Lymphoma Network of New Zealand

Post-transplant Lymphoproliferative Disorder (PTLD)

This is defined as lymphoid and/or plasmacytic proliferations in immunosuppressed hosts following solid or allogeneic stem cell transplantation. More than 80% of them are Epstein-Barr virus (EBV) driven. Up to 60% occur within first six months following transplant.

Incidence:

Solid organ transplant (SOT):

- Renal <1%
- Hepatic or cardiac 1-5%
- Heart-lung or lung >5%

Haematopoietic stem cell transplant (HSCT): 1-2%

PTLD Categories:

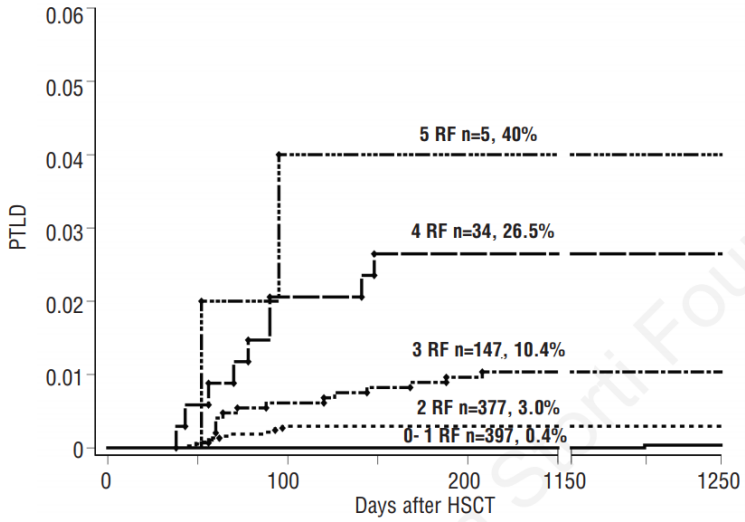
There are four categories of PTLD according to 2016 World Health Organisation classification system.

- **Non destructive PTLD** – This includes plasmacytic hyperplasia, infectious mononucleosis-like and florid follicular hyperplasia categorised by polyclonal B proliferation with architectural preservation and no evidence to suggest malignant lymphoma.
- **Polymorphic PTLD** – Polyclonal lymphoid infiltration with effacement of lymph node architecture or destructive masses but does not fulfil diagnostic criteria for any subtype of lymphoma in immunocompetent patients.
- **Monomorphic PTLD** – This is the most common subtype of PTLD with monoclonal lymphoid proliferation which fulfil criteria for one of the B-cell or T/NK-cell neoplasm recognised in immunocompetent patients.
    - **Monomorphic B-cell PTLD** includes diffuse large B cell lymphoma, Burkitt lymphoma, plasma cell myeloma and plasmacytoma. Small B-cell lymphoid neoplasm arising in post-transplant setting are not considered PTLD except EBV+ extranodal MALT.
    - **Monomorphic T-cell PTLD** includes peripheral T-cell lymphoma NOS, Hepatosplenic T cell lymphoma.
- **Classic Hodgkin lymphoma PTLD** – This is least common subtype of PTLD. They are usually mixed cellularity subtype.

Risk factors following haematopoietic stem cell transplant (HSCT):

A large, retrospective analysis identified the following independent risk factors associated with post-transplant lymphoproliferative disorder following haematopoietic stem cell transplant:

- Antithymocyte globulin
- Human leukocyte antigen mismatch
- Reduced intensity conditioning
- Acute GvHD Grade II-IV
- Splenectomy
- Mesenchymal stromal cell treatment
- EBV seronegative recipient and seropositive donor



EBV Monitoring

Performance of prospective monitoring of EBV DNA by quantitative PCR is recommended following haematopoietic stem cell transplantation. This should start within the first month after HSCT at least weekly until reconstitution of cellular immunity which is around 4 months following HSCT. Longer period of monitoring is recommended in patients considered to have poor T-cell reconstitution: on treatment for GvHD, haplo-transplantation, T-cell depletion or use of ATG/Alemtuzumab.

The evidence of routine use in adult patients after solid organ transplantation is controversial and this should be referred to local guidelines on organ-specific transplantation.

EBV DNA can be performed on whole blood and plasma samples. The preferred sample for EBV monitoring for PTLD remains controversial. While whole blood EBV DNA allows early detection, plasma EBV DNA can help to differentiate between PTLD onset and asymptomatic viraemia and has better correlation with disease response following treatment and relapse.

Recommendation:

- Whole blood EBV DNA for routine surveillance and early detection of EBV viraemia.
- Plasma EBV DNA should be used with established PTLD for monitoring of treatment response and remission.

Treatment of EBV viraemia/Suspected PTLD

Pre-emptive therapy for EBV viraemia should be considered particularly in patients with high risk for developing PTLD.

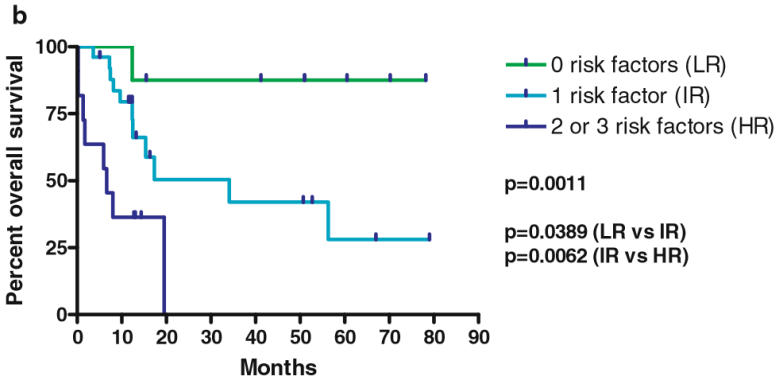
There is no consensus on EBV DNA threshold for consideration of pre-emptive treatment due to lack of standardised laboratory assays. The rate of increase of EBV copy number can be helpful. Local experience based on correlation of clinical and laboratory data might be a rationale for centre specific cut-off value.

- ***Rituximab:***
  Rituximab, dose 375mg/m^2, once weekly, 1-4 doses until EBV DNA negativity.

- ***Reduction of immunosuppression*:**
  Rituximab therapy should be combined with reduction of immunosuppression, if possible, except in patients with severe acute or chronic GvHD.

Prognostic factors (PTLD Prognostic Index):

- Age >60 years old
- ECOG PS >1
- Elevated LDH



Risk category	1 year survival	2 year survival
Low risk (no RF)	100%	88%
Intermediate (1 RF)	79%	50%
High risk (>1 RF)	36%	0%

Treatment of PTLD

Reduction of immunosuppression:

- Reduction of immunosuppression (RIS) should be incorporated in all patients with PTLD.
- RIS alone is recommended in Non Destructive PTLD.
- Increase risk of graft failure or GvHD.

Rituximab monotherapy:

- Rituximab 375mg/m^2 weekly for four weeks.

- Recommended in Polymorphic PTLD, early stage Monomorphic B-cell PTLD.
- Can be considered in Non Destructive PTLD with residual disease despite RIS or for those who cannot tolerated reduction of immunosuppression.
- Maintenance Rituximab therapy ranging from three weekly to six monthly post induction for further 4 doses of Rituximab can also be considered.

Combined chemoimmunotherapy:

- R-CHOP therapy is recommended for
    - patients who fail to achieve response following Rituximab monotherapy,
    - bulk disease
    - high-risk disease
- Subtype specific therapy is recommended for monomorphic PTLD including Burkitt lymphoma, T cell lymphoma and Classic Hodgkin PTLD.

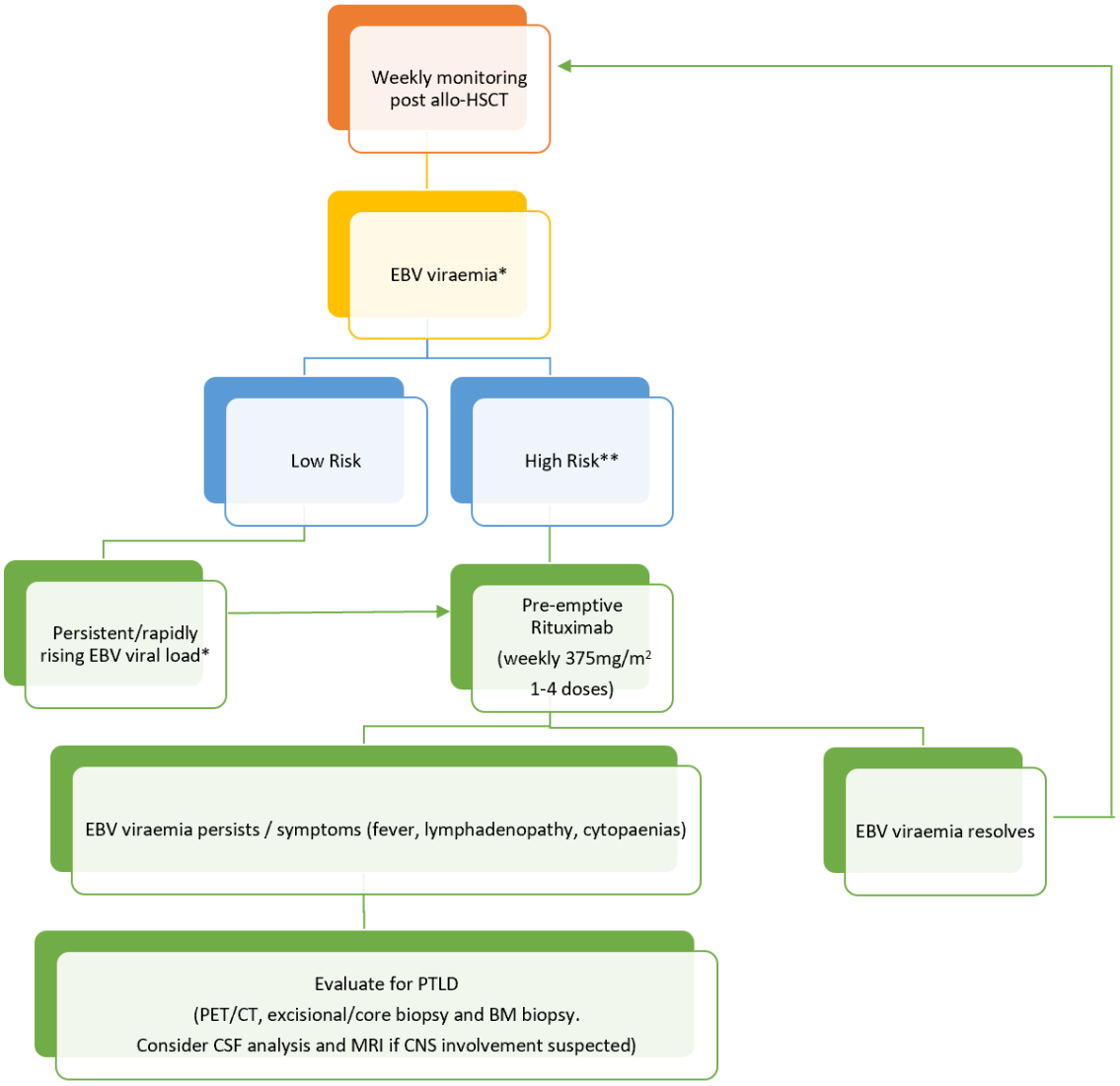
Other treatment options:

- Involved field Radiotherapy – localised disease or CNS involvement.
- EBV specific cytotoxic T lymphocytes (EBV-CTLs) if available.

CNS PTLD

- CNS involvement occurs in 20% of PTLD.
- Primary CNS PTLD represents 5-15% of all PTLD.
- CNS involvement is associated with significantly inferior survival.
- The optimal treatment for primary CNS PTLD is unknown.
- High dose Methotrexate is recommended as first line therapy.
- Surgical debulking and whole brain radiotherapy (WBRT) can also be considered.

Diagnostic approach to PTLD post allogeneic HSCT



*Consider Plasma EBV viral load

High risk: >2 of the following risk factors

- Antithymocyte globulin
- Human leukocyte antigen mismatch
- Reduced intensity conditioning
- Acute GvHD Grade II-IV
- Splenectomy
- Mesenchymal stromal cell treatment
- EBV seronegative recipient and seropositive donor

PTLD Treatment Algorithm