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# Post-Transplant Lymphoproliferative Disorder: A Clinical Perspective

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## ABSTRACT

Post-transplant lymphoproliferative disorder remains a rare but highly significant complication following both stem cell and solid organ transplantation. The highly variable clinical presentation may result in significant diagnostic delays requiring close supervision and vigilance of patients at high risk of developing the condition. Treatment of established disease becomes a clinical challenge due to the fine balance required in reducing immunosuppression to control the disease while safeguarding allograft function. Despite major advances made in overall management to improve outcomes, the associated morbidity and mortality remains high.

**Keywords:** Kidney transplant, Lymphoma, Malignancy, Lymphoproliferative disorder, Chemotherapy

## INTRODUCTION

Post-Transplant Lymphoproliferative Disorder (PTLD) is a rare but well-recognized, potentially fatal complication of both solid organ transplantation (SOT) as well as haematopoietic stem cell transplantation (HSCT). PTLD is the commonest post-transplant malignancy among children and second commonest among adults after non-melanoma skin cancer. It is a heterogenous clinical entity with a wide disease spectrum, ranging from indolent lymphoid proliferation to aggressive lymphoma. Despite numerous therapeutic measures, the overall mortality remains high around 50% [1].

## INCIDENCE AND RISK FACTORS

The incidence of PTLD following SOT varies according to the organ transplanted. The incidence is highest following heart, heart-lung, intestinal and multi-organ transplants (8-25%), while it's relatively low following renal transplants (1-3%) [1,2]. The highest incidence has been reported in the first year after transplantation. However, the cumulative risk increases with each passing year, demonstrating a steady increase with the progression of time post-transplant, compared to a matched non-transplant population [3].

Furthermore, the risk of PTLD is proportionately higher with the degree of cumulative immunosuppression and T-cell depletion. Anti-thymocyte globulin (ATG) as an induction agent has been associated with a significantly higher risk of PTLD compared to Interleukin-2 receptor antagonist (basiliximab), which has not been directly associated with PTLD. The initial reports of PTLD occurred prior to the cyclosporine era, indicating that any type of immunosuppression carries a risk of PTLD [4]. ATG, calcineurin inhibitors, tacrolimus and cyclosporine have all been implicated with PTLD while basiliximab, mycophenolate and alemtuzumab appear to pose no increased risk [5]. Mammalian target of Rapamycin (mTOR) inhibitors such as sirolimus and everolimus may actually reduce the risk of PTLD due to their anti-proliferative effect and have even been used as a therapeutic option, as discussed below.

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The vast majority (85%) of PTLD affect the B-cell lineage, primarily related to Epstein Barr Virus (EBV) infection. EBV infection could be either primary or reactivation following post-transplant immunosuppression. Primary EBV infection can either donor derived or less frequently, acquired from environmental exposure post-transplant. Primary donor derived EBV infection may develop with a sero-negative host receiving a graft from a sero-positive donor, which remains the commonest risk factor for PTLD. This explains the higher incidence of PTLD amongst pediatric transplant recipients who are more likely to be EBV sero-negative [6,7]. Regardless of age, pre-transplant EBV sero-negativity has been clearly shown to be a risk factor for development of PTLD [8,9].

Pediatric recipients, especially those transplanted before 10 years of age, have been consistently shown to have a higher risk of PTLD. According to the Organ Procurement and Transplantation Network (OPTN) database (2012), the reported cumulative incidence of PTLD after renal transplantation was 4.4-6.9% among children, compared to 0.6-1.5% among adults (10). Similarly, the risk is also higher among elderly recipients (>60 years), possibly due to decreased immune surveillance in old age [11,12].

Some reports have also implicated donor-recipient mismatch of other viral serologies as a potential risk factor for PTLD. Cytomegalovirus (CMV) sero-negative recipients, receiving a sero-positive donor organ can have up to a seven-fold increased risk of PTLD. Other reports have also implicated Hepatitis C and Herpes Virus-8 infection as possible risk factors, especially when coinciding with EBV infection [13,14]. Smith et al. [15] also demonstrated that Caucasian ethnicity carried a higher risk compared to other ethnicities while there was no demonstrable difference in incidence between the two genders **(Table 1)**.

**Table 1.** Common risk factors for development of PTLD.

| Degree of immunosuppression | Greater the cumulative immunosuppression and T-cell depletion, higher the risk |
|---|---|
| EBV sero status of recipient and donor | Highest risk with seronegative recipient receiving a seropositive organ |
| Recipient age | Highest risk with children (<10 year's), elderly (>60 years) |
| Time since the transplant | Highest risk in the 1st year post-transplant. Cumulative risk increases thereafter with each passing year. |
| Ethnicity | Caucasian have a higher risk than Afro-Americans and Asians |
| Type of organ transplanted | Highest risk with heart, heart-lung and intestinal |
| Pre-transplant malignancy | History of pre-transplant malignancy is associated with a higher risk of PTLD |

## PATHOPHYSIOLOGY

PTLD affecting the T-cell lineage is rare where only 30% are EBV related. This is in contrast to the B-cell lineage PTLD where over 80% are related to EBV infection. EBV-related PTLD is caused by anti-viral resistant 'latent-type' infection as opposed to anti-viral sensitive 'lytic-type' infection [9,16]. As discussed later, this becomes relevant in the management of PTLD and associated EBV infection. Post-transplant immunosuppression results in suppression of the host T-cell function which includes the ability to destroy EBV infected B-cells. This results in uncontrolled proliferation of EBV-infected B-cells, which become immortal, culminating in B-cell hyperplasia or frank lymphoma. The initial proliferation is polyclonal and is often responsive to immunosuppression reduction while as the disease progresses; it becomes monoclonal, with poor response to therapy.

The exact pathophysiology of EBV-negative PTLD is poorly understood. The postulated mechanisms include EBV infection that is no longer detectable or other non-EBV viral infections that cause antigenic stimulation. EBV-negative PTLD has a distinctly different clinical course with late onset, more aggressive disease compared to EBV-positive PTLD. The impact of EBV status on overall survival is unclear. While most historical studies reported poor survival with EBV-negative disease, Luskin et al. [17] followed up 176 SOT recipients and demonstrated no significant difference in overall survival based on EBV status.

## CLINICAL PRESENTATION

Clinical presentation of PTLD is heterogeneous, ranging from non-specific symptoms to features of advanced organ failure. The common presentation is with non-specific B-symptoms such as fever, night sweats, anorexia and weight loss requiring a high index of clinical suspicion and a low threshold for further investigation.

While peripheral lymphadenopathy is rare, extra-nodal involvement may be common, affecting the gastro-intestinal tract (GIT), bone marrow, lungs, skin and central nervous system (CNS-PTLD). Extra-nodal disease results in symptoms related to the relevant affected system. Accordingly, GIT disease can present with nausea, vomiting, diarrhea and abdominal cramps. Pulmonary involvement may result in cough, shortness of breath and reduced air entry. CNS-PTLD may result in features such as confusion, hallucinations and altered consciousness.

Following renal transplantation, commonest affected organ is the GIT. Approximately 15% may present with GIT related emergencies such as perforation and intestinal obstruction [18]. Rarely, fulminant PTLD disease can present with features mimicking septic shock.

**Diagnosis and evaluation**

The highly variable clinical presentation requires a high degree of clinical suspicion and low threshold for targeted investigation. Basic blood biochemistry may reveal cytopenia, elevated lactate dehydrogenase (LDH), hyperuricemia and hypercalcemia. Definitive diagnosis is by histological confirmation of lympho-proliferation with demonstration of EBV-DNA, RNA, or protein in biopsy tissue. Needle aspiration cytology is often inadequate and requires image-guided tru-cut biopsy or excision biopsy for histological confirmation of lymphoid proliferation.

Once the diagnosis is confirmed by histology, staging of disease by imaging is mandatory. The imaging modality of choice for staging is computed tomography (CT) of neck, thorax, abdomen and pelvis **(Figures 1 and 2)**.

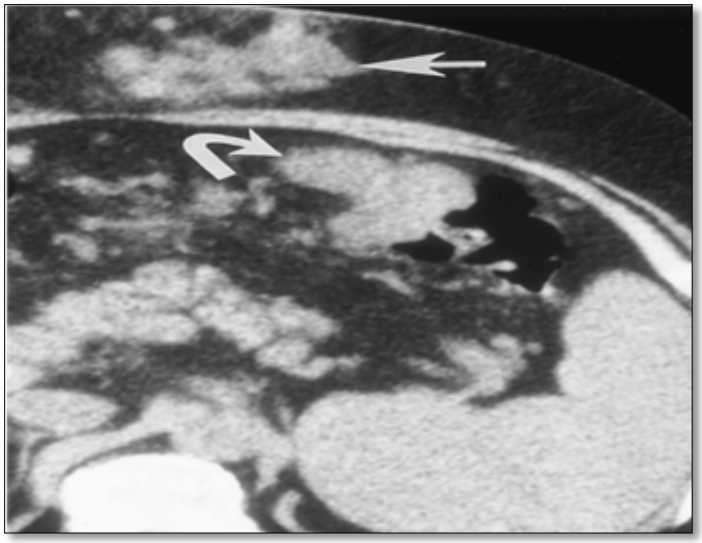

**Figure 1.** PTLD affecting the abdominal wall and peritoneum following renal transplantation.

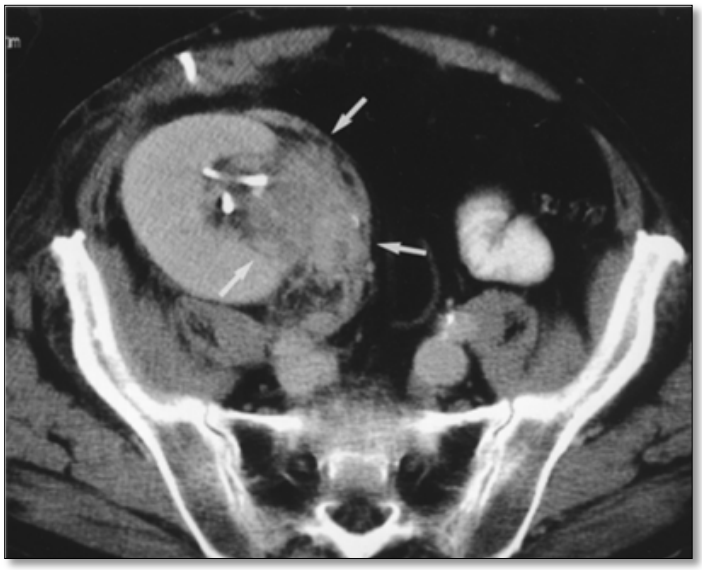

**Figure 2.** CT images showing PTLD affecting the renal allograft.

Positron emission tomography (PET) may be used in specific instances but lacks definitive data of benefit over CT. Bone marrow aspiration or lumbar puncture to evaluate cerebrospinal fluid (CSF) may be required to exclude CNS-PTLD [2]. CSF examination can be used to examine for the presence of malignant cells as well as for the presence of EBV proteins.

## MANAGEMENT

Management of PTLD requires a multi-disciplinary approach with a team including transplant clinicians, surgeons, radiologists, histopathologists and oncologists. Management aim should be successful regression of disease while safeguarding graft function.

The exact management approach should be individualized to the patient. This depends on several factors including; general health condition, clinical and pathological stage of disease, function and necessity of the graft and local availability of expertise in the management.

## REDUCTION OF IMMUNOSUPPRESSION (RIS)

Reduction of Immunosuppression (RIS) or complete withdrawal of immunosuppression remains the first-line approach and mainstay in management. An initial reduction of 25-50% of baseline as tolerated should be followed by complete withdrawal with minimal steroid maintenance, if response is poor or in the critically ill [19]. Response to treatment is monitored by resolution of constitutional symptoms, drop in LDH levels and tumor size reduction on imaging. Tsai et al. [20] have defined possible indicators of poor response to RIS. These include raised pre-treatment LDH levels, multi-organ involvement and pre-treatment allograft dysfunction.

Poor response within 2-4 weeks should prompt second-line therapy. RIS alone has shown response rates of 90% in low-grade PTLD without multi-organ involvement [20]. However, it carries the risk of allograft rejection and needs to be carefully weighed against the dangers of PTLD progression. Where the immunosuppression cannot be reduced beyond 50% of the baseline as in life-preserving grafts (heart and lung transplants), an early decision needs to be made regarding second line therapy.

Conversion to m-TOR inhibitor (sirolimus or everolimus) maintenance therapy with their 'anti-tumor' effects has been studied with conflicting reports. While some studies have shown successful PTLD regression with sirolimus, others have shown higher incidence of PTLD with its use [3,21-23]. Several small volume studies including *in vitro* experiences have shown possible tumor regression potential in PTLD with the use of mTOR inhibitors. Both sirolimus and everolimus have been shown to possess an inhibitory effect on PTLD cell line growth, thereby inhibiting tumor progression as well as inducing tumor regression. Pascual [24] reviewed the limited pooled data from European centers with experience of using mTOR inhibitors in post-renal transplant PTLD. There were 19 recipients with post renal transplant PTLD converted to sirolimus or everolimus. Calcineurin inhibitors (CNIs) were either completely withdrawn or minimized. Concomitant PTLD treatment was carried out with rituximab or chemotherapy in some of the recipients. Fifteen patients demonstrated complete remission of PTLD.

### Rituximab

Rituximab is an anti-CD-20 monoclonal antibody with demonstrated efficacy against CD-20 positive PTLD. Rituximab has been postulated to cause destruction of pathological malignant cells by several mechanisms including; antibody dependent cytotoxicity, complement dependent cytotoxicity, direct programmed cell death (apoptosis) and adaptive immune mechanisms **(Figure 3)**. Rituximab is considered second line therapy for those who fail to respond to RIS alone or where complete immunosuppression withdrawal in not possible [25]. It may be used as stand-alone therapy or in combination with systemic chemotherapy. Rituximab monotherapy has reported response rates between 50-60% in CD-20 positive PTLD [26]. However, it has a higher risk of relapse and slower response rate in aggressive disease, requiring combination therapy. Hence, it is most often used in combination with systemic chemotherapy to achieve early disease remission and lower relapse rates. Factors linked to poor rituximab response are CNS-PTLD, late-onset detection and multi-visceral disease.

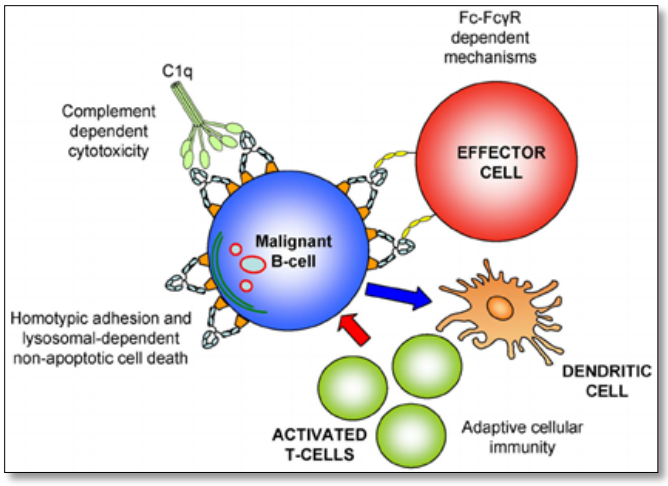


**Figure 3.** Rituximab; possible mechanisms of action.

*1. Antibody dependent cytotoxicity: The Fc arm of anti-CD20 mAb recruits and activates Fc-R-expressing immune effector cells, including macrophages and Natural Killer (NK) cells, which in turn eliminate the target cell by release of cytotoxic mediators, 2. Complement dependent cytotoxicity: Complement fixation occurs when C1q, the globular head of C1, binds the Fc portion of 2 IgG molecules, which triggers a series of enzymatic reactions that generate pores in the cell membrane (membrane attack complex) leading to cell lysis, 3. Direct programmed cell death: induced primarily by type II anti-CD20 mAbs through an actin-dependent, lysosomal pathway after homotypic adhesion, and 4. Adaptive cellular immunity: Anti-CD20 mAbs promote the uptake of tumour antigens by dendritic cells and cross-presentation to T cells, which differentiate into cytotoxic T cells that evoke an antitumor cellular immune response [27]*

## SYSTEMIC CHEMOTHERAPY

Chemotherapy with CHOP (cyclophosphamide, hydroxy-doxorubicin, vincristine, prednisolone) regime and its modifications remain an effective treatment for disseminated PTLD [19]. Chemotherapy may be considered either as stand-alone therapy or in combination with rituximab as discussed above. The overall response rates are higher than rituximab monotherapy with 1 year survival rates >65% [28] while sequential treatment with rituximab has shown response rates of 90% [29]. However, the chief drawback and limiting factor has been the drug toxicity with treatment related morbidity. Some studies have reported systemic chemotherapy induced infection related mortality to be as high as 30-50% [30]. Chemotherapy related infectious morbidity and mortality can be successfully reduced with the prophylactic use of granulocyte colony stimulating factor (G-CSF), antibiotics, antifungals and antivirals. This strategy has shown to reduce chemotherapy induced infection related mortality rates to <30% [31].

In CNS-PTLD, the treatment options are limited, and the overall prognosis remains poor. Standard systemic chemotherapy regimens do not cross the blood brain barrier, thus limiting their efficacy in CNS-PTLD. Hence, higher doses of methotrexate or direct intrathecal therapy have been used with limited success. However, radiotherapy remains the best available therapeutic modality in established CNS-PTLD.

## ADOPTIVE IMMUNOTHERAPY

Adoptive immunotherapy is a novel approach and has been used especially in HSCT recipients where conventional therapies for PTLD have failed. It aims at increasing EBV-specific cytotoxic T-cells (EBV-Tc) by either donor derived infusions (DDI) or banked, *in vitro* expanded "third-party" EBV-Tc [32,33]. The use of DDI is limited by the risk of graft-versus-host disease and slow response compared to third-party EBV-Tc.

DDI of cytotoxic T-cells as adoptive immunotherapy has been reported with success rates as high as 68% without significant risk of graft versus host disease. However, these successes have been largely limited to HSCT and have not been reproduced in PTLD following SOT **(Figure 4)**.

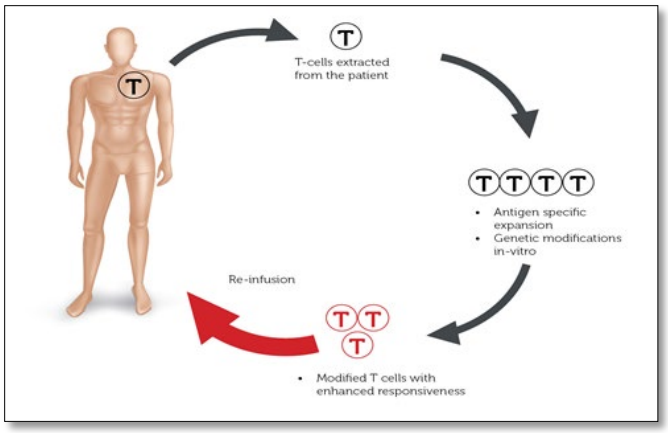


**Figure 4.** Adoptive immunotherapy simplified in a schematic representation.

## SURGICAL CARE AND RADIOTHERAPY (RT)

Surgery in PTLD is mainly useful in diagnosis to obtain tissue for histological confirmation.

Surgical excision can rarely be therapeutic in well-localized PTLD or during surgical emergencies such as GIT-related PTLD causing intestinal perforation, obstruction or bleeding [19].

In PTLD after renal transplantation, where the graft itself is affected by the disease, graft nephrectomy with RIS can be considered as first-line therapy.

Local radiotherapy has been used following surgical excision for peripheral PTLD while it remains a primary treatment modality in CNS-PTLD [34].

### Antivirals

PTLD is primarily caused by 'latent-type' EBV infection where antivirals are considered ineffective. Hence, the place of anti-viral therapy in the management of PTLD is limited to pre-emptive treatment of patients who demonstrate rising EBV antibody titres during post-transplant surveillance.

Addition of arginine butyrate with ganciclovir increases the drug efficacy against EBV infected cells that are otherwise resistant to ganciclovir therapy, and has been with limited experience [35].

### Interferon (IFN-alfa)

IFN-alfa has shown efficacy in direct destruction of EBV-infected B-cells and blunting the activity of T-helper cells, which promote B-cell proliferation [36]. However, there is no definitive prospective studies comparing its safety and efficacy in PTLD and it remains largely experimental based on few anecdotal reports.

### Post-treatment surveillance

Surveillance with EBV viral loads and renal functions provide valuable information regarding disease response, progression, recurrence and allograft function. Serial imaging with CT is also being done to assess disease recurrence.

### Prophylaxis

The Seville expert workgroup consensus (2012) has published recommendations regarding the prevention of PTLD [37]. The summary of these recommendations are as follows:

- The EBV serology status of both donor and recipient should be established prior to all transplants.
- EBV sero-negative recipients should ideally be preferentially allocated EBV sero-negative donor organs.
- Minimize overall immunosuppression so as to minimize the risk of PTLD while maintaining allograft function and avoiding rejection.
- Consider periodic EBV viral load measurement in those deemed at high risk for PTLD.
- A documented rise in EBV viral load (10 to 50 fold rises above baseline or a rise over short time duration) should prompt possible pre-emptive RIS. Furthermore, these patients may be considered for immunosuppression conversion to sirolimus or everolimus.

## PROGNOSIS

Despite all the advances in management of PTLD have improved overall outcomes compared to several decades ago, reports still indicate fairly high rates of disease related mortality. Most current studies have reported PTLD related mortality after SOT between 22-26% [38].

Despite numerous attempts to standardize a prognostic scoring system for PTLD, there is no consensus in this regard. Factors included in the International Prognostic Index for Non-Hodgkin Lymphoma in non-transplant setting have not been found to correlate accurately with prognosis

of PTLD. Different study groups have attempted to define possible poor prognostic indicators based on their individual patient cohorts. Some of the identified poor prognostic indicators are poor general health, EBV-ve disease, hypoalbuminaemia, CD-20 positive disease, primary CNS disease, graft involvement and monomorphic pathology [16,39,40] **(Figure 5)**.

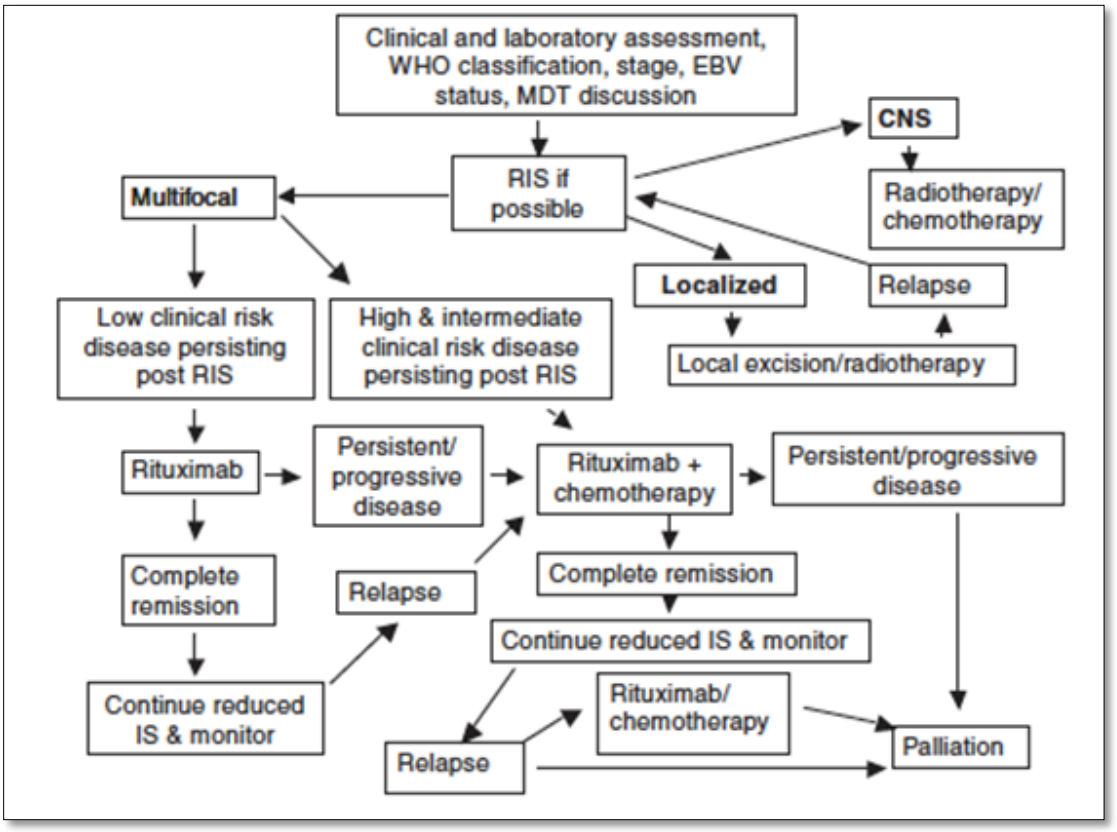


**Figure 5**. Algorithm for management of PTLD.
*RIS: Reduction in Immunosuppression; MDT: Multi-Disciplinary Team*
*Adopted from Parker et al. [2]*

## CONCLUSION

PTLD is one of the commonest malignancies following transplantation. Despite numerous advances in diagnosis and treatment, the associated mortality remains high. The presentation is highly variable and requires a high degree of clinical suspicion to avoid fatal delays in diagnosis. Treatment should be individualized with inputs from a multi-disciplinary team aiming at reversal of disease progression while preserving allograft function. While immunosuppression reduction remains the cornerstone in management, numerous novel therapeutic options have also been explored in an effort to safeguard graft function while achieving disease remission. Further studies will be needed to verify the efficacy and safety of such novel approaches with a view to reducing the associated mortality.

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