Medical Oncology, vol. 24, no. 2, 125–136, 2007

1357-0560/(Online)1559-131X/07/24:125–136/$30.00

Review

The Management of Posttransplant Lymphoproliferative Disorder

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Abstract

Posttransplant lymphoproliferative disorder (PTLD) is a life-threatening complication of allogeneic hematopoietic stem cell and solid organ transplantation. Most cases are EBV-positive B-cell neoplasms, which occur in the setting of pharmacologically impaired cellular immunity. Several different treatment strategies including cytotoxic antitumor therapy, anti-B-cell monoclonal antibody therapy, antiviral therapy, and modalities aimed at restoration of EBV-specific cellular immunity have been employed. In addition, efforts to identify patients at high risk for PTLD have resulted in attempts at prophylactic and preemptive therapies. In this review we discuss the available literature on differing approaches to PTLD management, identify areas in need of further investigation, and, when possible, make general recommendations. Reduction of immunosuppression remains the mainstay of first-line treatment. Accumulating evidence supports the role of rituximab as second-line therapy with cytotoxic chemotherapy reserved for specific circumstances. Further investigations are needed to better define the role of more novel and less widely available therapies such as the adoptive transfer of EBV-specific T cells and optimization of antiviral therapies.

Key Words: PTLD, rituximab; transplantation; lymphoma; chemotherapy; EBV.

Introduction

The term posttransplant lymphoproliferative disorder (PTLD) is commonly applied to a group of heterogeneous and potentially life-threatening lymphoproliferative disorders arising in a pharmacologically immunocompromised host after solid organ or allogeneic stem cell transplantation. Pathologically, the World Health Organization has described PTLD as a spectrum of diseases that range from polyclonal EBV-driven lymphoid expansions to monomorphic lymphomas (Table 1) *(1).* Approximately 90% of cases are Epstein-Barr virus (EBV)–related CD20 positive B-cell neoplasms, which proliferate in an environment of impaired T cell immunity *(2,3).* PTLD tends to be of host origin for solid organ transplant recipients and donor origin for stem cell transplant recipients *(4).*

EBV belongs to the herpes virus family and latently infects over 90% of the world's adult population. Nearly all seropositive patients shed virus in the saliva and transmission occurs through contact with oral secretions. Primary infection usually occurs during childhood or adolescence and can be asymptomatic or associated with the more clinically apparent but usually benign mononucleosis syndrome *(5).* Primarily infected naïve B-cells undergo polyclonal expansion and can differentiate into memory B-cells, which establishes the compartment for latent infection. The host cellular immune response, as mediated by cytotoxic CD4 and CD8 positive T cells (CTLs), is critical to controlling

Received December 19, 2006; Accepted December 24, 2006
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Table 1
World Health Organization Classification of PTLD *(1)*

1. Early lesions
Reactive plasmacytic hyperplasia
2. Polymorphic PTLD
3. Monomorphic PTLD
B-cell neoplasms
Diffuse large B-cell lymphoma
Burkitt/Burkitt like-lymphoma
Plasma cell myeloma
Plasmacytoma like lesions
T-Cell neoplasms
Peripheral T-cell lymphoma
Other
4. Hodgkin-like PTLD

EBV-infected B-cell proliferation during both primary and latent infections *(6,7)*. An illustration of the vigorous T-cell response to EBV infection is the lymphocytosis, comprised of cytotoxic EBV-specific T cells, often seen with infectious mononucleosis *(8)*.

EBV has been implicated to play a causative role in several malignancies including Burkitt's lymphoma, nasopharyngeal carcinoma, Hodgkin's lymphoma, AIDS-related non-Hodgkins lymphoma, and certain T-cell lymphomas *(6,9,10)*. Its association with PTLD has been well established and is present in approx 90% of cases. In the pediatric population, PTLD usually arises as a result of primary EBV infection. This is in contrast to adults where it is often from reactivation of latent EBV infection.

Many risk factors for the development of PTLD after transplantation have been identified. High degrees of T-cell immunosuppression predict a higher likelihood for the development of PTLD in both the hematopoietic stem cell transplant (HSCT) and solid organ transplant populations *(11–13)*. The risk of developing PTLD is also greatest within the first year of transplant, when the degree of immune dysregulation is highest *(11,12)*. In solid organ transplant recipients, younger age and transplantation from an EBV+ donor to an EBV– recipient have also been shown to be predictive. Allograft type is also strongly correlated with the incidence of PTLD due to both the differing degrees of immunosuppression and extent of lymphoid tissue transplanted. The Collaborative Transplant Database was recently used to describe the risk of developing PTLD among nearly 200,000 kidney, pancreas, heart, lung, and heart–lung transplant recipients. Combination heart–lung transplant recipients were at the highest risk followed by (in decreasing order of risk) recipients of lung, heart, liver, pancreas, and kidney transplants *(12)*. An analysis of 3796 solid organ transplant patients at our institution identified PTLD in 1.3% of renal transplant recipients and 8.2% of lung transplant recipients *(14)*. Recipients of intestinal transplants are at extremely high risk of developing PTLD with incidence rates up to 30% reported *(15)*.

In this article we will review the different strategies available to treat or prevent PTLD (Table 2). The different therapeutic approaches discussed target different aspects of PTLD's pathogenesis. One method is aimed at restoration of EBV specific cellular immunity. This is the method employed by reduction in immunosuppression and newer methods that adoptively transfer autologous or allogeneic EBV-specific cytotoxic T cells to patients with PTLD. A second method of attack is to give antitumor therapy, which includes nonspecific cytotoxic chemotherapy and the more targeted anti-B-cell monoclonal antibody therapy, rituximab. A third method employs attempts to target the EBV viral genome with antiviral agents such as ganciclovir. Throughout this review we suggest a certain treatment approach but emphasize the importance of an individualized approach to care. Treatment considerations for an individual patient include degree of immunosuppression, type of allograft, personal risk of allograft rejection, tumor histology, EBV status of tumor, extent of PTLD, and rapidity of response time required of treatment.

Antiviral Agents

Acyclovir, valacyclovir, and ganciclovir are nucleoside analogs, which have been shown to inhibit the replication of EBV DNA through inhibition of viral DNA polymerase. Their activity is dependent on intracellular phosphorylation by virally encoded thymidine kinase. Cells latently infected with EBV and cells of EBV+ lymphomas do not express thymidine kinase, making them poor candidates for antiviral therapy. Not surprisingly, attempts to treat PTLD with these agents have proven ineffective. Recently, exciting results have

Table 2
Summary of Treatment Strategies for PTLD in HSCT and Solid Organ Transplant Recipients

Treatment Strategy	Comments
Antitumor	
Local therapy: surgical excision or radiation therapy	Very effective. Low toxicity. Limited to localized presentation of disease.
Rituximab	Very effective. Limited to CD20+ disease.
Systemic chemotherapy	Very effective. Rapid Response. Associated with high morbidity and mortality.
Anti IL-6 antibody	Moderately effective. Experimental.
Antiviral	
Antivirals	Ineffective to treat active PTLD. Possible prophylactic benefit for high-risk patients.
Acyclovir, Ganciclovir	
Arginine Butyrate + Ganciclovir	Moderately Effective. Experimental.
Restoration of Cellular Immunity	
Reduction of Immunosuppression	Very effective. Slow onset of action. Limited use for patients with highly aggressive disease and high risk rejection.
Interferon-α	Moderately effective. Associated with a high incidence of graft rejection and systemic side effects.
EBV-specific cytotoxic T cells (CTLs)	Effectiveness dependent on transplant and CTL type. Limited by availability and length of time to generate EBV-specific CTLs.

been obtained treating refractory EBV+ lymphomas and PTLD with concurrent arginine butyrate and ganciclovir. Arginine butyrate selectively induces expression of thymidine kinase, making latently infected B cells and EBV+ neoplasms vulnerable to antiviral treatment. In one study, of six patients with chemotherapy and radiation therapy refractory disease, five patients achieved a partial or complete response with combination ganciclovir and arginine butyrate *(16).* Further evaluation with this mode of therapy is ongoing.

The conventional antiviral agents discussed above do have activity in EBV+ cells undergoing lytic replication during primary EBV infection or EBV reactivation in the immunocompromised host. The ability to identify patients at high risk for developing PTLD has thus led many investigators to explore the role of prophylactic antiviral therapy *(17–23).* Several large retrospective analyses comparing outcomes for high-risk patients treated with prophylactic acyclovir or ganciclovir to historical controls have suggested a decrease in the incidence of PTLD. One study treated 198 solid organ transplant recipients with prophylactic ganciclovir or acyclovir and compared the incidence of PTLD with 179 institutional controls; 0.5% of patients in the antiviral group developed PTLD compared with 3.9% of controls ($p < 0.03$) *(18).* Another study reported outcomes for 206 kidney and liver transplant recipients who were prophylactically treated with high-dose ganciclovir followed by high-dose oral acyclovir. Only three patients (1.5%) developed PTLD compared with 8% of historical controls *(19).* Another center treated high-risk pediatric liver transplant patients (donor EBV+, recipient EBV–) with 100 d of intravenous ganciclovir. None of 18 patients developed PTLD compared with 10% of institutional controls *(22).* While suggestive, these studies should be interpreted with caution as they are all retrospective and compare the incidence of PTLD to unmatched institutional or historical controls. Prospective trials are needed to better define the role of antiviral prophylaxis in transplant recipients. Currently, prophylaxis in certain high-risk patients may be appropriate.

Reduction of Immunosuppression

When feasible, reduction of immunosuppression (RI) remains the most appropriate step in the initial

management of PTLD *(14,24).* The goal of treatment is to restore EBV-specific (and thus tumor-specific) cellular immunity without instituting graft rejection. The optimal method for RI is unclear and is dependent on certain patient characteristics such as allograft type, relative risk of allograft rejection, severity and extent of PTLD, and the immunosuppressive regimen. Many centers favor the reduction of calcinuerin inhibitors and steroids with the cessation of azathioprine or mycophenolate mofetil *(14,25,26).* Aggressive reduction in immunosuppressive medications can be performed in renal and liver transplant patients due to the ease of monitoring the patients for rejection, relatively lower risk for allograft rejection, and the patients' ability to tolerate rejection. Success has been reported with complete cessation of immunosuppression in liver transplant recipients with careful monitoring for evidence of graft rejection *(27).* Reduction of immunosuppression cannot be as aggressively pursued in heart and lung transplant patients due to the consequences of acute rejection and the difficulty in diagnosing early rejection. Regardless, careful monitoring of allograft function during RI is imperative.

Overall, RI is a very effective therapy with research efforts focused on identifying predictors of a poor response. A retrospective analysis of 42 PTLD patients at our institution treated with either RI alone or RI in conjunction with surgical excision of all the tumor showed a complete response rate of 74%. Multivariable analysis identified three factors predictive of poor response to RI including elevated LDH (lactate dehydrogenase), organ dysfunction, and multiorgan involvement of PTLD. Patients with no risk factors had an 89% chance of response, patients with one risk factor had a 60% chance of response, and patients with two or three of these risk factors had a 0% chance of response *(14).* Compared to other therapies, clinical response time to RI is slow with clinical improvement noted between 1.5 and 4 wk of initiation of therapy *(14,28).* Rare patients with aggressive disease may require concomitant cytotoxic chemotherapy *(29).* It has been purported that patients with late onset or EBV– disease have a poorer prognosis and are less likely to respond to RI alone *(30).* However, successful treatment of EBV– disease and late onset PTLD with RI alone has been reported *(14,31,32).* Prospective trials to optimize upfront treatment for patients at high risk for failing RI need to be performed. In the meantime we support upfront treatment with RI for most patients with PTLD especially those with low risk for allograft rejection, low LDH, no multiorgan PTLD involvement, and indolent disease. Frontline active therapy with other agents such as rituximab or systemic chemotherapy should be reserved for clinically aggressive disease or high relative risk of allograft rejection.

Local Therapy

Patients who present with localized disease are candidates for either surgical excision of their tumor or involved field radiation therapy. Overall this mode of therapy has been very successful when used in combination with reduction of immunosuppression or rituximab *(14,33–36).* When PTLD presents localized to a renal allograft, complete surgical excision of the affected allograft with complete cessation of immunosuppression is often performed. Many of these patients may undergo retransplantation with no recurrence of their PTLD *(37).* Localized radiation therapy is also appropriate for certain patients with more advanced disease who require emergent or palliative treatment to a particular area *(38).*

Systemic Chemotherapy

Systemic chemotherapy is commonly used to treat patients with PTLD who do not respond to or are ineligible for reduction in immunosuppression and whose disease is not amenable to local therapy. It is also used in conjunction with RI when a rapid response rate is required. In general, these cytotoxic regimens are effective and associated with a rapid response rate but at considerable cost. Owing to comorbid disease and chronic immunosuppression, high morbidity and mortality rates are observed in the PTLD population compared to the non-Hodgkin's lymphoma population treated with similar regimens *(33,39–41).* One retrospective analysis evaluated outcomes for 18 patients with late-onset PTLD who were treated with systemic chemotherapy either concurrently with RI or after failed RI. A response rate of 33% was observed and 50% of patients died from complications of chemotherapy related to end organ toxicity or infection *(33).* A

large retrospective review of the Israel Penn International Transplant Tumor Registry examined outcomes of 193 heterogeneous patients with PTLD who received various chemotherapeutic regimens. Overall mortality rates after treatment were high with many deaths attributed to chemotherapeutic toxicity. Five-year overall survival for recipients of RCHOP was 25%, which was similar to other combination chemotherapies employed. Recipients of single-agent chemotherapy had a statistically significant worsened 5-yr overall survival rate (5%) when compared to recipients of multiagent regimens although no adjustments were made for underlying functional status or other clinical factors *(41).*

Pilot studies have investigated the roles of reduced intensity chemotherapy with encouraging results *(42,43).* A recent multicenter study prospectively treated pediatric patients with PTLD who failed frontline treatment (RI, rituximab, local therapy, or interferon-α) with cyclophosphamide (600 mg/m^2 iv for 1 d) and prednisone (2mg/kg × 5 d) every 3 wk for six cycles. The overall response rate was 83%. Of note, none of the five patients with fulminant, disseminated disease achieved a response *(44).* Further investigations are needed comparing reduced-intensity chemotherapy regimens with conventional lymphoma regimens for patients who end up requiring cytotoxic therapy.

Owing to its high morbidity and mortality, we believe that initial treatment with systemic chemotherapy should be reserved for specific clinical situations only. These include rare cases of Burkitt's lymphoma–type PTLD, which are aggressive, require fast-acting therapy, and do not respond well to RI alone *(29).* Hodgkin's disease should also be considered for upfront chemotherapy due to the high cure rate with systemic chemotherapy and the relative low-intensity chemotherapy that is used. In addition, some authors have purported that delayed onset, advanced stage, monomorphic, EBV– PTLD should be treated with up front chemotherapy as well due to its poor prognosis and low response rate to RI *(30,31).* In general, however, the goal when approaching patients with PTLD should be to avoid systemic chemotherapy if possible in favor of other less toxic interventions such as a trial or reduction in immunosuppression or rituximab. Of note, patients with refractory disease after induction chemotherapy have been cured with salvage chemotherapy followed by autologous or allogeneic stem cell transplantation *(45–48).*

Cytokine Therapy

Owing to its immunomodulatory and antiviral activities, interferon-α has been used successfully to treat PTLD. Unfortunately, this mode of therapy is also associated with a significant degree of graft rejection owing to its nonspecific stimulation of T cells *(49,50).* Interleukin-6 (IL-6) is a multifunctional cytokine that plays a role in the growth and maturation of B cells. It has also been shown to promote growth of EBV-infected cells and high levels of IL-6 have been found in patients with PTLD *(51,52).* One study prospectively treated 12 patients with PTLD who failed RI with anti-IL-6 antibody. 8/12 patients achieved a partial or complete response with no increased incidence of graft rejection *(53).* Further studies using anti- IL-6 antibodies are anticipated.

Rituximab

Rituximab is a chimeric IgG monoclonal antibody which is specific to the CD20 surface protein on mature B cells. Evidence suggests that it mediates cell death in several ways including the direct stimulation of apoptosis, the targeting of CD20+ cells for destruction through complement fixation, and recruitment of cytotoxic effector cells *(54–56).* Rituximab's safety and efficacy as monotherapy and in combination with systemic chemotherapy to treat CD20+ B-cell non-Hodgkin's lymphomas has been well established *(57–61).* Recently, 399 elderly patients with diffuse large B-cell lymphoma were randomized to receive RCHOP versus CHOP alone. At 5 years of follow up 47% of patients in RCHOP arm and 28% of patients in the CHOP alone arm were alive without disease ($p = 0.0037$) *(59).* While not curative, good overall response rates (72%) have been observed for rituximab as a monotherapy for low-grade follicular lymphomas.

Rituximab has also been shown to be an effective and safe addition to the armamentarium of agents to treat PTLD. Large case series and phase II clinical trials assessing efficacy of single-agent rituximab after failure of RI report overall response rates of 44–75% and complete response rates of 35–69%

(36,62–64). Clinical response as manifested by reduction in tumor size is typically seen within days of initiation of therapy although delayed responses have been reported. A large retrospective French study identified 30 patients with PTLD who were treated with rituximab after reduction of immunosuppression. In this study the median age of patients analyzed was 34 (range 6–67) and the median time to diagnosis of PTLD after transplant was 5 mo (range 1–156). Overall response rates were 69% and even higher (83%) in the subset of patients eight who received HSCT. Overall complete response rates were 60%. Of 10 patients who progressed through rituximab, 50% were salvaged with systemic chemotherapy *(63).* One recently published phase II study prospectively treated 46 adults and children with PTLD who failed RI with rituximab 375mg/m^2 weekly for 4 wk; 43 of these patients were analyzed at 80 days of follow up, with a 44% response rate and 35% complete response rate *(62).* Of note, this study reports lower response rates than other published reports, perhaps due to the fact that 65% of patients enrolled had delayed onset PTLD, which is known to have a poorer prognosis. Rituximab has also been used successfully for preemptive treatment of PTLD *(65,66).* One study treated 17 patients who were at high risk of developing PTLD after HSCT (as demonstrated by high EBV viral load indicative of EBV reactivation) with a one time infusion of rituximab. Only two of these patients (18%) developed PTLD compared with 48% of historical controls in this high-risk group. Of interest, EBV viral load became undetectable in the patients who did not develop PTLD *(66).* Rituximab has also been successful in treatment of patients who failed systemic chemotherapy *(63)* and as an adjunct to systemic chemotherapy *(42).* No randomized trials have compared rituximab alone to rituximab plus systemic chemotherapy for patients who fail reduction of immunosuppression. Retrospective analysis suggest similar response rates with less toxicity and improved overall survival for recipients of rituximab *(36,67,68).*

As a B-cell directed therapy concern has been raised about rituximab's potential infectious complications after long-term use especially in a posttransplant population on other chronic immunosuppressive therapies. To date over 500,000 people have been treated with this agent and only rare cases of serious infectious complications (all viral) have been reported *(69).* These include reactivation of hepatitis B infection (resulting in fulminate hepatic failure), parvo B19 infection (resulting in pure red cell aplasia), and disseminated CMV (in a patient with PTLD on concurrent immunosuppressive medication) *(70–72).* An interesting observation is that unlike the treatment of non-Hodgkin's lymphomas, monotherapy of PTLD with rituximab has been shown to be curative. It has been postulated that rituximab may be particular efficacious in treating PTLD by paradoxically enhancing cellular immunity directed at EBV+ PTLD cells through the cytotoxic cell recruitment mechanisms discussed above *(25).* However, a recent report to test this hypothesis found no improvement in the degree of EBV-specific T-cell immunocompetence in patients treated with rituximab who experienced a clinical response and reduction in EBV viral load *(73).*

Owing to rituximab's efficacy, low-side-effect profile, and rapid-treatment effect, we recommend its use for the treatment of CD20+ PTLD that does not initially respond to reduction of immunosuppression. It is also an appropriate first-line treatment choice for patients in whom reduction of immunosuppression is not appropriate. In cases where it is deemed clinically appropriate to treat initially with systemic chemotherapy (such as a delayed onset aggressive or EBV– PTLD), rituximab should be used as adjunctive therapy *(61).* Rituximab should be the subject of focused, prospective, randomized clinical trials to better define its role as preemptive therapy and as second-line treatment compared with systemic chemotherapy for PTLD that fails RI.

Cellular Immunotherapy

An attractive treatment strategy for EBV+ PTLD is restoration of EBV-specific cellular immunity through the adoptive transfer of EBV-specific CTLs. This new modality of therapy has successfully been used to approach PTLD arising in both solid organ and hematopoietic stem cell transplantations. Attempts to restore EBV-specific cellular immunity have involved the transfer of non-selected allogeneic and autologous CTLs (which contain EBV-specific T cells as part of their pooled

lymphocytes) and the infusion of selected EBV-specific T cells. Overall this is a promising area of investigation with the infusion of selected EBV-specific T cells associated with improved efficacy, less side effects [graft-vs-host disease (GVHD) and graft rejection] but also decreased availability and prolonged processing time compared to nonselected CTL infusions.

HSCT Population

Cytotoxic T-cell therapy (in the nonselected form) was first used to treat PTLD occurring in the allogeneic HSCT population *(74,75).* In one reported series, 18 patients who acquired PTLD after HSCT received donor lymphocyte infusion (DLI) from their original donors. Fifty-four percent of patients achieved a complete remission but 62% of patients also experienced acute or chronic GVHD *(75).* Subsequently, EBV-specific cytotoxic T-cell therapy has been used by several investigators to maximize PTLD-directed therapy while minimizing the incidence of GVHD due to the presence of other alloreactive T cells. Rooney and colleagues reported their experience in which 39 patients at high risk of developing PTLD after HSCT received prophylactic EBV-specific cytotoxic T-cell infusions. Because PTLDs in HSCT recipients are of donor origin, EBV-transformed B cells generated from the donor are antigenically identical to the malignant cells in the host making them an effective antigen-presenting cell for generation of EBV-specific cytotoxic T cells (also of donor origin). In this study none of the 39 patients developed PTLD, compared to 12% of institutional controls in this high risk population. Also of significance, all 6 patients with high EBV viral loads prior to therapy experienced 2-4 log reductions in their viral load 2-3 weeks after therapy. Of significance, none of the patients experienced increased GVHD after infusion *(76).* The same authors also reported their experience with six patients who did not receive prophylaxis who went on to develop PTLD and received EBV-specific cytotoxic T cell therapy. Five of the six patients achieved complete remissions. The patient who did not respond had a tumor that had been transformed with a virus whose genome contained deletions of epitopes for which the donor CTLs were directed *(77,78).*

Solid Organ Transplant Population

The success of EBV-specific cytotoxic therapy to treat PTLD in the HSCT population has led several investigators to examine the potential role of this mode of therapy in the treatment of PTLD in solid-organ-transplantation recipients. Because PTLD arising in the solid-organ-transplantation setting is usually of host origin and donors are often not HLA matched or available, cytotoxic T cells of donor origin are of limited utility as they are unlikely to survive in the host and are unlikely to recognize tumor cells of host origin *(4).* Options for the source of T cells for manipulation and adoptive transfer of EBV-specific cellular immunity therefore include autologous T cells from the host or allogeneic T cells from an HLA matched donor.

One group infused autologous lymphocytes (nonselected) after culturing them with IL-2 into seven patients with PTLD. Four of four patients with EBV+ tumors experienced complete remissions but two developed graft rejection. Interestingly, the three patients with EBV– tumors had no response *(79).* Many investigators have explored the role of autologous EBV-specific CTLs to prevent or treat PTLD in recipients of solid organ transplantation *(79–85).* Overall this method is safe (no increased incidence of graft rejection) and effective with reduction in tumor size and EBV viral load. One group examined the role of preemptive therapy with autologous EBV-specific CTLs in patients with high EBV viral loads posttransplant. Of seven patients treated, five experienced a significant reduction in their EBV viral load, and none developed PTLD *(80).* Case reports have shown dramatic PTLD regression and EBV viral load reduction after EBV-specific autologous CTL infusions *(83,84).* The safety and feasibility of using autologous EBV-specific T cells in conjunction with conventional chemotherapy has been shown as well *(81).* Thus far, the use of autologously derived EBV-specific CTLs have depended on patients to be EBV seropositive. Patients who are EBV seronegative are, unfortunately, at high risk for developing PTLD and efforts to generate EBV-specific CTLs from this group are underway *(85,86).*

Some investigators have evaluated the role of allogeneic T-cell infusions from HLA identical donors to treat PTLD in solid-organ-transplant recipients *(87–89).* The University of Miami

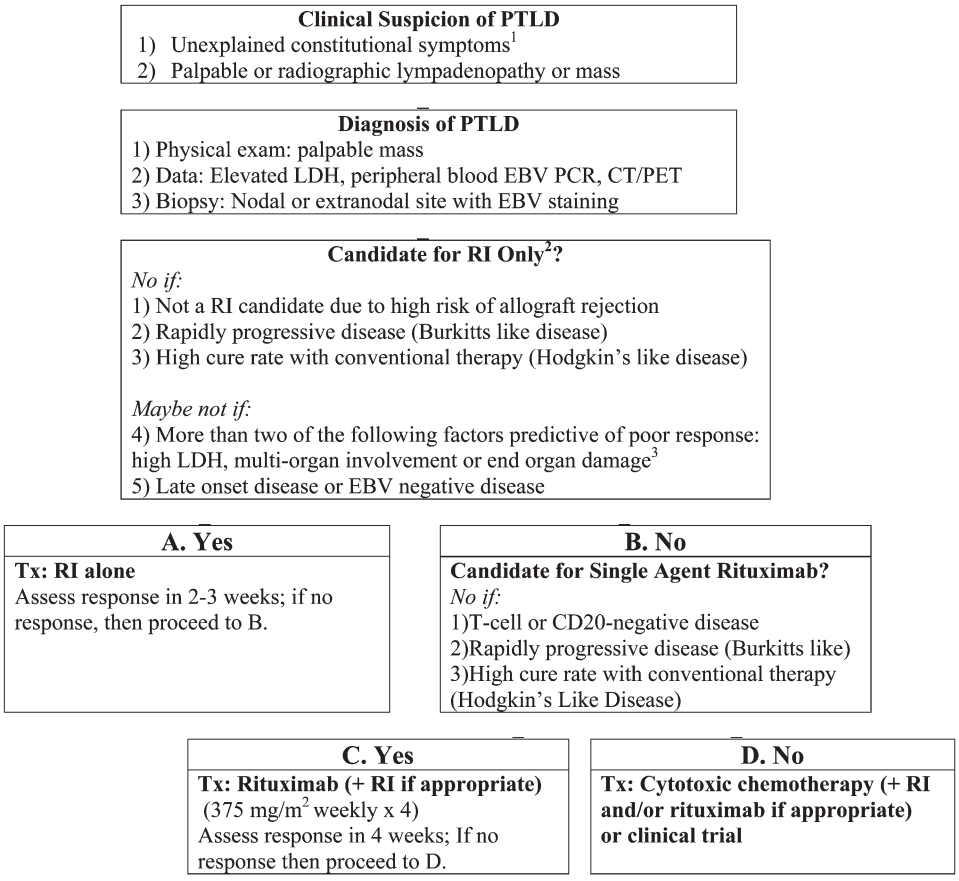
reports their experience with 568 liver transplant patients, 164 who received subsequent infusion of donor bone marrow cells as part of an institutional protocol to decrease the side effects of immunosuppressive therapy. While not achieving statistical significance, they noted that none of these 164 patients developed PTLD compared with 5 of 394 patients who did not receive subsequent donor bone marrow infusions *(90)*. One case report describes a child who developed PTLD in his central nervous system after an HLA mismatched cadaveric lung transplantation and received DLI (nonselected) from an EBV+ HLA identical sibling. The patient achieved a prolonged complete remission but experienced episodes of graft rejection *(89)*. To avoid complications of graft rejection, some investigators have explored the role of allogeneic EBV-specific CTLs *(87,88)*. Haque and colleagues have established a bank of approx 100 EBV-specific T cell lines of known HLA type generated from EBV+ donors. They report their experience with eight patients who had refractory PTLD after solid organ transplantation who received EBV specific CTL infusions from the best HLA-matched cell line available from the bank. Of the five patients who completed therapy three had a response and none witnessed graft rejection or GVHD *(87,91)*. The establishment of such a bank makes this line of therapy more feasible for general use.

Conclusions

The heterogeneity in pathologic and clinical presentations of PTLD makes it difficult to recommend a general treatment paradigm (Fig. 1). Several factors including allograft type, relative risk of allograft rejection, comorbid disease, extent of PLTD, EBV status of tumor, and desired clinical response time affect treatment decisions. Ideally the chosen treatment strategy should optimize antitumor activity while minimizing systemic toxicity and allograft rejection. In general, RI remains the appropriate first-line treatment for most patients with PTLD with the following exceptions. Patients with very aggressive Burkitt's-like disease who require a rapid response time of treatment and are at high risk of RI failure and those with Hodgkin's disease, which has a very high cure rate with chemotherapy, should be treated with upfront systemic chemotherapy (and rituximab if CD20+) in addition to RI. RI may also not be appropriate for patients with a high relative risk of graft rejection and they may require upfront treatment with rituximab or chemotherapy depending on other clinical factors. Prospective trials to evaluate to role of adding rituximab or systemic chemotherapy to RI for upfront therapy in certain populations at high risk for failing RI are needed.

It is a subject of great debate how to best approach a patient who fails or is not eligible for RI. Patients who present with localized disease should be treated with localized therapy. While no randomized trials comparing rituximab to systemic chemotherapy for patients with more disseminated disease who fail RI have been performed, the body of evidence to date suggests rituximab is similarly effective and potentially less toxic than chemotherapy *(36)*. Also of importance, patients who fail rituximab remain candidates for cytotoxic therapy. For these reasons we recommend rituximab as second-line therapy for patients with CD20+ lymphomas who fail RI. Patients who are CD20 negative or who fail rituximab should then be considered for systemic chemotherapy. Further prospective trials comparing conventional chemotherapy regimens to less aggressive regimens are needed.

It remains to be seen how other emerging prophylactic and treatment strategies will be incorporated into the PTLD prevention and treatment paradigm. Prophylactic antiviral therapy may be appropriate for certain high-risk groups although prospective randomized trials are needed to better define these groups. EBV viral load monitoring with preemptive therapy (rituximab, RI, CTLs) is a reasonable approach for high-risk populations as well. Novel therapies for treatment of PTLD such as combination arginine butyrate with ganciclovir and anti-IL6 antibodies are promising and need further investigation. The adoptive transfer of EBV-specific CTLs has proven to be an effective therapy although it remains to be seen whether the wide spread application of this therapy will be practical and cost effective. The number of treatment options for PTLD is large and continues to grow. Organizing and optimizing these treatments for the individual transplant patient remains a challenge.



1 Weight loss, anorexia, malaise, pain, fever, fatigue, & gastrointestinal complaints.
2 For local disease: RI plus local therapy (surgery/radiation) if appropriate
For CNS involvement: Radiation therapy in addition to other therapy.
3 Tsai DE, Hardy CL, Tomaszewski JE, et al. Reduction in immunosuppression as initial therapy for posttransplant lymphoproliferative disorder: analysis of prognostic variables and long-term follow-up of 42 adult patients. Transplantation 2001; 71:1076-1088.

Fig. 1. Treatment algorithm for multifocal PTLD in solid-organ-transplant recipients.

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