Frontline Management of Post-Transplantation Lymphoproliferative Disorder in Adult Solid Organ Recipient Patients

A British Society for Haematology Guideline

Writing group: on behalf of the Haemato-Oncology Task Force of the British Society for Haematology and the British Transplantation Society

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Methodology

This guideline was compiled according to the BSH process at https://b-s-h.org.uk/media/16732/bsh-guidance-development-process-dec-5-18.pdf and represents best practice in both teaching and district hospitals in the UK. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) nomenclature was used to evaluate levels of evidence and to assess the strength of recommendations. The GRADE criteria can be found at http://www.gradeworkinggroup.org.

Grade nomenclature; Strength of recommendations;

Strong (grade 1): Strong recommendations (grade 1) are made when there is confidence that the benefits do or do not outweigh harm and burden. Grade 1 recommendations can be applied uniformly to most patients. Regard as 'recommend'.

Weak (grade 2): Where the magnitude of benefit or not is less certain a weaker grade 2 recommendation is made. Grade 2 recommendations require judicious application to individual patients. Regard as 'suggest'.

Quality of evidence

The quality of evidence is graded as high (A), moderate (B) or low (C). To put this in context, it is useful to consider the uncertainty of knowledge and whether further research could change what we know or our certainty.

(A) High: Further research is very unlikely to change confidence in the estimate of effect. Current evidence derived from randomised clinical trials without important limitations.

(B) Moderate: Further research may well have an important impact on confidence in the estimate of effect and may change the estimate. Current evidence derived from

randomised clinical trials with important limitations (e.g. inconsistent results, imprecision wide confidence intervals or methodological flaws e.g. lack of blinding, large losses to follow up, failure to adhere to intention to treat analysis), or very strong evidence from observational studies or case series (e.g. large or very large and consistent estimates of the magnitude of a treatment effect or demonstration of a dose-response gradient).

(C) Low: Further research is likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate. Current evidence from observational studies, case series or just opinion.

Literature review details

Recommendations included a systematic review of published English language literature from publication of previous British Society for Haematology (BSH) Management of Post-Transplantation Lymphoproliferative Disorder (PTLD) in Adult Solid Organ Transplant (SOT) Recipients (16 April 2010) up to 30 June 2020. In addition there are some additional pertinent references and a consensus of expert opinion where no published data are available. PubMed, MEDLINE, EMBASE, Cochrane databases and Web of Science were searched using the preliminary search terms; adult, chemotherapy, rituximab, immunosuppression, post-transplant lymphoproliferative disorder, solid organ transplant and lymphoma.

Review of the manuscript

Review of the manuscript was performed by the BSH Guidelines Committee, Haemato-oncology Task Force, Haemato-oncology sounding board of BSH and the British Transplant Society

Introduction

This document is an updated guideline and details the recommendations for the frontline management of adult patients with an established diagnosis of post-transplant lymphoproliferative disorder (PTLD) following solid organ transplantation (SOT).

PTLD represents a spectrum of disorders resulting from lymphoid proliferations that occur as a result of immunosuppression following SOT. Lymphoproliferative disorders account for 21% of all cancers of SOT recipients, as compared with 4–5% within the immunocompetent population[1]. In adult SOT recipients, PTLD is a common malignancy after skin cancer and is associated with a significant cancer-related mortality[1]. The reported incidence varies according to patient age, transplant type and the degree of immunosuppression. Historically, PTLD has been reported to occur most frequently in the first year following transplantation[2-4]. However, these studies also report a similar incidence of PTLD beyond one-year, suggesting the late occurrence is as prevalent post SOT[2–5].

The majority of cases in the western world are derived from B lymphocytes and are Epstein–Barr Virus (EBV) associated, particularly in the first year post-SOT. EBV-negative cases account for approximately 20–40% of PTLD and usually occur after the first year of transplantation, with a second peak of incidence occurring at 10 years[6,7].In the adult population, recipients of multi-organ and intestinal transplants have the highest incidence of PTLD (up to 20%) followed by lung transplants (3.0 to 10%), heart transplants (2.0 to 8.0%), liver transplants (1.0 to 5.5%), pancreatic transplants (0.5 to 5.0%), and renal transplants recipients having the lowest incidence of PTLD (0.8 to 2.5%) [8,9].

PTLDs are sub-classified into four histopathological categories as shown in Table 1[10].

Table 1: Categories of PTLD

PTLD Type	Description
Non-destructive	Encompasses plasmacytic hyperplasia, lymphocytes representing infectious mononucleosis-like changes and florid follicular hyperplasia. Most cases are EBV-associated and usually present as early PTLD.
Polymorphic	A spectrum of B-cell maturation stages with admixture of T cells, EBV-associated in >90% cases.
Monomorphic	Classified according to the lymphoma sub-type they resemble, comprising 60–80% of PTLD; diffuse large B-cell lymphoma(DLBCL), Burkitt lymphoma, plasma cell myeloma, plasmacytoma. Much less commonly indolent B-cell lymphomas, usually mucosa-associated lymphoid tissue lymphoma[5,11,12] and T-cell neoplasms are diagnosed. Monomorphic PTLD can be EBV-negative. Approximately 70% of these lesions are reported to have cytogenetic abnormalities, including trisomy 9 and 11 or both, loss of 17p, and rearrangement of 8q24 (MYC).
Classical Hodgkin Lymphoma	Morphologically this fulfils the conventional criteria for the diagnosis of classical Hodgkin lymphoma and is generally (>90%) associated with EBV.

Abbreviations: EBV, Epstein-Barr Virus

Diagnosis and Staging

Establishing a tissue diagnosis of PTLD can be challenging and all diagnostic material should be accompanied by relevant clinical information including the date of transplant, immune suppression regimen and organ type. Where possible, excision biopsy samples are recommended to enable accurate PTLD sub-classification and to provide sufficient material for subsequent ancillary investigations.

Patients with PTLD require a comprehensive pre-treatment evaluation as shown in Table 2. Accurate staging and response assessments are crucial for patient

management. Staging should be recorded using the Ann Arbor classification or the Lugano classification[13] which is the recommended classification for staging following Positron Emission Tomography – Computed Tomography (PET-CT) in ^{18}F-fluorodeoxyglucose -avid (FDG-avid) nodal lymphomas.

Table 2: Essential pre-treatment baseline evaluation for all patients diagnosed with PTLD

Baseline investigations:		
Full blood count, Electrolytes, Renal function, Glucose, Liver enzymes, Urate, Lactate dehydrogenase (LDH) **Virology:** HIV type 1 & 2, Hepatitis B and C and EBV serology, CMV/EBV DNA titres Bone marrow biopsy is indicated and some selected patients it may not be clinically needed or appropriate[14].	Echocardiography where appropriate and potentially when cardiotoxic agents are being used. Fertility-preserving treatments, such as sperm cryopreservation for male and referral to a fertility specialist in female patients, should be considered for eligible patients. Details should include; date of transplant, organ type, and immunesuppresion regimen. All patients require assessment of the function of the transplanted organ, ideally directed by the transplant physician.	All patients should have a staging CT- scan of neck, chest, abdomen and pelvis at diagnosis to inform the treatment decisions and to act as a baseline for the assessment of response. Where available, PET-CT scan should be utilised for staging over CT scan.

Abbreviations: CMV, cytomegalovirus; CT, computed tomography; DNA, Deoxyribonucleic acid; EBV, Epstein-Barr Virus; HIV, Human immunodeficiency virus;

The role of PET-CT in the staging of PTLD is less well defined when compared to lymphoma in the immunocompetent. A recent systematic review and meta-analysis where the majority of the cases (215/269) were of the monomorphic subtype of PTLD has confirmed the utility of PET-CT for staging. PET-CT detected additional

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sites of disease in 28% of cases, resulting in upstaging in 15% when compared to CT alone. End of treatment PET-CT appears to have moderate sensitivity (71%) and specificity (73%) for predicting relapse but a higher negative predictive value of 92%[15]. In addition, PET-CT may also have a role in the diagnostic work up as demonstrated in a retrospective study published by Montes de Jesus *et al*. They reported a sensitivity of 85% and specificity of 90% with a positive predictive value of 83% and a negative predictive value of 92% in PTLD[16]. Despite the limitations of these PTLD data, a staging PET-CT, where available, should be performed in line with recommendations for FDG-avid lymphomas in the immunocompetent patients[17,18].

Magnetic resonance imaging (MRI) or CT imaging of the brain, orbits and sinuses is recommended for patients with suspected central nervous system (CNS) or craniofacial disease. Diagnostic lumbar puncture for cerebrospinal fluid (CSF) analysis, including cytology and flow cytometry, is recommended for patients with suspected CNS involvement.

Recommendations:

- **Where possible a surgical excisional or incisional biopsy is recommended to establish a diagnosis. Where this is not possible, a core needle biopsy is an alternative (1A).**
- **Staging with a CT is recommended in all patients where PET-CT is not available (1A).**
- **Where available a PET-CT should be utilised for staging in line with recommendation for FDG-avid lymphoma (1B).**

Multidisciplinary Approach to Care

Patients with PTLD present a multifaceted clinical challenge. It is essential to consider not only the patient's general health, but also the histological subtypes and clinical stage of the lymphoproliferative disorder, the SOT function, the degree of immunosuppression, and the modalities of therapy available. A management plan should be agreed by a core multidisciplinary team (MDT) which should include transplant physicians, haemato-oncologists, haematopathologists, radiation-oncologist and radiologists[19]. The MDT process should be in line with the 2016 NICE guideline (NG47), 'Haematological cancers: improving outcomes'. It is recommended that the lead MDT should be the lymphoma MDT and where possible, a representative of the transplant team should attend.

Recommendations:

- **All cases should be discussed at a haemato-oncology MDTM with experience in PTLD management, with input from the organ transplant physicians (1A).**
- **All diagnostic material should be reviewed by a haematopathologist (1A).**

Prognostic Scoring

There is no universally accepted prognostic scoring system specific for PTLD. This is a result of most prognostic scores included varying risk factors, heterogeneous patients or treatments and are often retrospective or single institution series. However, a number of adverse risk factors have been identified in various prognostic scoring systems including poor performance status, EBV-negative tumour, graft involvement, monomorphic histology, older age, CNS or bone marrow involvement, raised LDH, and hypoalbuminaemia[2,6,20,21,22].

The Ghobrial prognostic score allocated one point for ECOG >2, monomorphic disease and graft involvement to demonstrated significant for overall survival (OS) but its utility was limited due to majority of patient having monomorphic disease (96%) and only 16% has graft involvement[22,23]. Another prognostic scoring system utilised in PTLD is the International Prognostic Index (IPI) for non-Hodgkin lymphoma. Although, it was not specifically developed for PTLD[24], it has validity in this setting[25- 28]. IPI is based on the baseline parameters age, stage of disease, EGOG performance status, extranodal site involvement and LDH. IPI in relation to PTLD is separated into two groups low (0,1,2 points) and high (3,4,5 points) which has a significant effect on OS (p=0.006) and treatment related mortality, but did not have an effect on progression free survival (PFS)[28]. In addition, another prognostic score, the PTLD Prognostic Index is a variation of the IPI with baseline factors of age, ECOG performance status and LDH. Similar to the IPI is had significant effect on the OS (p=0.032) but not the PFS and a large bias towards one risk group [27,28]. More recently, real world analysis of CD20-positive B-cell PTLDs incorporated the IPI to demonstrate its utility. The IPI was statistically significant, with low IPI risk (0-2 points) exhibiting a superior OS compared to high IPI risk (≥3 points) at 3yrs (OS 78% versus 54%, respectively, p=0.0003)[27]. Thus, the IPI is a pragmatic choice of upfront score to use[26–28].

Management of PTLD

Given the rarity of the diagnosis and the histological heterogeneity together with the medical complexity of the patients, there are no data available from randomised trials to inform management. For the rarer subtypes and in the relapsed/refractory setting, treatment decisions are informed by small case series and case reports. However,

for the commonest monomorphic subtype, DLBCL, there is robust data from prospective phase II studies that have informed existing treatment algorithms[23,24].

Reduction of Immunosuppression

Where safe to do so, immediate reduction in immunosuppression (RIS) should be instituted under the direction of the transplant team. RIS aims to partially restore T-cell function. This may be the only treatment required for a select group of patients with low-risk patients which have early lesions, low stage disease and non-bulky disease[21,27,29].

Where RIS is being considered as the sole initial treatment, response should be assessed within 2–4 weeks so that alternative strategies can be promptly initiated in those patients that fail to respond. If a complete remission (CR) is obtained, then no other therapy may be required in patients with low risk factors[29–31]. Close monitoring for rejection of the SOT by the relevant transplant team is crucial in these patients who are in CR and maintained at RIS[29,31,32]. Patients that achieve a PR by RIS alone can either be monitored and reassessed within a further 2-4 weeks or further rituximab based treatment may be considered as described in the section Rituximab +/- chemotherapy[29-31].

The most recent SOT guidelines support the recommendation for RIS[33–35] but none give specific guidance on how this should be achieved. The European Renal Guidelines have been outlined in Table 3, however there have been no recent updates[36].

The American guidelines recommend an alternative approach according to the clinical picture and the extent of the disease[37,38] . A prospective study of sequential RIS according to the clinical picture conducted by the Southwest Oncology Group

(SWOG) on Protocol S9239 had a similar approach, which was then considered best practice[32] as shown in Table 3. Historically, some guidelines suggest stopping all immune suppression in certain clinical scenarios. However, this should only be done with guidance from the transplant team and only if absolutely necessary.

A more pragmatic approach that should be adopted for RIS is to follow the criteria used for entry into the prospective phase II PTLD-1 trial. PTLD-1 trial inclusion criteria included failure of upfront RIS, where the recommendation was to stop antimetabolites (azathioprine and mycophenolate mofetil [MMF]) and reduce calcineurin inhibitors (CNIs) by 30% to 50% while maintaining corticosteroids, if feasible. The response to RIS was assessed early between 2 and 4 weeks and failure of RIS was followed by sequential treatment with rituximab and subsequently by CHOP chemotherapy in adult B cell PTLD[39].

RIS should be considered in conjunction with other therapies, in patients who have risk factors which include clinically aggressive PTLD Ann Arbor stage ≥III, elevated LDH, and more than one extranodal site or a high-risk IPI[27,39,40]. Significant reduction or even interruption of immunosuppression, is more realistic following a renal SOT than a lung or heart transplant, where alternative support strategies for acute rejection are not available[41,42]. Therefore, in patients where RIS is not possible, alternative therapies are indicated.

241 **Table 3: RIS following the American, SWOG and European Renal Guidelines**

Extent of PTLD disease	RIS recommendations
American Guidelines on RIS	
Limited disease	Reduction by 25% of all immunosuppression.
Extensive disease – not critically ill	Reduction of CNIs by 50%. Consider stopping azathioprine/MMF. Maintain prednisolone 7.5/10mgs/day.
Extensive disease – critically ill	Stop all agents except for maintaining prednisolone 7.5/10 mg/day.
SWOG Protocol S9239	
Clinically urgent	Stop azathioprine / methotrexate / cyclophosphamide. Initial reduction of CNIs by 75%. Prednisolone to 7.5 mg/day (glucocorticoid to physiological maintenance dose).
Non-clinically urgent	Stop azathioprine and methotrexate Reduction of CNIs by 50% and further reduction by 50% if not in complete remission by day 14. Reduce glucocorticoids by 50%, with a lower limit of prednisone of 7.5 mg/day.
European Renal Guidelines on RIS	
As per clinical need	Stop azathioprine and cyclophosphamide Reduce CNIs by 50% and maintain steriods. Or withdrawal of all immune-suppressant drugs except for corticosteroids

Abbreviations: CNIs, calcineurin inhibitors; MMF, mycophenolate mofetil

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Recommendations:

- **Reduction in immunosuppression by stopping azathioprine and MMF and reduction of CNIs by 30–50% whilst maintaining or reducing corticosteroids, is recommended in all patients whenever possible, under the guidance of the transplant physician with surveillance of graft function (1B).**
- **Early disease response assessment (at 2–4 weeks) is recommended in those patients following RIS alone so that further treatment can be initiated in those that fail to respond (1B).**

Rituximab +/- Chemotherapy

Front line therapy for monomorphic CD20-positive B-cell PTLD (Figure 1)

The commonest form of PTLD has a CD20-positive, B-cell monomorphic histology similar to DLBCL (see later sections for management of other subtypes).

Rituximab is a monoclonal anti-CD20 antibody that has become a standard of care in patients with polymorphic PTLD, or monomorphic DLBCL-like PTLD, who are unresponsive to initial RIS. The international phase II PTLD-1 trial[39] established sequential therapy of 4 cycles of weekly intravenous rituximab at standard dose (375 mg/m^2) followed by 4 cycles of standard dose CHOP-21 chemotherapy (50 mg/m^2 doxorubicin; 750 mg/m^2 cyclophosphamide, 1.4 mg/m^2 vincristine, 50 mg/m^2 prednisolone) every 21 days alongside mandatory granulocyte colony-stimulating factor (G-CSF). This approach resulted in a median OS of 6.6 years and a clear plateau on the progression-free survival (PFS) curve. Although it is difficult to compare studies, these outcomes compared favourably with those of patients treated with rituximab monotherapy alone, where the median OS was

approximately 1.2–3.5 years[43-45]. Treatment-related mortality (TRM) was reduced to 13% compared to retrospective case series with frontline CHOP therapy which documented TRMs of up to 31%[46] (see Table 4 for a summary of key studies).

In light of the TRM documented in PTLD-1 and the efficacy of rituximab monotherapy, the third amendment of the PTLD-1 study introduced a response-adapted treatment strategy in an attempt to limit the exposure to patients to R-CHOP-21 whilst retaining acceptable response rates and long-term cures. In the PTLD-1/3 trial schema, patients with CD20-positive PTLD who had failed RIS received 4 weekly standard-dose rituximab followed by interim CT restaging around day 50. Patients obtaining a CR were considered 'low risk' and received a further 4 doses of 3-weekly rituximab and then stopped therapy. Patients failing to obtain CR by CT criteria or who progressed during the initial rituximab monotherapy were considered 'high risk' and were switched to 4 cycles of R-CHOP-21. G-CSF was mandated during chemotherapy and prophylaxis against *Pneumocystis jirovecii* (PJP) was recommended. 25% of patients achieved CR at interim CT with rituximab monotherapy and continued with rituximab therapy alone. In the intention to treat population the median time to progression (TTP) was not reached and the 3-year proportion without progression was 75%. Median OS was 6.6 years. TRM was reduced to 8%. On multivariable analysis, initial response to 4 doses of rituximab and a baseline IPI <3 were strongly significant independent favourable prognostic factors[28].

Based on the data available from PTLD-1 and PTLD-1/3 the low-risk group was refined further in the ongoing PTLD-2 study taking into account the initial response to rituximab monotherapy and the IPI at diagnosis. Patients with a low risk of disease progression are defined as those who achieve a CR after the first four courses of

rituximab monotherapy and those with an IPI of 0 to 2 who achieve a partial remission at interim staging. This strategy increases the number of PTLD patients who only require rituximab monotherapy and is likely to reduce grade 3-4 leucopenia, infection, and subsequently the TRM, but retaining a similar OS. This is not an unreasonable approach to adopt in selected patients and furthermore, González-Barca E,*et al,* demonstrated good responses in a prospective phase II trial where 83.3% of patients that achieved PR after rituximab monotherapy progressed to CR with extended treatment with rituximab only[45].

Not all patients will be fit for combination chemotherapy as described above. Using dose-attenuated treatment or alternative less toxic treatment regimens (such as single agent rituximab, corticosteroids, oral etoposide and alkylating agents) can be considered in selected patients[47–50]. Particular attention should be given to cardiac transplant patients with allograft vasculopathy. These patients often develop heart failure with preserved left ventricular ejection fraction (LVEF) on standard echocardiography. Therefore, a normal LVEF does not necessarily indicate good function in this particular group of patients. Liaison with the transplant team to obtain an individual assessment of the current cardiac allograft structure and function is recommended.

In patients where there is an urgent clinical need to treat with immunochemotherapy, rituximab plus anthracycline-based therapy (typically R-CHOP-21) is recommended with RIS as per the treatment algorithms used in DLBCL for the immunocompetent patients[51]. However this should be done with caution as there is a significant risk of TRM with this approach as outlined during the evolution of the PTLD-1 trial[39,45,46,51]. In case of clinical signs of disease progression at any time during rituximab monotherapy or before interim staging, restaging should be performed prematurely,

and R-CHOP-21 should be considered to commence immediately if disease progression is confirmed[43-45].

Response to treatment can be assessed by CT, however, even though the role of interim PET-CT is not yet established it can be considered a more sensitive tool for interim response assessment and should be utilised where available[17,51].

Polymorphic CD20 positive B cell PTLD

Data on the management of polymorphic CD20 positive B-cell PTLD is limited and these cases have been included in the PTLD-1 trial. Therefore, they are treated with the same algorithm as monomorphic CD20 positive B-cell PTLD as described above[28,30,39]. Rarely, polymorphic PTLD can have an overlap with Hodgkin Lymphoma-PTLD and thus the management would be as described in the Hodgkin Lymphoma-PTLD section.

Recommendations:

- **Rituximab monotherapy is recommended for patients with CD20-positive PTLD who fail to respond adequately to RIS as initial therapy (1B).**
- **4 further 3-weekly cycles of rituximab is recommended in patients who obtain CR or complete metabolic remission (CMR) (with Deauville ≤3) after 4 cycles of weekly standard dose rituximab (1B).**
- **4 cycles of R-CHOP-21 immunochemotherapy is recommended in patients who fail to obtain CR or CMR (with Deauville ≤3) after 4 cycles of weekly standard dose rituximab or who clinically progress during these 4 cycles (1B).**

- **Rituximab plus anthracycline-based therapy (typically R-CHOP-21) is recommended with RIS for patients at any time following diagnosis with clinically aggressive lymphoma with critical organ compromise (1B).**
- **Formal assessment of cardiac and renal function should be undertaken in all patients with SOT or in patients where renal or cardiac impairment is suspected (1B).**
- **PET-CT should be considered as end of treatment (EoT) response assessment where available (1C).**
- **PET-CT should be considered for interim assessment where available (1C).**

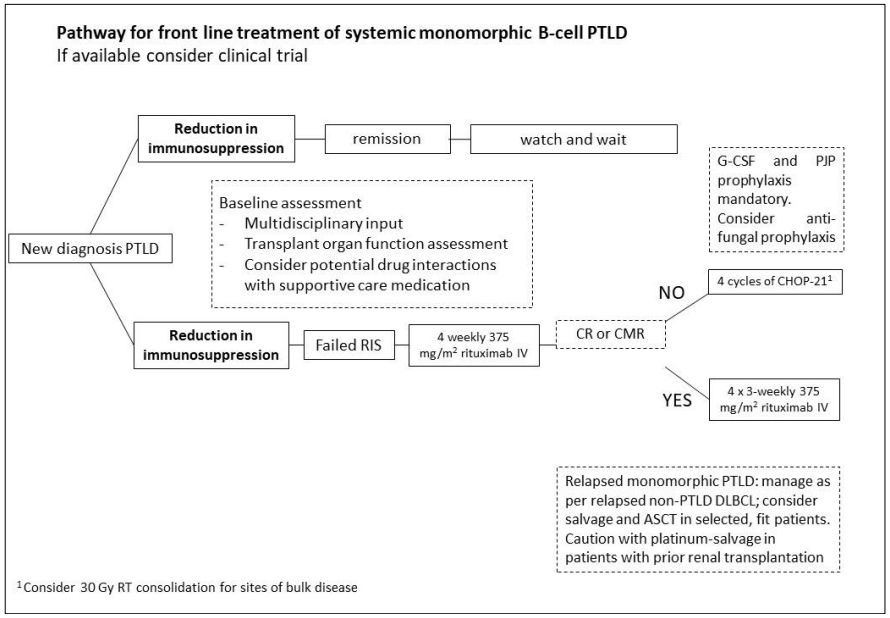

Figure 1: Pathway for front line treatment of systemic monomorphic B-cell PTLD.

All patients with a confirmed diagnosis of PTLD should have clinical and laboratory assessment and adequate staging. All patients with PTLD should be considered for RIS and early assessment of response at 2–4 weeks need to be undertaken. Sequential therapy with rituximab should be started in patients with CD20 positive PTLD, who fail to achieve adequate response to RIS alone. Following re-assessment after initial rituximab treatment, patients in CR should be considered for a further 4 cycles of rituximab and those not in CR should be treated with 4 cycles of R-CHOP-21.

Abbreviations: ASCT, autologous stem cell transplant; CR, complete remission; DLBCL, diffuse large B cell lymphoma; G-CSF, granulocyte-colony stimulating factor; IPI, international prognostic index; PR, partial remission; PJP, *Pneumocystis jirovecii*; RIS, reduction of immune-suppresion; IV, intravenous; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine and prednislone.

Radiotherapy

The role of radiotherapy as a component of treatment for PTLD is undefined. Retrospective, non-randomised heterogeneous case series include patients treated predominantly with RIS and/or chemotherapy, with 7–25 % of cases having radiotherapy included in their initial management[4,30,52]. A retrospective analysis suggested that adults with limited stage disease, regardless of the histological subtype, can obtain durable CRs after surgical resection or radiotherapy, usually with concurrent RIS[53].

Localised monomorphic type DLBCL and Hodgkin lymphoma (HL) PTLD could be considered for treatment with RIS and combined modality treatment in line with standard practice outside the setting of PTLD[51,54,55], or in combination with RIS +/- rituximab in DLBCL if the patient is not eligible for intensive chemotherapy. Radiotherapy may be considered for some extranodal sites, such as the orbit, isolated CNS relapse[56,57] and is an effective therapy in localised extranodal marginal zone lymphomas of the mucosa-associated lymphoid tissue (MALT) type[60–64].

In rare forms of PTLD, radiotherapy tends to be incorporated with the chemotherapy regimens such as in nasal natural killer/T-cell lymphoma[58,59].

The dose and fractionation regimen tends to follow normal lymphoma protocols[51,54,65–67].

Antivirals, intravenous immunoglobulin and interferon-alpha treatment

There remains a paucity of data or further developments to demonstrate effective response of established EBV-positive lymphoproliferative disorders to antiviral agents [68–74] or immunoglobulins either as single agent or in combination with antivirals[75].

The use of interferon alfa (IFNα) remains historical and there are no new developments to recommend its use outside of clinical trials[32].

Recommendations:

- **Involved-field radiotherapy may be offered for selected patients with PTLD in line with standard protocols for specific histological subtypes (2C).**
- **In localised disease, radiotherapy may be offered concurrently with RIS (2C).**
- **Treatment with anti-viral agents and/ or arginine butyrate, IVIG and IFNα is not recommended outside clinical trials (1C).**

Table 4: Front line phase II clinical trials in monomorphic B-cell, CD20-positive PTLD

Reference	Patient number	Years	Treatment approach	Histological subtypes	Overall response	TRM	Survival
PTLD-1/3 Trial [23]	N = 152	2006-2014	Response adapted design: 4 x weekly rituximab (375mg/m^2). If CR 4 further 3-weekly rituximab doses; if non-CR >4 cycles RCHOP-21	85% monomorphic (112/129 DLBCL type) 15% polymorphic	88% (CR 70%) of 126 evaluable	8%	Median OS 6.6 years
PTLD-1 Trial[39]	N = 70	2002-2008	4 x weekly rituximab (375 mg/m^2) followed by 4 cycles of CHOP-21	96% monomorphic	90% (68% CR)	13%	Median OS 6.6 years
Oertel, *et al*, 2005[43]	N = 17	1999-2002	4 x weekly rituximab (375 mg/m^2)	18% polymorphic 82% monomorphic (10/13 DLBCL type)	59% (CR 53%)	Nil	Median OS 3.1 years
Choquet, et al, 2006[44]	N = 43	2000-2001	4 x weekly rituximab (375 mg/m^2)	Of 37 evaluable: 76% monomorphic 11% polymorphic 14% unclassifiable	44.2% (CR/Cru 25.6%)	1 infusion-related death	1-year OS 67% 1-year EFS 72%. Median OS 1.2 years
González-Barca E, et al, 2007[45]	N = 38	2000-2005	Response-adapted design: 4 x weekly rituximab (375 mg/m^2) followed by 4 further doses if PR but not CR	18% polymorphic 82% monomorphic (28/31 DLBCL type)	79% (CR 60%)	3 infective deaths	EFS 42% and OS 47% a 27.5 months

Abbreviations: (R) CHOP, (Rituximab) cyclophosphamide, doxorubicin, vincristine, prednisolone; CR/CRu, complete remission/response/unconfirmed complete response; DLBCL, diffuse large B cell lymphoma; EFS, event-free survival; OS, overall survival; PR, partial remission; PTLD, post-transplantatio lymphoproliferative disease

Therapy for Relapsed or Refractory PTLD

There is no prospective data to guide the treatment of patients with refractory or relapsed (R/R) PTLD. The evidence base is limited to case reports across various histological subtypes[77–79]. In patients who are unresponsive to rituximab, using R-CHOP is a reasonable and logical approach[23,24,80]. A sequential approach as in frontline therapy can be considered if relapse post-rituximab monotherapy occurs late.

Patients with R/R PTLD post R-CHOP have a poor long-term survival with OS <20% as conventional salvage approaches with consolidation autologous stem cell transplantation (ASCT) are challenging to deliver in SOT patients[79,80]. Extrapolating treatments from R/R DLBCL in immunocompetent patients is reasonable[81–84] but this approach has little evidence in R/R PTLD. Particular attention should be paid to the toxicities of salvage chemotherapy in relation to the underlying SOT and patient comorbidities.

Patients should be offered enrolment in a clinical trial where available.

Adoptive Immunotherapy

EBV-specific cytotoxic T-lymphocyte (CTL) immunotherapy potentially offers another approach in the treatment of EBV-positive PTLD whilst avoiding the risk of graft rejection. EBV-specific CTLs utilise either the recipient's own cells to generate autologous EBV-directed CTLs or a bank of partially HLA-matched EBV-specific CTLs to generate a T-cell immune mediated response to these abnormal B cells[85–89].

If available, autologous or allogeneic EBV-directed CTLs should be considered in patients with R/R EBV positive PTLD. An overall response rate (ORR) of 52% has been described in 33 patients who had failed initial therapy, and remission at 5 years

of 14 patients who achieved an initial CR[86]. A recent updated report from the same group using 3rd party allogeneic EBV-specific CTLs has shown ORR of 75% and 3-year OS of 60% in patients with refractory PTLD following SOT[90] . Similar to the results demonstrated by Prockop *et al* where a 54% ORR in 13 PTLD patients who were refractory to rituximab was reported[91].

Trials using CTL specifically for PTLD are small, but the results appear promising and the recent development of chimeric antigen receptor T cells (CAR) T cells reported for B cell malignancies[92,93] suggest that this technology could have a future role in the treatment of PTLD.

Recommendations:

- **Patients that relapse post-R-CHOP should be carefully selected for intensive second line chemotherapy followed by autologous stem cell transplant if a good remission is achieved (2B).**
- **Treatment of PTLD with EBV-specific CTLs should be considered where available with R/R EBV-positive PTLD (1C).**
- **Patients with relapsed/refractory PTLD should be offered clinical trials where available (1C).**

Burkitt Lymphoma-like PTLD

Burkitt-like PTLD has many features in common with sporadic Burkitt lymphoma, but some differences can be observed. A strong association with EBV is described[94], along with an association with 11q aberrations in patients presenting with typical histopathological features but without a demonstrable *MYC* rearrangement[95].

The largest series of 20 patients with Burkitt-like monomorphic PTLD demonstrated that rituximab monotherapy was inadequate at inducing sustained remission (n=3).

Seventy-three percent (8/11) of patients receiving an R-CHOP-like regimen (R-CHOP n=9; R-EPOCH n=1; CHOP n=1) with concurrent RIS attained a CR, which was similar to results obtained with more dose-intensive chemotherapy and concurrent RIS (LLA/LB97 protocol n=2; CODOX-M/IVAC n=1; Burkimab regimen n=3 (5/6) 83% CR)[96]. These results are supported by a small sub-analysis of 7 patients pooled from the PTLD-1 trial and a German PTLD registry[97].

In view of these small series, R-CHOP with concurrent RIS could be considered a reasonable option for Burkitt-like PTLD as in diffuse large B cell lymphoma in the immunocompetent patient. However, dose-adjusted EPOCH-R with appropriate CNS prophylaxis may also represent a clinically appropriate option in selected patients aiming to achieve curative therapy, given clear data for efficacy and tolerability outside the PTLD setting[98,99].

The CNS should always be assessed for overt or occult involvement at baseline and CNS prophylaxis should be strongly considered.

Plasmablastic and plasma-cell myeloma PTLD

There is a paucity of data on these subtypes to recommend a standardised approach and therefore it is reasonable to treat as for the plasmacytoid dyscrasia disease in the immunocompetent . RIS should be incorporated in the management algorithm[100]

T-Cell Lymphoma–PTLD

Peripheral T-cell lymphomas (PTCL) are a rare form of PTLD. They typically occur later after SOT and are often associated with poor outcome. The published evidence base is limited to case reports. A reasonable approach in patients with adequate cardiac function is to combine RIS with anthracycline-based chemotherapy. Treatment algorithms used in immunocompetent patients with T cell lymphoma can

be reasonably adopted on T cell lymphoma-PTLD patients[101]. There are no published cases describing the use of ASCT in first remission in the setting of PTCL-NOS PTLD.

Hodgkin Lymphoma–PTLD

Classical Hodgkin lymphoma-type PTLD (HL-PTLD) is rare and data on optimal therapy are lacking. Patients with PTLD are typically excluded from clinical trials with data largely from cases series[79,102,103]. SEER-Medicare population-level US data suggests that HL-PTLD occurs late, at a median of 88 months post-SOT[102]. HL-PTLD had a 5-year OS of 57% compared to 80% for HL immunocompetent patients treated outside the SOT setting, however patients receiving chemotherapy, particularly HL-specific combination chemotherapy, demonstrated a superior OS[102]. As such, standard combination chemotherapy with ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) with or without radiotherapy may represent a safe and efficacious option alongside RIS in HL-PTLD patients with normal cardiac and pulmonary function [67]. BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisolone), Escalated BEACOPP or BEACOPDac (procarbazine substituted for dacarbazine) should only be considered and used with caution in patients with particularly high-risk disease given the known associated haematological and infection-related toxicities with these regimen(s)[67,104].

Extra-nodal Marginal Zone Lymphoma – PTLD

SOT is estimated to increase the risk of extra-nodal marginal zone lymphoma by 2–3 fold[104]. The predominant site of involvement of mucosa associated lymphoid tissue (MALT) lymphoma is gastric, although isolated cases of colonic and small bowel involvement are described[10,61]. Treatment algorithms are heterogeneous and poorly

standardised. Occasionally EBV-positive MALT lymphoma occurs in the skin and may respond well to RIS in the first instance[12]. Rituximab monotherapy has been shown to be effective and can be a reasonable treatment option[43].

Radiotherapy is an effective treatment in this setting as discussed in the radiotherapy section above. Radiotherapy may be adopted as per the treatment algorithms used in immunocompetent patients with Extra-nodal Marginal Zone Lymphoma[60-64].

PTLD affecting the Central Nervous System

Although the risk of CNS lymphoma is elevated in SOT recipients, it remains between 10-20% of PTLD[106,107]. The histology of CNS-PTLD is typically monomorphic, high grade B-cell lymphoma and all are EBV-positive[108,109]. The disease is usually multi-focal and detectable by MRI but tissue biopsy is recommended given that opportunistic infections may present with similar radiological findings[110].

The overall prognosis is generally considered poor. However, in several recent case series, ORR appear higher than expected (55–75%) regardless of treatment modality, with a median OS in the range of 33–47 months[108,111].

The optimal therapy for CNS-PTLD has not been established and co-morbidity may limit treatment options in many patients. RIS is routinely performed usually alongside radiotherapy resulting in an ORR of 75% in one series[111] and others have reported a median OS of 47 months[108]. The use of RIS, intrathecal chemotherapy and whole brain radiotherapy yielded an ORR of 75% and OS of 62% at 5 years in one series with no serious cognitive impairment in survivors[113].

Intensive, systemic chemotherapy with CNS penetration, such as regimes including high dose methotrexate (HD-MTX) with rituximab, is the standard for

immunocompetent primary CNS lymphoma[114,115] but may be challenging to administer safely due to comorbidities typically renal failure or SOT dysfunction in CNS-PTLD patients. Nonetheless, this approach has been adopted in CNS-PTLD patients with some success[111]. Extrapolating regimens from immunocompetent primary CNS lymphoma can be considered on a case by case basis however, most trials excluded CNS-PTLD patients. The addition of rituximab to chemotherapy in primary CNS lymphoma has shown to improve outcomes and thus in selected patients unfit for chemotherapy single agent rituximab with concurrent RIS may be considered[114–116].

Recently, Prockop *et al*. demonstrated responses with donor and 'third party' (Tabelecluecel) EBV-specific CTLs in patients with EBV-positive CNS-PTLD in patients following haemopoietic stem cell transplant or SOT demonstrating ORR of 63% and 1year OS of 60% in 19 patients[91]. Currently larger studies are ongoing to evaluate this promising therapy, but it may be an option in selected patients where available.

Recommendations:

- **It is recommended that all patients with the less common forms of PTLD be considered for RIS as part of their initial management (1C).**
- **Treatment of less common forms of PTLD with standard of care therapies as per the algorithms outside PTLD setting may be offered with caution due to potential toxicity and patient comorbidity (2C).**
- **Patients with CNS-PTLD should be offered treatment with RIS (it may not always be possible to wait for response to initial RIS before embarking on secondary therapy) followed by combination chemotherapy with rituximab**

in suitable patients depending on adequate organ function and comorbidity (1C).

- **Local radiotherapy +/- corticosteroids with RIS where fitness and comorbidity are limiting factors may be offered in CNS-PTLD (2C).**
- **Where available EBV-specific CTL can be considered for EBV positive CNS-PTLD (1C).**

Supportive Care

Significant TRM has been described in patients with PTLD treated with combination immunochemotherapy, with reports of up to 50% mortality following infection[42,53]. It is therefore appropriate to use G-CSF as primary prophylaxis in this patient group. Prophylactic administration of G-CSF if the risk of febrile neutropenia (FN) is >20% for all planned cycles of treatment should be considered[117,118]. Age is an important risk factor for developing FN which can partly be prevented by G-CSF[117,118].

Given the degree of immunosuppression in patients with PTLD, strong consideration should be given to antibiotic, antifungal (e.g. fluconazole) and antiviral (e.g. acyclovir) prophylaxis during therapy, particularly if treatment is associated with neutropenia as per local protocols. Prophylaxis with co-trimoxazole or equivalent should be considered in all patients and especially in those with a past history of *Pneumocystis jirovecii* pneumonia (PJP). Surveillance for CMV infections should continue in patients with PTLD with guidance from the transplant physician or team.

Patients with past hepatitis B or C infection should be managed in conjunction with a hepatologist[119]. Regular monitoring of liver function is required through treatment, and monitoring of hepatitis B viral load should be considered as per the guidance outlined by NICE CG165[119] or as directed by the hepatologist. Patients with HIV

should be managed under joint care with their HIV physician. The advent of highly active antiretroviral therapy (HAART) has made chemotherapy much more tolerable in the HIV infected non-transplant population with lymphoma[120].

Recommendation:

- **G-CSF is recommended for patients receiving chemotherapy and PJP prophylaxis should be offered to all patients with diagnosis of PTLD (1B).**

Re-transplantation

Re-transplantation may be considered after successful control of PTLD as the risk of recurrence of PTLD after re-transplantation is low[121–123]. The Organ Procurement and Transplant Network/United Network analysis reported favourable outcomes in 69 patients who underwent re-transplantation (27 renal, 22 liver, 9 lung, 6 heart, 4 intestine and 1 pancreas)[124]. Of the 27 renal re-transplants, all patients were alive and 89% of grafts were functioning after a mean follow up of approximately two years. A more recent review of 52 patients reported that recurrence of PTLD after re-transplantation was rare, with only one patient developing PTLD at two years[6].

The timing of re-transplantation depends on the specific organ and clinical need. A number of small studies have examined relisting for renal transplantation between 29 and 100 months following successful treatment of PTLD[124]. In patients where re-transplantation has been successful there has been no reported recurrence of PTLD at 5 year[125].

Therefore, it is sensible to allow adequate time for the patient's immune system to recover to maximise the probability of successful re-transplantation. A period of one year should be considered as a minimum before re-transplantation depending on the organ and clinical need.

Recommendation:

- **Re-transplantation is dictated by clinical need and organ type. A minimum of one year may be considered before re-transplantation, but a longer period may be needed (2C).**

Acknowledgements

The BSH Haemato-Oncology task force members at the time of writing this guideline were Professor Guy Pratt (Chair), Dr Nilima Parry-Jones (Secretary), Dr Simon Stern, Dr Shireen Kassam, Dr Matthew Cullen, Dr Alastair Whiteway, Dr Oliver Miles, Dr Elspeth Payne, Dr Toby Eyre. The authors would like to thank them, the BSH sounding board, and the BSH guidelines committee for their support in preparing this guideline. We would also like to acknowledge Jacky Wilson for the initial literature search and Madeleine Parker who is medical writer from Niche Science and Technology for help with the formatting.

Declaration of Interests

The BSH paid the expenses incurred during the writing of this guidance.
All authors have made a declaration of interests to the BSH and Task Force Chairs which may be viewed on request. NS has received speaker fee/consultancy, advisory board from ROCHE, Janssen and ABBVIE, DT has received financial reimbursement, advisory board from Takeda, Amgen, TE has received financial reimbursement, advisory board and / or research funding from ROCHE, Gilead, Takeda, Janssen, ABBVIE. CF has received consultancy/speaker fees from Abbvie, Addienne, AstraZeneca, Atarabio, Celgene, Gilead, Roche, Sunesis, Takeda and research funding from Abbvie, Adienne, Gilead, Roche,Takeda. TM has received consultancy/speaker fees from Amgen, AstraZeneca, Atarabio, Celgene, Kite/Gilead, Janssen, Novartis, Roche, Takeda and research funding from AstraZeneca and Janssen. SC has received consultancy fees from Roche and advisory board for Atara Bio. The following members of the writing group AS, EA, PA, JP KB have no conflicts of interest to declare.

Review Process

Members of the writing group will inform the writing group Chair if any new evidence becomes available that would alter the strength of the recommendations made in this document or render it obsolete. The document will be reviewed regularly by the relevant Task Force and the literature search will be re-run every three years to search systematically for any new evidence that may have been missed. The document will be archived and removed from the BSH current guidelines website if it becomes obsolete. If new recommendations are made an addendum will be published on the BSH guidelines website (https://b-s-h.org.uk/guidelines/).

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Author Contribution

All authors reviewed the literature and contributed to the drafting and editing of this manuscript. NS developed Tables 1, 2 & 3. TE developed Figure 1 and Table 4.

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