in 68% of patients treated with EBV-CTLs. Acute graft-versus-host disease (GvHD) occurred in 17% of DLI recipients, but not at all in patients treated with EBV-CTLs.

The efficacy of EBV-CTLs was also analyzed in a phase II study, which included patients with HCT-PTLD after previous failure of conventional therapies [109]. In this study, lymphocytes were obtained from a CTL bank and selected individually for the patient based on the HLA assessment (A, B, DR) and *in vitro* cytotoxicity tests. Patients received a maximum of four doses of lymphocytes at weekly intervals, with a single dose of 1×10^6 CD3+ EBV-CTLs/ /kg bw. No treatment-related toxicity was observed during the study, and the ORR was 64% at 5 weeks and 52% at 6 months.

Kazi et al. [110] summarized the results of CTLs treatment in 59 patients. Lymphocytes were obtained from an independent third-party donor from a CTLs bank. The study group included 28 patients after allo-HCT and 20 after SOT. The remaining patients suffered from inborn errors of immunity, immune disorders secondary to immunosuppressive therapy, EBV-positive T/NK cell lymphoma, or DLBCL of the elderly. The overall response rate (ORR) was 59%, including 46% for HCT-PTLD and 75% for SOT-PTLD, and CR was 18% and 50%, respectively. Median overall survival was 0.1 years for patients with HCT-PTLD and 3.87 years for SOT-PTLD.

One of the critical issues limiting the use of EBV-CTLs is their low availability [79]. A promising alternative is tabelecleucel (tab-cel, Ebvallo®), a commercially available allogeneic T lymphocyte product targeted at eliminating EBV-infected cells, referred to as 'off-the-shelf'. In the phase III ALLELE study, the results of tab-cel treatment in a poor prognosis population were excellent. The estimated 1- and 2-year survival rates in all treated patients were 65.8% (95% CI 53.6–75.5) and 57.8% (95% CI 45.4–68.5), respectively. The 2-year OS rates in responders were 86.2% (95% CI 67.0–94.6) for CR, and 86.5% (95% CI 55.8–96.5) for PR [111].

Recommendations

- The use of EBV-CTLs is recommended in the treatment of patients with EBV-PTLD after failure of conventional treatment methods (IIC).

- Tabelecleucel (Ebvallo®) is indicated as monotherapy for the treatment of adult and pediatric patients aged two and older with relapsed or refractory EBV-induced PTLD who have received at least one prior therapy (IIA). This treatment is currently available in Poland only within the Emergency Access to Drug Technology programme.

Treatment of selected monomorphic PTLDs

CD20+ DLBCL-PTLD

The first step in the treatment of patients with DLBCL-PTLD is RIS and initiation of sequential RSST in cases of failure of RIS. Alternatively, RIS and simultaneous initiation of RSST can be used in patients with a low probability of successful RIS [93].

Starting the treatment with immunochemotherapy without previous rituximab monotherapy should be limited only to exceptionally aggressive cases, due to the high mortality associated with such a procedure [71, 93].

Recommendations

- In most patients, the reduction of immunosuppression (RIS) is insufficient, and therefore it is necessary to simultaneously start sequential RSST (IIA).
- It is recommended to use primary prophylaxis of febrile neutropenia during the use of R-CHOP (IIB).
- Additionally, prophylaxis of *Pneumocystis jiroveci* infection is recommended (IVC).

Prevention of central nervous system involvement

In patients considered to be at high risk of relapse in the CNS, the BCSH and BTS recommendations suggest implementing prophylaxis according to the local guidelines [93, 100]. In such cases, intrathecal prophylaxis with dexamethasone, methotrexate with or without cytosine arabinoside seems to be the preferred option, especially in patients with impaired liver or kidney function. This approach minimizes the risk of complications associated with the use of high-dose methotrexate.

Recommendation

- Prevention of CNS involvement (intrathecal treatment) in patients at high risk of recurrence (IVB).

cHL-PTLD

Data on the treatment of cHL-PTLD comes mainly from retrospective studies and case reports. In Rosenberg et al.'s analysis [112], which included the largest series to date of 192 patients with cHL-PTLD reported to the HL-PTLD Scientific Registry of Transplant Recipients, patients were treated primarily with RIS and protocols typical for classical Hodgkin lymphoma (cHL), such as ABVD or ABVD-like. Some patients (24%) received CHOP chemotherapy, and none of the patients received rituximab monotherapy. Eight patients (4%) received rituximab in combination with ChT.

The outcomes in cHL-PTLD patients were significantly worse than in patients with non-PTLD classical Hodgkin lymphoma. The 5-year overall survival was 57% for cHL-PTLD and 78% for cHL. The poorer prognosis for cHL-PTLD was due to both higher cHL-PTLD-related mortality (23% *vs.* 13% at 5 years) and higher mortality not related to cHL-PTLD (20% *vs.* 6% at 6 years). The use of typical ChT protocols for cHL was associated with improved OS compared to CHOP regimen, other 'non-typical' cHL protocols, or no ChT.

Median overall survival was as follows:

- median not reached for typical protocols,
- 93 months for CHOP,
- 88 months for other protocols,
- 15 months for patients not treated with ChT.

Similar differences were observed in DSS. Five-year DSS was:

- 91% for typical protocols,
- 68% for CHOP,
- 72% for other protocols,
- 53% for patients not treated with ChT (p <0.001).

The improved prognosis in the competing risks analysis was due to the reduction in cHL-PTLD-related mortality.

Experience with new drugs in the treatment of cHL-PTLD is currently limited to case reports reporting high efficacy of brentuximab vedotin (Bv) monotherapy [113, 114].

It is also worth emphasizing that the use of immune checkpoint inhibitors (ICIs) in patients after SOT is a significant challenge. In analysis by Portuguese et al. [115], summarizing the efficacy and safety of ICI therapy in patients after SOT treated for various cancers, it was found that 41.2% of patients experienced organ rejection, 23.5% experienced organ failure, and 18.5% experienced immune-related adverse events [115].

Recommendations

- Reduction in immunosuppression is recommended in patients with cHL-PTLD (IIIB).
- Treatment protocols typical for classical Hodgkin lymphoma (cHL) should be used (IIIB).
- Brentuximab vedotin in combination with AVD (Bv-AVD) should be used with caution due to the increased risk of infectious complications (IVC).
- In cases of resistant disease, the use of brentuximab vedotin is recommended (IIIC).

Treatment of refractory/relapsed disease

There are no precise definitions for relapsed or refractory PTLD. This is partly due to the variety of PTLD subtypes

and differences in their treatment. As previously mentioned, PTLD therapy is multi-step, with adjustment of intensity based on the efficacy of prior treatment. In the management of monomorphic forms, criteria related to the treatment of non-transplant lymphomas are often applied.

Due to the difficulties in defining resistance, it is not possible to clearly define the therapeutic methods used in such cases. In later treatment stages, it is possible to use EBV-CTLs, but only in EBV-positive patients. There are also reports of the effective re-use of rituximab in patients after the failure of previous chemotherapy [116].

There have been a few reports of salvage chemotherapy used in this group of patients. Examples include the CE regimen (carboplatin, etoposide), administered to nine patients, and CHOP [116, 117]. Some patients may also be eligible for high-dose chemotherapy supported by autologous hematopoietic cell transplantation (auto-HCT) [118].

One of the most promising therapeutic options for EBV-positive PTLD is tabelecleucel, which is characterized by high efficacy and low toxicity [119]. Brentuximab vedotin has been shown to be effective in CD30+ PTLD, and it is also used outside cHL-PTLD [114].

In addition, there have been anecdotal reports of achieving response in patients with rituximab-resistant PTLD after the use of an anti-CD20 antibody (ofatumumab), a PD1 inhibitor (nivolumab), or Bruton's kinase inhibitors (ibrutinib and zanubrutinib) [120].

Role of auto-HCT in patients with SOT-PTLD

Auto-HCT in patients with SOT-PTLD is associated with a high risk of non-relapse mortality (NRM). Therefore, qualification for this type of therapy should be performed with the utmost caution. In the largest analysis published to date, by the European Society for Blood and Marrow Transplantation (EBMT), including only 21 patients with SOT-PTLD. 100-day non-relapse mortality was 14%, and 1-year mortality was 24%. The main cause of death was infectious complications [121].

CAR-T therapy in PTLD

CAR-T therapy is a promising treatment option for refractory PTLD. Analysis of available published data, including 17 PTLD patients treated with CAR-T, showed a high success rate (76.5%) [120], even in difficult cases such as lung transplantation [122]. In the RWE study, including 22 patients, the overall response rate was 64%, with 55% of patients achieving CR. The 2-year progression-free survival and overall survival rates were 35% and 58%, respectively. Achieving CR with CAR-T therapy was strongly associated with improved survival.

In summary, the safety and efficacy of CD19 CAR-T therapy in relapsed or refractory SOT-PTLD appear to be comparable to the data from the pivotal CAR-T trials [123]. However, it should be noted that CAR-T therapy may increase the risk of graft rejection; in the RWE study, rejection occurred in 14% of patients [123].

The efficacy of CAR-T in PTLD may also be limited by immunosuppression. Therefore, it is recommended to consider temporary discontinuation of CNIs both before T-cell apheresis and after CAR-T administration [122].

Recommendations

- Auto-HCT can be used in patients with refractory or relapsed SOT-PTLD (classification IIIC).
- CAR-T therapy is a therapeutic option for refractory or relapsed disease (classification IIIC).

Treatment of rare subtypes of PTLD

Burkitt lymphoma accounts for c.5% of PTLD cases. It is characterized by rapid growth, extranodal locations, and a high proliferative index [124, 125]. Despite many features overlapping with sporadic BL, there are some differences. This lymphoma is almost always EBV-positive. Previous analyses often found forms with 11q aberration but without *MYC* rearrangement [126]. According to the 2017 WHO classification, as well as both 2022 classifications, these cases are no longer classified as BL and constitute a separate disease entity.

The largest series, including 20 patients with monomorphic Burkitt-type PTLD, suggests that rituximab monotherapy is insufficient in achieving durable remission (n = 3). Patients require ChT as treatment intensification. In total, 73% of patients (8/11) receiving a regimen similar to R-CHOP (R-CHOP, n = 9; EPOCH-R, n = 1; CHOP, n = 1) with concomitant RIS achieved CR. These results were comparable to those achieved with more intensive ChT combined with RIS (LLA/LB97 protocol, n = 2; CODOX-M/IVAC, n = 1; Burkimab trial regimen, n = 3), where CR was achieved in 5/6 (83%) patients.

Similarly, superior results of Burkitt-PTLD treatment were reported in the subanalysis of the PTLD-1 study [125]. Data has also been published of R-CHOP regimen efficacy, as well as R-CE regimen (rituximab, carboplatin, etoposide) efficacy, in cases of refractory and recurrent disease [124].

The role of CNS prophylaxis with intrathecal methotrexate administration remains unclear. Due to the aggressive clinical course and high proliferative index, simultaneous RIS and immunochemotherapy are recommended.

Primary central nervous system PTLD

Post-transplant lymphoproliferative disorders of the central nervous system accounts for approximately 10–20% of all

PTLD cases [127]. It is usually diagnosed within the first year after transplantation, most often with DLBCL morphology and associated with EBV reactivation. Treatment involves RIS and regimens based on the combination of rituximab with systemic methotrexate (MTX) or high doses of cytosine arabinoside. However, the optimal sequence of therapy is not established [124]. The prognosis is usually unfavorable, but according to recent reports, the overall response rate is 55–75%, regardless of the therapy used, with median overall survival of 33–47 months [66, 93].

A major limitation in the treatment of PTLD with CNS involvement is renal function, which makes it difficult to use high doses of methotrexate (>3 g/m^2) and increases the risk of transplant loss. In such cases, it is worth considering the use of glucarpidase in patients with delayed methotrexate elimination. In patients with impaired renal function or poor performance status (ECOG >2), in whom high doses of MTX cannot be used, RIS, rituximab monotherapy, and adjuvant RT are recommended. A promising therapeutic option for this group of patients consists of EBV-specific T lymphocytes (tabelecleucel) [111].

Plasmacytoma-like PTLD

Plasmacytoma-like PTLD is a rare form of PTLD, accounting for about 4% of all cases. It is characterized by the expression of the CD138 antigen in the absence of CD38 expression. The disease rarely generalizes, most often without bone marrow involvement, with frequent extranodal locations. Recommended treatment includes RIS and radiotherapy, which allow for long-term complete remission. In cases of generalized disease, RIS therapy has been shown to be effective in combination with PAD (bortezomib, doxorubicin, dexamethasone) treatment [128]. The prognosis in this form of PTLD is good.

Plasmablastic PTLD

Plasmablastic PTLD is very rare (<1% of all cases). It develops very late, a median of 12.8 years after transplantation, mainly in HIV-infected patients. It is characterized by an aggressive course and resistance to RIS and local RT. Of patients treated with a CHOP regimen, complete remission was achieved by 3/8 (37.5%) [124]. Due to the high aggressiveness of this form of PTLD, RIS therapy is recommended in combination with CHOP-21 chemotherapy, supported by G-CSF use and prophylaxis of *Pneumocystis jiroveci* infection.

PTLD from T cells or NK cells

PTLD from T cells or NK cells is diagnosed late after transplantation (usually >5 years). Histopathologically, they encompass the entire spectrum of malignancies analogous to those occurring in the non-transplanted patient population. In most cases (90%), they are EBV-negative. The prognosis is poor, except for T-cell large granular lymphoma. Treatment includes RIS and standard protocols used in T- and NK-cell lymphomas, including CHOP [124]. In the case of resistance, therapy with L-asparaginase, vincristine and dexamethasone, or their combination with high doses of cytosine arabinoside, has been shown to be effective. In addition, individual patients have been successfully treated with bexarotene, lenalidomide and brentuximab vedotin [113]. A therapeutic alternative may be transplantation of autologous or allogeneic hematopoietic cells [74].

Recommendations regarding rare PTLD subtypes

- All patients with rare PTLD subtypes should receive RIS as the initial treatment (IC).
- Patients with rare PTLD subtypes may be offered treatment similar to that used for analogous lymphomas, though with caution due to potential toxicity and comorbidity (IIC).
- In patients with CNS-PTLD, RIS should be used with concurrent ChT combined with rituximab, provided there is proper function of the remaining organs (kidneys)
- In patients who are not candidates for systemic treatment, RT combined with rituximab may be considered (IIC).
- In refractory patients, adoptive immunotherapy should be considered, if available (IIC).

Summary of recommendations in Polish conditions

Figure 1 presents a PTLD treatment algorithm, depending on the type and stage of the disease. In Polish conditions, the basic methods of therapy are reduction of immunosuppression (RIS), immunotherapy, and immunochemotherapy. Due to the limited availability of EBV-specific T lymphocytes (CTLs), this therapy is currently not commonly used or reimbursed. It is worth emphasizing however that CTLs were used in Poland for therapeutic purposes outside the transplant indications [129].

Follow-up after treatment completion

After completing therapy and assessing the response tailored to the PTLD type, patients should be monitored every 2–3 months for the first year after achieving treatment response, and then every 4–6 months, depending on their clinical situation. Due to a lack of clear guidelines, imaging tests should be performed based on the patient's current clinical status.

Article information and declarations

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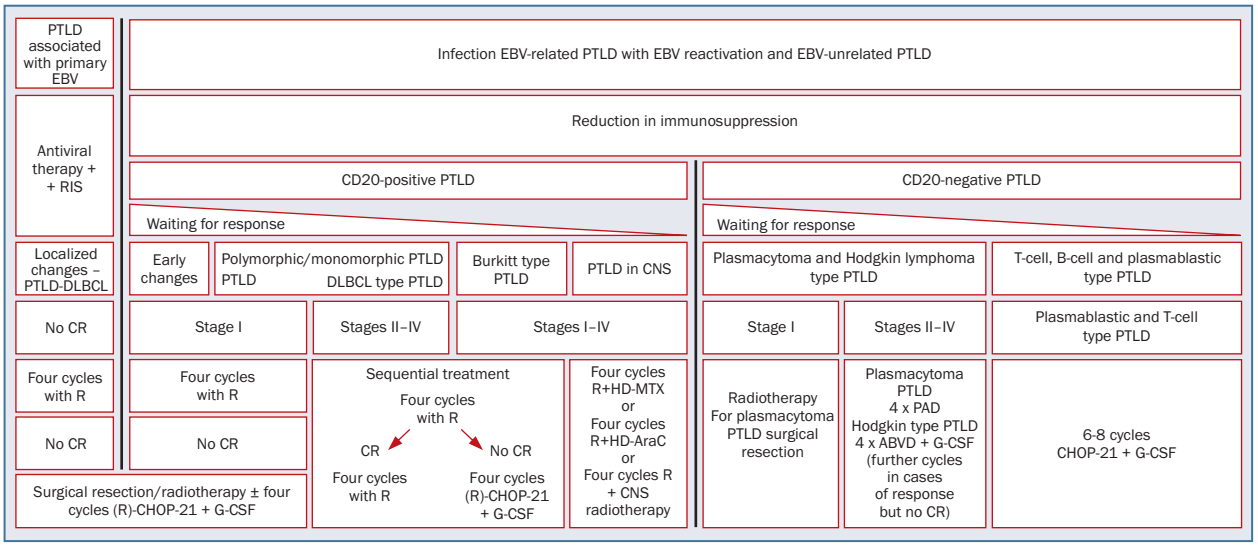

Figure 1. Illustrative scheme of prevention and treatment of post-transplant lymphoproliferative disorders (PTLD), modified after Trappe and Zimmerman [124]. In patients with DLBCL type PTLD who achieve PR in CT scan and have low IPI (<3), rituximab monotherapy can also be continued as in patients who achieved CR or CMR; ABVD — adriamycin, bleomycin, vinblastine, dacarbazine; CHOP — cyclophosphamide, doxorubicin, vincristine, prednisone; CNS — central nervous system; CR — complete response; DLBCL — diffuse large B-cell lymphoma; EBV — Epstein-Barr virus; G-CSF —granulocyte-colony stimulating factor; HD-MTX — high-dose methotrexate; PAD — bortezomib, doxorubicin, dexamethasone; R — rituximab; RIS — reduction of immunosuppression

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