Post-Transplant Lymphoproliferative Disorders
NCCN Guidelines Version 2.2015
Post-Transplant Lymphoproliferative Disorders

**DIAGNOSIS**

**ESSENTIAL:**
- Histopathology and adequate immunophenotype to establish diagnosis. Rebiopsy if consult material is nondiagnostic.
  - IHC panel: CD3, CD5, CD10, BCL6, BCL2, IRF4/MUM1, CD20, CD79a, PAX5, Ki-67, kappa, lambda
  - Cell surface marker analysis by flow cytometry: CD3, CD5, CD7, CD4, CD8, CD19, CD20, CD10, Kappa, lambda
- Epstein-Barr virus evaluation by EBV-LMP1 or EBER-ISH (if EBV-LMP1 negative, EBER-ISH is recommended)

**USEFUL UNDER CERTAIN CIRCUMSTANCES:**
- Additional immunophenotyping
  - IHC panel: CD15, CD30, CD45, CD7, CD4, CD8, ALK, TIA-1, Granzyme B, CD57, CD56, CD138
  - Cell surface marker analysis by flow cytometry: CD138, cytoplasmic Kappa and lambda, CD30, CD57, CD56, CD16, CD25, CD52.
- Molecular analysis to detect: IgH gene rearrangements
  - BCL6 gene mutation analysis\(^a\)
  - EBV by southern blot

\(^a\)BCL6 positivity has been associated with a poor response to reduction in immunosuppressive therapy.

**WORKUP**

**ESSENTIAL:**
- Performance status
- Albumin
- Immunosuppressive regimen
- LDH, electrolytes, BUN, creatinine
- CBC, differential
- Hepatitis B testing\(^b\)
- Chest/abdomen/pelvis CT

**USEFUL IN SELECTED CASES:**
- MUGA scan/echocardiogram if treatment includes regimens containing anthracyclines or anthrancenediones
- Bone marrow evaluation
- PET-CT scan
- Brain MRI
- EBV PCR
- CMV PCR
- EBV serology for primary versus reactivation

**Note:** All recommendations are category 2A unless otherwise indicated. Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

\(^b\)Hepatitis B testing is indicated because of the risk of reactivation with immunotherapy + chemotherapy. Tests include hepatitis B surface antigen and core antibody for a patient with no risk factors. For patients with risk factors or previous history of hepatitis B, add e-antigen. If positive, check viral load and consult with gastroenterologist.
PTLD SUBTYPE

Early lesions
- Reduction of immunosuppressive (RI)\textsuperscript{d}
  - Systemic
  - Polymorphic
  - Localized

Monomorphic\textsuperscript{c}
- Reduction of immunosuppressive (RI)\textsuperscript{d}
  - \textit{if possible} and/or:
    - Rituximab alone\textsuperscript{f}
    - Chemotherapy\textsuperscript{g}

INITIAL RESPONSE
- Complete response
  - Manage immunosuppression\textsuperscript{g} and monitor EBV PCR
  - Rituximab and monitor EBV PCR

SECOND-LINE THERAPY
- Persistent or progressive disease
  - Complete response
    - Observation
    - Continue RI, if possible ± maintenance rituximab
  - Persistent or progressive disease
    - Chemoimmunotherapy\textsuperscript{e}
    - Clinical trial
    - EBV-specific cytotoxic T-cell immunity (if EBV driven)

CONSIDERATION
- Monitor EBV PCR and:
  - Observation
  - Continue RI, if possible ± maintenance rituximab
  - Chemoimmunotherapy\textsuperscript{e}
  - Clinical trial
  - EBV-specific cytotoxic T-cell immunity (if EBV driven)

\textsuperscript{c} Treatment is based on the unique histology.
\textsuperscript{d} Response to RI therapy is variable and patients need to be closely monitored; RI should be coordinated with the transplant team.
\textsuperscript{e} Concurrent or sequential chemoimmunotherapy, See Suggested Treatment Regimens (PTLD-A).
\textsuperscript{f} As part of a step-wise approach in patients who are not highly symptomatic or cannot tolerate chemotherapy secondary to comorbidity.
\textsuperscript{g} Re-escalation of immunosuppressive therapy should be individualized, taking into account the extent of initial RI and the nature of the organ allograft. These decisions should be made in conjunction with the transplant team.
SUGGESTED TREATMENT REGIMENS
(in alphabetical order)

Concurrent chemoimmunotherapy
- RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone)
- RCHOEP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone, etoposide)\(^a\)
- For frail patients who cannot tolerate anthracycline, no specific regimen has been identified but options may include:
  - RCVP (rituximab, cyclophosphamide, vincristine, prednisone)\(^a\)
  - RCEPP (rituximab, cyclophosphamide, etoposide, prednisone, procarbazine)\(^a\)
  - RCEOP (rituximab, cyclophosphamide, etoposide, vincristine, prednisone)\(^a\)

Sequential chemoimmunotherapy
- Rituximab 375 mg/m\(^2\) weekly x 4 weeks followed by CHOP-21 ± rituximab starting Day 1 of week 9 x 4 cycles

Consider prophylaxis for tumor lysis syndrome (See NHODG-B)
See monoclonal antibody and viral reactivation (NHODG-B)

\(^a\)There are no published data regarding the use of these regimens; however, they are used at NCCN Member Institutions for the treatment of PTLD.
Post-Transplant Lymphoproliferative Disorders

Post-transplant lymphoproliferative disorders (PTLD) are a heterogeneous group of lymphoid neoplasms associated with immunosuppression following solid organ transplantation (SOT) or allogeneic hematopoietic stem cell transplantation (HSCT). \(^1\) PTLD following autologous HSCT is very rare. The majority of PTLD following both allogeneic HSCT and SOT are of B cell origin, and are usually associated with the Epstein Barr virus (EBV). \(^2\) Although rare, PTLD of T cell or NK cell origin can also occur (EBV-associated in approximately 30% of cases), and tend to occur late (median 6 years post-transplant in one series). \(^9\) EBV-negative PTLD has been shown to be a late serious complication of transplantation, and tend to occur later (>2 years) after SOT than EBV-positive disease. \(^10\) Gene expression profiling studies have shown that EBV negative PTLD are biologically distinct from their EBV associated counterparts. \(^13\) PTLD following HSCT are usually of donor origin, whereas PTLD following SOT are of recipient origin in the majority of cases, with a minority of donor derived cases that often involve the grafted organ. \(^2,3,15-20\)

The incidence of PTLD following allogeneic HSCT ranges from about 1% to 3% with a slightly higher incidence in patients who are recipients of cord blood transplant. \(^1,21-24\) The large majority of these PTLD occur early, within 6 to 12 months of transplant. \(^1,21-23\) The incidence of PTLD following SOT ranges from about 1% to 10% depending upon the type of organ transplant. \(^2,25-28\) Small bowel transplant appears to be associated with the highest incidence of PTLD, at about 20%. \(^2,29\) More than 50% of PTLD cases following SOT are diagnosed beyond 12 months from the time of transplant. \(^26,28,30,31\) The incidence of PTLD is generally higher among pediatric patients compared with adults. \(^2,8,21,29,31\)

Median survival following a diagnosis of PTLD (after SOT) ranges from about 10 to 32 months. \(^8,26,28,32,33\) Survival outcomes for PTLD occurring after allogeneic HSCT are poor. \(^21\)

Factors such as EBV and cytomegalovirus (CMV) serology status (of the recipient and the donor), age, type of organ transplant, type of immunosuppressive agents (likely correlated with degree of immunosuppression), and time from transplant, contribute to variations in the risks for developing PTLD. \(^2,34-37\) In patients undergoing allogeneic HSCT, factors associated with increased risks for PTLD included T-cell depletion of the allograft, unrelated or HLA-mismatched grafts, and anti-T-cell therapy (e.g., antithymocyte globulin [ATG] or anti-CD3 monoclonal antibody) for prophylaxis or treatment of graft-versus-host disease (GVHD). \(^1,20-21\) In recipients of SOT, factors associated with increased risks for PTLD included the type of organ transplant (e.g., highest risks in bowel, lung, heart/lung transplants), EBV serology mismatch (i.e., negative recipient/positive donor), CMV serology mismatch (i.e., negative recipient/positive donor), HLA mismatch, and anti-T-cell therapy (e.g., ATG or OKT3) for prevention or treatment of graft rejection. \(^2,10,31,36-38\) Moreover, the use of tacrolimus (compared with cyclosporin) as primary immunosuppressive therapy appeared to increase the risk of PTLD in SOT recipients. \(^31,38-40\) Although CMV disease has also been associated with risks for EBV-positive PTLD, the correlation between CMV infection and development of PTLD is unclear. \(^37,41,42\) In patients with PTLD following SOT, factors such as older age, poor performance status, elevated lactate dehydrogenase (LDH), organ dysfunction, multiple involved lymph nodes, and multi organ involvement were identified as prognostic factors for poorer survival. \(^7,32,43,44\)

The diagnosis and classification of PTLD can be challenging given the nonspecific clinical presentation, and heterogeneity in histopathologic and immunophenotypic presentations. Moreover, subtypes of PTLD
may overlap within the same individual. In the 2008 WHO classification, PTLD are classified into 4 major categories: early lesions, monomorphic PTLD, polymorphic PTLD and classical Hodgkin lymphoma (cHL) type PTLD. Early lesions typically develop within a year of transplantation and are more common in transplant recipients who are EBV naive. Early lesions consist of 2 histological subtypes, plasmacytic hyperplasia and infectious mononucleosis like PTLD. Monomorphic histologies appear to be the most common subtype of PTLD, and resemble one of the B-cell lymphomas (except for indolent lymphomas) or T-cell/NK cell lymphomas seen in immunocompetent individuals. EBV serology status can vary according to lineage; most monomorphic B-cell PTLD are EBV positive whereas most T-cell PTLD are EBV negative.

Monomorphic B-cell PTLD most commonly resembles diffuse large B-cell lymphoma (DLBCL), but some lesions, although less common, can resemble Burkitt lymphoma, plasma cell myeloma or plasmacytoma. Polymorphic PTLD is mostly EBV positive, and can be either polyclonal or monoclonal; this represents the most common type of PTLD among children. cHL-type PTLD is almost always EBV-positive, and is the least common of the PTLD categories.

Diagnosis

Histopathology and adequate immunophenotyping are essential to confirm the diagnosis of PTLD. Immunophenotyping should include both B-cell and T-cell (as well as NK cell) associated markers. Among B-cell PTLD, expression of BCL6, MUM1 and CD138 can be useful in distinguishing between the histological subtypes of PTLD. BCL6 expression was detected in cases of monomorphic PTLD (71% of centroblastic DLBCL), whereas it was consistently absent in polymorphic PTLD. MUM1 was preferentially expressed in 92% of polymorphic PTLD. Overall, BCL6−, MUM1+ and CD138− phenotype is associated most frequently with polymorphic PTLD; BCL6+, MUM1+/− and CD138− is mostly associated with monomorphic PTLD. The recommended panel for immunohistochemistry (IHC) includes the following markers: CD3, CD5, CD10, BCL6, BCL2, IRF4/MUM1, CD20, CD79a, PAX5, Ki67, and kappa, lambda light chains. Cell surface markers CD3, CD5, CD7, CD4, CD8, CD19, CD20, CD10, and kappa, lambda are recommended for flow cytometric analysis. Under certain circumstances, the following additional markers may be useful for an IHC panel: CD15, CD30, CD7, CD45, CD10, and kappa, lambda are recommended for flow cytometric analysis.

Evaluation of EBV infection status is another essential component of the diagnostic workup. EBV can be detected by either IHC for latent membrane protein 1 (LMP 1) or EBV encoded RNA in situ hybridization (EBER ISH). EBER ISH is more sensitive than immunohistochemistry, and is recommended if EBV-LMP-1 is negative. If immunostaining for EBV-LMP 1 is positive, EBER ISH is not required. Under certain circumstances, EBV evaluation by Southern blot may also be useful.

Immunoglobulin heavy chain (IGH) gene mutations are seen in the majority of B-cell PTLD cases, with the exception of early lesions. Genetic alterations in MYC, NRAS and TP53 are seen only in monomorphic PTLD. BCL6 mutations have been associated with shorter survival and poor response to therapy. In certain situations, molecular genetic analysis to detect IGH rearrangements and BCL6 gene mutations could be useful.

Workup

The initial workup for PTLD should include a physical examination and evaluation of performance status. Laboratory assessments should
include standard blood work including CBC with differential and a metabolic panel (to include albumin, electrolytes, BUN, and creatinine), in addition to measurements of serum LDH levels. Bone marrow evaluations may be useful in selected cases. Prior history of immunosuppressive therapy should also be assessed. CT scans of chest, abdomen and pelvis should be performed. PET CT scan and brain MRI may be useful in selected cases. In addition, MUGA scan/echocardiogram may be useful in cases where treatment with anthracycline or anthracenedione-containing regimens is being considered. Hepatitis B virus (HBV) testing should be performed prior to initiation of treatment with immunotherapy (with or without chemotherapy) given the potential risks for viral reactivation with such regimens. Evaluation of EBV viral load by quantitative PCR can aid in the diagnosis as well as monitoring of treatment responses in patients with PTLD. Plasma or peripheral blood mononuclear cells (PBMC) are useful for measuring EBV viral load, although some studies have shown that viral load in plasma is more sensitive than PBMC in the diagnosis of PTLD. 55-57 EBV serology to assess primary infection versus reactivation may be useful. As previously mentioned, CMV infection has also been associated with an increased risk of PTLD in EBV seronegative patients. 37,41 Thus, PCR for the measurement of EBV and CMV can be useful for selected patients.

Treatment

While guidelines have been published, the optimal treatment for PTLD is not well defined due to the lack of randomized controlled trials and the heterogeneity of the disease. 58 Published reports of treatment for PTLD have included reduction in immunosuppression (RI), use of antiviral agents, single-agent treatment with rituximab, chemotherapy, and/or chemoimmunotherapy regimens; treatment approaches are largely dependent on the PTLD subtype. In general, RI remains the initial step in the management of nearly all cases of PTLD. 2,44,58,59 In a prospective phase II study that evaluated a sequential approach to therapy (i.e., RI first, then interferon-alfa for less than complete remission (CR), then multiagent chemotherapy if less than CR to interferon) for adults with PTLD following SOT (N=20; n=16 evaluable), RI alone resulted in only one partial remission (PR). 60 The remaining patients experienced either disease progression or graft rejection. One patient achieved a CR with interferon, and among patients eligible for multiagent chemotherapy, 67% achieved a CR. Rituximab was not evaluated as part of this study. 60 The role of antiviral therapy is controversial since the majority of PTLD are associated with latent EBV. Replicating EBV DNA has been reported in about 40% of EBV associated lymphoproliferative disorders in immunocompromised patients. 61,62 Antiviral drugs targeting EBV replication may be beneficial in this subset of patients with early or polymorphic PTLD. 63

Several phase II studies and retrospective analyses have confirmed the efficacy of rituximab monotherapy in the treatment of patients with B-cell PTLD. 64-70 In a prospective multicenter phase II study in patients with PTLD after SOT (N=46; n=43 evaluable), rituximab induced responses in 44% of patients (CR in 28%) with a 1-year overall survival (OS) rate of 67%. 65 Another prospective multicenter phase II study demonstrated that extended treatment with rituximab (e.g., 2 courses of rituximab) induced a high rate of CR (60.5%; including patients treated with a second course) in patients with PTLD after SOT (N=38) without increasing toxicity. 71 Among the patients who could not achieve a CR with rituximab alone and subsequently received rituximab combined with chemotherapy (R-CHOP or R-EPOCH; n=8), 6 patients achieved a CR (75%). At a median follow up of 27.5 months, the event-free survival and OS rates were 42% and 47%, respectively. 71 In a multicenter retrospective analysis of data from patients with PTLD following SOT
(N=80), all patients had received initial RI, and 74% were treated with rituximab with or without chemotherapy. The 3-year progression-free survival (PFS) and OS rates for all patients were 57% and 62%, respectively. Inclusion of rituximab as part of initial therapy significantly improved both 3-year PFS (70% vs. 21%) and OS (73% vs. 33%) rates compared with the group who did not receive rituximab.

Anthracycline based chemotherapy with or without rituximab has also been effective in the treatment of patients with PTLD. In a retrospective analysis, CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) induced an overall response rate (ORR) of 65% (CR in 50%) in patients with PTLD after SOT (N=26) who were unresponsive to RI alone. With a median follow up of nearly 9 years, the median OS was 14 months. Treatment-related mortality rate was high, at 31%. Chemotherapy and RT, with or without rituximab has also been reported to induce durable CR with reduced risk of graft impairment when used as first line treatment.

As mentioned above, rituximab with or without chemotherapy was shown to improve outcomes in patients with PTLD in a retrospective study. More recently, a prospective multicenter phase II study evaluated the role of sequential chemoimmunotherapy with rituximab (4 weekly doses) followed by CHOP-21 (4 cycles) combined with G-CSF in patients with PTLD who failed initial RI (N=74; n=70 evaluable). The large majority of patients presented with monomorphic histology (primarily DLBCL), and 44% of cases were EBV positive. The ORR with rituximab (n=70) was 60% (CR in 20%), which improved to 90% (CR in 68%) in the patients who received subsequent CHOP chemotherapy following rituximab (n=59). Median response duration has not yet been reached. The median PFS and OS were 4 years and 6.6 years, respectively; the 5-year PFS and OS rates were 50% and 55%, respectively. The most common grade 3 or 4 toxicities included leukopenia (68%) and infectious events (41%). Treatment-related mortality associated with CHOP was reported in 11% of patients. This trial was amended to introduce a risk-stratified treatment strategy based upon initial response to rituximab, whereby low-risk patients (defined as those achieving CR after initial rituximab) received consolidation with rituximab monotherapy and high-risk patients (defined as non-CR after initial rituximab) received chemoimmunotherapy with R-CHOP-21 (4 cycles) combined with G-CSF. Among the patients enrolled in the risk-stratified protocol (N=91; n=80 evaluable), the ORR was 93% (CR in 78%). The CR rate after initial rituximab alone was 27%. In this low-risk group (who subsequently received rituximab consolidation; n=23), the rate of relapse after a median follow up of more than 3 years was 13%. Among patients with progressive disease after initial rituximab (n=23), sequential therapy with R-CHOP resulted in CR in 65%; this CR rate was higher than that of patients with progressive disease (following initial rituximab) who received sequential CHOP in the original study protocol (CR in 27%).

Adoptive immunotherapy using autologous or allogeneic EBV specific cytotoxic T lymphocytes (EBV CTLs) has been investigated in several studies. In small studies, the use of autologous EBV-CTLs has been shown to prevent the occurrence of PTLD in SOT recipients who were considered at high risk for developing PTLD. In patients who underwent allogeneic HSCT, the use of allogeneic EBV-CTLs successfully prevented PTLD in all patients (N=39). In a subsequent study that evaluated the effectiveness of allogeneic EBV-CTLs in a
larger series of patients (including those reported in the earlier Rooney et al, 1998 study) who underwent allogeneic HSCT (N=114), EBV-CTLs prevented PTLD in all patients (n=101) and induced a durable CR in 85% of patients in the subgroup with existing PTLD (n=13). This study also showed that during long-term follow up, functional EBV-CTLs persisted up to 9 years. A prospective multicenter phase II study evaluated allogeneic EBV-CTLs in the treatment of patients with PTLD that failed conventional therapy (N=33). The majority of patients (94%) had received SOT; the remaining patients had undergone allogeneic HSCT. All patients had RI as part of initial therapy for PTLD, and some patients had also received treatment with rituximab, anti-virals, or chemotherapy. The ORR at 6 months was 52% (CR in 42%). The OS rate at 6 months was 79%. Results from this study suggest that immunotherapy with EBV-CTLs may be a promising strategy in patients with PTLD who fail conventional treatments. However, further prospective studies are needed to better define the role of adoptive immunotherapy in the prevention and management of PTLD.

**NCCN Recommendations**

**First-line Treatment and Initial Response**

Treatment options for PTLD depend on the histological subtype and should be individualized. RI, if possible, should be a part of the initial treatment approach for all patients with PTLD. It should be noted that response to RI is variable, and patients should be closely monitored during RI. Importantly, RI should be initiated and managed in coordination with the transplant team in order to minimize risks for graft rejection.

For patients with early lesions, first-line management could involve RI alone. For patients who achieve a CR with this approach, re-escalation of immunosuppressive should be individualized, taking into account the extent of initial RI and the nature of the organ allograft; these decisions should be made in conjunction with the transplant team. EBV viral load can be monitored by PCR assays. Patients with early lesions who have persistent or progressive disease with RI alone should be managed with second-line therapy options (see section below).

For patients with localized polymorphic PTLD, treatment should include RI, if possible, along with RT with or without rituximab, surgery with or without rituximab, or rituximab alone. For patients with systemic polymorphic PTLD, the NCCN Guidelines panel recommends RI, if possible, along with rituximab alone or rituximab as part of a chemoimmunotherapy regimen (concurrent or sequential combination). In patients with (systemic or localized) polymorphic PTLD who achieve a CR with initial therapy, the patient should either be observed or continue RI (if possible) with or without rituximab maintenance. Patients who have persistent or progressive disease with initial therapy should be managed with second-line treatment options (see section below).

The treatment approach for patients with monomorphic PTLD should be based on the standard treatment regimens used for the unique histology. The treatment options include RI, if possible, and/or rituximab alone or rituximab as part of a chemoimmunotherapy regimen (concurrent or sequential regimen); rituximab alone should only be considered as part of a step-wise approach to treatment in patients who are not highly symptomatic or in those who cannot tolerate chemotherapy due to comorbid conditions. Patients who achieve a CR with initial therapy should undergo surveillance/follow up according to the Guidelines specific for the histology. Patients who have persistent or progressive disease with initial therapy should be managed with second-line treatment options (see section below).
Second line Treatment

Treatment options in the second-line setting are dependent on the response to initial treatment and the histological subtype. For patients with early lesions who have persistent or progressive disease with RI alone, rituximab is recommended as second-line therapy.

For polymorphic PTLD, chemoimmunotherapy or EBV CTL infusion (if EBV positive) are included as options for patients who experience persistent or progressive disease with initial therapy. Participation in a suitable clinical trial, where available, should also be considered in this setting.

For patients with monomorphic PTLD with persistent or progressive disease with initial therapy, second line treatment options are dependent on prior therapy. Rituximab or chemoimmunotherapy regimens are options for patients who received RI alone as initial treatment, whereas patients who received single-agent rituximab as initial therapy should be treated with chemoimmunotherapy. In both situations, other options include participation in a suitable clinical trial, if available, or incorporation of EBV CTL infusion (if EBV positive).