bjh guideline

Management of post-transplant lymphoproliferative disorder in adult solid organ transplant recipients – BCSH and BTS Guidelines

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Summary

A joint working group established by the Haemato-oncology subgroup of the British Committee for Standards in Haematology (BCSH) and the British Transplantation Society (BTS) has reviewed the available literature and made recommendations for the diagnosis and management of post-transplant lymphoproliferative disorder in adult recipients of solid organ transplants. This review details the therapeutic options recommended including reduction in immunosuppression (RIS), transplant organ resection, radiotherapy and chemotherapy. Effective therapy should be instituted before progressive disease results in declining performance status and multi-organ dysfunction. The goal of treatment should be a durable complete remission with retention of transplanted organ function with minimal toxicity.

Keywords: lymphoproliferative, transplant, therapy, chemotherapy.

These recommendations are based on Guidelines on the Surveillance, Diagnosis and Management of Post-Transplant Lymphoproliferative Disorders in Adult Solid Organ Transplant recipients produced under the auspices of the British Committee for Standards in Haematology (BCSH) and British Transplantion Society (BTS) (Parker *et al*, 2009). The group has made recommendations based on a review of key literature to December 2007 with some additional pertinent references and a consensus of expert opinion where no published data is available. This document is part of the guideline and details the recommendations for the management of post transplant lymphoproliferative disorder once the diagnosis has been made.

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The recommendations were made using the Agree instrument (http://www.agreecollaboration.org) and were further reviewed by members of the BCSH and BTS sounding boards, representing practice in both teaching and district hospitals in the UK. The levels of evidence used were those of the US Agency for Health Care Policy and Research (see Tables I and II).

Post-transplant lymphoproliferative disorder (PTLD) is the commonest cause of cancer-related mortality post-solid organ transplant. The reported incidence varies depending on age, transplant type and degree of immunosuppression. The majority of cases in the UK are derived from B lymphocytes and are Epstein Barr Virus (EBV) driven, particularly in the first year post-transplant. In order to determine appropriate therapy a tissue diagnosis should be obtained and reviewed by an experienced lymphoma pathologist using the World Health Organization (WHO) diagnostic criteria (Swerdlow *et al*, 2008).

The optimal treatment of PTLD is still not clearly defined due to lack of randomized phase III trials. Most published data are in the form of case series and must be interpreted with caution, as results will be affected by selection criteria.

Multidisciplinary approach to care

Patients with PTLD present a multifaceted clinical challenge. For optimum outcomes it is essential to consider not only the patient's general health, but also the histological and clinical stage of the lymphoproliferative disorder, the function and necessity of the transplanted organ and, finally, the modalities of therapy available. To this end a management plan should be agreed by a core multidisciplinary team (MDT) of experienced physicians, which should include transplant physicians, haemato-oncologists, histopathologists, and radiologists with particular experience of treating solid organ transplant patients and/or aggressive lymphoproliferative disorders. In some cases the team may require input from transplant surgeons, radiation oncologists, microbiologists and/or palliative care

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Table I. Classification of evidence levels.

I.	a. Evidence obtained from meta-analysis of randomized controlled trials
	b. Evidence obtained from at least one randomized controlled trial
II.	a. Evidence obtained from at least one well-designed controlled study without randomization
	b. Evidence obtained from at least one other type of well-designed quasi-experimental study*
III.	Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case studies
IV.	Evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities

*Refers to a situation in which implementation of an intervention is out with the control of the investigators, but an opportunity exists to evaluate its effect.

Table II. Classification of grades of recommendations.

A.	Requires at least one randomized controlled trial as part of a body of literature of overall good quality and consistency addressing specific recommendation. (Evidence levels Ia, Ib)
B.	Requires the availability of well conducted clinical studies but no randomized clinical trials on the topic of recommendation. (Evidence levels IIa, IIb, III)
C.	Requires evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities. Indicates an absence of directly applicable clinical studies of good quality. (Evidence level IV)

physicians as appropriate. It is suggested that the lead MDT should be the lymphoma MDT and that, where possible, a representative of the transplant team should attend. However, it is appreciated that by the nature of the centralization of solid organ transplant services, patient care will frequently extend across more than one hospital site and often region, and therefore particular care should be taken to ensure adequate communication and discussion between all team members.

Pre-treatment assessment and staging

Patients with PTLD require a comprehensive pre-treatment evaluation. All patients require assessment of the function of the transplanted organ, which is most appropriately directed by the transplant physician. Baseline blood tests should include full blood count, electrolytes, glucose, liver enzymes, urate, lactate dehydrogenase (LDH) and virology (human immunodeficiency virus [HIV] type 1 & 2, hepatitis B, hepatitis C), Furthermore, because of the potential cardiotoxicity of some chemotherapy drugs e.g. anthracyclines, patients require echocardiography and ejection fraction measurement if these agents are considered. All patients should have a staging computed tomography (CT) scan of neck, chest, abdomen and pelvis at diagnosis to inform treatment strategy and act as baseline for later response assessment. The role of positron emission transmission (PET)-CT in altering staging or in providing additional prognostic information remains unproven in this setting and its use should be considered on a case-by-case basis. Some patients may need a bone marrow, imaging of the central nervous system and lumbar puncture as clinically indicated. Patients should be staged using the Ann Arbor staging system (Carbone *et al*, 1971). Many of these investigations can frequently be planned on suspicion of PTLD and carried out whilst awaiting results of the biopsy.

Prognostic scoring

There is no universally accepted prognostic scoring system for PTLD, although a number of groups have identified some poor risk factors for PTLD including poor performance status, EBV-negative tumour, graft involvement (Leblond *et al*, 2001; Tsai *et al*, 2001). The Mayo Clinic analysed their cohort of 107 PTLD patients post-solid organ transplant and identified three factors: poor performance status, monomorphic pathology and graft organ involvement. Patients having two or more factors were five times more likely to die after diagnosis of PTLD when compared with patients with one or none of the risk factors (Ghobrial *et al*, 2005). These poor risk factors are not all included in the International Prognostic Index (IPI) (stage, performance status, extra medullary disease, LDH and age), developed for Non-Hodgkin lymphoma (NHL) in the non-transplant setting. These differences suggest that the use of the standard IPI score in PTLD is inappropriate and that a specific PTLD prognostic index should be developed for this type of lymphoma as has been done with the Follicular Lymphoma Prognostic Index. It may be that other factors, such as presence of B symptoms, disease stage and pathology, may be significant if analysed in a large cohort of patients.

Manipulation of immunosuppressive therapy

Once the diagnosis is suspected immediate reduction in immunosuppression (RIS) should be considered under the direction of the transplant team. As soon as the diagnosis is confirmed it is essential that RIS is commenced. In some patients this may be adequate therapy to achieve complete remission, whilst facilitating further treatment in others. The rationale for RIS should be discussed with the patient, in particular the risks of rejection *versus* PTLD. It is possible, but not recommended, to stop immunosuppression completely in organs where alternative support is available, such as renal and renal/pancreas and in liver, which is relatively resistant to rejection. Ideally RIS should be done over several months, but this is not always possible particularly in aggressive disease (Heim-Duthoy *et al*, 1994). Tsai *et al* (2001) identified a number of features that predicted those patients who would not achieve complete remission (CR) with this as the sole

means of treatment. These were raised LDH, organ dysfunction, and multi-organ involvement. A 90% response rate was achieved with RIS reduction alone in those with no risk factors (Tsai *et al*, 2001).

As part of RIS all myelosuppressive agents, such as azathioprine and mycophenolate should be stopped if possible. There are both European and American Guidelines (European Best Practice Guidelines (EBPG) Expert Group on Renal Transplantation 2002; Paya *et al* 1999) with the former recommending steroid maintenance alone or reducing calcineurin inhibitors e.g, ciclosporin by 50% and stopping all other agents e.g. mycophenolate or azathioprine. The American guidelines recommend;

- Limited disease: a 25% reduction in immunosuppression;
- Extensive disease and critically ill: stop all agents except prednisone 7·5–10 mg/d;
- Extensive disease not critically ill: decrease ciclosporin/tacrolimus by 50%, discontinue azathioprine/mycophenolate and maintain prednisone 7·5–10 mg/d.

Patients need to be monitored, by the transplant team on a weekly basis, for organ function while immunosuppression is reduced; for heart and lung transplants the maximum reduction is to 75–50% of baseline. There will be some cases where immunosuppression cannot be reduced, and in these there should be a low threshold for moving to alternative therapies.

It is important to measure the response to RIS by assessing change in tumour size, reduction in LDH, and resolution of constitutional symptoms. A response to RIS is usually seen within 2–4 weeks (Tsai *et al*, 2001). If the PTLD fully resolves with RIS, then no further treatment may be required. If only a partial response is observed, further treatment is required. Aggressive tumours that fail to respond or progress, despite RIS, require urgent chemotherapy.

Recommendation

- **Reduction in immunosuppression to the lowest tolerated levels (usually by 25–50% of baseline) should be initiated in all patients under the guidance of the transplant physician whenever possible (Grade B, level 3).**

Surgery and radiotherapy

Only a minority of heart, liver and kidney PTLDs are localized at presentation (Leblond *et al*, 1995; Libertiny *et al*, 2001; Taylor *et al*, 2005). PTLD post-lung transplant, appears frequently to involve the transplant alone, with approximately 40% of cases in the first year and 10% of cases more than 1 year following transplant reported to affect the transplanted organ only (Paranjothi *et al*, 2001). If PTLD appears to be localized surgical resection or radiotherapy may result in long-term disease-free survival. However, this may not be an option in tumours involving life-preserving grafts (e.g. heart) and may result in loss of graft function in non-life preserving grafts (e.g. kidney). The decision for graft resection or radiotherapy has to be balanced against the risks of alternative strategies, such as RIS alone, with the risk of progression of disease or the short and long term risks of chemotherapy, but where graft preservation is expected (Swinnen, 2001; Taylor *et al*, 2006; Buadi *et al*, 2007).

Surgery

Surgery plays a role in the management of a minority of patients with PTLD. First, surgical excision may be required in order to establish a tissue diagnosis, particularly if needle core biopsy is not practicable. Excision biopsy of isolated lesions undertaken for diagnostic purposes may, in some cases, be an effective component of first-line treatment, although surgery alone is not sufficient treatment and should be used in combination with other therapies (Foroncewicz *et al*, 2006). Surgical intervention is also usually required for the emergency management of gastrointestinal PTLD that presents acutely with perforation, intestinal obstruction or intractable haemorrhage. In such situations laparotomy and surgical excision of the affected segment of bowel is needed to avoid early mortality. It is also important to note that perforation of gastro-intestinal PTLD may occur during treatment of gastro-intestinal PTLD with anti-CD20 antibodies or chemotherapy and requires prompt laparotomy and, ideally, surgical resection of the affected intestine (Kollmar *et al*, 2002; Hsu *et al*, 2009). Surgery (or radiotherapy) may also be required for other local complications of PTLD.

Apart from aiding diagnosis or dealing with local complications of PTLD as outlined above, the value of surgical resection of PTLD or de-bulking of tumour as a component of first-line treatment has not been demonstrated. Publications documenting the treatment of PTLD typically state that surgical excision, often combined with RIS has a role in the initial treatment of those patients with localized PTLD, particularly where the disease is readily amenable to surgical excision, e.g. localized lesions of the gastrointestinal tract (Tsai *et al*, 2001). However, there is little or no comparative information on the effectiveness of surgical excision *versus* other treatment modalities, such as chemotherapy and anti-CD20. The largest experience of PTLD after cardiac transplantation (274 cases) is provided by the Israel Penn International Transplant Tumour Registry of US centres (Aull *et al*, 2004). 11·5% of patients underwent monotherapy comprising 'surgical debulking' and a further 10% underwent RIS along with surgical resection. Patient survival was higher overall in those patients who received surgery than those who did not (33% vs. 17%) but this may simply reflect patient selection bias. In a recent single institution study of 27 adults in the US who developed PTLD after thoracic or abdominal organ transplantation, surgery was the initial therapy in nine (33%) patients and comprised resection of localized disease or, in four patients with extensive disease and graft involvement

(kidney or pancreas), surgical removal of the graft and discontinuation of immunosuppression (Buadi *et al*, 2007).

In patients with extensive disease and a non-life supporting graft (kidney or pancreas transplant) surgical removal of the graft and discontinuation of immunosuppression is an option, particularly if chemotherapy would not be tolerated or the graft has been failing for another cause. However, there is no evidence that early removal of the transplant is essential and, if PTLD responds adequately to non-surgical first-line therapy, removal of a functioning graft should prove unnecessary.

Radiotherapy

The role of radiotherapy as a component of first-line treatment for PTLD is difficult to determine as there are no randomized controlled trials. Reports, of retrospective, non-randomized case series include a heterogeneous group of patients treated predominantly with RIS and/or polychemotherapy, with 0–18% of cases having radiotherapy included in their initial management (Dotti *et al*, 2002; Bates *et al*, 2003; Reams *et al*, 2003; Aull *et al*, 2004). One retrospective analysis suggested that adults with limited disease, regardless of the histological subtype, can obtain a complete and sustained remission after surgical resection or radiotherapy, usually associated with RIS (Dotti *et al*, 2002). This may be considered in monoclonal polymorphic disease or low grade follicular lymphoma.

Monoclonal, monomorphic disease is typically aggressive with poor prognosis and, like Burkitt lymphoma, should be primarily treated with chemotherapy, with radiotherapy reserved for palliation. Localized Diffuse Large B-Cell and Hodgkin lymphoma could be considered for treatment with RIS and radiotherapy, especially where patients are not eligible for intensive chemotherapy because of organ compromise. Radiotherapy should be considered for specific sites, such as orbit and isolated central nervous system (CNS) relapse (Douglas *et al*, 2002; Buell *et al*, 2005) and rarer tumours such as nasal Natural Killer T-cell (Kwong *et al*, 2000; Kwong, 2005) and extranodal marginal zone lymphomas of the mucosa-associated lymphoid tissue (MALT) type (Wotherspoon *et al*, 1996; Hsi *et al*, 2000; Aull, *et al* 2003). A study of 136 patients with CNS disease suggests that radiotherapy should be considered for isolated CNS relapse.(Buell *et al*, 2005).

For those with life-threatening symptoms due to obstructive symptoms or cord compression emergency radiotherapy should be considered. Radiotherapy is useful as palliation for those patients with obstructive symptoms who fail to respond to chemotherapy and monoclonal antibodies (Kang *et al*, 2004; Webber & Naftel, 2006).

A case report on the use of radioimmunotherapy has been published, but there is no strong evidence to recommend this approach (Jaeger *et al*, 2005).

The dose and fractionation regimen used tends to follow normal lymphoma protocols, using up to 4000 cGy in 20 fractions over 4 weeks to sites of involved disease (Aull *et al*, 2004). Lower doses should be used for CNS radiotherapy and palliation. Acceptable regimens used for palliation are 2000 cGy in five fractions over 1 week, or 400–450 cGy in 2–3 fractions (Girinsky *et al*, 2000; Kang *et al*, 2004).

In conclusion, radiotherapy is recommended for consideration as part of therapy in localized disease, but in higher grade disease is not appropriate as sole therapy with or without Rituximab, although it may be used for patients who are unsuitable for chemotherapy and in palliative situations.

Recommendation

- **Resection or radiotherapy may be adequate treatment of localized PTLD. In patients with life-preserving grafts or those with non-life preserving grafts in whom resection would mean loss of the transplanted organ, and who are deemed suitable, alternative treatment, such as rituximab and/or chemotherapy are preferred (Grade C, level 3).**

Rituximab and/or chemotherapy

Rituximab

Rituximab is a monoclonal antibody directed against CD20, an antigen expressed on the surface of mature and immature B lymphocytes. It has been shown to have significant efficacy and survival benefit in many B cell lymphomas (Campbell & Marcus, 2003). Single agent rituximab is rarely effective in high grade B cell lymphoma in the non-transplant population. However, there are a number of anecdotal reports of successful use of single agent rituximab in the management of PTLD in recipients of lung, liver, kidney, intestine and heart transplants (Cook *et al*, 1999; Oertel *et al*, 2000; Zilz *et al*, 2001; Berney *et al*, 2002; Pham *et al*, 2002).

Case series and phase II studies of rituximab monotherapy following RIS have confirmed its efficacy in inducing remission in 44–65% of PTLD patients (Milpied *et al*, 2000; Blaes *et al*, 2005; Jain *et al*, 2005; Oertel *et al*, 2005; Choquet *et al*, 2006). Toxicity appears to be low, but significant numbers of patients progressed on therapy or relapsed after rituximab (Choquet *et al*, 2006). Therefore, while an effective strategy in some, for most, rituximab monotherapy is inadequate.

In order to refine patient selection for the different modalities of therapy some groups have tried to identify at diagnosis patients likely to have a poor response to rituximab monotherapy. One study suggested that good response in late PTLD was only seen when rituximab was used after either surgical resection or radiotherapy (Dotti *et al*, 2001) and, in another, EBV-negative PTLD did not respond to rituximab and subsequently required chemotherapy (Oertel *et al*, 2005). Other reports have found no difference in response between EBV and non-EBV associated PTLD (Trappe *et al*, 2007). Choquet *et al* (2006) have proposed a risk score for identifying patients with PTLD most likely to respond to RIS with

rituximab monotherapy. They propose a prognostic score of the following three factors:

- age >60 years
- Eastern Cooperative Oncology Group (ECOG) performance status 2–4
- raised LDH

In the low risk group (0 risk factors), intermediate risk group (1 risk factor) and high risk group (more than 1 risk factor) the 1- and 2-year survival was 100%, 79%, 36% and 88%, 50% and 0%, respectively (Trappe *et al*, 2007). The authors suggested that rituximab monotherapy is inadequate for intermediate and high risk groups and recommend rituximab in combination with chemotherapy as initial treatment for such patients.

Chemotherapy

Increasing intensity of treatment for PTLD results in higher response rates but increased toxicity. Anthracycline-based chemotherapy in combination with rituximab (e.g. R-CHOP; rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone) is now generally considered to be the standard of care in non-transplant DLBCL patients (Coiffier *et al*, 2002; Campbell & Marcus, 2003; Feugier *et al*, 2005; Pfreundschuh *et al*, 2008). Such treatment strategies have also been shown to be effective in achieving long-term disease-free survival in patients with PTLD (Jain *et al*, 2005; Elstrom *et al*, 2006; Taylor *et al*, 2006; Buadi *et al*, 2007). Overall response rates are higher than those reported for rituximab monotherapy and range from 65% to 100%. Therapies that result in high complete remission rates are associated with high cure rates with overall survival approximately 65% at 1 year (Orjuela *et al*, 2003; Gross *et al*, 2005; Jain *et al*, 2005; Elstrom *et al*, 2006; Fohrer *et al*, 2006; Taylor *et al*, 2006; Choquet *et al*, 2007). Concerns about loss of graft function on chemotherapy have generally not been borne out with very low rates of graft loss reported.

In a retrospective analysis of patients in whom anthracycline-based chemotherapy was used as first-line therapy with RIS for all patients with monomorphic PTLD, complete response rate of 69% and 5-year disease-free survival of 62% were reported with little toxicity (Taylor *et al*, 2006). The authors of this study suggested patients with morphological high grade malignant lymphoma should receive prompt treatment with an anthracycline-based chemotherapy regimen. In a separate retrospective study comparing RIS, rituximab alone, chemotherapy and rituximab plus chemotherapy, the data suggests that rituximab plus chemotherapy may result in better outcomes for patients with late onset PTLD, with all six patients alive and in complete remission after a median of 34·5 months (range 8–48 months) follow up (Tulpule *et al*, 2005). The above stratification has yet to be tested prospectively, but the approach seems reasonable, non-toxic, and may reduce the need for intensive chemotherapy in good risk patients.

Rituximab plus chemotherapy appears to be effective and well tolerated in selected patients with low risk of transplant organ loss. Despite appearing more effective, rituximab plus chemotherapy is more toxic than RIS ± rituximab alone. Rituximab plus anthracycline-based chemotherapy (where not relatively contraindicated – see below) is therefore recommended for patients with B cell PTLD who fail to respond adequately to reduction RIS and rituximab monotherapy. We suggest that rituximab plus chemotherapy should be used for patients who fail to respond within 8 weeks of rituximab alone and it should be considered immediately at any stage following diagnosis for patients with clinically aggressive disease or those with critical organ compromise.

PTLD affecting the central nervous system

The treatment of PTLD in the CNS is problematic and the prognosis poor. Rituximab and the chemotherapeutic drugs discussed above do not cross the blood brain barrier. Steroids may improve symptoms in the short term but are not curative. A review of 289 patients with primary CNS NHL after solid organ transplant reports a mortality of 88%, of which 67% died of lymphoma (Penn & Porat, 1995). In that report local radiotherapy was the most successful treatment modality and 32 of the 39 patients in whom a complete response was observed were treated this way. However, 69 patients treated with radiotherapy did not respond to treatment and died. There is a single case report of complete remission of CNS PTLD following intrathecal anti B cell antibody administered through an Ommaya reservoir (Stephan *et al*, 1992).

High dose methotrexate (HD-MTX) 3–5 doses >3 g/m^2 delivered over a maximum of 2–3 h at intervals of not more than 2–3 weeks is the treatment of choice in the non-transplant population with primary CNS lymphoma (Marcus *et al*, 2007; Ferreri *et al*, 2009). It has been used in PTLD patients with some success (Taj *et al*, 2008; Nabors *et al*, 2009). Methotrexate is renally excreted and should be avoided in patients with renal or liver impairment. Even in the non-transplant population morbidity and mortality is significant and only a minority of patients with cerebral PTLD will be suitable for such treatment.

Recommendation

- **Rituximab monotherapy is recommended for clinical low risk PTLD who fail to respond adequately to RIS. Clinical low risk is defined as none of the following risk factors: age <60 years, raised LDH, performance status ECOG grade 2-4 (Grade B, level 3).**
- **Rituximab plus anthracycline-based chemotherapy is recommended for patients who fail to achieve an adequate remission or progress despite previous RIS and Rituximab monotherapy (grade B, level 3).**
- **Rituximab plus anthracycline-based therapy should be considered with RIS for patients at any time following diagnosis with clinically aggressive lymphoma or those with critical organ compromise (Grade C, level 4).**

- **PTLD affecting the CNS should be treated with RIS followed by local radiotherapy ± steroids although some young, fit patients may be considered for HD-MTX (Grade C, level 3).**

Less common forms of PTLD

T cell lymphoma

In the non-transplant population, T cell lymphoma is generally aggressive in its behaviour and prognosis poor when compared to B cell malignancy. Where possible, advanced stage T cell PTLD should be treated with chemotherapy (e.g. CHOP) with radiotherapy/surgery used for localized disease. The clonal proliferation of large granular T lymphocytes seen in some post-transplant patients is not thought to represent a true PTLD and should NOT be treated as such.

Burkitt lymphoma

Burkitt lymphoma is a clinically highly aggressive lymphoma with a short tumour doubling time (as little as 24 h) and is associated with a translocation involving the *MYC* oncogene. Such tumours are rare in the post-transplant setting, CNS disease at presentation is not uncommon and staging investigations should therefore include magnetic resonance imaging of the brain and lumbar puncture.

The CODOX-M/IVAC (cyclophosphamide, vincristine, doxorubicin, high-dose methotrexate/lifosfamide, etoposide and high-dose cytarabine) regimen is extensively used in non PTLD Burkitt Lymphoma and is regarded by many as the standard regimen. However, it is associated with significantly greater toxicity than CHOP-like regimens and as such may not be suitable for the majority of patients with Burkitt lymphoma or Burkitt-like lymphoma occurring in the post transplant setting (Mead *et al*, 2008). Regimens that may be preferable in Burkitt Lymphoma PTLD, with a similar toxicity profile to CHOP, include dose adjusted (da) EPOCH-R (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, rituximab) (Wilson *et al*, 2002). Although the efficacy and toxicity of da-EPOCH specifically in Burkitt Lymphoma/PTLD are largely unknown it has been found to be highly efficacious in HIV-associated lymphoma (Little *et al*, 2003). In such cases consideration should be given to one of these more intensive regimens mentioned above or others identified as effective in Burkitt lymphoma if patients are deemed fit enough to undergo this type of therapy.

Low grade B cell lymphoma

Extranodal marginal zone lymphomas, MALT-type may occur in any mucosal tissue and have been described post transplant (Hsi *et al*, 2000). MALT lymphoma is commonly localized to the stomach and is usually *Helicobacter pylori*-related. Antibiotic eradication therapy is often effective in the non-transplant population, however, patients with persistent symptomatic disease post-antibiotics or *Helicobacter pylori*-negative MALT lymphoma of the stomach may respond well to localized radiotherapy, rituximab or alkylator monotherapy. When considering treatment for symptomatic low-grade lymphoma post-transplant, rituximab, alkylators and radiotherapy should be used in preference to toxic therapies, such as combination chemotherapy, although in stage III-IV disease R-CVP (rituximab, cyclophosphamide, vincirstine, prednisolone) may be appropriate.

Hodgkin lymphoma

Advanced stage Hodgkin lymphoma (HL) should be managed with ABVD chemotherapy (which has a similar toxicity profile to CHOP in the non-transplant population) with a view to curing suitable patients (Diehl *et al*, 2003). ABVD contains an anthracycline drug and platinum or gemcitabine or alkylator-based therapies, e.g CHlVPP (chlorambucil, vinblastine, procarbazine, prednisone) may be substituted in patients with cardiac dysfunction or following cardiac transplant (Vose *et al*, 1991). Localized HL may be successfully treated with radiotherapy alone; although less effective than chemotherapy plus radiotherapy it is associated with less treatment-related toxicity and chemotherapy can be reserved for the patients that relapse.

Chemotherapy in patients with cardiac disease

Anthracycline drugs are effective in PTLD, but cardiotoxic, and relatively contraindicated in patients with impaired cardiac function. In patients where physicians elect to avoid anthracycline-based chemotherapy (e.g CHOP), but in whom a curative approach is deemed an appropriate therapeutic goal, then alternative regimens to consider include platinum-based combinations. In one pilot study carboplatin in combination with etoposide produced durable complete remissions in five out of nine patients treated for relapsed or refractory PTLD (Oertel *et al*, 2003). The combination of gemcitabine, cisplatin and steroid has clinically significant activity in the non-transplant population with aggressive lymphoma (Chau *et al*, 2003) and seems a reasonable alternative in patients with cardiac disease. An alternative is to omit the anthracycline and use CVP (cyclophosphamide, vincristine and prednisone) although this is known to be less effective than CHOP in non-transplant associated DLBCL but has been used in the setting with some success (Orjuela *et al*, 2003).

In cardiac transplant patients the ejection fraction is usually normal, but this may not accurately reflect sensitivity to anthracycline toxicity. Therefore, if an anthracycline is deemed necessary it is suggested that a reduced dose should be considered, such as in the PMitCEBO (prednisolone, mitoxantrone, cyclophosphamide, etoposide, bleomycin, vincristine) regimen.

Chemotherapy in patients with renal disease

Platinum drugs are nephrotoxic and renally excreted, therefore, when considering such regimens, special care must be taken. In kidney transplant recipients even with 'normal' kidney function, platinum-based drugs should be used with caution and preferably avoided, so that if physicians do elect to use platinum (at the appropriately adjusted dose for the glomerular filtration rate) then provision should be made for the potential need for renal replacement therapy.

Fludarabine (also renally excreted) based combinations can be very effective in lymphoma but its effectiveness in PTLD is largely unknown and care should be used in the face of renal impairment.

Central nervous system prophylaxis

For patients perceived to have an increased risk of CNS relapse during local MDT discussions then standard CNS chemoprophylaxis should be employed as per local policy. If it is to be used, then particular consideration should be given to the use of intrathecal methotrexate rather than high dose intravenous methotrexate where there are concerns with regard to patient suitability due to renal or liver function or frailty.

Poor performance status

Not all patients will be fit for combination chemotherapy as described above. In such patients with poor performance status and aggressive lymphoma, who fail RIS, then alternative less toxic treatment regimens to consider would include rituximab monotherapy, steroids, oral etoposide, alkylating agents, or combination chemotherapy such as R-CVP (Orjuela *et al*, 2003). Outcome with this therapy is likely to be poor and radiotherapy for symptomatic localized disease may be the best option.

Supportive care

Significant treatment-related morbidity and mortality has been described in patients with PTLD treated with combination chemotherapy, with up to 50% mortality from infection reported. Recent reports incorporating the use of prophylactic granulocyte colony-stimulating factor (G-CSF) and/or prophylactic antibiotics have shown death from infection rates during chemotherapy from 0–30% with chemotherapy. American Society of Clinical Oncology (ASCO) guidance for the use of colony stimulating factors suggests primary prophylaxis in patients with high risk of febrile neutropenia based on coexisting medical problems (Smith *et al*, 2006). Therefore, it would seem appropriate to use G-SCF as primary prophylaxis in this patient group.

Given the degree of immunosuppression in patients with PTLD, consideration should be given to antibiotic, antifungal and antiviral prophylaxis during therapy, particularly if treatment is associated with neutropenia. Drugs to consider include ciprofloxacin, triazole antifungal drugs and aciclovir. Some physicians may wish to consider the use of co-trimoxazole prophylaxis in patients with a past history or perceived susceptibility to *Pneumocystis jeroveci* pneumonia (PCP). Surveillance for cytomegalovirus (CMV) infections should continue to occur in patients with PTLD although initiation of surveillance because the patient has developed PTLD does not seem warranted.

Patients with chronic viral infections require special consideration. Patients with past hepatitis B or C infection should be managed in conjunction with a hepatologist. Those with hepatitis B should receive at least lamivudine prophylaxis starting 1 week before immuno-chemotherapy and for up to a year following completion of chemotherapy to reduce the risk of hepatitis flare. Regular monitoring of liver function is required through treatment, and monitoring of hepatitis B viral load should be considered.

Patients with HIV infection 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.

Recommendation

- **Prophylactic GCSF and anti infective agents are recommended for patients receiving chemotherapy (Grade C, level 4).**

Adoptive immunotherapy

Manipulation of the transplant recipient's immune system to reduce the risk of developing PTLD and to improve response to therapy for PTLD has many attractions. A number of different techniques have been used, unfortunately with somewhat limited success to date although some areas are looking promising.

In this treatment the recipient's own cells are used to generate autologous EBV-directed cytotoxic Tcell (CTL) lines. Alternatively, a bank of partially HLA-matched EBV CTLs can be maintained. The advantage of this approach includes avoiding the risk of graft rejection that follows immunosuppressive therapy reduction and good patient tolerance of the infusion of cytotoxic T-lymphocytes.

It may be that this approach is most applicable as a prophylactic treatment particularly for high-risk cases. In one group of 23 paediatric solid organ recipients autologous EBV-specific CTLs were generated from peripheral blood. The recipients were defined as being at high risk of PTLD because of the finding of high EBV DNA load. In five of the seven patients treated there was between a 1·5–3 log decrease in EBV-specific DNA, whereas in two there was no reduction in EBV load (Comoli *et al*, 2002). In a similar study in a paediatric

population of heart and liver transplant recipients, 12 recipients defined as high risk for PTLD received autologous CTL infusions without significant toxicity. In this report there was no decrease in viral load in peripheral blood mononuclear cells, no patients developed de novo disease, the four cases with previously treated disease remained in remission and one with liver PTLD showed a complete response, and the one case with ocular PTLD showed a partial response (Savoldo *et al*, 2006). The development of a patient-specific autologous cell line is inevitably a relatively slow progress. The alternative is a bank of EBV CTLs harvested from healthy EBV seropositive donors that are then cryopreserved and the closest possible human leucocyte antigen (HLA) match infused into the recipients. This approach has been reported by one group (Haque *et al*, 2002). Eight patients were treated with three achieving a complete and one a partial response. A further report of a phase II study by the same group in a population of 33 PTLD patients, who had failed conventional therapy, showed that 64% of patients had a response at week 5 after adoptive therapy that persisted for up to 6 months. Although a complete response was only observed in 14 patients and was related to the degree of HLA match between the patient and donor lymphocytes, the data provides some encouragement for larger clinical trials using this approach to manage PTLD especially in patients who have failed conventional therapy (Haque *et al*, 2007).

Recommendation

- **At present, treatment with EBV-specific cytotoxic T lymphocytes is not recommended outwith a clinical trial. However, further studies using either autologous or allogeneic banks of EBV CTLs are warranted (Grade C, level 3).**

Anti-viral treatment

There has been a scattering of case reports showing a response by EBV-positive lymphoproliferative disease (LPD) to antiviral agents, such as ganciclovir and aciclovir (Pirsch *et al*, 1989; Delone *et al*, 1995). Whilst it is known that EBV-transformed cells do not express thymidine kinase, which is essential for these agents to be metabolized into the active drug within the cell, there remains debate as to whether ongoing active EBV replication also contributes to the pathogenesis of PTLD. Pre-emptive use of antiviral agents, such as ganciclovir and valganciclovir, have also been evaluated in patients with EBV replication, but who have not developed overt LPD, with mixed results. A new anti-CMV compound, maribavir, which targets the cytomegalovirus UL97 protein kinase has been shown to have substantial *in vitro* activity against EBV (Williams *et al*, 2003).

More promising than the currently available anti-viral agents alone, has been some work combining arginine butyrate with ganciclovir. *In vitro*, this chemical induces the expression of cellular thymidine kinase thus making EBV-infected cells susceptible to the actions of ganciclovir (Mentzer *et al*, 1998). There has been a phase 1/2 clinical trial of this combination in 15 chemotherapy refractory patients, with 10 showing significant antitumor responses, four complete responses and six partial responses within one treatment cycle (Perrine *et al*, 2007).

Recommendation

- **Treatment with anti-viral agents and/or arginine butyrate is not recommended outwith a clinical trial (Grade C, level 3).**

Immunological agents

Intra-venous immunoglobulin (IVIg)

There is a paucity of published case experience for the use of IVIg post-solid organ transplantation to treat PTLD. It was included as part of combination therapy in three recipients of autologous stem cell transplants along with ganciclovir, steroids and Interferon and, in one case, rituximab (Jenkins *et al*, 2002). It is not possible to assess the contribution of IVIg and therefore any role in PTLD management.

Interferon alpha

There is a phase II trial of RIS and with a concomitant antiviral therapy progressing to interferon and then chemotherapy if there was failure of tumour regression. Of 20 patients entered only one achieved a durable complete response with interferon, seven went on to receive chemotherapy and five achieved complete response (Swinnen *et al*, 2008).

The majority of data relating to this agent are anecdotal case reports with 57 cases collected in one review (Davis, 2001). The reviewing author, who has significant clinical experience, emphasized that regression is seen within 3 weeks if Interferon is going to be effective. Although less toxic than chemotherapy, interferon is commonly associated with fatigue, myalgia, arthralgia, anorexia and marrow suppression. In renal transplants interstitial oedema resulting in graft dysfunction can be seen. In addition, acute graft rejection occurs in about a third of patients. The contribution of interferon and RIS is impossible to separate (Davis *et al*, 1987). The risk of rejection, which is usually steroid-responsive, is of course of particular concern with recipients of life-sustaining transplants. In the 2001 update none of the newly recruited patients had achieved a complete remission.

Recommendation

- **Treatment with Interferon or intravenous immunoglobulin is not recommended outwith a clinical trial (Grade B, level 3).**

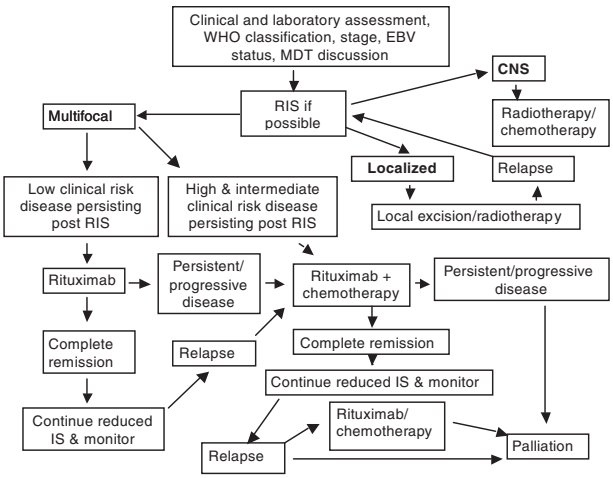

Fig 1. Algorithm for management and treatment of PTLD. Clinical risk assessment is based on age >60 years, raised LDH, ECOG 2–4; if none of these factors treat as low risk (Choquet *et al*, 2007). RIS should be started as soon as the diagnosis is suspected. Patients, for whom reduction in immunosuppression is inappropriate, should move directly to the appropriate therapy. MDT, multidisciplinary team; RIS, reduction in immunosuppression; IS, immunosuppression.

Treatment algorithm for PTLD

An algorithm for the treatment of PTLD after solid organ transplantation is shown in Fig 1. All patients should be staged and tumours histologically classified according to WHO criteria. The EBV status of the tumour should be established. Surgical resection and or radiotherapy should be considered for localized stage I disease. Immunosuppression should be reduced, where possible, by the transplant team to a minimum level consistent with organ retention. Patients with EBV-positive lymphoma may respond to this measure alone whereas EBV-negative lymphomas are unlikely to respond. Patients with clinically low risk B cell disease i.e. age <60 years, Low LDH, good performance status (ECOG < 2), who fail to respond completely to RIS, should be treated with rituximab monotherapy (Choquet *et al*, 2007). Patients with low risk disease, who fail to respond to these measures, and all patients with high risk disease or with critical organ compromise should immediately be considered for chemotherapy (plus rituximab in B cell malignancies). Following response to treatment patients should be maintained on the lowest possible dose of immunosuppression without resulting in graft rejection. Further prospective studies are needed to better define the patient populations who will benefit most from each treatment modality.

Management of re-transplantation

Treatment of PTLD, especially RIS, may result in graft failure from rejection. Re-transplantation after control of PTLD is an option, but may risk recurrence of PTLD when full immunosuppression is reintroduced. However, The risk of recurrent PTLD after re-transplantation is apparently less than might be expected, and there are several reports of successful re-transplantation following treatment for PTLD in patients with various types of organ transplantation (Chapchap *et al*, 1991; Demircin & Rees, 1997; Birkeland *et al*, 2003; Raj & Frost, 2005; Buadi *et al*, 2007). The largest experience of re-transplantation after graft loss in patients successfully treated for PTLD is recorded by the Organ Procurement and Transplant/United Network for Organ Sharing database in the US and suggests that re-transplantation is generally accompanied by a good outcome (Johnson *et al*, 2006). A total of 69 patients who underwent re-transplantation were reported (27 renal, 22 liver, nine lung, six heart, four intestine and one pancreas). Immunosuppression for re-transplantation appeared broadly in line with that used in the general transplant population. Overall the reported outcomes after re-transplantation were good: in the case of the 27 renal re-transplants, all recipients were alive and 24 (89%) of grafts were functioning after a mean follow up time of around 2 years. If re-transplantation is envisaged, the optimal time needed to ensure long-term control of PTLD before listing for transplantation is clearly an important issue. In the case of life-supporting transplants (liver, heart and lung), the timing for re-transplantation is dictated largely by the clinical need. In the case of kidney transplantation, the optimal time from control of PTLD to re-listing for transplantation to minimize the risk of recurrence of PTLD is not known. However, a period of at the very least 1 year seems appropriate. A recent survey of French transplant centres (Karras *et al*, 2004) identified a series of six patients with PTLD, including four in whom the disease was confined to the kidney transplant. After successful treatment (which in all cases involved transplant nephrectomy) re-transplantation was undertaken between 50 and 128 months after diagnosis of PTLD and 29–97 months (mean 46 months) after graft nephrectomy. All patients received standard immunosuppression and patient survival was 100% after a median follow up of 30 months (range 24–47 months), with one graft loss and no recurrence of PTLD.

Recommendations

- **In cases where the grafts have failed/been removed re-transplantation should be considered (Grade B, level 3).**
- **A period of at least 1 year from control of PTLD to re-transplantation should be allowed to minimize risk of PTLD recurrence if clinical need allows (Grade B, level 3).**

References

Aull, M.J., Buell, J.F., Peddi, V.R., Trofe, J., Beebe, T.M., Hanaway, M.J., Roy-Chaudhury, P., Alloway, R.R., First, M.R., Woodle, E.S. & Israel Penn International Transplant Tumor Registry (2003) MAL-Toma: a Helicobacter pylori-associated malignancy in transplant

patients: a report from the Israel Penn International Transplant Tumor Registry with a review of published literature. *Transplantation*, **75,** 225–228.

Aull, M.J., Buell, J.F., Trofe, J., First, M.R., Alloway, R.R., Hanaway, M.J., Wagoner, L., Gross, T., Beebe, T. & Woodle, E.S. (2004) Experience with 274 cardiac recipients with posttransplant lymphoproliferative disorder: a report from the Israel Penn International Transplant Tumor Registry. *Transplantation*, **78,** 1676–1682.

Bates, W.D., Gray, D.W.R., Dada, M.A., Chetty, R., Gatter, K.C., Davies, D.R. & Morris, P.J. (2003) Lymphoproliferative disorders in Oxford renal transplant recipients. *Journal of Clinical Pathology*, **56,** 439–446.

Berney, T., Delis, S., Kato, T., Nishida, S., Mittal, N.K., Madariaga, J., Levi, D., Nery, J.R., Cirocco, R.E., Gelman, B., Ruiz, P. & Tzakis, A.G. (2002) Successful treatment of posttransplant lymphoproliferative disease with prolonged rituximab treatment in intestinal transplant recipients. *Transplantation*, **74,** 1000–1006.

Birkeland, S., Hamilton-Dutoit, S. & Bendtzen, K. (2003) Long-term follow-up of kidney transplant patients with posttransplant lymphoproliferative disorder: duration of post-transplant lymphoproliferative disorder-induced operational graft tolerance, interleukin-18 course, and results of re-transplantation. *Transplantation*, **75,** 153–158.

Blaes, A.H., Peterson, B.A., Bartlett, N., Dunn, D.L. & Morrison, V.A. (2005) Rituximab therapy is effective for posttransplant lymphoproliferative disorders after solid organ transplantation: results of a phase II trial. *Cancer*, **104,** 1661–1667.

Buadi, F.K., Heyman, M.R., Gocke, C.D., Rapoport, A.P., Hakimian, R., Bartlett, S.T. & Sarkodee-Adoo, C. (2007) Treatment and outcomes of post-transplant lymphoproliferative disease: a single institution study. *American Journal of Hematology*, **82,** 208–214.

Buell, J.F., Gross, T.G., Hanaway, M.J., Trofe, J., Roy-Chaudhury, P., First, M.R. & Woodle, E.S. (2005) Posttransplant lymphoproliferative disorder: significance of central nervous system involvement. *Transplantation Proceedings*, **37,** 954–955.

Campbell, P. & Marcus, R. (2003) Monoclonal antibody therapy for lymphoma. *Blood reviews*, **17,** 143–152.

Carbone, P.P., Kaplan, H.S., Musshoff, K., Smithers, D.W. & Tubiana, M. (1971) Report of the Committee on Hodgkin's Disease Staging Classification. *Cancer Research*, **31,** 1860–1861.

Chapchap, P., Carone, F.E., Porta, G., Miura, I., Zerbini, M., Gayotto, L. & JG., M. (1991) Posttransplant lymphoproliferative disease of the liver successfully treated by retransplantation. *Transplantation*, **52,** 736–737.

Chau, I., Harries, M., Cunningham, D., Hill, M., Ross, P.J., Archer, C.D., Norman, A.R., Wotherspoon, A., Koh, D.M., Gill, K., Uzzell, M., Prior, Y. & Catovsky, D. (2003) Gemcitabine, cisplatin and methylprednisolone chemotherapy (GEM-P) is an effective regimen in patients with poor prognostic primary progressive or multiply relapsed Hodgkin's and non-Hodgkin's lymphoma. *British Journal of Haematology*, **120,** 970–977.

Choquet, S., Leblond, V., Herbrecht, R., Socie, G., Stoppa, A.M., Vandenberghe, P., Fischer, A., Morschhauser, F., Salles, G., Feremans, W., Vilmer, E., Peraldi, M.N., Lang, P., Lebranchu, Y., Oksenhendler, E., Garnier, J.L., Lamy, T., Jaccard, A., Ferrant, A., Offner, F., Hermine, O., Moreau, A., Fafi-Kremer, S., Morand, P., Chatenoud, L., Berriot-Varoqueaux, N., Bergougnoux, L. & Milpied, N. (2006) Efficacy and safety of rituximab in B-cell post-transplantation lymphoproliferative disorders: results of a prospective multicenter phase 2 study. *Blood*, **107,** 3053–3057.

Choquet, S., Oertel, S., LeBlond, V., Riess, H., Varoqueaux, N., Dorken, B. & Trappe, R. (2007) Rituximab in the management of post-transplantation lymphoproliferative disorder after solid organ transplantation: proceed with caution. *Annals of Hematology*, **86,** 599–607.

Coiffier, B., Lepage, E., Briere, J., Herbrecht, R., Tilly, H., Bouabdallah, R., Morel, P., Van Den Neste, E., Salles, G., Gaulard, P., Reyes, F., Lederlin, P. & Gisselbrecht, C. (2002) CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. *New England Journal of Medicine*, **346,** 235–242.

Comoli, P., Labirio, M., Basso, S., Baldanti, F., Grossi, P., Furione, M., Vigano, M., Fiocchi, R., Rossi, G., Ginevri, F., Gridelli, B., Moretta, A., Montagna, D., Locatelli, F., Gerna, G. & Maccario, R. (2002) Infusion of autologous Epstein-Barr virus (EBV)-specific cytotoxic T cells for prevention of EBV-related lymphoproliferative disorder in solid organ transplant recipients with evidence of active virus replication. *Blood*, **99,** 2592–2598.

Cook, R.C., Connors, J.M., Gascoyne, R.D., Fradet, G. & Levy, R.D. (1999) Treatment of post-transplant lymphoproliferative disease with rituximab monoclonal antibody after lung transplantation. *Lancet*, **354,** 1698–1699.

Davis, C. (2001) Interferon and cytotoxic chemotherapy for the treatment of post-transplant lymphoproliferative disorder. *Transplation and Infectious Disease*, **3,** 108–118.

Davis, C., Wood, B., Sabath, D., Joseph, J., Stehman-Breen, C. & Broudy, V. (1987) Interferon-alpha treatment of posttransplant lymphoproliferative disorder in recipients of solid organ transplants. *Transplantation*, **66,** 1770–1779.

Delone, P., Corkill, J., Jordan, M., Krapiva, P., Ghasemian, R., Sasaki, T. & Light, J. (1995) Successful treatment of Epstein-Barr virus infection with ganciclovir and cytomegalovirus hyperimmune globulin following kidney transplantation. *Transplantation Proceedings*, **27,** 58–59.

Demircin, G. & Rees, L. (1997) Retransplantation after post-transplant lymphoproliferative disease. *Pediatric Nephrology*, **11,** 358–360.

Diehl, V., Stein, H., Hummel, M., Zollinger, R. & Connors, J.M. (2003) Hodgkin's lymphoma: biology and treatment strategies for primary, refractory, and relapsed disease. *Hematology*, **2003,** 225–247.

Dotti, G., Rambaldi, A., Fiocchi, R., Motta, T., Torre, G., Viero, P., Gridelli, B. & Barbui, T. (2001) Anti-CD20 antibody (rituximab) administration in patients with late occurring lymphomas after solid organ transplant. *Haematologica*, **86,** 618–623.

Dotti, G., Fiocchi, R., Motta, T., Mammana, C., Gotti, E., Riva, S., Cornelli, P., Gridelli, B., Viero, P., Oldani, E., Ferrazzi, P., Remuzzi, G., Barbui, T. & Rambaldi, A. (2002) Lymphomas occurring late after solid-organ transplantation: influence of treatment on the clinical outcome. *Transplantation*, **74,** 1095–1102.

Douglas, R.S., Goldstein, S.M., Katowitz, J.A., Gausas, R.E., Ibarra, M.S., Tsai, D., Sharma, A. & Nichols, C. (2002) Orbital presentation of posttransplantation lymphoproliferative disorder: a small case series. *Opthalmology*, **109,** 2351–2355.

EBPG Expert Group on Renal Transplantation (2002) European best practice guidelines for renal transplantation. Section IV: long-term management of the transplant recipient. IV.6.1. Cancer risk after renal transplantation. Post-transplant lymphoproliferative disease

(PTLD): prevention and treatment. *Nephrology Dialysis Transplantation*, **17,** 31–33, 35–36.

Elstrom, R.L., Andreadis, C., Aqui, N.A., Ahya, V.N., Bloom, R.D., Brozena, S.C., Olthoff, K.M., Schuster, S.J., Nasta, S.D., Stadtmauer, E.A. & Tsai, D.E. (2006) Treatment of PTLD with rituximab or chemotherapy. *American Journal of Transplantation*, **6,** 569–576.

Ferreri, A.J.M., Reni, M., Foppoli, M., Martelli, M., Pangalis, G.A., Frezzato, M., Cabras, M.G., Fabbri, A., Corazzelli, G., Ilariucci, F., Rossi, G., Soffietti, R., Stelitano, C., Vallisa, D., Zaja, F., Zoppegno, L., Aondio, G.M., Avvisati, G., Balzarotti, M., Brandes, A.A., Fajardo, J., Gomez, H., Guarini, A., Pinotti, G., Rigacci, L., Uhlmann, C., Picozzi, P., Vezzulli, P., Ponzoni, M., Zucca, E., Caligaris-Cappio, F. & Cavalli, F. (2009) High-dose cytarabine plus high-dose methotrexate versus high-dose methotrexate alone in patients with primary CNS lymphoma: a randomised phase 2 trial. *The Lancet*, **374,** 1512–1520.

Feugier, P., Van Hoof, A., Sebban, C., Solal-Celigny, P., Bouabdallah, R., Fermé, C., Christian, B., Lepage, E., Tilly, H., Morschhauser, F., Gaulard, P., Salles, G., Bosly, A., Gisselbrecht, C., Reyes, F. & Coiffier, B. (2005) Long-term results of the R-CHOP study in the treatment of elderly patients with diffuse large B-cell lymphoma: a study by the Groupe d'Etude des Lymphomes de l'Adulte. *Journal of Clinical Oncology*, **23,** 4117–4126.

Fohrer, C., Caillard, S., Koumarianou, A., Ellero, B., Woehl-Jaegle, M.L., Meyer, C., Epailly, E., Chenard, M.P., Lioure, B., Natarajan-Ame, S., Maloisel, F., Lutun, P., Kessler, R., Moulin, B., Bergerat, J.P., Wolf, P. & Herbrecht, R. (2006) Long-term survival in post-transplant lymphoproliferative disorders with a dose-adjusted ACVBP regimen. *British Journal of Haematology*, **134,** 602–612.

Foroncewicz, B., Mucha, K., Usiekniewicz, J., Chmura, A., Kryst, P., Sołdacki, D. & Paczek, L. (2006) Posttransplant lymphoproliferative disorder of the lung in a renal transplant recipient treated successfully with surgery. *Transplantation Proceedings*, **38,** 173–176.

Ghobrial, I.M., Habermann, T.M., Maurer, M.J., Geyer, S.M., Ristow, K.M., Larson, T.S., Walker, R.C., Ansell, S.M., Macon, W.R., Gores, G.G., Stegall, M.D. & McGregor, C.G. (2005) Prognostic Analysis for Survival in Adult Solid Organ Transplant Recipients With Post-Transplantation Lymphoproliferative Disorders. *Journal of Clinical Oncology*, **23,** 7574–7582.

Girinsky, T., Benhamou, E., Bourhis, J.-H., Dhermain, F., Guillot-Valls, D., Ganansia, V., Luboinski, M., Perez, A., Cosset, J.M., Socie, G., Baume, D., Bouaouina, N., Briot, E., Beaudre, A., Bridier, A. & Pico, J.L. (2000) Prospective Randomized Comparison of Single-Dose Versus Hyperfractionated Total-Body Irradiation in Patients With Hematologic Malignancies. *Journal of Clinical Oncology*, **18,** 981–986.

Gross, T.G., Bucuvalas, J.C., Park, J.R., Greiner, T.C., Hinrich, S.H., Kaufman, S.S., Langnas, A.N., McDonald, R.A., Ryckman, F.C., Shaw, B.W., Sudan, D.L. & Lynch, J.C. (2005) Low-dose chemotherapy for Epstein-Barr virus-positive post-transplantation lymphoproliferative disease in children after solid organ transplantation. *Journal of Clinical Oncology*, **23,** 6481–6488.

Haque, T., Wilkie, G.M., Taylor, C., Amlot, P.L., Murad, P., Iley, A., Dombagoda, D., Britton, K.M., Swerdlow, A.J. & Crawford, D.H. (2002) Treatment of Epstein-Barr virus-positive post-transplant lymphoproliferative disease with partly HLA-matched allogeneic cytotoxic T cells. *Lancet*, **360,** 436–441.

Haque, T., Wilkie, G.M., Jones, M.M., Higgins, C.D., Urquhart, G., Wingate, P., Burns, D., McAulay, K., Turner, M., Bellamy, C., Amlot, P.L., Kelly, D., MacGilchrist, A., Gandhi, M.K., Swerdlow, A.J. & Crawford, D.H. (2007) Allogeneic cytotoxic T-cell therapy for EBV-positive posttransplantation lymphoproliferative disease: results of a phase 2 multicenter clinical trial. *Blood*, **110,** 1123–1131.

Heim-Duthoy, K., Chitwood, K., Tortorice, K., Massy, Z. & Kasiske, B. (1994) Elective cyclosporine withdrawal 1 year after renal transplantation. *American Journal of Kidney Diseases*, **24,** 846–853.

Hsi, E.D., Singleton, T.P., Swinnen, L., Dunphy, C.H. & Alkan, S. (2000) Mucosa-associated lymphoid tissue-type lymphomas occurring in post-transplantation patients. *American Journal of Surgical Pathology*, **24,** 100–106.

Hsu, Y.C., Liao, W.C., Wang, H.P., Yao, M. & Lin, J.T. (2009) Catastrophic gastrointestinal manifestations of post-transplant lymphoproliferative disorder. *Digestive and Liver Disease*, **41,** 238–241.

Jaeger, G., Linkesch, W., Temmel, W. & Neumeister, P. (2005) Anti CD20 monoclonal antibody-based radioimmunotherapy of relapsed chemoresistant aggressive posttransplant B-lymphoproliferative disorder in heart-transplant recipients. *Lancet Oncology*, **6,** 629–631.

Jain, A.B., Marcos, A., Pokharna, R., Shapiro, R., Fontes, P.A., Marsh, W., Mohanka, R. & Fung, J.J. (2005) Rituximab (chimeric anti-CD20 antibody) for posttransplant lymphoproliferative disorder after solid organ transplantation in adults: long-term experience from a single center. *Transplantation*, **80,** 1692–1698.

Jenkins, D., DiFrancesco, L., Chaudhry, A., Morris, D., Glück, S., Jones, A., Woodman, R., Brown, C., Russell, J. & Stewart, D. (2002) Successful treatment of post-transplant lymphoproliferative disorder in autologous blood stem cell transplant recipients. *Bone Marrow Transplantation*, **30,** 321–326.

Johnson, S., Cherikh, W., Kauffman, H., Pavlakis, M. & Hanto, D. (2006) Retransplantation after post-transplant lymphoproliferative disorders: an OPTN/UNOS database analysis. *American Journal of Transplantation*, **6,** 2743–2749.

Kang, S.K., Kirkpatrick, J.P. & Halperin, E.C. (2004) Low-dose radiation for posttransplant lymphoproliferative disorder. *American Journal of Clinical Oncology*, **26,** 210–214.

Karras, A., Thervet, E., Le Meur, Y., Baudet-Bonneville, V., Kessler, M. & Legendre, C. (2004) Successful renal retransplantation after post-transplant lymphoproliferative disease. *American Journal of Transplantation*, **4,** 1904–1909.

Kollmar, O., Becker, S., Schilling, M.K. & Maurer, C.A. (2002) Intestinal lymphoma perforations as a consequence of highly effective anti-CD20 antibody therapy. *Transplantation*, **73,** 669–670.

Kwong, Y.L. (2005) Natural-killer cell malignancies: diagnosis and management. *Leukaemia*, **19,** 2186–2194.

Kwong, Y.L., Lam, C.C.K. & Chan, T.M. (2000) Post-transplantation lymphoproliferative disease of natural killer cell lineage: a clinicopathological and molecular analysis. *British Journal of Haematology*, **110,** 197–202.

Leblond, V., Sutton, L., Dorent, R., Davi, F., Bitker, M.O., Gabarre, J., Charlotte, F., Ghoussoub, J.J., Fourcade, C. & Fischer, A. (1995) Lymphoproliferative disorders after organ transplantation: a report of 24 cases observed in a single center. *Journal of Clinical Oncology*, **13,** 961–968.

Leblond, V., Dhedin, N., Bruneel, M.-F.M., Choquet, S., Hermine, O., Porcher, R., Quoc, S.N., Davi, F., Charlotte, F., Dorent, R., Barrou, B., Vernant, J.-P., Raphael, M. & Levy, V. (2001) Identification of Prognostic Factors in 61 Patients With Posttransplantation Lymphoproliferative Disorders. *Journal of Clinical Oncology*, **19,** 772–778.

Libertiny, G., Watson, C.J., Gray, D.W., Welsh, K.I. & Morris, P.J. (2001) Rising incidence of post-transplant lymphoproliferative disease in kidney transplant recipients. *British Journal of Surgery*, **88,** 1330–1334.

Little, R., Pittaluga, S., Grant, N., Steinberg, S., Kavlick, M., Mitsuya, H., Franchini, G., Gutierrez, M., Raffeld, M., Jaffe, E., Shearer, G., Yarchoan, R. & Wilson, W. (2003) Highly effective treatment of acquired immunodeficiency syndrome-related lymphoma with dose-adjusted EPOCH: impact of antiretroviral therapy suspension and tumor biology. *Blood*, **101,** 4653–4659.

Marcus, R., Hodson, D., Coupland, S., Bessell, E., Mead, B. & Pettitt, A.R. (2007) Guidelines on the diagnosis and management of adult patients with primary CNS lymphoma (PCNSL) and primary intraocular lymphoma (PIOL). WWW document. URL http://www.bcshguidelines.com/pdf/PCNSL_guidelines.pdf.

Mead, G., Barrans, S., Qian, W., Walewski, J., Radford, J., Wolf, M., Clawson, S., Stenning, S., Yule, C. & Jack, A. (2008) A prospective clinicopathologic study of dose-modified CODOX-M/IVAC in patients with sporadic Burkitt lymphoma defined using cytogenetic and immunophenotypic criteria (MRC/NCRI LY10 trial). *Blood*, **112,** 2248–2260.

Mentzer, S.J., Fingeroth, J., Reilly, J.J., Perrine, S.P. & Faller, D.V. (1998) Arginine Butyrate-Induced Susceptibility to Ganciclovir in an Epstein-Barr-Virus-Associated Lymphoma. *Blood Cells, Molecules, and Diseases*, **24,** 114–123.

Milpied, N., Vasseur, B., Parquet, N., Garnier, J.L., Antoine, C., Quartier, P., Carret, A.S., Bouscary, D., Faye, A., Bourbigot, B., Reguerre, Y., Stoppa, A.M., Bourquard, P., Hurault de Ligny, B., Dubief, F., Mathieu-Boue, A. & Leblond, V. (2000) Humanized anti-CD20 monoclonal antibody (Rituximab) in post transplant B-lymphoproliferative disorder: a retrospective analysis on 32 patients. *Annals of Oncology*, **11**(Suppl 1)**,** 113–116.

Nabors, L.B., Palmer, C.A., Julian, B.A., Przekwas, A.M. & Kew, C.E. (2009) Isolated Central Nervous System Posttransplant Lymphoproliferative Disorder Treated with High-Dose Intravenous Methotrexate. *American Journal of Transplantation*, **9,** 1243–1248.

Oertel, S.H., Anagnostopoulos, I., Bechstein, W.O., Liehr, H. & Riess, H.B. (2000) Treatment of posttransplant lymphoproliferative disorder with the anti-CD20 monoclonal antibody rituximab alone in an adult after liver transplantation: a new drug in therapy of patients with posttransplant lymphoproliferative disorder after solid organ transplantation? *Transplantation*, **69,** 430–432.

Oertel, S., Papp-Váry, M., Anagnostopoulos, I., Hummel, M., Jonas, S. & Riess, H. (2003) Salvage chemotherapy for refractory or relapsed post-transplant lymphoproliferative disorder in patients after solid organ transplantation with a combination of carboplatin and etoposide. *British Journal of Haematology*, **123,** 830–835.

Oertel, S.H., Verschuuren, E., Reinke, P., Zeidler, K., Papp-Vary, M., Babel, N., Trappe, R.U., Jonas, S., Hummel, M., Anagnostopoulos, I., Dorken, B. & Riess, H.B. (2005) Effect of anti-CD 20 antibody rituximab in patients with post-transplant lymphoproliferative disorder (PTLD). *American Journal of Transplantation*, **5,** 2901–2906.

Orjuela, M., Gross, T.G., Cheung, Y.K., Alobeid, B., Morris, E. & Cairo, M.S. (2003) A pilot study of chemoimmunotherapy (cyclophosphamide, prednisone, and rituximab) in patients with post-transplant lymphoproliferative disorder following solid organ transplantation. *Clinical Cancer Research*, **9,** 3945S–3952S.

Paranjothi, S., Yusen, R.D., Kraus, M.D., Lynch, J.P., Patterson, G.A. & Trulock, E.P. (2001) Lymphoproliferative disease after lung transplantation: comparison of presentation and outcome of early and late cases. *Journal of Heart and Lung Transplantation*, **20,** 1054–1063.

Parker, A., Amlot, P., Bowles, K., Bradley, J.A., Emery, V., Featherstone, C., Gupte, G., Marcus, R., Parameshwar, J., Ramsay, A. & Newstead, C. (2009) Guidelines on the Surveillance, Diagnosis and Management of Post-Transplant Lymphoproliferative Disorders in Adult Solid Organ Transplant Recipients. WWW document. URL. http://www.bcshguidelines.com/pdf/pltd_finaldraft_071009.pdf.

Paya, C.V., Fung, J.J., Nalesnik, M.A., Kieff, E., Green, M., Gores, G., Habermann, T.M., Wiesner, R.H., Swinnen, L.J., Woodle, E.S., Bromberg, J.S. & for the ASTS/ASTP EBV-PTLD Task Force the Mayo Clinic organized International Consensus Development Meeting on Epstein Barr Virus-Induced Posttransplant Lymphoproliferative Disorders (PTLD) (1999) Epstein-Barr Virus-Induced Posttransplant Lymphoproliferative Disorders. *Transplantation*, **68,** 1517–1525.

Penn, I. & Porat, G. (1995) Central nervous system lymphomas in organ allograft recipients. *Transplantation*, **59,** 240–244.

Perrine, S.P., Hermine, O., Small, T., Suarez, F., O'Reilly, R., Boulad, F., Fingeroth, J., Askin, M., Levy, A., Mentzer, S.J., Di Nicola, M., Gianni, A.M., Klein, C., Horwitz, S. & Faller, D.V. (2007) A phase 1/2 trial of arginine butyrate and ganciclovir in patients with Epstein-Barr virus-associated lymphoid malignancies. *Blood*, **109,** 2571–2578.

Pfreundschuh, M., Schubert, J., Ziepert, M., Schmits, R., Mohren, M., Lengfelder, E., Reiser, M., Nickenig, C., Clemens, M., Peter, N., Bokemeyer, C., Eimermacher, H., Ho, A., Hoffmann, M., Mertelsmann, R., Trümper, L., Balleisen, L., Liersch, R., Metzner, B., Hartmann, F., Glass, B., Poeschel, V., Schmitz, N., Ruebe, C., Feller, A. & Loeffler, M. (2008) German High-Grade Non-Hodgkin Lymphoma Study Group (DSHNHL). Six versus eight cycles of bi-weekly CHOP-14 with or without rituximab in elderly patients with aggressive CD20+ B-cell lymphomas: a randomised controlled trial (RICOVER-60). *Lancet Oncology*, **9,** 105–116.

Pham, P.T., Wilkinson, A.H., Gritsch, H.A., Pham, P.C., Miller, J.M., Lassman, C.R. & Danovitch, G.M. (2002) Monotherapy with the anti-CD20 monoclonal antibody rituximab in a kidney transplant recipient with posttransplant lymphoproliferative disease. *Transplantation Proceedings*, **34,** 1178–1181.

Pirsch, J., Stratta, R., Sollinger, H., Hafez, G., D'Alessandro, A., Kalayoglu, M. & Belzer, F. (1989) Treatment of severe Epstein-Barr virus-induced lymphoproliferative syndrome with ganciclovir: two cases after solid organ transplantation. *American Journal of Medicine*, **86,** 241–244.

Raj, R. & Frost, A. (2005) Lung retransplantation after posttransplantation lymphoproliferative disorder (PTLD): a single-center experience and review of literature of PTLD in lung transplant recipients. *Journal of Heart and Lung Transplantation*, **24,** 671–679.

Reams, B.D., McAdams, H.P., Howell, D.N., Steele, M.P., Davis, R.D. & Palmer, S.M. (2003) Posttransplant lymphoproliferative disorder: incidence, presentation, and response to treatment in lung transplant recipients. *Chest*, **124,** 1242–1249.

Savoldo, B., Goss, J.A., Hammer, M.M., Zhang, L., Lopez, T., Gee, A.P., Lin, Y.-F., Quiros-Tejeira, R.E., Reinke, P., Schubert, S., Gottschalk, S., Finegold, M.J., Brenner, M.K., Rooney, C.M. & Heslop, H.E. (2006) Treatment of solid organ transplant recipients with autologous Epstein Barr virus-specific cytotoxic T lymphocytes (CTLs). *Blood*, **108,** 2942–2949.

Smith, T.J., Khatcheressian, J., Lyman, G.H., Ozer, H., Armitage, J.O., Balducci, L., Bennett, C.L., Cantor, S.B., Crawford, J., Cross, S.J., Demetri, G., Desch, C.E., Pizzo, P.A., Schiffer, C.A., Schwartzberg, L., Somerfield, M.R., Somlo, G., Wade, J.C., Wade, J.L., Winn, R.J., Wozniak, A.J. & Wolff, A.C. (2006) 2006 update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline. *Journal of Clinical Oncology*, **24,** 3187–3205.

Stephan, J.L., Le Deist, F., Blanche, S., Le Bidois, J., Peuchmaur, M., Lellouch-Tubiana, A., Hirn, M., Griscelli, C. & Fischer, A. (1992) Treatment of central nervous system B lymphoproliferative syndrome by local infusion of a B cell-specific monoclonal antibody. *Transplantation*, **54,** 246–249.

Swerdlow, S.H., Campo, E., Harris, N.L., Jaffe, E.S., Pileri, S.A., Stein, H., Thiele, J. & Vardiman, J.W. (eds.) (2008) *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues*. IARC, Lyon.

Swinnen, L.J. (2001) Organ transplant-related lymphoma. *Current Treatment Options in Oncology*, **2,** 301–308.

Swinnen, L., Leblanc, M., Grogan, T., Gordon, L., Stiff, P., Miller, A., Kasamon, Y., Miller, T. & Fisher, R. (2008) Prospective study of sequential reduction in immunosuppression, interferon alpha-2B, and chemotherapy for posttransplantation lymphoproliferative disorder. *Transplantation*, **86,** 215–222.

Taj, M.M., Messahel, B., Mycroft, J., Pritchard-Jones, K., Baker, A., Height, S., Hadzic, N. & Pinkerton, C.R. (2008) Efficacy and tolerability of high-dose methotrexate in central nervous system positive or relapsed lymphoproliferative disease following liver transplant in children. *British Journal of Haematology*, **140,** 191–196.

Taylor, A., Marcus, R. & Bradley, J. (2005) Post-transplant lymphoproliferative disorders (PTLD) after solid organ transplantation. *Critical Reviews in Oncology and Hematology*, **56,** 155.

Taylor, A.L., Bowles, K.M., Callaghan, C.J., Wimperis, J.Z., Grant, J.W., Marcus, R.E. & Bradley, J.A. (2006) Anthracycline-based chemotherapy as first-line treatment in adults with malignant posttransplant lymphoproliferative disorder after solid organ transplantation. *Transplantation*, **82,** 375–381.

Trappe, R.U., Choquet, S., Reinke, P., Dreyling, M., Mergenthaler, H.G., Jager, U., Kebelmann-Betzing, C., Jonas, S., Lehmkuhl, H., Anagnostopoulos, I., Leblond, V., Hetzer, R., Dorken, B., Riess, H. & Oertel, S. (2007) Salvage therapy for relapsed posttransplant lymphoproliferative disorders (PTLD) with a second progression of PTLD after Upfront chemotherapy: the role of single-agent rituximab. *Transplantation*, **84,** 1708–1712.

Tsai, D., Hardy, C., Tomaszewski, J., Kotloff, R., Oltoff, K., Somer, B., Schuster, S., Porter, D., Montone, K. & Stadtmauer, E. (2001) Reduction in immunosuppression as initial therapy for posttransplant lymphoproliferative disorder: analysis of prognostic variables and long-term follow-up of 42 adult patients. *Transplantation*, **71,** 1076–1088.

Tulpule, S., Mikhael, G., Kazmi, M., Nunan, T., Van Der Walt, J., Goldsmith, D. & Fields, P. (2005) B Cell Post Transplant Lymphoproliferative Disorder Complicating Solid Organ Transplantation (B-PTLD):a Single Centre Review Reporting 1) Results with Chemo-Immunotherapy (CHOP/R) and 2) the Predictive Ability of FDG-PET Scanning To Correlate with Long Term Overall Survival. *Blood (ASH Annual Meeting Abstracts)*, **106,** 1500.

Vose, J.M., Bierman, P.J., Anderson, J.R., Weisenburger, D., Moravec, D.F., Sorensen, S., Hutchins, M., Dowling, M.D., Howe, D. & Okerbloom, J. (1991) CHLVPP chemotherapy with involved-field irradiation for Hodgkin's disease: favorable results with acceptable toxicity. *Journal of Clinical Oncology*, **9,** 1421–1425.

Webber, S.A. & Naftel, D.C. (2006) Pediatric heart transplant study. Lymphoproliferative disorders after pediatric heart transplantation: a multi-institutional study. *Lancet*, **367,** 233–239.

Williams, S.L., Hartline, C.B., Kushner, N.L., Harden, E.A., Bidanset, D.J., Drach, J.C., Townsend, L.B., Underwood, M.R., Biron, K.K. & Kern, E.R. (2003) *In Vitro* Activities of Benzimidazole D- and L-Ribonucleosides against Herpesviruses. *Antimicrobial Agents and Chemotherapy*, **47,** 2186–2192.

Wilson, W., Grossbard, M., Pittaluga, S., Cole, D., Pearson, D., Drbohlav, N., Steinberg, S., Little, R., Janik, J., Gutierrez, M., Raffeld, M., Staudt, L., Cheson, B., Longo, D., Harris, N., Jaffe, E., Chabner, B., Wittes, R. & Balis, F. (2002) Dose-adjusted EPOCH chemotherapy for untreated large B-cell lymphomas: a pharmacodynamic approach with high efficacy. *Blood*, **99,** 2685–2693.

Wotherspoon, A., Diss, T., Pan, L., Singh, N., Whelan, J. & Isaacson, P. (1996) Low grade gastric B-cell lymphoma of mucosa associated lymphoid tissue in immunocompromised patients. *Histopathology*, **28,** 129–134.

Zilz, N.D., Olson, L.J. & McGregor, C.G. (2001) Treatment of post-transplant lymphoproliferative disorder with monoclonal CD20 antibody (rituximab) after heart transplantation. *Journal of Heart and Lung Transplantation*, **20,** 770–772.