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COMPREHENSIVE REVIEW

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The IPTA Nashville consensus conference on post-transplant lymphoproliferative disorders after solid organ transplantation in children: IV-consensus guidelines for the management of post-transplant lymphoproliferative disorders in children and adolescents

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Abstract

The International Pediatric Transplant Association convened an expert consensus conference to assess current evidence and develop recommendations for various aspects of care relating to post-transplant lymphoproliferative disorders (PTLD) after pediatric solid organ transplantation. This report addresses the outcomes of deliberations by the PTLD Management Working Group. A strong recommendation was made for reduction in immunosuppression as the first step in management. Similarly, strong recommendations were made for the use of the anti-CD20 monoclonal antibody (rituximab) as was the case for chemotherapy in selected scenarios. In some scenarios, there is uncoupling of the strength of the recommendations from the available evidence in situations where such evidence is lacking but collective clinical experiences drive decision-making. Of note, there are no large, randomized phase III trials of any treatment for PTLD in the pediatric age group. Current gaps and future research priorities are highlighted.

Abbreviations: CMV, cytomegalovirus; CNS, central nervous system; COP, cyclophosphamide, vincristine, prednisone; CR, complete response; CSA, cyclosporine; CTL, cytotoxic T lymphocyte; DLBCL-type, diffuse large B cell lymphoma type; EBV, Epstein–Barr virus; FDG, fluorodeoxyglucose; HLA, human leukocyte antigen; HSCT, hematopoietic stem cell transplant; IC50, half maximal inhibitory concentration; IFN, interferon; IgM, immunoglobulin M; IL, interleukin; IPTA, International Pediatric Transplant Association; IS, immunosuppression; IVIG, intravenous immunoglobulin; LMP-TC, latent-membrane-protein-specific T-cells; mTOR, mammalian target of rapamycin; NHL, non-Hodgkin lymphoma; NK, natural killer; OEPA, vincristine, etoposide, prednisone, and doxorubicin; OPPA, vincristine, procarbazine, prednisone, and doxorubicin; PD-(L)1, programmed death-ligand 1; PD-1, programmed cell death protein 1; PI3K, phosphoinositide 3-kinase; PR, partial response; PTLD, post-transplant lymphoproliferative disorder; R-CHOP, rituximab, cyclophosphamide, vincristine, doxorubicin, prednisone; RIS, reduction of immunosuppression; SOT, solid organ transplant; TRM, treatment-related mortality; VST, virus-specific T-cell.

For affiliations refer to page 14.

KEYWORDS
child, Epstein–Barr virus, management, PTLD, solid organ transplantation

1 | INTRODUCTION

Pediatric patients are typically at greater risk of developing post-transplant lymphoproliferative disorder (PTLD) because they are proportionately more likely to acquire primary Epstein–Barr virus (EBV) infection after transplantation. In this regard, the major risk factor for PTLD is primary EBV infection due largely to the absence of immunity derived from EBV-specific T lymphocytes. While different strategies for prevention have been proposed, they have variable effectiveness and so no single strategy has emerged to be associated with a high degree of effectiveness. Consequently, cases of EBV-driven PTLD will inevitably occur, necessitating varying approaches to management based on histopathologic characteristics of lesions, their location, and other factors. This report addresses consensus recommendations and research gaps that relate to the management of PTLD in children in the setting of solid organ transplantation. Reference is made to hematopoietic stem cell transplantation, where appropriate.

2 | METHODS

The methodological approach used to develop these consensus guidelines is described in detail in a separate publication of the Journal.[1] The goal was to produce evidence-based consensus guidelines on: (1) Definitions, Diagnosis, and Diagnostic Evaluation of Pediatric PTLD; (2) Prevention of Pediatric PTLD; (3) Management of Pediatric PTLD; and (4) Viral Load and Other Biomarker Assays in Pediatric PTLD; all based on a critical review of the literature and consensus of experts. The consensus conference included 29 international experts in organ transplantation and PTLD from the fields of hepatology, nephrology, cardiology, pulmonology, infectious diseases, immunology, hematology-oncology, surgery, virology, immunology, pathology, and clinical epidemiology. The Working Groups were supported by experts in systematic reviews from the Vanderbilt University Medical Center's Center for Knowledge Management (https://ckm.vumc.org/ckm/).

Prior to the conference, each writing group discussed goals, drafted key questions to be addressed by their group, and commenced literature reviews. The key questions to be addressed were discussed at the conference and further refined by consensus. After the conference, each writing group met via teleconference on multiple occasions. The first task was to finalize the structured literature search terms for each of their key questions with the assistance of the experts from the VUMC Center for Knowledge Management. Expert search strategies were defined for each of the key question subtopics by an information scientist and executed in MEDLINE® via the PubMed® interface. Each writing group's co-chairs, in consultation with their group's members, then finalized the list of articles for detailed data extraction and review.

Writing groups were provided with the Grading of Recommendations, Assessments, Development and Evaluation (GRADE) guidelines for classification of the direction and strength of their recommendations.[2–5] The groups were instructed to classify each of their recommendations as either "strong" or "weak" and the quality of evidence as high, moderate, low, or very low based on the GRADE system recommendations, which rates evidence quality across the body of evidence for an outcome rather than each study as a single unit.[2–5]

Final approval of each recommendation was provided by both the PTLD Management Working Group and all members of the full Consensus Conference. The final manuscripts reporting recommendations of the Consensus Conference were reviewed and approved in sequence by all working group members, all participating members of the Conference, and finally by the IPTA Board.

The PTLD management group addressed recommendations that relate to the effectiveness of specific treatment modalities, (reduction of immunosuppression [RIS], surgical resection/local irradiation, antiviral agents, immune globulin, monoclonal B cell antibody therapy [anti-CD20], cytotoxic chemotherapy, adoptive immunotherapy, immunomodulatory/anti-cytokine therapy), in addition to other specific scenarios in clinical practice.

3 | RESULTS/CONSENSUS OUTCOMES

3.1 | Recommendations relating to the efficacy of specific treatment modalities

3.1.1 | Question 1: What is the evidence for the efficacy of reduction of immunosuppression in the management of PTLD and when might withdrawal of immunosuppression be considered?

Recommendations

- We recommend RIS at the time of PTLD diagnosis, to as great a degree as possible, according to the risk of graft rejection and loss, as well as to the consequences of graft loss.

Evidence Grade: Strong recommendation/moderate-quality evidence.

- Complete withdrawal of IS may be feasible in select patients considered to have low rejection risk, principally after liver transplantation. Very close monitoring for rebound acute rejection is required.

Evidence Grade: Strong recommendation/low-quality evidence.

- Wherever feasible, we recommend considering temporarily stopping the administration of immunosuppressive agents in cases of PTLD that are not responsive to initial reduction in IS treatment (especially after liver and kidney transplantation), or which require chemotherapy.

Evidence Grade: Weak recommendation/low-quality evidence.

Supporting evidence

It is difficult to truly assess the effectiveness of withdrawal of immunosuppression as it is often combined with other treatment modalities. This excludes corticosteroids, which are usually continued. Transient withdrawal or reduction of immunosuppression should be interpreted in relation to the associated drug levels. It must be appreciated that the immunosuppressive effects of drugs might persist for several weeks beyond cessation of use, especially when PTLD is associated with significant liver dysfunction. While no firm recommendations can be made regarding how long RIS should be employed before moving to additional treatment in the sequential management of PTLD, most panel members felt that for heart, heart-lung, lung, intestinal, or kidney-intestinal transplants, it would be appropriate to delay subsequent treatment for no more than 6 weeks unless the clinical course dictated otherwise. For kidney and liver transplants, periods of reduced immunosuppression of up to 8–9 weeks or more were considered reasonable depending on the initial response to RIS. These guidelines are considered appropriate irrespective of EBV status, although it is acknowledged that most of the pediatric literature relates to EBV-driven PTLD.

The efficacy of RIS for PTLD management was first described in 1984 in 17 solid organ transplant (SOT) adult patients (eight kidney transplants, four liver, three heart, and two heart-lung) with outcome assessment at 2–68 months after transplantation.[6] Immunosuppression (IS) beyond steroid reduction was unchanged in four patients, and all died. RIS was the only treatment in 10 patients with a survival of 80% and four episodes of acute rejection. Chemotherapy with/without radiation was received by four patients (one of whom had no RIS) with one death in the patient with no concomitant reduction in immunosuppression. The first large pediatric report described 36 children with PTLD following liver transplantation.[7] All received anti-viral therapy (ganciclovir, acyclovir, or both); 3 had RIS and immunosuppression was stopped in 33. Interferon and/or chemotherapy were added in six patients and three underwent surgery. PTLD-related survival was 86%, 23 developed acute rejection after a median of 24 days; follow-up identified two patients with chronic rejection, one re-transplantation, and 2 PTLD relapses. Of the 33 patients with cessation of IS, tacrolimus was restarted as monotherapy in 14, and with corticosteroids in 8. Six children remained off IS.

RIS is the first step of treatment in most patients with PTLD in most centers.[8–21] Interestingly, the rate of rejection or graft loss is lower when compared to early reports. Overall survival is often good,[7] but death due to progressive PTLD and acute and chronic graft loss continue to occur.[8] In more recent series, the addition of rituximab is more frequently employed. Despite the frequency of RIS as first-line treatment, it remains difficult to estimate the true efficacy of this approach due to the lack of controlled trials comparing this approach to other treatments and due to the concomitant use of other therapies in many series (eg, antivirals). It should also be noted that there are rare cases in which allograft rejection may be seen concomitantly with active PTLD (mostly in the setting of intestinal transplantation). Active acute rejection is an impediment to reduction or cessation of IS in the initial management of PTLD, and other therapies such as rituximab may be important to consider in this setting.

Of note, establishment of EBV-specific T-cell immunocompetence, likely achieved through reduction or withdrawal of immune suppression, is likely essential for the long-term control of EBV-mediated PTLD. Treatment with rituximab alone has been shown to potentially "cure" PTLD, but it does not always improve the EBV-specific cellular immune response[22]; in contrast, improvement of EBV-specific cellular immunity has been reported after combination of RIS and rituximab.[23] Therefore, some level of RIS is probably necessary to achieve this goal, even if associated with other treatments.

In some specific presentations of PTLD, RIS in addition to surgery showed excellent results. In a prospective follow-up of 77 children following liver transplantation, eight developed "early" PTLD (ie, non-destructive PTLD in current classification). Seven had acute tonsillitis, and 1 had a pharyngo-laryngeal localization.[24] All patients underwent RIS, with surgery for the seven children with tonsillitis. All patients were "cured," and no deaths nor rejections were observed. Non-destructive PTLD, mostly involving tonsils/adenoids, were also described in 11 children after SOT,[25] all of whom underwent surgery, with no further treatment in 4 and RIS in 4. The precise treatment of the three remaining patients was not known and the authors reported 100% survival with no rejection.

The complete withdrawal of immunosuppression is not often reported and was associated with a high rate of rejection in the first reports.[26] However, this was proposed as the first-line treatment for PTLD after liver transplantation in children, where IS was withdrawn in 19 PTLD patients and 19 EBV disease patients, with mortality rates of 31.6% among those with PTLD and 6% among those with EBV disease.[26] In those surviving, six remained off IS. IS was restarted in 21 for acute rejection, with only one patient evolving to chronic rejection and re-transplantation. This option should also be discussed in cases of treatment failure in other SOT patients. When multi-agent chemotherapy was needed, withdrawal of IS avoided cumulative side effects without graft rejection in three children following liver transplant and in three pediatric kidney recipients.[27,28] Careful follow-up of graft function remains mandatory, especially when chemotherapy is administered in association with withdrawal of immunosuppression. While acute rejection is rare during chemotherapy, acute rejection can occasionally be seen

on treatment, and restoration of immune competence leading to acute rejection may develop shortly after cessation of chemotherapy. In general, physicians are more reluctant to withdraw IS following heart or lung transplantation due to the risk of sudden death with acute severe rejection in the former (and the absence of simple graft monitoring strategies) and the highly immunogenic nature of the lung allograft.

Research priorities for knowledge gaps

- Develop a large prospective, multi-center, international registry that includes all PTLD cases occurring after SOT in children, aiming to better determine optimal treatment of PTLD based on patient and PTLD characteristics. This should include development of an international repository of PTLD tissue.
- Development of simple, clinically applicable, biomarkers for serial assessment of alloimmune responses and immune responses against EBV/PTLD to help define optimal strategies for reduction/withdrawal of immunosuppression to optimize PTLD responses while maximally protecting the allograft.
- Define which patients can be managed long-term with CNI-free immunosuppression or complete withdrawal of immunosuppression after successful treatment of PTLD.

3.1.2 | Question 2: What is the role of surgery and radiotherapy in the management of patients with PTLD?

Recommendations

Surgery.

- Emergency surgery is recommended and required for select local complications (such as uncontrolled gastrointestinal hemorrhage, perforation, and bowel obstruction) of PTLD.

  Evidence Grade: Strong recommendation/low-quality evidence.

- Surgery is recommended when it is potentially curative (eg, complete excision biopsy of tonsils/adenoids, lingular tonsil PTLD, and isolated skin lesion(s)). Of note, some reduction in immunosuppression is generally also used.

  Evidence Grade: Strong recommendation/low-quality evidence.

- Surgical allograft removal (kidney or isolated intestinal transplant) may be considered in rare circumstances in which other treatment modalities for PTLD have failed or are contraindicated.

  Evidence Grade: Weak recommendation/low-quality evidence.

Radiotherapy.

- Radiotherapy may be part of the management plan in certain cases of PTLD. The indications for radiotherapy are driven by the location of specific lesions and is most commonly used in CNS disease.

  Evidence Grade: Weak recommendation/Very low-quality evidence.

Supporting evidence

Evidence from controlled trials confirming the role of surgery in the treatment of PTLD is lacking and is limited to case series and database registries.[29,30] At present, the role of surgery is defined by the clinical situation. For example, surgery might be needed because the patient presented with an acute surgical emergency such as acute hemorrhage, perforation, or obstruction. In other situations, surgery might be potentially curative when coupled with reduced immunosuppression (eg, tonsillar/adenoidal disease, lingular tonsil mass, isolated skin lesion(s)). Although it may be tempting to rely solely on surgical resection in the setting of isolated disease, the presence of PTLD infers impaired host CTL (and other) immune responses, and some degree of temporary reduction in immunosuppression is generally considered important for achieving durable complete responses. In kidney transplant recipients with PTLD confined to the graft, survival analyses from one study indicated that nephrectomy was associated with better outcomes compared with when graft removal was not done ($p = .03$).[30] However, there was no survival benefit in those patients who underwent allograft nephrectomy compared to those who did not when there was PTLD involvement of three or more sites. However, with an increasing armamentarium of treatment options, it is now generally considered appropriate to preserve the allograft whenever possible, given the many implications of graft loss in childhood. Graft nephrectomy seems appropriate when PTLD is not responsive to other therapies such as rituximab or low-dose chemotherapy. Similar considerations may apply to PTLD in isolated intestinal allografts.

The use of radiotherapy is influenced by the clinical scenario and no firm all-encompassing recommendations can be made. Radiotherapy is usually not part of first-line therapy but restricted to relapsed or refractory disease, special locations (eg, central nervous system [CNS]), or contraindications to other treatment modalities. Radioimmunotherapy may also play an occasional role in the management of refractory PTLD.[31]

Research priorities for knowledge gaps

- Further research is required to define when, if ever, allograft removal is required in the current era.
- The role of radiotherapy, particularly in relation to CNS lesions, requires further elucidation.

3.1.3 | Question 3: Should antiviral agents, with or without immunoglobulin, be employed as adjunctive treatment of PTLD?

Recommendations

- Anti-viral agents and/or IVIG should not be used in the management of PTLD in the absence of other interventions (ie, RIS,

rituximab and chemotherapy). There are insufficient data to recommend for or against their use as adjunctive therapy.

Evidence Grade: Strong recommendation/low-quality evidence.

Supporting evidence

Evidence addressing the role of antiviral agents and/or IVIG is lacking from controlled trials in organ transplant patients. Although frequently utilized, there is no definitive evidence to support the use of antiviral agents in the treatment of PTLD. Acyclovir and ganciclovir have been used in the management of non-destructive PTLD, alone or in combination with immune globulin and variable degrees of adjustments in the level of immunosuppression.[29,32] In such situations, the agent of choice is ganciclovir, since in vitro, it is several times more active against EBV than acyclovir,[33] with half maximal inhibitory concentration (IC50) values of 1–1.5 μM[34,35] compared with 4–10 μM for acyclovir.[36,37]

The above antiviral agents are only effective against the lytic phase of viral activity. However, although latent viral infection predominates in PTLD lesions, lytic virus genes and protein expression are also seen in a substantial proportion of cases,[38,39] particularly among those with an immunoglobulin M (IgM)+ phenotype.[40] Arginine butyrate, a histone deacetylase inhibitor induces the lytic cycle of EBV, making EBV-infected cells sensitive to ganciclovir. A Phase I/II trial of arginine butyrate combined with ganciclovir demonstrated an overall response in 10 of 15 patients with EBV+ lymphoid malignancies; one third had PTLD.[41] There are no other data to recommend the use of this agent, which in any event is no longer available for use in clinical settings. Another chemotherapeutic agent, the proteosome inhibitor bortezomib, also induces lytic virus replication in EBV-infected cells and is being evaluated in clinical trials of gamma-herpesvirus-associated malignancies including PTLD.[42]

As is the case with antiviral agents, immunoglobulin therapy has not been the subject of controlled trials as treatment of PTLD. While data from prophylaxis cannot necessarily be extrapolated to treatment, it should be noted that two prospective randomized placebo-controlled trials in EBV seronegative patients evaluating cytomegalovirus-intravenous immunoglobulin (CMV-IVIG) alone[43] or IVIG in recipients already receiving ganciclovir[44] failed to observe an effect on either EBV disease, PTLD rates, or EBV viral load kinetics.

Research priorities for knowledge gaps

- Studies evaluating the potential role of de-methylating agents coupled with antiviral agents in the treatment of PTLD.

3.1.4 | Question 4: When should monoclonal B-cell antibody therapy (typically anti-CD20) be used for the treatment of PTLD and what is the preferred regimen?

Recommendations

- Children with CD20+ B-cell PTLD who do not respond to the reduction of immunosuppression should receive 3–4 weekly doses of rituximab (375 mg/m^2).
- If a partial response (PR) is achieved, additional rituximab (3–4 doses) should be given with the goal of achieving complete response (CR).
- If PR is not achieved, or there is disease progression on treatment, other treatment modalities should be given.
- The role of additional therapy with rituximab if CR is achieved after 4–8 doses is not established in children at this time.

Evidence Grade: Strong recommendation/moderate-quality evidence.

- Rituximab may be used as the first-line therapy in conjunction with RIS for higher risk cases, such as monomorphic PTLD diffuse large B cell lymphoma type (DLBCL-type), multisystem disease, end-organ dysfunction, or in subjects with higher risk of allograft rejection during RIS.

Evidence Grade: Strong recommendation/low-quality evidence.

Supporting evidence

The first reported use of monoclonal B-cell antibody treatment in PTLD was in 1998 using anti-CD21 and CD24 antibodies.[45] Benkerrou et al. reported use in PTLD following SOT, achieving a CR rate of 64% with a 1-year overall survival (OS) of 55%. These agents were never commercialized; therefore, subsequent investigations utilized the monoclonal anti-CD20 antibody rituximab. In a Phase II study, adult patients with PTLD following SOT who failed RIS, received 4 weekly doses of rituximab and achieved CR of 28% and 1-year OS of 67%.[46] Two other Phase 2 studies among adults confirmed CR rates after 4 weekly doses of 20%–34%. They demonstrated that CR could be achieved in 40%–65% of patients who had PR when four additional doses of rituximab were given. Overall CR rates of 50%–60% and OS of 60%–70% can be achieved with the use of the single agent rituximab.[47,48] In two pediatric studies evaluating the efficacy of single agent rituximab in SOT patients with PTLD that failed RIS, patients received 3–4 weekly doses of rituximab and if CR or PR was achieved, patients received up to four additional doses. CR was achieved in 60%–70% and OS over 80%.[49,50] Rituximab was also studied in a small investigator-initiated prospective phase II open-label study after pediatric SOT. Among 15 patients with refractory disease unresponsive to RIS (73% with polymorphic PTLD), CR was achieved in 80% (12/15), with 67% (10/15) overall survival at 2 years.[51] The consistent results from Phase II studies in adults and at least equivalent, if not superior results, from two Phase II pediatric studies, provide strong evidence that single agent rituximab is effective in patients with CD20-positive PTLD that have failed treatment with RIS alone.

Importantly, there have been no Phase III randomized trials performed to compare the effectiveness of rituximab and reduced RIS versus RIS alone as *first-line* therapy for newly diagnosed PLTD in children. However, this approach has become the standard of care in most cases of PTLD in adults after SOT[52–54] and is an approach used in many pediatric centers, especially in cases deemed to be high risk for poor outcomes, such as monomorphic PTLD of DLBCL-type,

multisystem disease, end-organ dysfunction, or in subjects with higher risk of allograft rejection during RIS.

Research priorities for knowledge gaps

- What is the appropriate rituximab treatment regimen to achieve CR?
- What are the long-term adverse effects of rituximab therapy, for example, B-cell and immunoglobulin deficiencies?
- When should rituximab monotherapy be considered as front-line therapy with RIS?
- When should rituximab monotherapy not be considered?
- What is the role of next generation anti-B-cell monoclonal antibodies?
- What is the role of immunogenetic markers in predicting a likely response to rituximab?

3.1.5 | Question 5: What is the role of cytotoxic chemotherapy in the treatment of different categories of PTLD?

Recommendations

- Children with polymorphic and monomorphic CD20+ B-cell PTLD (of DLBCL-type) should receive low-dose chemotherapy (with or without rituximab) if they have failed to achieve CR with RIS and treatment with rituximab.

  Evidence Grade: Weak recommendation/low-quality evidence.

- Children with monomorphic CD20+ B-cell PTLD (of DLBCL-type) may receive low-dose chemotherapy with rituximab as first-line therapy (in lieu of RIS or RIS with rituximab). It is unknown if this will result in superior outcomes to sequential therapy, but this can be considered a suitable treatment option, especially if there is felt to be high risk for allograft rejection (eg, in the setting of recent acute rejection).

  Evidence Grade: Weak recommendation/low-quality evidence.

- Children with Burkitt PTLD should receive conventional chemotherapy as first-line therapy.

  Evidence Grade: Strong recommendation/low-quality evidence.

- Patients with a lack of response or a relapse after an initial response to low-dose chemotherapy may receive conventional high-dose chemotherapy.

  Evidence Grade: Weak recommendation/low-quality evidence.

- Patients with T-cell PTLD should receive intensive chemotherapy to the extent possible in the presence of comorbidities. Targeted therapies (eg, CD30, ALK) may be considered depending on tumor expression of these target molecules.

  Evidence Grade: Weak recommendation/very low-quality evidence.

- Patients with Hodgkin lymphoma PTLD should receive treatment analogous to Hodgkin lymphoma in non-immunocompromised patients.

  Evidence Grade: Strong recommendation/low-quality evidence.

- Patients with plasmacytoma-like PTLD should initially undergo RIS as for other forms of PTLD. There is insufficient evidence base to define optimal additional therapies. RIS can be combined with local surgery or irradiation (eg, for isolated skin or bone lesions). Chemotherapy and regimens utilized for multiple myeloma may be considered for aggressive and refractory cases.

  Evidence Grade: Weak recommendation/very low-quality evidence.

Supporting evidence

The majority of destructive PTLDs in children are polymorphic and monomorphic B-cell PTLDs (with the latter most often being of the DLBCL type).[8,55,56] Many programs do not discriminate between these two entities in terms of initial treatment. Almost all B-cell PTLDs are CD20+ and, therefore, potentially susceptible to treatment with anti-CD20 monoclonal antibodies. Thus, treatment has shifted over the last 20 years toward a more liberal use of rituximab as first-line therapy with RIS, or as second-line therapy after failure of RIS. None-the-less, chemotherapy still has a role in selected patient populations and clinical scenarios.

In the adult PLTD population, a number of trials have been reported using chemotherapy with or without rituximab. The European PTLD-1 trial employed a frontline 4-week rituximab treatment followed by four courses of CHOP (cyclophosphamide, vincristine, doxorubicin, and prednisone) in adult SOT patients with CD20+ PTLD.[57] Seventy-four patients were enrolled, with a median overall survival of 6.6 years, and 11% of patients experiencing treated-related mortality (TRM). In a subsequent trial, the group established that patients with complete response to front-line rituximab had a favorable survival if consolidated with rituximab alone, leading to a recommendation to avoid chemotherapy regimen in this patient group.[47] For salvage situations, more intensive chemotherapy regimens with the inclusion of anthracyclines and/or high-dose methotrexate have been used. These options need to be balanced against other treatment modalities, such as adoptive cellular immunotherapy or other targeted therapies (eg, CD30—brentuximab-vedotin). Current adult consensus recommendations suggest that most adults with PTLD after SOT receive initial treatment with RIS with or without rituximab, and those without CR, or with progressive disease on treatment, move to conventional chemotherapy, that is, R-CHOP.[52,54] While adult experiences have informed pediatric practice, it is important to remember that there are important differences between

adult and pediatric populations, including timing of PTLD onset, EBV positivity, spectrum of pathology (most adults having monomorphic disease), and also potential differences in tolerance to chemotherapy in immunocompromised populations. These observations have driven several pediatric studies of chemotherapy, including prospective phase II trials that focus on lower toxicity regimens.

Some pediatric centers favor low-dose chemotherapy (with or without rituximab) as second-line therapy after failure of RIS. While chemotherapy is not typically given as first-line therapy, some groups have even utilized low-dose chemotherapy as the initial treatment for polymorphic PTLD[8]; a strategy to achieve CR of PTLD while protecting the allograft from the effects of RIS. This has not been considered a standard of care, in part because the superiority of low-dose chemotherapy over RIS with/without rituximab as first-line treatment has not been demonstrated in direct head-to-head randomized trials. Furthermore, for disease not responding to RIS, OS, CR, and relapse rates appear similar between low-dose chemo-based regimens (with or without rituximab) compared to rituximab protocols.[49–51] Earlier use of chemotherapy might be justified if long-term follow-up studies were to demonstrate superior graft function and outcomes.

Chemotherapy for pediatric PTLD can be divided into different intensity levels. High-intensity regimens used for lymphoma in immunocompetent children (eg, NHL/BFM regimen, FAB/LMB type regimen) are often not tolerated as treatment of PTLD after SOT and can lead to high morbidity and mortality.[58] Therefore, chemotherapy regimens of low to moderate intensity have been developed for pediatric B-cell PTLD based on prospective trials, although with none employing randomization. A multicenter Phase II study tested a low-dose chemotherapy regimen (prednisone + cyclophosphamide) in 36 children with an overall response rate of 83% and a 2-year overall and failure-free survival of 73% and 67%, respectively.[59] Treatment was well tolerated with acceptable rates of TRM (5.5%) and graft loss (8.3%). In a subsequent COG Phase II trial, six cycles of rituximab were added to the chemotherapy.[60] Fifty-five patients were enrolled, survival was improved to 83% (2-year OS) and 71% (2-year failure free survival [FFS]). A German trial of 49 children with B-cell PTLD used sequential rituximab and moderate chemotherapy (mCOMP: cyclophosphamide, vincristine, prednisone, low-dose methotrexate) only in patients not responding to rituximab and achieved similar survival rates.[61] In summary, rituximab (Section 3.1.4) or low-dose chemotherapy (with or without rituximab) have emerged as the second-line treatment for most children with CD20+ B-cell PTLD unresponsive to first-line therapies (including those with polymorphic disease or monomorphic DLBCL-type PTLD).

In the case of Burkitt lymphoma PTLD, aggressive multi-agent protocols are typically used, similar or identical to those used for the management of Burkitt lymphoma in the non-transplant setting. This is due to the aggressive nature of this form of PTLD, which typically progresses rapidly. Results using aggressive chemotherapy have been encouraging[61–64] and has led to multi-agent chemotherapy becoming the standard of care in almost all centers.

Classical Hodgkin lymphoma PTLD (HL PTLD) is usually a late event (>5 years) after SOT. It is commonly EBV-positive. A case series of 17 pediatric patients with classical HL PTLD reports an excellent outcome (86% OS and 81% event free survival at 5 years) using chemotherapy regimens (OEPA/OPPA for induction and COP/COPDAC for consolidation) similar to non-immunocompromised patients.[65] Similar results were obtained in a series of adult HL PTLD, in which patients receiving specific Hodgkin lymphoma treatment had an improved probability of survival compared to no chemotherapy or other chemotherapy regimens.[66]

T-cell PTLDs comprise a heterogeneous group of EBV+ (30%) and EBV− lymphomas occurring late after transplantation.[67] While ALK+ anaplastic large cell lymphoma has a reasonable prognosis, other entities like peripheral T-cell lymphoma not otherwise specified or hepatosplenic T-cell lymphoma have an extremely poor prognosis.[68] EBV+ cases tend to do better than EBV−. No prospective trials are available for T-cell PTLD patients. Most patients (adults and children) reported to have survived T-cell PTLD received intensive chemotherapy of various kinds in conjunction with radiation therapy.[67] However, both TRM and mortality due to PTLD are high in this patient cohort. Occasionally, targeted therapies (ALK inhibitors, CD30-targeted therapies such as brentuximab-vedotin) have been added to, or were substituted for, intensive chemotherapy with promising outcomes.[69]

There are very few reports on plasmacytoma-like PTLD in children, and thus there is minimal evidence base for defining optimal therapy.[70,71] This rare entity is very distinct from others and disease activity can be monitored by quantifying paraproteinemia and Ig light chains. Typically, they do not show bone marrow involvement. Treatments that have been utilized in children include: RIS, high dose dexamethasone, dexamethasone plus thalidomide, vincristine, adriamycin and dexamethasone, and dexamethasone with bortezomib.[70,71] Overall, prognosis has been favorable with patients entering remission and with disappearance of paraproteinemia. Given reports of favorable outcomes in children,[70,71] initial consideration should be given to less aggressive therapy, including RIS potentially combined with local surgery or irradiation in select cases (eg, for localized skin or bone lesions). As treatment of this condition evolves, clinicians should weigh the risk of over treatment when regimens are adapted from myeloma protocols for adults in the non-transplant setting. However, the latter may be suitable for aggressive disease refractory to first-line interventions.

Research priorities for knowledge gaps

- Define which patients with polymorphic or monomorphic B-cell PTLD might best be treated with upfront low-dose chemotherapy.
- Define which patients should be treated with low-dose chemotherapy/rituximab versus rituximab alone after failure of first-line therapy with RIS.
- Define the toxicity of sequential regimens with/without rituximab.
- Determine the optimal immuno-chemotherapy regimens for different subtypes of T-cell PTLD.

- Determining optimal salvage therapy regimens for recurrent disease after prior chemotherapy.

3.1.6 | Question 6: What is the role of adoptive immunotherapy in the treatment of different categories of PTLD?

Recommendations

- EBV-specific T-cell therapy from third-party donors may be considered in individual patients with EBV+ PTLD refractory to other treatment modalities or unable to receive intensive chemotherapy, if needed. Virus-specific T-cell (VST) therapy should be administered to patients who are stable on a minimal tolerable dose of immunosuppression. It is also recommended that patients are receiving <0.5 mg/kg/day steroids at the time of VST administration. Weaning of immune suppression should not occur within the 6 weeks post-VST infusion.

  Evidence Grade: Weak recommendation/low-quality evidence.

- Children with EBV+ PTLD who do not respond to reduction of immunosuppression and 3–4 weekly doses of rituximab (375 mg/m^2) can be considered for third-party VST therapy in the setting of a clinical trial. If stable disease or partial remission is achieved, additional third-party VSTs could be given possibly from another donor. If disease progression occurs, other treatment modalities should be given.

  Evidence Grade: Strong recommendation/low-quality evidence.

Supporting evidence

Unlike the situation with hematopoietic stem cell transplant (HSCT) patients, data on the use of adoptive immunotherapy for SOT patients with PTLD are limited.[72–76] This third-party approach was first tested in the clinic by Haque and colleagues,[73] who manufactured a bank of polyclonal EBV-specific T-cell products for the treatment of EBV-associated diseases in patients undergoing HSCT or solid organ transplantation. The T-cell products were generated from unrelated third-party blood donors and selection of the T-cells were based primarily on the best human leukocyte antigen (HLA) match.[73] Using this approach, in a larger Phase II multicenter trial enrolling 33 patients with EBV-positive PTLD from 19 transplant centers who had not responded to conventional therapy and were given the best-HLA-matched "off-the-shelf" product,[74] overall response rates of 64% at 5 weeks, and 52% at 6 months were reported.

The above results are further supported by reports from other centers including from Memorial Sloan–Kettering Cancer Center which administered, in collaboration with Atara Biotherapeutics, third-party EBV T-cells to patients with PTLD post-SOT.[75] Third-party EBV cytotoxic T lymphocyte (EBV-CTL) therapy was given to 46 recipients of HSCT ($n=33$) and 13 with SOT who had established EBV-PTLD and who had failed rituximab therapy. Treatment cycles consisted of 3 weekly infusions of EBV-CTLs and 3 weeks of observation. CR or sustained PR was achieved in 68% of HSCT recipients and 54% of SOT recipients. The product (tabelecleucel) has recently received approval by the U.S. Food and Drug Administration and the EU European Medicines Agency for treatment of EBV+ PTLD refractory to at least one prior treatment. Most recently, the Children's Oncology Group (COG) completed their ANHL1522 study which evaluated outcomes in pediatric patients with PTLD after solid organ transplant treated with rituximab followed by third-party latent-membrane-protein-specific T-cells (LMP-TC). In this study, newly diagnosed patients received three cycles of rituximab followed by 1–2 cycles of LMP-TC if they had not achieved a complete remission. This newly diagnosed cohort achieved an overall response rate (ORR) following LMP-TC cycle 1 of 70% (7/10).[76]

Overall, the interpretation of the results across all these studies is not straightforward as many of the patients with relapsed/refractory disease who responded also had their immunosuppressive treatments reduced and received other therapies. Hence the encouraging benefits in patients with relapsed/refractory disease cannot be solely attributed to the third-party VST. The role of VST in relapsed or refractory prior to the use of chemotherapy remains unknown. For this reason, the consensus of conference participants was that use in this setting should be limited to the setting of formal clinical trials. In addition, as for most phase I and II studies, experience to date has mostly been for the most challenging patients who have failed other therapies. There is intrinsic logic to enhancing anti-EBV immunity early in the course of disease, perhaps even at the time of initial RIS at first presentation. Such studies have yet to be performed. Nevertheless, the use of VST has shown considerable promise, warranting further testing in definitive studies.

Research priorities for knowledge gaps

- If CR is achieved after treatment with VST, should additional third-party VSTs be given?
- What are the optimal monitoring techniques to evaluate for the persistence of the adoptively transferred VSTs?
- When might VST therapy with RIS be considered as front-line therapy?
- When should VST not be considered (eg, recent history of graft rejection, on steroids >0.5 mg/kg/day)?
- Defining whether VST should be used before chemotherapy in patients failing RIS/rituximab.
- What is the role of autologous VSTs?

3.1.7 | Question 7: What is the evidence for the efficacy of immunomodulatory/anti-cytokine therapy in the management of PTLD?

Recommendations

- Interferon therapy cannot be recommended for treatment of PTLD due to low anti-tumor activity and related toxicity (eg, myelosuppressive and neurological side effects, allograft rejection).

Evidence Grade: Strong recommendation/low-quality evidence.

- Monoclonal anti-IL6 antibodies cannot be generally recommended for PTLD treatment at this time. However, administration of anti-IL6 antibodies may be considered as salvage therapy.

Evidence Grade: Strong recommendation/low-quality evidence.

- PD-(L)1 blockers cannot be recommended for PTLD treatment given limited experience and data.

Evidence Grade: Strong recommendation/low-quality evidence.

Supporting evidence

Immunomodulatory/anti-cytokine therapy used in PTLD management include interferon treatment, administration of monoclonal anti-interleukin-6 (anti-IL-6) antibodies, and checkpoint inhibitors such as programmed death-ligand 1 (PD-(L)1) blockers.

Historically, positive responses have been reported in small numbers of PTLD patients receiving interferon (IFN)-alpha[77] and anti-IL-6 therapy,[78] but these agents are no longer commonly employed in the treatment of PTLD. IFN-alpha is potentially able to enhance cytotoxic T-cell activity against the tumor, as it modulates the immune system by several mechanisms including (i) preventing B lymphocytes from producing immunoglobulins, (ii) reducing IL-6 receptor density, and (iii) augmenting the inhibition of IL-4 by IL-12.[79,80] IFN-alpha has been administered as therapy of EBV-associated PTLD in case reports and a few case series using IFN-alpha alone or mostly in combination with other treatment strategies in adult heart or kidney transplant recipients as well as in pediatric kidney or liver transplant patients.[77,81–85] Based on these results, IFN-alpha is associated with a relatively low anti-tumor activity but considerable toxicity. In the transplant setting, there is especially a high risk of triggering allograft rejection or aggravation of an autoimmune disease which may be the underlying disease leading to transplantation. Hence, PTLD treatment with IFN cannot be generally recommended and is no longer commonly used at this time.

Since IL-6 plays an important role in the proliferation and maturation of virus-infected B cells, administration of monoclonal anti-IL-6 antibodies has the theoretical potential to induce remission in patients with PTLD. In a multicenter Phase I-II trial, treatment with an anti-IL-6 monoclonal antibody was assessed in one pediatric liver allograft patient and 11 adult SOT recipients with PTLD.[86] CR was achieved in 5/12 (42%) patients, partial remission in 3/12 (25%) of whom one relapsed 5 months after therapy. Stable disease occurred in one patient; the remaining three patients showed no response to therapy.[86] No major anti-IL-6 monoclonal antibody-associated side effects were reported. However, data are insufficient to generally recommend therapy of PTLD with IL-6 antibodies.

There is biological plausibility for disease response to PD-(L)1 blockade using immune checkpoint inhibitors in the setting of PTLD positive for these markers.[87] Pembrolizumab, a programmed cell death protein 1 (PD-1) blocker inhibits the interplay between PD-1 on T-cell and PD-L1 on tumor cells. In the non-transplant setting, one study analyzed the outcome of 30 relapsed or refractory NHL patients treated with pembrolizumab and compared the outcome between EBV-positive and EBV-negative subtypes because EBV infection of tumor cells can upregulate PD-L1 expression.[88] The authors concluded that pembrolizumab could be useful as a salvage treatment for relapsed or refractory EBV-positive NHL, especially natural killer (NK)/T-cell lymphoma.[87] Nivolumab, another checkpoint inhibitor, was administered as salvage therapy to an 11-year-old patient who developed CNS PTLD after allogeneic HSCT[89] and did not respond to all other therapeutic approaches, namely cessation of immunosuppression, treatment with EBV-specific cytotoxic T-cells, rituximab, and chemotherapy. Treatment with nivolumab led to CR without cytopenia, graft versus host disease, graft failure, or other alloimmune complications.[89] So far, experience with PD-(L)1 blockers in transplant recipients is limited and lacking in SOT patients. Although published reports in NHL and HSCT patients are promising, in the SOT setting potential safety concerns are significant in the form of precipitating rejection or exacerbating autoimmune disease that is one of the causes of end organ failure requiring transplant.

Research priorities for knowledge gaps

- Future studies should prospectively evaluate the efficacy and safety of monoclonal anti-IL6 antibodies and PD-(L)1 blockers in this patient population.

3.2 | Recommendations relating to specific clinical scenarios

Several important clinical scenarios are encountered in the management of PTLD. In this section, we summarize key recommendations for their management.

3.2.1 | Question 8: How should CNS PTLD be treated?

Recommendations

- Radiation therapy may be used in selected patients where risk/benefit ratio appears acceptable, for example, in the older child with small numbers of discrete lesions. When the risk of long-term toxicity is deemed high, alternate treatments should be considered.

Evidence Grade: Weak recommendation/very low-quality evidence.

Supporting evidence

CNS involvement is a relatively rare manifestation of PTLD and, consequently, has not been clearly classified in the current published literature.[90–93] CNS disease may be primary or associated with systemic PTLD. Most reports of CNS disease describe cases where involvement first became clinically evident with neurologic

symptoms prompting subsequent evaluations establishing the presence of CNS disease.[94] In contrast, there are very few reports where patients were evaluated with radiologic imaging and lumbar punctures to establish whether CNS disease was present when PTLD was first diagnosed. Thus, it is unclear whether patients described in the literature are patients manifesting CNS recurrence, progression of previously established CNS disease, or clinical manifestations of pre-existing disease that may have not clinically advanced. Given that patients often present with a substantial disease burden, an important question remains as to whether early detection and treatment, before clinical symptoms develop, would alter the prognosis of these patients. Currently, the outcome of patients with CNS disease is poor, with a survival ranging from 9.4% to 43%.[90–93]

There is currently a lack of studies that include uniform treatments and evaluations, thus evaluating the efficacy of any therapy is difficult. Therapies cover a broad scope of interventions including (1) reduction of immunosuppression[95]; (2) administration of antiviral agents[96]; (3) administration of rituximab, both intravenously and intrathecally[97–100]; (4) high-dose chemotherapy administered intravenously[101]; (5) intrathecal chemotherapy[102,103]; (6) adoptive immunotherapy[104]; and (7) radiation.[90–93] Stereotactic radiotherapy has also been used.[105] Every intervention is associated with some level of success, but the lack of structured clinical trials makes it impossible to discern the efficacy of any modality as published reports are likely biased toward successful outcomes. Furthermore, many of these interventions are administered in different combinations, making interpretation difficult. However, reports encompassing larger numbers of patients provide some indications of which therapies are associated with higher survival rates. Radiation therapy is associated with the highest level of success with response rates ranging from 53% to 87%.[90–93] Of note, despite the wide variety of therapies that have been utilized in this disease, there are virtually no reports utilizing conventional therapies for CNS lymphoma or lymphoma with CNS involvement. It is unclear whether such therapy would be tolerated in this population, nor how effective they would be. In addition, prognostic risk factors that could be used to stratify patients and direct therapy have not been established for CNS PTLD.

In the absence of high-level evidence, depending upon the urgency of therapy, we recommend that less aggressive/toxic therapy be initiated for CNS PTLD prior to advancing to more aggressive therapy to minimize toxicity, with radiation therapy having the highest reported efficacy but the greatest risk of long-term toxicity in children.

Research priorities for knowledge gaps

- Development of standardized nomenclature and classification of CNS PTLD.
- Standardized imaging approaches at diagnosis, during treatment, and at disease relapse to understand the prevalence at initial diagnosis and its development on therapy.
- Prospective trials are also needed to deliver standard treatment regimens to gain insight into response and survival rates.
- A comprehensive international registry might identify successful treatment strategies using comparative effectiveness methodologies.

3.2.2 | Question 9: What is the role of treatment of "presumed PTLD" (based on imaging) when biopsy is not feasible?

Recommendation

- We recommend that treatment be considered for lesions that are presumed to be PTLD if a biopsy is not feasible or is deemed too risky. This should be done when radiographic imaging is characteristic, and ideally, when there is supporting evidence (such as very elevated EBV viral loads), along with the absence of evidence for alternate diagnoses (eg, infectious etiologies).

Evidence Grade: Weak recommendation/very low-quality evidence.

Supporting evidence

This recommendation was largely consensus-based and recognizes that it is essential to biopsy PTLD lesions to make the histopathological diagnosis whenever feasible. With advances in interventional radiology, it is rare that a biopsy cannot be obtained. However, in some situations, it may be necessary to initiate treatment empirically if other diagnoses are not likely and a biopsy poses too great a risk to the patient based on its location. In such situations, extensive work up should be performed to look for subclinical evidence of other sites of disease more amenable to biopsy (eg, by PET-CT), to rule out other possible etiologies (eg, infectious), and to look for corroborative evidence of PTLD (eg, elevated EBV viral loads, serum/urine paraproteinemia). If additional lesions develop after commencing therapy, biopsy should be obtained.

Research priorities for knowledge gaps

- The development and validation of specific biomarkers, gene expression profiles, or molecular assays that might help in differentiating PTLD from other potential etiologies in cases where biopsy is not feasible.

3.2.3 | Question 10: What is the role of mammalian target of rapamycin (mTOR) inhibitors in patients with active or recently treated PTLD

Recommendation

- Changing from CNI-based immunosuppression to mTOR inhibitors (mTORi) as primary immunosuppression may be considered in select patients with PTLD on a case-by-case basis.

Evidence Grade: Weak recommendation/very low-quality evidence.

Supporting evidence

Inhibiting the mTOR pathway suppresses growth of EBV (+) and EBV (−) B-cell lymphoma cells.[106,107] Either PI3K or Akt pathway inhibition also diminishes the growth of B-cell lymphoma cells with synergistic effects when used in combination with sirolimus.[108,109] In vitro treatment of antigen-specific T-cells with rapamycin results in increased functional activity of virus-specific T-cells compared to bulk T-cell cultures.[110] The combination of mTOR inhibitor (everolimus) in combination with cyclosporin A (CSA) also has a suppressive effect on Burkitt lymphoma cells while tacrolimus abolished everolimus-mediated suppressive effects.[111] This would support the combination of the calcineurin inhibitor CSA with everolimus in preference to the combination of tacrolimus and everolimus. Interestingly, the combination of mTOR inhibitor with tacrolimus was associated with increased risk of PTLD as compared to mTOR inhibition combined with CSA in primary kidney transplant recipients.[112] In addition, patients only on mTORi maintenance therapy have developed PTLD.[113] There are several relatively small retrospective reviews or case series, with no controlled studies, that suggest that replacing calcineurin inhibitors with an mTOR inhibitor for a variety of reasons including the development of PTLD or high EBV load may be an effective immunosuppressive therapy.[114–118] However, it should be noted that a prospective study of everolimus and reduced calcineurin inhibitors therapy in pediatric liver transplant patients was stopped prematurely due to high rates of PTLD, presumably due to over immunosuppression.[119] Thus, although there appear to be some theoretical benefits to mTORi following diagnosis of PTLD, much more knowledge is required to make definitive recommendations. It is possible that studies to date have merely identified which patients no longer need CNI treatment after diagnosis of PTLD, rather than those who truly benefit specifically from an mTORi. This is supported by the knowledge that a significant number of patients (mostly with liver allografts) can be managed long-term after PTLD completely free of immunosuppression, having achieved operational tolerance.[26,120–122]

Research priorities for knowledge gap

- Defining which patients can be managed post-PTLD diagnosis with CNI withdrawal and substitution with mTORi.
- Defining which patients after PTLD (typically liver recipients) can be managed long-term free of any immunosuppression.

3.3 | Recommendations related to prognostic factors in PTLD

3.3.1 | Question 11: Are there prognostic factors that can be used to guide management of PTLD?

Recommendation

- Prognostic factors may be selectively used to guide the management of PTLD.

Evidence Grade: Weak recommendation/very low-quality evidence.

Supportive information or evidence

Patients with T-cell PTLD,[123,124] CNS disease,[125] and advanced disease with bone marrow involvement[126] appear to have a poorer prognosis than other PTLD patients. PTLD confined to tonsillar/adenoidal tissue has been shown to be associated with a more favorable prognosis compared with other forms of PTLD.[127] Among adult kidney patients with PTLD, a prognostic index has been developed based on age, lactate dehydrogenase level, creatinine, disease site, and histologic features.[128] Several other factors have been inconsistently associated with PTLD outcomes in retrospective case series. Prognostic factors relating to the location and histopathology of lesions that have been reported in one or more series include the following:

1. Based on location of lesions
   Less favorable prognosis: Multisite disease, central nervous system disease, bone marrow involvement.
   More favorable prognosis: Disease localized to tonsillar/adenoidal tissue.
2. Based on histopathology and related features
   Less favorable prognosis: T or NK cell PTLD, EBV-negative PTLD, Burkitt lymphoma.

However, in a large cohort of 56 cases of PTLD from among 1184 primary heart transplants in the Pediatric Heart Transplant Study, no robust predictors of outcome were identified and patients with monomorphic disease (generally considered more "aggressive") had outcomes comparable to those with polymorphic disease.[8] However, it should be noted that treatment approaches were not comparable among histological groups and thus the histological "aggressiveness" may drive more aggressive treatment (such as chemotherapy), which in turn may improve outcomes for certain histologies. For example, Burkitt PTLD is extremely rapidly growing but several series report excellent outcomes comparable to other forms of PTLD when Burkitt chemotherapy protocols are used in the transplant setting.[64]

In summary, despite recognition of a small number of risk factors for adverse outcomes in retrospective studies, no prognostic index or risk prediction model has been developed and validated for children, and many children with multisite disease, including those with monomorphic histology, still do very well with modern treatment regimens. It must also be noted that up to half of deaths after diagnosis of PTLD are related to graft dysfunction/loss due to acute and chronic rejection, and therefore graft protection is also a key determinant of overall patient outcomes.[8] Thus, prognosis must take into account not only PTLD response (goal being complete response of PTLD without relapse) but also graft outcomes (goal of freedom from acute and chronic rejection and graft loss) (see Section 3.4.1 below).

Research priorities for knowledge gap

- Development of a Prognostic Index in children

3.3.2 | Question 12: Which children can be re-transplanted, and when, after being diagnosed with PTLD and allograft failure? What is the risk of developing PTLD in subsequent allografts?

Recommendations

- Patients with complete remission of PTLD and chronic allograft failure/loss can be suitable candidates for re-transplantation.

  Evidence Grade: Strong recommendation/low-quality evidence.

- Wherever possible, patients who are being considered for re-transplantation should wait 2 years from complete remission of PTLD before being re-transplanted and retransplant should be performed when viral loads are low or undetectable.

  Evidence Grade: Weak recommendation/low-quality evidence.

- Kidney transplant recipients should be considered for the removal of the allograft before being re-transplanted to allow for a period of complete cessation of immunosuppression if feasible.

  Evidence Grade: Weak recommendation/very low-quality evidence.

Supporting evidence

Data on re-transplantation after PTLD are limited.[129–132] Data from the French PTLD registry provides some guidance. Among 52 patients with kidney transplants who underwent 55 re-transplantations after post-transplant lymphoproliferative disorder, the time from PTLD diagnosis to re-transplantation was 100 ± 44 months. PTLD developed in one patient (1.9%) at 24 months after re-transplantation.[132] In the analysis of the OPTN/UNOS database, most retransplants for PTLD were in children and interestingly, a quarter of retransplants for PTLD occurred within a year of PTLD diagnosis.[129] At latest follow-up (784 ± 82 days), patient and second-graft survival after re-transplantation were 85.5% and 73.9% respectively, with no recurrence of PTLD. The authors concluded that "Patient/graft survival is excellent and re-transplantation in PTLD subjects should be considered acceptable." It is acknowledged that for non-kidney transplant patients, clinicians would likely make the decision to re-transplant at intervals shorter than 2 years after the initial transplant since there are limited opportunities to support patients after allograft loss for these organs. Decisions will need to be individualized based on many factors.

Research priorities for knowledge gap

- Evaluation of the impact of viral load levels (prior to re-transplantation) on re-transplantation outcomes after PTLD.
- Investigation of risk factors for adverse outcome after very early re-transplantation (first year) for graft failure after PTLD.
- Optimal immunosuppression strategies at time of re-transplantation for PTLD.

3.4 | Monitoring response to treatment of PTLD

3.4.1 | Question 13: How should clinical response to treatment of PTLD by monitored?

Recommendations

- Clinical assessment, including assessment of graft function, should be performed to evaluate response to PTLD treatment; however, the specific assessments vary depending on the clinical features on presentation and the affected organs.

  Evidence Grade: Weak recommendation/very low-quality evidence.

Supporting evidence

Evidence is limited on the value of clinical criteria singly or in combination with other criteria in assessing the response to PTLD treatment. At the very minimum, it would be expected that patients should be evaluated for changes in the symptoms and signs that were associated with their initial presentation of PTLD as described in current guidelines.[52,54,133] Resolution of fever and constitutional symptoms may occur days to weeks before reduction in size of mass lesions and may offer early suggestion that therapy is working. In addition, relapse or recurrence may be associated with new clinical findings that were not part of the initial presentation. Evaluation will usually include selective radiographic imaging to complement the physical examination of the patient. In addition, assessment of graft function is important following treatment of PTLD. First, to assess for rejection or compromised graft function in response to a specific treatment modality (eg, reduced immunosuppression). Second, to assess for improvement in function where such was compromised by PTLD. Third, to assess for possible complications of treatment. For example, rituximab treatment of patients with intestinal PTLD might be associated with bowel perforation. Assessment of graft function will be specific to the organ in question (eg, serum creatinine, echocardiography, chest radiography, and pulmonary function testing), comparing serial evaluations to pre-PTLD baseline values. Frequency of testing will depend on numerous factors including time from transplant, past rejection history, and intensity, and length of reduction (or withholding) of immunosuppression. Many centers use protocol biopsies for acute rejection monitoring when reduction in immunosuppression is sustained, especially when the PTLD arises early after transplantation or when there is recent history of rejection. Clinical assessments during treatment for PTLD should also incorporate monitoring for complications of therapy, including infectious and non-infectious complications of chemotherapy and hypogammaglobulinemia and neutropenia following rituximab. Management of complications of therapy is outside the scope of these review; for chemotherapy, this will typically follow standard guidelines for the same protocol when used in the non-transplant setting.

Research priorities for knowledge gap

- Development of standardized clinical response criteria for monitoring treatment response in PTLD.
- Optimal methods and frequency of monitoring graft function in response to PTLD treatment.

3.4.2 | Question 14: How should virologic response to treatment of PTLD be monitored?

Recommendation

- Clinicians should be aware of the limitations of viral load monitoring post-treatment of PTLD, including but not limited to scenarios where rituximab treatment has been used.

  Evidence Grade: Strong recommendation/low-quality evidence.

- The use of peripheral blood viral load as the sole measure of response to treatment of EBV+ PTLD is not recommended.

  Evidence Grade: Strong recommendation/low-quality evidence.

- Serial monitoring of EBV DNA in peripheral blood or plasma may be considered to monitor the response to PTLD therapy where loads are elevated at the time of diagnosis. While no firm recommendations can be made on the frequency and duration of monitoring, most experts using post-treatment monitoring would consider it of most value during the immediate post-treatment phase and in the absence of recent rituximab usage.

  Evidence Grade: Weak recommendation/very low-quality evidence.

- Low viral load states post-treatment should not be relied upon as a predictor of sustained disease remission.

  Evidence Grade: Strong recommendation/very low-quality evidence.

Supporting evidence

Epstein–Barr virus DNA levels often fall in response to treatment that includes RIS, adoptive immunotherapy, or rituximab. The compartment that is sampled influences the utility of the loads to predict disease remission, progression, or relapse. However, loads may remain low in the presence of progressive disease or relapse.[67,134] High viral loads often fall in peripheral blood in association with clinical and histologic regression in response to interventions that include RIS and adoptive immunotherapy.[67,134] However, it has been observed that among individuals treated with rituximab, viral load measured in cellular blood components may fall and remain low even in the face of progressive disease and relapse.[135,136]

Plasma loads seem to correlate better with treatment response and relapse than loads measured in the cellular compartment.[137,138] One study found that while measurement of EBV DNA in plasma or peripheral blood mononuclear cells differentiated between untreated cases of EBV+ PTLD, EBV+ PTLD in remission and untreated EBV− PTLD, plasma loads were more reliable in separating the three groups.[139] However, individual patients were not serially monitored in this study.

Among adult PTLD patients, it has been observed that EBV in whole blood after solid organ transplantation does not correlate with the clinical course.[136] In this regard, viral loads may remain elevated in the presence of clinical remission or may remain low in the presence of progressive disease. Further studies correlating serial monitoring in different sample types to individual PTLD patient outcomes are required to confirm the optimal specimen type that should be used for this purpose.

Research priorities for knowledge gap

- The correlations between viral load levels and treatment responses in PTLD in various clinical settings.
- The optimal specimen type for monitoring virologic response in PTLD needs to be determined. Studies should compare the usefulness of measuring viral load in peripheral blood versus plasma, as well as other sample types like peripheral blood mononuclear cells.
- The optimal frequency and duration of monitoring during the various post-treatment phases.

3.4.3 | Question 15: How should radiologic response to PTLD treatment be monitored?

Recommendation

- While radiologic evaluation complements clinical and virologic evaluation of patients following treatment of PTLD, it is recommended that the choice of modality to use to monitor response to treatment be individualized and should depend in part on the location of lesion, the historical sequence of imaging modalities and concerns regarding radiation dosage in the patient.

  Evidence Grade: Weak recommendation/very low-quality evidence.

Supporting evidence

Pulmonary lesions that are visible on chest radiographs may require high-resolution CT scanning for better delineation, including the presence of mediastinal adenopathy and small pulmonary nodules that are not visible on plain chest radiographs.[140] Suspected intra-abdominal lesions may be followed with ultrasonography and computerized tomography (CT) scanning. In the case of fluorodeoxyglucose (FDG)-avid lymphomas, 18-FDG-positron emission tomography (PET)/CT has become the standard to assess treatment response.[141] Data in PTLD patients are limited and are largely confined to reports from single centers, where PET/CT has been used in diagnosis and more selectively in the follow-up of PTLD.[142,143] However, a report from a German registry of adult PTLD cases reported that end of treatment PET-CT had a 92% negative predictive

TABLE 1 Summary of management based on pathological findings at presentation.

Histopathological criteria or clinical entity	First line of treatment	Second line of treatment	Discussion points
Non-destructive PTLDs	• Reduction of IS (RIS) • Surgery for selected localized disease	• Rarely required	• How much RIS and for how long? • Role of withdrawal IS? • Replacement of CNI with other agents?
Polymorphic PTLD	• RIS • Rituximab for select high risk scenarios (if CD20+) • Surgery for selected localized disease	• Rituximab (CD20 +ve) for refractory disease • Chemotherapy (CD20 −ve or refractory to rituximab/RIS)	• When should rituximab be used as first-line therapy? • Consider third-party VST for refractory EBV +ve disease (*preferably in clinical trials*)
Monomorphic PTLDs			
Diffuse large B-cell	• RIS • Rituximab (CD20 +ve) • Surgery for selected localized disease	• Rituximab (CD20 +ve) • Chemotherapy (CD20 −ve or refractory to rituximab/RIS)	• When should rituximab be used as first-line therapy? All cases? • Consider third-party VST for refractory EBV+ disease (*preferably in clinical trials*)
Burkitt	• Multidrug chemotherapy including rituximab	• Alternate chemotherapy regimens	• Optimal regimen not defined
T-cell PTLDs	• Multidrug chemotherapy • Targeted biologics in selected cases • Consolidation with RT?	• Alternate chemotherapy regimens	• Optimal regimen not defined
Classical Hodgkin lymphoma	• Treat per HL in non-transplant setting	• Treat per HL in non-transplant setting	• Role of VST in Tx EBV+ CHL?

Note: 1. Second line of treatment modalities may be employed singly, sequentially or in combination, as appropriate. 2. Conventional immunosuppression is typically withheld during chemotherapy.

value for disease relapse.[144] A major disadvantage is the amount of radiation delivered by PET-CT, which makes it difficult to make all-encompassing recommendations for all patients.

Research priorities for knowledge gap

- Determination of the effectiveness and limitations of different imaging modalities for monitoring radiologic response to PTLD treatment.
- Development of standardized imaging protocols for PTLD patients to ensure consistency in monitoring treatment response across different patient groups and centers.

3.5 | Summary of management based on histopathological findings at presentation

To provide a summary of treatment for purposes of teaching and clinical practice, we have summarized a stepwise approach to treatment based on the sequential use of specific treatment modalities (Table 1). In this regard, it is widely accepted that this initial step in management is RIS to minimize the net state of immunosuppression to the extent feasible. It must be appreciated that the recommended strategies do not represent exclusive courses of action, as several factors influence the choice of treatment and the timing of introduction of a particular treatment modality.

AUTHOR CONTRIBUTIONS

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DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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