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REVIEW

- 29 Post-transplantation lymphoproliferative disorders: Current concepts and future therapeutic approaches
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Post-transplantation lymphoproliferative disorders: Current concepts and future therapeutic approaches

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Abstract

Transplant recipients are vulnerable to a higher risk of malignancy after solid organ transplantation and allogeneic hematopoietic stem-cell transplant. Post-transplant lymphoproliferative disorders (PTLD) include a wide spectrum of diseases ranging from benign proliferation of lymphoid tissues to frank malignancy with aggressive behavior. Two main risk factors of PTLD are: Firstly, the cumulative immunosuppressive burden, and secondly, the oncogenic impact of the Epstein-Barr virus. The latter is a key pathognomonic driver of PTLD evolution. Over the last two decades, a considerable progress has been made in diagnosis and therapy of PTLD. The treatment of PTLD includes reduction of immunosuppression, rituximab therapy, either isolated or in combination with other chemotherapeutic agents, adoptive therapy, surgical intervention, antiviral therapy and radiotherapy. In this review we shall discuss the prevalence, clinical clues, prophylactic measures as well as the current and future therapeutic strategies of this devastating disorder.

Key words: Lymphoproliferative disorders; Epstein-Barr virus; Solid organ transplant; Hematopoietic stem cell transplant; Post-transplant lymphoproliferative disorder prevention; Future therapies

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Core tip: Post-transplant lymphoproliferative disorders (PTLD) is a serious complication related to the intensity of post-transplant immunosuppression. The role of Epstein-Barr virus (EBV) in PTLD evolution is well established; however, development of PTLD in EBV negative patients is not uncommon. The key step in the management of PTLD is to reduce the immunosuppressive load. Transplant clinicians should be vigilant to the possibility of this complication, particularly in patients with past history of exposure to immunosuppression during treatment of the primary renal disease. High index of suspicion is crucial for timely diagnosis. Therapeutic options include rituximab, chemotherapy, antivirals, adoptive therapy and surgery.

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INTRODUCTION

Post-transplant lymphoproliferative disorders (PTLD) are one of the most important malignancies after solid organ transplantation (SOT) and hematopoietic stem-cell transplant (HSCT)^[1], and it develops as a result of uncontrolled B cell proliferation due to blunted immunological surveillance. B cells may get infected by Epstein-Barr virus (EBV) either by: (1) Post-transplant viral reactivation; and (2) Primary EBV infection, through the donated organ or via environmental exposure. The majority of PTLD cases (> 85%) are usually observed in the first post-transplant year. On the other hand, PTLD as a result of T-cell proliferation is seen much less commonly and is mostly EBV-negative. The magnitude of cumulative immunosuppressive burden has a crucial role in PTLD evolution^[2]. Lymphoma accounts for 21% of all malignancies in SOT recipients as compared to 4% and 5% in immunocompetent individuals, respectively in men and women^[3,4]. Clinically, PTLD may manifest either as localized lesion or as systemic disease. Lowering the clinical threshold of PTLD diagnosis is fundamental. Transplant clinicians should be vigilant to this serious disorder. Tissue diagnosis (histopathology) is crucial for PTLD diagnosis, in addition to a clear evidence of EBV DNA, RNA, or protein material^[2].

The mainstay of PTLD primary management is reduction of immunosuppression (RI). Complete cessation of the immunosuppressive drugs may be necessary to stop the disease progression. However, RI is not always feasible; a potential risk of allograft loss or graft dysfunction has to be considered particularly for vital organ transplants (e.g., heart transplant). A variety of therapeutic options include surgical clearance, anti-viral agents, local radiotherapy, intravenous immunoglobulin (IVIG), chemotherapeutic agents, monoclonal antibodies and cytotoxic T lymphocytes with variable success^[2]. A combination of the above treatment modalities offers better results rather than when used in isolation.

Epidemiology of PTLD

Penn *et al*^[5] described five cases of PTLD in 1969 for the first time. Since that time, an increased recognition of PTLD has been observed in both SOT as well as in HSCT^[6,7]. Many explanations have been suggested to elucidate the increased awareness of PTLD prevalence e.g., better diagnostic technology, older age of donors and recipients, increased awareness of this disorder, the advent of new immunosuppressive strategies and introduction of the haplo-identical (HSCT).

The increased risk is expressed as “standardized incidence ratios” (SIRs) *i.e.*, the incidence of lymphoma in transplant cohort divided by its incidence in general population (non-transplant cohort)^[8]. SIRs of 10 (non-Hodgkin’s lymphoma) and 4 (Hodgkin’s lymphoma) have been reported among SOT recipients^[8]. On the other hand, a reported incidence of PTLD in 3.2% of HSCT recipients has been observed in multicenter studies^[7].

Risk factors

Risk factors are, reportedly, varied according to the type of the transplant organ:

(1) SOT: In adults, the incidence of PTLD has been reported to range from 0.8%-2.5% in kidney transplant recipients (KTR), 0.5%-5.0% in pancreatic TRs, 1.0%-5.5% in liver TRs, 2.0-8.0% in heart TRs, 3.0-10.0% in lung TRs, and $\leq 20\%$ in multi-organ and intestinal TRs^[9,10] (Figure 1). These figures suggest that the amount of lymphatic tissue in an allograft and the degree of immunosuppression are key factors.

(2) Allogeneic HSCT: PTLD incidence is primarily related to the degree of HLA matching with consequent introduction of T-cell depleting agents prior to transplant. Higher risk, however, has been observed with particular T-cell depleting strategies (relative risk: 8.4-15.8). On the other hand, its incidence has been relatively lower with the use of non-specific broad lymphocyte depleting agents (T- and B-cells) (relative risk = 3.1)^[11]. Hence, the magnitude of increased risk of PTLD can be graded as follows: (1) HSCT (zero in patients who received cyclophosphamide for GVHD and $> 20\%$ with selective T-cell depletion); (2) Umbilical-cord transplantation (4%-5%); (3) Transplant from unrelated donors (4%-10%); and (4) Transplant from matched, related donors (1%-3%)^[7,10-13] (Figure 2).

Impaired immune surveillance has been considered to be the explanation for infection-related malignancy a phenomenon similar to the predisposition of malignancy in patients with human immunodeficiency virus^[14]. The role of immunosuppressive agents is less clear due to variability in timing, duration, and dosage in different immunosuppressive strategies. Whereas the type of induction therapy has a fundamental role in the early developed PTLD, the one that develops late PTLD is largely determined by cumulative immunosuppressive burden. A number of PTLDs in allogeneic HSCT are donor-driven (EBV-infected lymphocytes) and are usually observed in 1st post-transplant year, with almost 100% being EBV positive. The most crucial contributing factors for PTLD evolution were the “donor type” as well as the “T-cell depleting strategy”^[11]. However, sharing role of other factors is less evident (Figure 3).

The lack of long-term follow up of TRs may result in underestimation of actual incidence of PTLD. On the other hand, the registry data might result in overestimation of this cohort of patients^[15]. Compared to EBV seropositive TRs, the seronegative patients in SOT are more vulnerable to develop PTLD with an increased estimated risk of 10-75^[16,17]. This observation explains the high prevalence of PTLD in pediatric TRs. By far, the primary EBV infection is considered the most effective factor triggering PTLD development in pediatric age group. Considering the improving patient and allograft survival, two peaks of PTLD incidence have been observed, first peak: In the first post-transplant year (mostly EBV seropositive), and, second peak: Usually present 5-15 years after transplant (mostly EBV seronegative). Furthermore, the evolution of the late PTLD (> 20 years post-transplant) has been on rise^[10,18].

(3) It is noteworthy to mention that the presence of previous exposure to the immunosuppressive load during treatment of the primary renal disease in the native kidney is an unnoticed risk factor for PTLD evolution.

(4) Oncogenic EBV: EBV may alter cell growth via several mechanisms: (1) With lack of immune recognition, EBV may induce highly regulated growth transformation with expression of all of its growth inducing proteins. (2) Induction of the potent oncogenes *e.g.*, LMP1 and LMP2 *via* environmental factors. (3) EBV induced proliferating cells as well as EBV variant/HLA types combination may permit these proteins to by-pass immune control and go unrecognized. And (4) Growth alterations with the right levels of expression of cell targets and viral and cellular mRNA^[19].

Serology *via* viral capsid antigens (VCA-IgG) antibody detection is the best solitary serological test to indicate previous EBV exposure. Molecular testing: essential diagnostic technique in immunocompromised TR, where serology can be confusing and unclear owing to the erratic humoral response. Consequently, (molecular plus serological methods) combination may allow early detection of EBV with prompt diagnosis of infection^[19]. Healthy donors may carry the high-risk variants of LMP-1 that predispose to malignant evolution. Understanding EBV molecular epidemiology in various populations and recognition of virulent strains can help in institution of a robust preventive strategies of PTLD^[20]. In view of the better understanding of these underlying mechanisms, each one may admit a potential therapeutic target, *e.g.*, cytotoxic T-cell immunotherapeutic agents targeting EBV proteins. Critical pathways (activated by EBV) blockers *e.g.*, NF κ B, PI3kinase, EGFR, can also block critical activation locations of EBV oncogenes^[19].

Pathogenesis

Role of EBV: For decades, PTLD development was attributed mainly to EBV infection, however, recent reports suggest that as many as 50% PTLD in SOT are not accompanied by EBV infection^[21]. For EBV-positive TRs, the development of PTLD can be attributed to immunosuppressive-induced decline in the T-cell immune-surveillance. EBV can integrate into normal B-cell program leading to proliferation

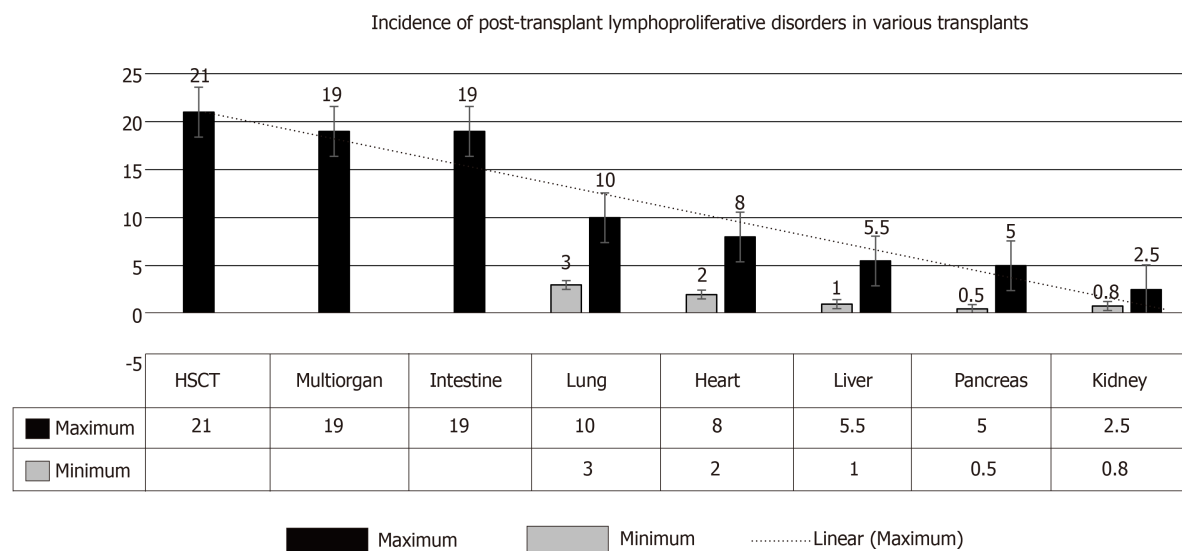


Figure 1 The range increased incidence of post-transplant lymphoproliferative disorders in various transplants. Incidence in intestinal transplant and in multi-organ transplants it is < 20%, while in hematopoietic stem-cell transplant it is > 20% with selective T-cell depletion^[4]. HSCT: Haplo-identical allogeneic hematopoietic stem-cell transplant.

and transformation of these cells. Normally, these antigens would trigger a T-cell response capable of destruction of most of the EBV-infected B cells. However, this immune defense mechanism has been compromised in TRs leading to unlimited B-cell transformation and the evolution of lymphoma^[22]. On the other hand, pathogenesis of PTLD in EBV-negative patients is less evident. Several hypotheses have been postulated *e.g.*, CMV or another viral infection, prolonged immunosuppression, allograft-driven persistent antigenic triggering, hit-and-run hypothesis *i.e.*, EBV commences the pathogenic process leading to the development of PTLD and then vanishes.

EBV-positive vs EBV-negative PTLD: In the light of molecular-genomic data of diffuse large B-cell lymphoma subtype, a range of distinguishing features have been identified to discriminate between EBV+ve and EBV-ve PTLD (Table 1)^[25]. However, there is a lack of clear distinction between clinical consequences of different EBV serotypes and their response to therapy. Further studies are warranted to recognize more precise molecular-genomic classification of both types.

T-cell subtype PTLD (usually EBV-ve), a rare tumor, and presents with manifestations that are dissimilar to those of T-cell lymphoma in immunocompetent subjects^[25]. However, molecular-genomic information would help to define best therapeutic strategies for both types^[24].

Classification: The main differences between early and late onset PTLD have been shown in Tables 2 and 3. However, depending mainly on histopathological classification, diagnosis of PTLD can be categorized according to WHO 2017 Classification, as follows: (1) Three nondestructive PTLD: plasmacytic hyperplasia, florid follicular hyperplasia, and infectious mononucleosis-like PTLD. (2) Polymorphic PTLD. (3) Monomorphic PTLD (B-cell, T-cell, or natural killer-cell types). And (4) classic Hodgkin's lymphoma-like PTLD.

An associated EBV infection could be currently seen in almost all TRs with non-destructive PTLD, in > 90% of patients with polymorphic PTLD and Hodgkin's lymphoma-like PTLD, and in only 50% of monomorphic PTLD (Figure 4). Pathologically, monomorphic PTLD cannot be discriminated from lymphomas in immunocompetent patients^[26,27].

Gene-expression profile and immunohistochemical staining have been used to classify the diffuse large B-cell lymphoma in immunocompetent subjects depending on the cell of origin into "germinal center" B cell or "non-germinal" center B cell^[28-30]. In PTLD, EBV+ve cases are mostly non-germinal center B-cell type, in contrary to the EBV-ve cases that are more likely to be "germinal center B-cell type"^[31,32]. The presence of EBV infection is not necessary for PTLD diagnosis; however, the EBV-encoded RNA (EBER) *in-situ* hybridization assessment is mandatory for all the cases^[33]. Despite wide-spread application of preemptive monitoring of peripheral-blood EBV viral load, it seems to be devoid of any diagnostic benefit. The pathological classification by

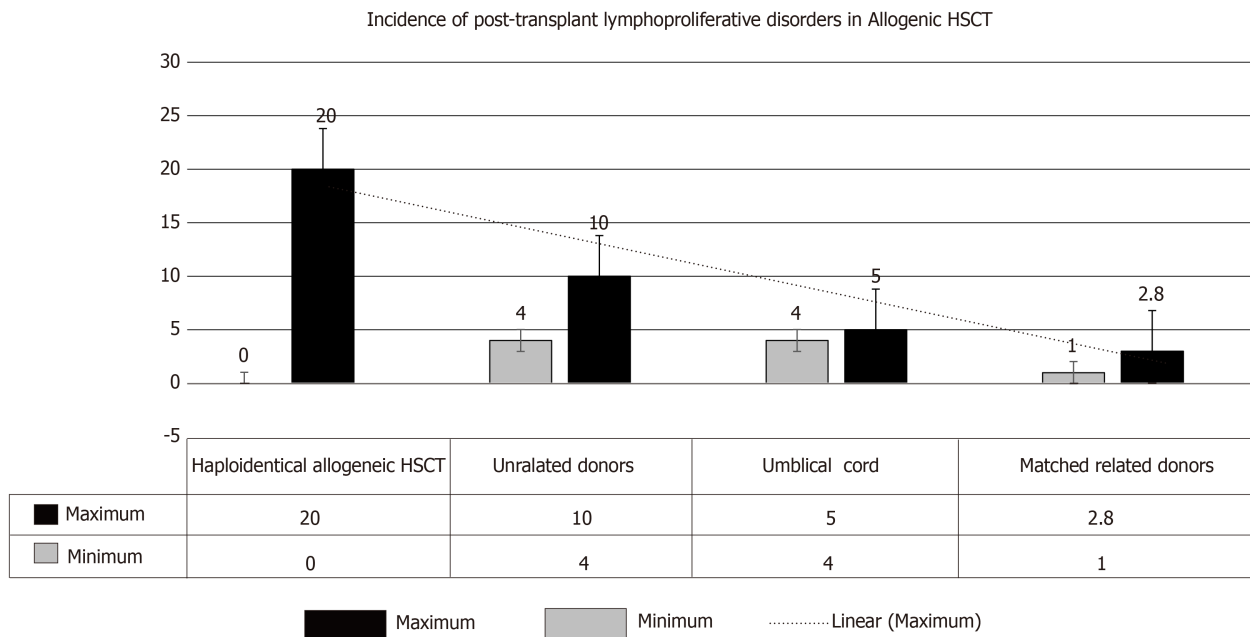


Figure 2 Incidence of post-transplant lymphoproliferative disorders after allogeneic hematopoietic stem-cell transplant. An additional risk factor in hematopoietic stem-cell transplantation is: recipient age of > 50 yr^[4]. HSCT: Haplo-identical allogeneic hematopoietic stem-cell transplant.

the WHO aims for more consistency for better PTLD diagnosis, however, several aspects are currently missing: EBV sero-status, molecular-genomic criteria and transplant organ type (SOT *vs* HSCT)^[34]. Once the histopathologic configuration is confirmed, prompt staging for PTLD is obtained *via* application of the currently used staging for lymphoma.

Clinical presentation: Clinically, PTLD manifestations vary from symptomless lesions to fulminating disease with multi-organ failure.

Salient features: PTLD may present as a local or disseminated disease. In either form, the tumor can behave aggressively in a rapidly progressive manner. Clinical manifestations include: Pyrexia (57%)^[1], weight loss (9%)^[35], neurological manifestations (13%)^[36], nodal lesions (38%)^[37], gastrointestinal manifestations (27%)^[27], pulmonary manifestations (15%)^[38] and infectious mononucleosis-like syndrome that could be fulminant (19%)^[39], refer to **Figure 5**. An allograft dysfunction may ensue due to graft involvement. Lowering the threshold for PTLD diagnosis is crucial, as TR may present with nonspecific symptoms (*e.g.*, fever, asthenia). An associated high EBV viral load by PCR should make one suspect PTLD^[40-42]. The most common locations of PTLD involvement are as follows^[43,44]: Lymph nodes, liver, lung, kidney, bone marrow, gastrointestinal tract (GIT), spleen, central nervous system (CNS), tonsils and salivary glands, refer to **Figure 6**^[1,2].

Differential diagnosis: Any high-risk TR who presents with pyrexia, pharyngitis and cervical lymphadenopathy would make one consider other diagnoses *e.g.*, streptococcal infections or Infectious mononucleosis^[2].

Time to PTLD for different transplanted organs: The time to PTLD is longest for the heart recipients and shortest for the lung and heart/lung in pediatric TR. Early PTLD is often of diffuse large B-cell or other B-cell lymphoma histology; whereas Burkitt's lymphoma and Hodgkin's disease are late events^[46] (**Table 3**).

EBV monitoring for preemptive therapy: The risk of EBV+ve PTLD has been postulated to be related to three factors: Type of transplant organ, time elapsed until diagnosis of post-transplant PTLD and EBV serological status of both recipient and donor before transplant^[16]. An estimation of the viral load *via* PCR amplification of peripheral blood EBV DNA is mandated to monitor preemptive PTLD therapy. It has been observed that TR with PTLD usually expresses an increased EBV viral load as compared to PTLD free TR. This higher viral load invites more risk for PTLD evolution^[50-52]. However, several pitfalls have emerged in preemptive strategy monitoring: First, cut-off values are not clear, second, sources of samples are not universal and third, absence of standard points of time to perform the monitoring.

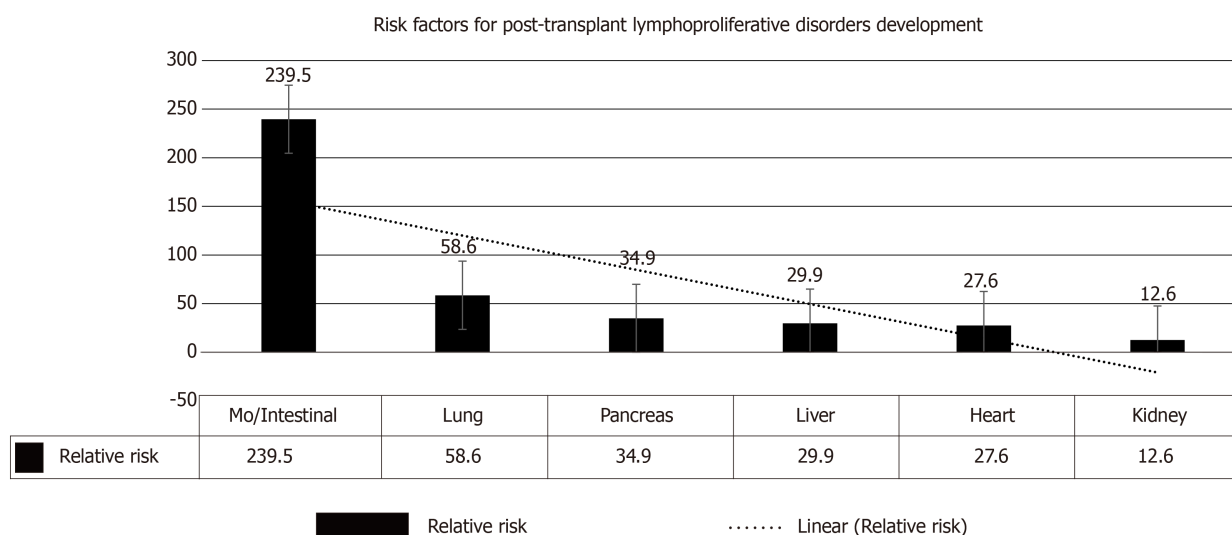


Figure 3 Risk factors for the development of post-transplant lymphoproliferative disorders after solid-organ transplantation^[4]. MO: Multi-organ.

This disparity, however, has been reflected in positive and negative predictive of EBV viral load values for both SOT (28%-100% and 75%-100%, respectively) and allogeneic HSCT (25%-40% and 67%-86%, respectively)^[53-56]. Compared to the reliability of EBV DNA *via* peripheral-blood mononuclear cells, the “cell-free plasma EBV DNA” has been reported as a better marker of EBV activity^[41,57]. In order to limit the risk of PTLD development in SOT and HSCT, a variety of preemptive strategies have been suggested^[58,59], *e.g.*, RI, rituximab therapy, and adoptive transfer of EBV-specified T cells. Considering a suitable preemptive approach should be confined to the high-risk group of PTLD patients, however, the precise definition of the cohort of patients at high risk has not been established yet^[3].

Prophylaxis: In order to limit the risk of developing PTLD, it is worthwhile quoting a consensus statement on classification and risk factors for PTLD^[39]. Primarily, EBV sero-status of both donor and recipient should be recognized before donor selection. EBV-negative TR is better receiving grafts from EBV-negative donors whenever available. A fine-tuning the immunosuppressive burden to as low as clinically possible. Reactivation of other viruses, *e.g.*, CMV or BK should trigger initiation of RI since viral application of other viruses might herald over-immunosuppression. Preemptive/prophylactic antiviral therapy in potentially high-risk groups should be also considered. Maintenance of high titers anti-EBV antibodies *via* IVIG/CytoGam administration is also recommended. The preemptive therapy should be considered in select groups that are at high-risk for developing PTLD. Furthermore, monitoring EBV viral load in a high-risk case and considering preemptive RI with rising titers, and close monitoring of allograft function have been also recommended^[2].

TREATMENT OF PTLD

RI

The mainstay of primary PTLD management is to ameliorate the immunosuppressive burden, so that EBV-specific cellular immunity can be partially restored with no additional risk of acute rejection. RI can reverse 20%-80% of patients with PTLD^[60-62]. RI plan includes 50% reduction of calcineurin inhibitors (CNI), either tacrolimus (Tac) and cyclosporine (CyA) doses in addition to withdrawal of the antimetabolites such as azathioprine or mycophenolate mofetil (MMF), despite the lack of evidence demonstrating any relation between MMF and PTLD development^[62]. With the exception of glucocorticoids, withdrawal of all immunosuppressive medications in critically ill cases should be considered.

Considering their early response, TR can be restaged within two to four weeks in contrary to lymphoma staging in immunocompetent patients. Monitoring allograft function is mandated during the trial of RI to recognize any manifestations of early rejection. An acute rejection rate of 37% has been observed in a prospective trial entailed the RI strategy as a sequential plan for post-SOT PTLD therapy^[61]. Compared to EBV positive disease, the EBV negative cases are less responsive to RI^[10,24].

Table 1 Epstein-Barr virus-positive vs Epstein-Barr virus-negative post-transplant lymphoproliferative disorders^[25]

	EBV-positive PTLD	EBV-negative PTLD
Molecular-genomic studies	Fewer genomic abnormalities	Share many genomic/ transcriptomic features with diffuse large B-cell lymphoma in IC patients
Origin	Mostly B-cell proliferative lesions	Mostly T-cell proliferative lesions
Gene-expression	"Non-germinal" center B-cell	"Germinal center B-cell type" ^[4]
Prevalence	More common (first peak)	Less common (second peak)
Risk of PTLD	Less risk compared to seronegative TR	Seronegative SOT pediatric TR are more vulnerable to develop PTLD with increased estimated risk of 10-75 ^[16,17]
SOT vs HSCT	Almost all cases of HSCT (100%) are EBV positive	In SOT, both EBV positive and negative are present
Clinical consequences of EBV status	Less clear	Less clear
Prognosis/response to therapy in adults.	Not prognostic/predictive of response to therapy ^[21,23]	
Common criteria	A considerable proportion of both EBV+ve and -ve PTLD respond to RI as a sole intervention ^[24]	
Future studies	Whole-exome/genome wide sequencing and studies of role of EBV-associated microRNAs, may further define PTLD pathogenesis with more precise molecular-genomic classification of both EBV+ve and EBV-ve PTLD	

RI: Reduction of immunosuppression; IC: Immunocompetent; PTLD: Post-transplant lymphoproliferative disorders; EBV: Epstein-Barr virus; HSCT: Haplo-identical allogeneic hematopoietic stem-cell transplant; KTR: Kidney transplant recipients; TR: Transplant recipients; SOT: Solid organ transplantation.

However, a complete lack of response to RI has been observed in old aged patients (> 50 years), bulky lesions (> 7 cm), as well as in advanced stages of the disease (*Ann Arbor* stage III/IV)^[60].

Rituximab therapy

Rituximab (Rtx) is a potent chimeric anti-CD20 monoclonal antibody that binds CD-20 antigen, leading to B cell depletion via several mechanisms *e.g.*, phagocytosis (macrophages), complement mediated cytotoxicity, and through natural killer cells (antibody-dependent cell-mediated toxicity)^[63]. Of note, CD20-positivity in B-cell PTLD approached 75% of TR in the prospective phase 2 trial (largest subgroup)^[64].

However, Rtx has been approved as a standard therapeutic agent in PTLD for three types of the WHO classification: (1) Nondestructive PTLD, (2) Polymorphic PTLD, and (3) Monomorphic diffuse large B-cell lymphoma-like PTLD not responding to RI. The overall response to Rtx monotherapy (375 mg/m² body-surface area, weekly for 4 wk, single agent) in addition to RI, approached 44%-79% with a complete remission has been observed in 20%-55% of cases^[23,65-68]. Adding 4 doses of Rtx, can raise the rate of complete remission to 34%-60.5%^[66]. In the PTLD-1 trial (prospective, multicenter trial including post-SOT PTLD), the complete remission rate approached 25% after standard induction augmented by another four doses of 3 weekly Rtx (low-risk patients)^[23]. The complete response can be interpreted as three associated benefits: Better overall survival, extended time to progression, and better progression-free survival.

Furthermore, in comparison with the group of TRs with complete remission with Rtx followed by CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone), the low-risk group in the cohort receiving risk-stratified sequential expressed longer disease-free survival at 3 year, despite no change in overall survival^[68,69], please see [Figure 7](#). More recent prospective trial PTLD-2 is registering TRs with the "risk stratification" based on the following parameters: Type of the allograft, response to Rtx therapy, and international prognostic index (IPI) scoring^[4].

Chemotherapy

Indications of Immunochemotherapy include: Burkitt's lymphoma, Hodgkin's lymphoma, peripheral T-cell lymphoma, primary CNS lymphoma and other uncommon lymphomas, and B-cell PTLD unresponsive to Rtx and RI^[23].

Considering the standard-of-care approaches related to specific histologic features in the rare subtype lymphomas^[4,5], have mostly improved patient's outcome^[43,65,70-75]. Despite unproven efficacy, a reduction of the immunosuppressive burden should be evaluated by transplant physicians in view of the immunosuppressive effect of chemotherapy agents and their toxicity. In all CD20+ve subtypes (75% or more), Rtx should be included. The poor outcome of chemotherapy-treated PTLD patients between 1980 and 1990 was partially attributed to the high rates of therapy related

Table 2 Early vs late onset post-transplant lymphoproliferative disorders in adults^[4]

	Early PTLD	Late onset PTLD
General characteristics	EBV positivity Graft involvement Less often: Extranodal disease Nondestructive PTLD ¹ : Present early Less often: Monomorphic subtype ^[3] Origin: higher % of donor-derived PTLD especially in 1 st post-tx year)	Frequent EBV negative tumors Less often graft involvement ^[3] Extra-nodal disease: Common High incidence of late onset Hodgkin's lymphoma after allogeneic HSCT Specific tumorigenic events: C-myc translocations Elevated LDH level
Risk factors	Same	Same
Response to therapy	Same	Same
Patient survival (at 1- and 5- yr)	65% and 46%, (In adult heart/lung tx) ^[1,45]	53% and 41% (In adult heart/lung tx) ^[1,45]
Future therapy	Proteasome inhibition (bortezomib) may be useful after allogeneic HSCT ^[3]	
Role of immun-osuppression	Induction therapy has a role	Cumulative immunosuppression is crucial
Prevalence	Majority of PTLD cases	Less prevalent

¹Non-destructive post-transplant lymphoproliferative disorders includes plasmacytic hyperplasia post-transplant (according to the Classification of PTLD by the WHO). Tx: Transplantation; PTLD: Post-transplant lymphoproliferative disorders; EBV: Epstein-Barr virus; HSCT: Haplo-identical allogeneic hematopoietic stem-cell transplant; LDH: Lactate dehydrogenase.

mortalities^[76]. However, their outcomes greatly improved after the advent of the proper supportive care and administration of granulocyte colony-stimulating factors (G-CSF). Safety and efficacy of Rtx (375 mg/square meter/ week/4 wk), followed by CHOP regimen every 3 wk and G-CSF support have been elucidated in the PTLD-1 trial^[68].

A risk-stratified sequential therapeutic approach has been admitted in the second part of this trial as follows: Rtx + CHOP (R-CHOP) given over 3 wk for 4 cycles with G-CSF support in cases with no complete response to isolated Rtx therapy. Overall response rate approached 88%, with 70% of cases with any response achieved a complete response at the end of therapeutic program. Of note, post-R-CHOP supportive G-CSF was mandated in all patients with anti-Pneumocystis jirovecii prophylactic therapy^[23]. Considering an excellent outcome reported of this trial, a reduction of the immunosuppressive load and risk-stratified sequential therapy are widely considered the standardized care of polymorphic and monomorphic diffuse large B-cell lymphoma-like PTLD (regardless to EBV status) after SOT.

Adoptive immunotherapy

Infusion of donor lymphocytes, to achieve adoptive immunotherapy, has been shown to manage PTLD in HSCT patients that is primarily originating from donor cells. This situation is in contrast to PTLD developing in TRs of SOT. A robust EBV-specific cellular immune response is induced by EBV-specific cytotoxic lymphocytes (CTLs)^[22,77]. The major risk of this therapeutic modality, however, is GVHD development^[77,78].

Expanded EBV-specific CTLs have been an effective therapeutic option in autologous (recipient-derived PTLD) as well as in donor-derived PTLD^[79]. A variety of recent approaches *e.g.*, adoptive transfer of "pamidronate-expanded Vγ9Vδ2 T cells" and Tac-resistant, engineered CTLs has been admitted as new therapeutic options for PTLD with no need to decrease the immunosuppressive load^[80].

Outpatient care

In light of serial follow up of the EBV viral load in identifying the patients at risk and in monitoring the response to therapy, the following steps have been suggested: (1) Weekly monitoring of EBV viral titers^[81] in higher risk patients. Monthly monitoring initially followed by three monthly monitoring for low risk groups. (2) Whilst viral load drop denotes a response to therapy, persistently high or continuous rise in viral load indicates disease development or progression. (3) Serial physical examination, radiology testing and monitoring allograft function should be viewed as a part of comprehensive clinical picture that includes EBV viral load assessment. The latter does not necessarily correlate with PTLD status. (4) Optimum balance between PTLD management and avoidance of allograft acute rejection is crucial. (5) Therapeutic options should be tailored as per multidisciplinary team discussion. And (6) The

Table 3 Early vs late onset post-transplant lymphoproliferative disorders in pediatrics^[46]

	Early PTLD	Late PTLD
General criteria	Diffuse large B-cell or other B-cell lymphoma	Burkitt's lymphoma and Hodgkin's disease are late events ^[47]
Time to PTLD	Atypical presentation (graft dysfunction, abdominal pain, frequent extra-nodal involvement in > 80% of TR) ^[46] Shortest for lung, heart/lung TR. Early PTLD is quite frequent in liver TR (Late PTLD beyond 5 yr is rare, immunosuppression can be tapered/hold due to tolerance)	Frequent EBV negative tumors. Specific tumorigenic events <i>e.g.</i> , C-myc translocations are restricted to late PTLDs Longest for the heart TR and at risk for late PTLD even > 10 yr after trans-plantation
Patient survival	No significant difference in most published studies ^[20,47-49]	
Distinct criteria	B-cell origin, almost exclusively EBV+ve, reflecting reduced immunosurveillance as major pathogenetic factor	Resembles tumors with distinct pathogenetic alterations and nodal appearance ^[46]
Role of immunosuppression	Induction therapy has a role. More likely to develop graft rejection and switch to Tac before PTLD diagnosis	Cumulative immunosuppression is crucial

Tx: Transplantation; TR: Transplant recipient; PTLD: Post-transplant lymphoproliferative disorders; EBV: Epstein-Barr virus; HSCT: Haplo-identical allogeneic hematopoietic stem-cell transplant; LDH: Lactate dehydrogenase.

initial therapeutic step is RI or cessation of immunosuppression, after which further therapeutic options is tailored according to the response and clonality^[2].

Future strategies

A list of newer therapeutic medications has been proposed^[80-87]. However, their efficacy remains to be validated via randomized controlled trials: (1) Bruton's tyrosine kinase (BTK) inhibition^[80] (Ibrutinib): Virtually active in GVHD and allograft rejection; remarkably active in activated B cells (ABC) type diffuse large B cell lymphoma (DLBCL). (2) Inhibition of PI3K and mTOR^[82] [Idelalisib (PI3K inhibitor)]; SRL and everolimus: Evident - *in vitro* evidence - of involved pathways; mTORi also have robust immunosuppressive impact, introduction in PTLD therapy still controversial. (3) Proteasome inhibition^[83] (Bortezomib): Particularly efficacious in the early presented PTLD post allogeneic HSCT. (4) Radioimmunotherapy^[84], (90Y)ibritumomab, tiuxetan): Apparent efficacy seen only in a small pilot trial. (5) Checkpoint inhibitors^[85] (Pembrolizumab, nivolumab): Cytotoxic T lymphocyte-associated antigen 4 pathway: Contraindication, given high risk of (fatal) acute rejection; programmed death 1 (PD1) or programmed death ligand 1 (PDL1) pathway: Lower risk of acute rejection; recommended only in clinical trials. And (6) Anti-CD30 therapy^[86] (Brentuximab vedotin): Expression of CD30 in 85% of all PTLD subtypes; the given effects is only limited to case reports.

To summarize

Reduction of immunosuppression is the cornerstone of PTLD management. Rituximab therapy is indicated in nondestructive PTLD, polymorphic PTLD, and, monomorphic diffuse large B-cell lymphoma-like PTLD not responding to RI. Chemotherapy is indicated for: Burkitt's lymphoma, Hodgkin's lymphoma, peripheral T-cell lymphoma, primary CNS lymphoma, and B-cell PTLD unresponsive to Rtx/RI with variable results. However, "risk-stratified sequential" therapeutic approach seems to be promising. Other modalities may include adoptive immunotherapy and outpatient care. Investigational agents that're currently under trials have been shown above.

Prognosis

Outcome of PTLD patients has greatly improved owing to the advent of new lymphoma-specific protocols as well as to the better supportive care. Seventy percent of the PTLD-1 patients had achieved a complete remission with median survival of approximately 6.6 years^[23,74,75]. IPI has been universally applied by most hematologists and oncologists to recognize the prognostic attitude in aggressive lymphoma^[88]. IPI is a prognostic scoring system that includes the following: Patient's age, performance attitude, current stage, lactate dehydrogenase (LDH), and number of extra-nodal locations. Another scoring system has been also given in a French registry system that relies primarily upon patient's age, serum creatinine concentration, LDH level, PTLD localization, and histopathologic criteria^[89], however, it is not superior to the IPI^[90].

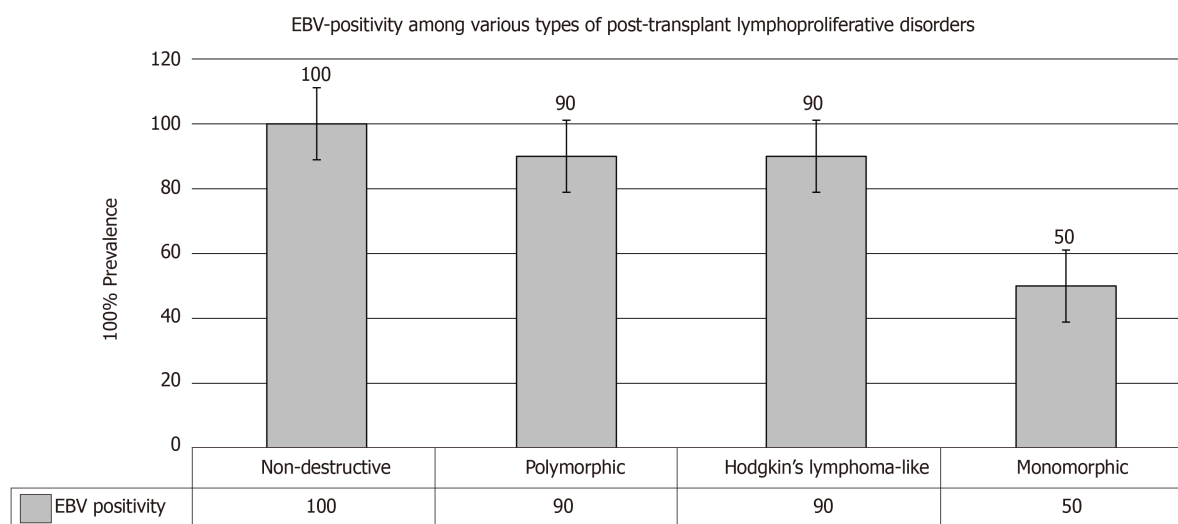


Figure 4 Epstein-Barr virus positivity among various types of post-transplant lymphoproliferative disorders^[4]. EBV: Epstein-Barr virus.

The PTLD-1 trial has settled the prognostic validity of IPI^[69]. However, PTLD-2 trial is currently in progress to optimize the role of these prognostic factors. Evens *et al*^[72], concluded that hypoalbuminemia is a robust prognostic factor in a multicenter study. Khedmat *et al*^[91] reported that CD20-positivity in PTLD indicates poorer outcome. LeBlond *et al*^[92], on the other hand, applied IPI to adult TR with PTLD following SOT to identify criteria for poor survival. Using univariate analysis, the poor prognostic criteria have been postulated^[44,91,92] that include the following: Monoclonality, negative EBV serology, primary CNS involvement, tumor originated from T-cell, performance status ≥ 2 , chemotherapy-based therapy (plus RI), and, multiple involved locations (*i.e.*, > 1 vs 1).

Re-transplantation and PTLD recurrence

Feasibility of re-transplantation after successful management of PTLD has been reported in particular cases; however, one-year disease free survival is necessary after control of PTLD before re-transplantation^[93]. In one French study involving 55 cases with re-transplantation, average time between PTLD recognition and re-transplants was 90 mo. Fortunately, PTLD recurrence has been reported in only one case^[94]. An anti-EBV partially acquired immunity has been proposed as a potential protective mechanism^[94]. To limit the possibility of PTLD recurrence the following recommendations are worth noting^[95]: (1) Time to retransplant: Approximately two years of time should elapse after successful PTLD management. Many transplant physicians recommend 12 to 24 mo after complete PTLD remission, before commencing a new kidney transplant. Dierickx *et al*^[4] reported a mean time of 76 mo for registration in waiting list and a mean of 99 mo between disease remission and the retransplantation. (2) EBV: The following recommendations is currently suggested in the literature: (a) TR should experience Epstein-Barr nuclear antigen IgG positivity (an anti-EBV indicator of robust cytotoxic response) before retransplantation. (b) Low/absent EBV viral load is recommended at the time of retransplantation. (c) Close monitoring of TRs with persistently high EBV viral load is advised. (d) Anti-viral therapy: Long-term prophylactic antiviral therapy with serial estimation of EBV viral load is crucial to limit the incidence of PTLD recurrence^[96]. Ganciclovir has been suggested for this purpose^[97]. (3) Role of immunosuppression: There is general consensus that PTLD is disease of post-transplant immunosuppression. However, it is the magnitude of immunosuppressive intensity that is the fundamental trigger for PTLD evolution. Of note, the intensity of immunosuppression cannot be calculated as a priori information^[98]. Consequently, RI/withdrawal of immunosuppression has been the cornerstone of PTLD management. Retransplantation after PTLD cure remains controversial due to the re-exposure of immunosuppression. (4) Induction therapy: The following agents are considered: (a) ATG *vs* IL-2 receptor antagonists: The T cell-depleting agents should be excluded from the induction strategies with IL-2 receptor antagonists appeared to have the first priority. Of note, ATG induction significantly triggers the risk of lymphoma evolution as compared to other agents^[99]. The latter agents, however, may provide two benefits, first, a lower risk of PTLD development, and, second, TRs are more amenable to avoid long-term excessive immunosuppression after retransplantation. (b) Rituximab in induction therapy: Rtx

Clinical manifestation of post-transplant lymphoproliferative disorders

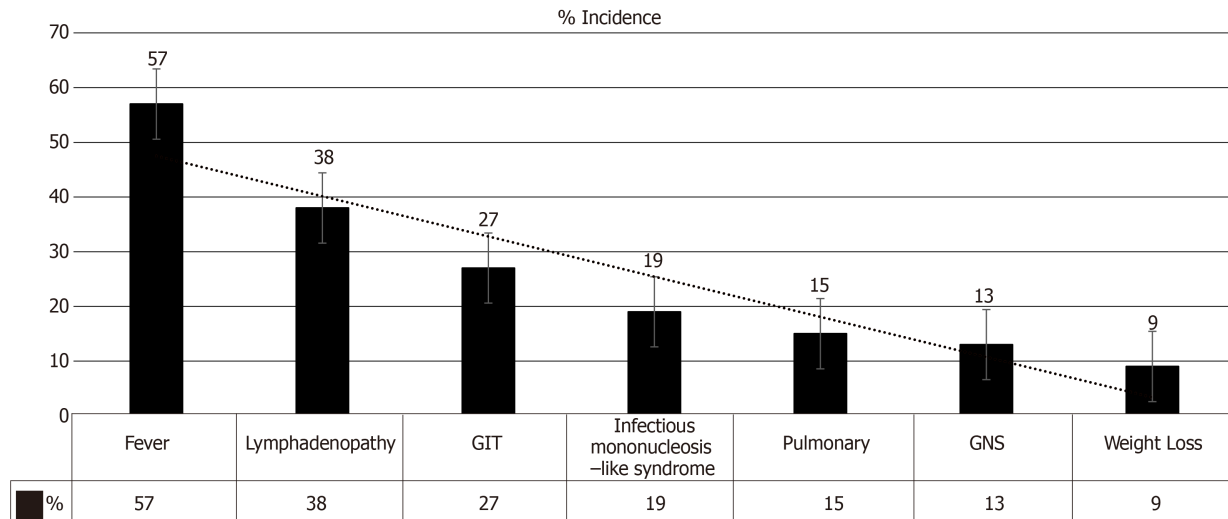


Figure 5 Clinical manifestations of post-transplant lymphoproliferative disorders^[2]. GIT: Gastrointestinal tract; CNS: Central nervous system.

may be introduced as an element of desensitization regimen in high-risk TR. Rtx has been used before in bone marrow or heart TR with seriously high EBV loads in order to inhibit EBV proliferation within lymphocytes, consequently limiting the risk of PTLD development^[58,100]. (5) Maintenance immunosuppression: The fundamental target in regard to maintaining immunosuppression is to avoid the intense state of immunosuppression so that the recovered immune system can promote the evolution of the anti-EBV cytotoxic T lymphocyte, thereby, hampering EBV-triggered B cell proliferation^[101]. However, the potential risk of PTLD development should not impede/interfere with our choice of proper immunosuppressive regimen (grade B, level 3)^[58]: (a) Triple therapy (CNI, MMF and steroids) use is very common in the current post-transplant maintenance therapy, therefore, the lowest safe dosages monitored by target trough levels should be considered. (b) MMF: Considering the safety of MMF in regard to PTLD evolution, MMF can be included safely in the immunosuppressive protocols with no more added risk^[102]. (c) mTOR inhibitors: Their role in PTLD development remains debatable. These agents may inhibit the development of lymphomas *in vitro*, but their clinical application in human still warrant the proper evidence^[103]. (d) Graft PTLD: Is very intriguing (Figure 8) and usually has a good prognostic outcome, furthermore, graft nephrectomy is almost curative^[91,104]. (6) Monoclonal gammopathy: Whilst the presence of monoclonal gammopathy may indicate incompletely remitted PTLD, its complete resolution is an obvious indicator of complete remission. And (7) Origin of PTLD (donor vs recipient): Identification of the tumor source is crucial for future therapeutic plans and recognition of the biology of the next PTLD, if any^[28]. Of note, Olagne *et al*^[101], reported an obvious trend to a better outcome in TRs with “donor” lymphomas. Clinical clues about the origin of lymphoma cell line (*i.e.*, either donor derived or of recipient origin) is an important therapeutic guide in using cytotoxic Tcell infusions in PTLD management.

CONCLUSION

PTLD is a disease of immunosuppression. Recent progress in our understanding of the underlying pathophysiology of PTLD as well as the role of EBV has led to a better management. PTLD recurrence has been rarely reported after re-transplantation that requires careful planning of immunosuppression. An ever-improving molecular-genomic technology has had its impact on upgrading our diagnostic and therapeutic strategies that will be reflected in improved recipient’s outcome. However, close liaison with hemato-oncology team of key importance since the lessons learnt from lymphoma management in the general population can be applied to the management of patients who develop PTLD.

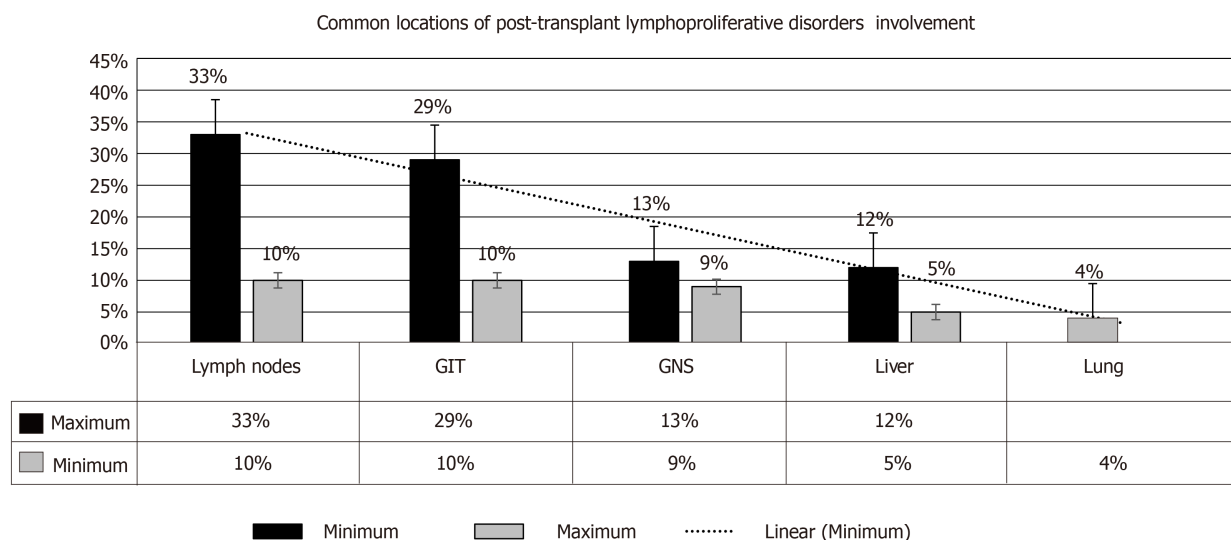


Figure 6 Common locations of post-transplant lymphoproliferative disorder involvement^[1]. GIT: Gastrointestinal tract; CNS: Central nervous system.

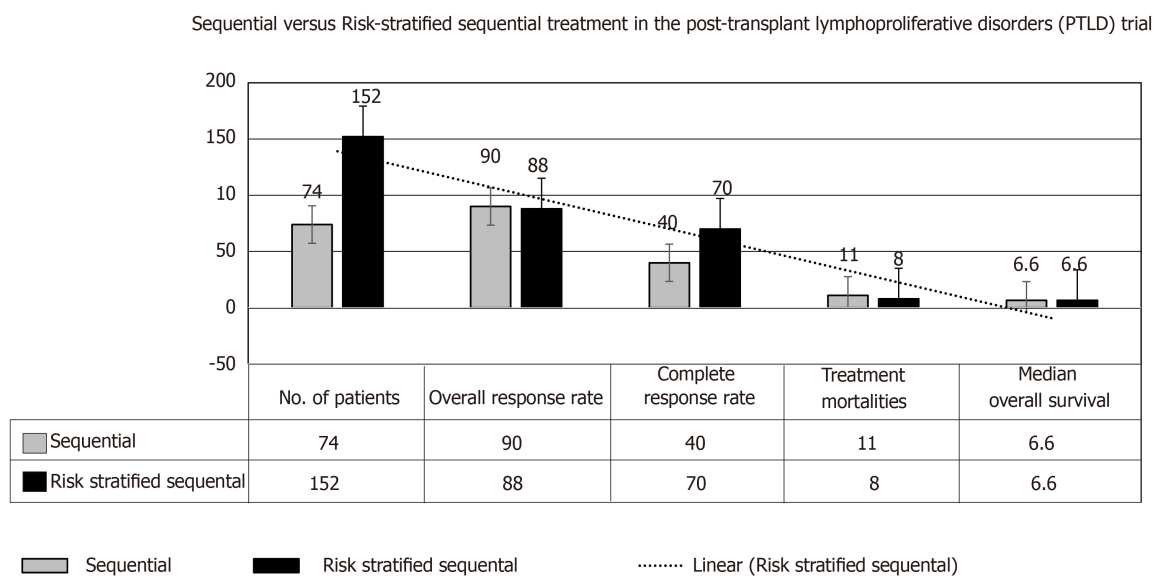


Figure 7 Development of rituximab-based treatment strategies for post-transplant lymphoproliferative disorders after solid organ transplantation: Sequential (2002-2008) vs risk-stratified sequential (2006-2014) treatment^[23,65].

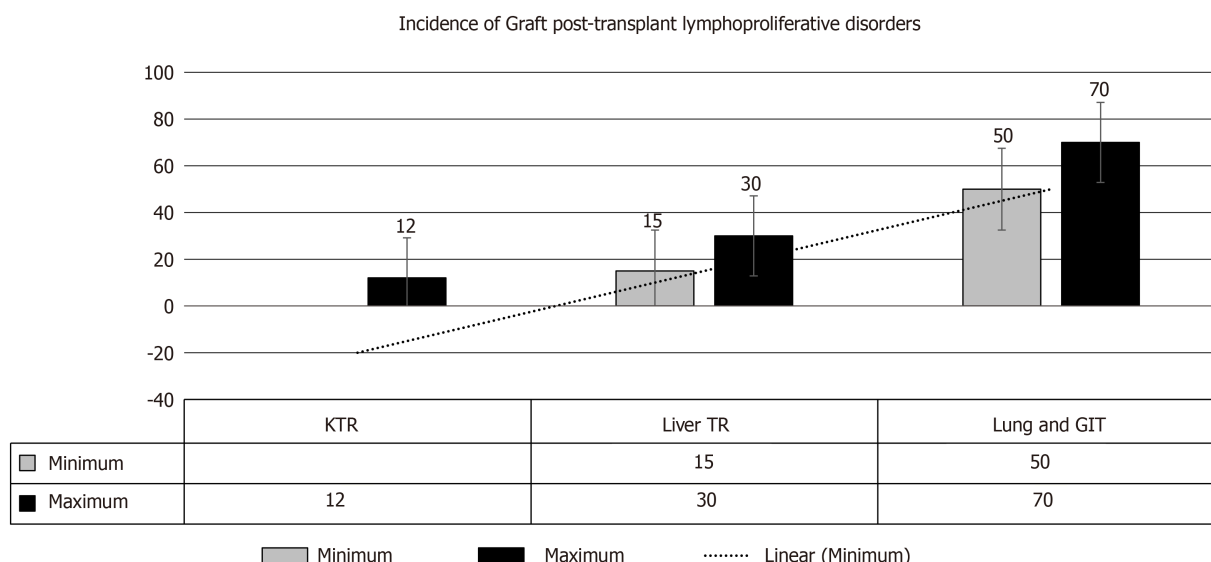


Figure 8 Incidence of graft post-transplant lymphoproliferative disorder involvement^[4,27]. KTR: Kidney transplant recipients; GIT: Gastrointestinal tract; TR: Transplant recipients.

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