

CHAPTER 16 IMMUNODEFICIENCY ASSOCIATED LYMPHOMA

16.1 Introduction

It has long been recognised that disturbances of the immune system may be associated with an increased incidence of lymphoma. The extent to which this occurs varies according to the specific underlying immune disturbance and has been documented with variable clarity and certainty.

The WHO¹ classification is:

- 1 Lymphoproliferative diseases (LPDs) associated with primary immune disorders
- 2 Human immunodeficiency virus-related lymphomas
- 3 Post-transplant lymphoproliferative disorders
- 4 Methotrexate-associated lymphoproliferative disorders

Lymphomas occurring in these settings share a number of features that differ from those occurring in the general population. These include the distribution of specific histologies, the incidence of extranodal disease, the greater frequency of Epstein Barr virus (EBV) integration in the lymphoma, and importantly, the potential for disease regression without specific therapy when manipulation of the immune system is possible, for example, by the withdrawal of immunosuppressive drugs. These features are common to the four subtypes of immunodeficiency-associated LPDs, although to greater and lesser extents. In counterpoint to these broad similarities are the many specific differences, as illustrated by the heterogeneity among LPDs, complicating the many rare but distinct primary immunodeficiency syndromes. In this chapter, generalisations are made where applicable but are not intended to obviate the need to consider each entity and clinical scenario independently. Where management recommendations are the same as for lymphomas occurring in the non-immunocompromised host, they are cross-referenced.

16.2 Lymphoproliferative diseases associated with primary immune disorders

16.2.1 Predisposing conditions

There is good epidemiologic evidence that patients with a variety of primary immunodeficiency syndromes are at risk for the development of lymphoma. It has been difficult to quantitate that risk accurately, with a variety of estimates based on case series published in the literature. These range from as little as 1.4% to one series reporting that 25% of patients with genetically determined immunodeficiencies will develop primary B-cell lymphomas in their lifetimes.²⁻⁶

The predisposing conditions are^{2,4,7,8}:

- ataxia telangiectasia (AT)
- Wiskott-Aldrich syndrome (WAS)
- common variable immune deficiency (CVID)
- severe combined immune deficiency (SCID)
- x-linked lymphoproliferative disorder (XLP or Duncan syndrome)
- Nijmegen breakage syndrome (NBS)

- hyper-IgM syndrome (HIM)
- autoimmune lymphoproliferative syndrome (ALPS)

While the evidence of increased risk of lymphoma is firm, the benefit of early detection and intervention is less well documented. The presumption that surveillance for lymphoma and early intervention is beneficial is an extrapolation from general cancer medicine principles.

16.2.2 Clinical presentation

The clinical presentation commonly involves extranodal sites of disease, predominantly gastro intestinal tract (GIT), central nervous system (CNS), lung and kidney.^{2,3} Presenting symptoms may resemble infection and commonly include fevers, infectious mononucleosis-like syndrome, and fatigue. Benign lymphoid hyperplasia may precede the development of lymphoma², as may the development of monoclonal gammopathy.⁹

16.2.3 Management

Management of the primary immune disorder usually entails consideration of allogeneic bone marrow transplantation (BMT) from a sibling donor.¹⁰ The clinical decision to proceed to transplant depends on the severity of the clinical phenotype, including the perceived risk of developing lymphoma. BMT is, in general, curative of the underlying disorder, and appears to reduce the risk of developing lymphoma.¹¹

Diagnosis and staging of lymphoma follows standard guidelines (see Chapter 8). Special considerations include:

- monoclonal B-cell populations may be self limited in some primary immune disorders (PIDs) (e.g. in CVID) and are not diagnostic of lymphoma¹²
- some non-clonal proliferations of B-cells (e.g. in XLP) or plasma cells (e.g. in hyper IgM syndrome) may be fatal
- extranodal sites may require specific investigations

It is unknown whether standard risk factor assessment or evaluation of IPI are helpful in the setting of PID-related lymphoma. The underlying immune status is an important predictor of outcome. T-cell count and T-cell function correlated with outcome in a series of 18 patients with PID and LPD.¹³

The most common histologic subtype is DLBCL, although polymorphic LPDs also occur frequently. Rarely described are Burkitt's lymphoma, follicular lymphoma, peripheral T-cell lymphoma, and Hodgkin lymphoma.²⁻⁶

There is a paucity of data documenting the treatment and outcome of PID patients with lymphoma. Retrospective analyses of case reports predominate.^{7,14,15} There are no randomised controlled trials within this rare patient group to provide evidence for specific recommendations. More recent data suggest that standard treatment with curative intent, stratified along the currently recommended lines according to histology and prognostic index, be attempted in patients with PID¹⁶, although confirmation of this approach is needed. As PID lymphoma usually occurs in paediatric patients, the specific approach should be appropriate to the paediatric patient.

Special considerations include continuing specific treatment of the underlying immunodeficiency, for example, immunoglobulin replacement, antibiotic prophylaxis, etc. The option of allogeneic BMT should be considered and fully explored, if not already done in the context of the primary disorder. Toxicity from standard lymphoma therapies may be considerably greater than in the non-

immunocompromised lymphoma patient population and strict attention to supportive care measures must be maintained.

Guidelines — Immune deficiency — treatment	Level of evidence	Refs
Patients with primary immune deficiency (PID) should be under close clinical surveillance for the development of lymphoproliferative disease. Maintain a high index of suspicion with prolonged symptoms of unidentified infection; symptoms referable to common sites of extranodal lymphoma; and precursor lesions such as lymphoid hyperplasia and monoclonal gammopathy.	V	2, 3
Standard curative intent therapy appropriate for the specific lymphoma should be administered, with special attention to supportive care for expected treatment-related toxicity.	IV	16
Primary immune deficiency (PID) patients with lymphoma should be assessed for potential allogeneic bone marrow transplant.	opinion	10, 11

16.2.4 Recommendations for future research

- Cancer registries should prospectively collect data on lymphoma patients to document the incidence of underlying PID and determine the outcome for this subset of patients.
- PID-related lymphoma patients should be eligible to participate in the large lymphoma clinical trials, and identified as a specific subset for the prospective collection of information on outcomes and comparison with the non-immunocompromised lymphoma patient. Ideally, laboratory information including EBV status should be incorporated into such trials.

16.3 Management of lymphomas associated with infection by the human immunodeficiency virus (HIV)

16.3.1 Background

Lymphoma is a common complication of HIV infection, correlating with both the degree and duration of immunosuppression. Incidence rates vary from 1.6% to 6% per year.¹⁷ The introduction of highly active anti-retroviral therapy (HAART) has seen a reduction in the incidence of lymphoma, particularly primary CNS lymphoma.

16.3.2 WHO classification

The WHO categories are as follows:

- Lymphomas also occurring in immunocompetent patients
 - Burkitt lymphoma
 - Classical
 - With plasmacytoid differentiation
 - Atypical
 - Diffuse large B-cell lymphoma

- Centroblastic
- Immunoblastic
- Extranodal marginal zone B-cell lymphoma (MALT lymphoma) (rare)
- Peripheral T-cell lymphoma (rare)
- Classical Hodgkin lymphoma
- Lymphomas occurring more specifically in HIV-positive patients
 - Primary effusion lymphoma
 - Plasmablastic lymphoma of the oral cavity
- Lymphomas also occurring in other immunodeficiency states
 - Polymorphic B-cell lymphoma (PTLD-like)

16.3.3 Clinical

The lymphomas are predominantly aggressive B-cell lymphomas¹⁸, most commonly Burkitt lymphoma, diffuse large B-cell lymphoma (DLBCL), primary effusion lymphoma (PEL) and plasmablastic lymphoma of the oral cavity. EBV positivity is higher than in the same entities in the non-HIV lymphomas. It varies from 30% to 100%, depending on the specific histology and site.¹⁸ In general, pathologic features are similar to the non-HIV counterparts. Burkitt lymphoma with plasmacytoid differentiation, PEL, and plasmablastic lymphoma of the oral cavity are rarely reported outside the HIV setting. PEL has been associated with Kaposi's sarcoma and HHV8 infection. Primary CNS lymphoma is more common in HIV-lymphoma than in non-HIV lymphomas, although the incidence has fallen dramatically since the introduction of HAART (see Chapter 2).

The incidence of Hodgkin lymphoma also increases in the HIV population in the order of eight-fold.¹⁸ There is a predominance of the poorer prognostic histological subtypes (lymphocyte depleted and mixed cellularity) and presentation is usually with advanced-stage disease. It is almost always EBV positive and is associated with a poorer prognosis than in HIV-negative patients.

16.3.4 Therapy for systemic NHL

Chemotherapy

There have been three prospective randomised trials in HIV-positive lymphoma patients, all conducted in the pre-HAART era (see Table 16.1). These studies examined dose intensity. The AIDS Clinical Trials Group compared standard-dose mBACOD with reduced dose of the same protocol (mostly 50%) and were unable to demonstrate any benefit for response or survival for either group.¹⁹ Toxicity was greater in the standard-dose arm despite the routine use of GM-CSF.

Table 16.1 Randomised chemotherapy trials for HIV lymphoma

Study	Number	Regimens	Median CD4 cells/ul)	CR rate	Survival
Kaplan et al. 1997 ¹⁹	94	100% mBACOD	100	45	7.2m (median)
	98	50% mBACOD		40	8.2m
Tirelli et al. 1999 ²⁰	80	ACVB	200	65	51% at 2yr
	79	CHOP		56	43% at 2yr
Tirelli et al. 1999 ²⁰	59	100% CHOP	60	63*	35% at 2yr
	51	reduced CHOP		39*	28% at 2yr

*statistically significant

The French–Italian Co-operative Group stratified patients according to adverse prognostic factors defined as prior history of AIDS, CD4 <100 cells/uL, and ECOG performance status of two or more.²⁰ In 159 patients with no adverse factors, full-dose CHOP was compared to a more intensive regimen (ACVB). All patients were given G-CSF support. There were no significant differences for response, event-free or overall survival. There was greater haematological toxicity in the ACVB group but no difference in death rate. For patients with one adverse factor, standard-dose CHOP was compared to reduced-dose CHOP (50% doxorubicin and cyclophosphamide). The complete response rate was significantly better in the full-dose CHOP arm at 63%, compared to 39% for the reduced dose ($p = 0.001$), but there was no difference in overall survival.

Preliminary evidence suggests that infusional therapy may be a promising approach in primary and salvage treatment of patients in the HAART era.¹⁷ Two regimens have shown promising results, CDE²¹ and EPOCH.²² In 39 patients EPOCH was reported to achieve an impressive 74% complete response rate, 92% disease free survival and 60% overall survival with median follow up beyond four years. However there are no randomised data comparing infusional to standard therapy.

Since CHOP is equivalent to more intensive regimens in lymphoma patients who are HIV negative²³, it is reasonable to expect the same for patients with HIV-related lymphoma. Consequently, CHOP could be considered the standard of care. This is supported by the French–Italian Group study. Whether all patients should be treated with full-dose CHOP is not clear. The French–Italian Group study suggests full dose is more likely to be effective even in patients with poor prognostic factors.²⁰ It is recommended that full-dose CHOP be given with HAART to maximise response and reduce secondary complications of immune failure. An infusional regimen such as EPOCH may be a reasonable alternative, however, randomised comparative studies with CHOP are needed in the HAART era. There are no current data for accelerated CHOP (CHOP 14) or CHOP with rituximab specific to the HIV population.

CNS prophylaxis

This has not been extensively studied in the context of HIV-related lymphoma. However, a high incidence of CNS involvement has been reported from early studies and some treatment centres recommend all patients receive CNS prophylaxis.¹⁷ It is recommended in the absence of specific data that guidelines for similar lymphoma subtypes in the non-HIV population be adopted.

Rituximab

One preliminary study of CDE and rituximab in 29 patients has reported an 86% complete response rate and 80% actuarial two-year overall survival.²⁴ The AIDS Malignancy Consortium completed a randomised study of CHOP plus rituximab compared to CHOP alone, in September 2002. The results are awaited with great interest.

Highly active anti-retroviral therapy (HAART)

To date, there have been only preliminary studies of the interaction of chemotherapy and HAART. The EPOCH study demonstrated that didanosine used with chemotherapy was associated with reduced haematological toxicity.²² The AIDS Malignancy Consortium studied the HAART combination of stavudine, lamivudine and indinavir with either low or standard-dose CHOP, and found no increase in toxic side effects.²⁵ Cyclophosphamide clearance was reduced by 50% compared to historical controls, with no difference in expected clearance of doxorubicin or indinavir. Zidovudine should be avoided in HAART protocols because of its well recognised haematological toxicity.^{21,25} Since HAART substantially reduces morbidity and mortality of AIDS complications, and pre-HAART studies of chemotherapy for HIV-related NHL demonstrated as many as 25% of complete remission patients dying of these complications, it is recommended that HAART be given either during or after the completion of chemotherapy. A number of recent small prospective studies have demonstrated improved survival for patients on HAART. One non-randomised study has reported an improvement in median survival from 8.2 months to 17.8 months for patients with HIV-related NHL treated in the post-HAART era.²⁶ This study demonstrated a CR rate of 71% for HAART responders compared to 30% for non-responders. In another study, HAART treatment was associated with improved survival, with an 84% reduction in risk of death.²⁷ A retrospective risk factor study in more than 200 patients found response to HAART was independently associated with improved survival.²⁸

It is therefore recommended AIDS–lymphoma patients should receive HAART or have their existing antiretroviral therapy changed to maximise improvement in immune function.

16.3.5 Therapy for primary CNS lymphoma

Before the introduction of HAART, the prognosis for patients with primary CNS lymphoma was exceptionally poor, with many patients too ill to consider either radiotherapy or chemotherapy. The introduction of HAART has led to a number of anecdotal reports of improvement in prognosis. Hoffman et al. reported dramatic improvement in survival of these patients when HAART achieved immune recovery.²⁹ In general, treatment guidelines should follow those for patients without HIV infection.

16.3.6 Therapy for Hodgkin lymphoma

There are no randomised treatment studies. Most reports have only small numbers of patients and describe clinical experience with well-known protocols such as ABVD. Since the introduction of HAART, more intensive protocols have been tried. Recently, successful and safe use of the Stanford V regimen has been reported.³⁰ If immune reconstitution can be achieved with HAART, then treatment guidelines similar to those for HIV-negative patients with Hodgkin lymphoma may be considered.

Stem cell transplantation

The success of immune reconstitution using HAART has led to the investigation of high-dose chemotherapy and stem cell transplantation as salvage therapy for patients with refractory or relapsed lymphoma. The prognosis for these patients is very poor. Gabarre et al. reported the results of autologous marrow and blood stem cell transplants in eight such patients, with five achieving a CR and survivals reported from 5 to 15+ months.³¹ Krishnan et al. reported nine similar patients, with seven achieving CR and median survival 19 months. These modest results represent a remarkable improvement on the previously expected results for such patients.³²

Allogeneic stem cell transplantation has generally been unsuccessful, with one case report of a relapsed lymphoma patient surviving in remission after a syngeneic transplant.³³ Non-myeloablative allogeneic stem cell transplantation has been reported in two patients, one with lymphoma and one

with acute myeloid leukaemia.³⁴ Both survived the therapy. The lymphoma patient died of relapsed disease at one year; the other patient remained in remission at two years.

Extra-nodal lymphoma

This is a more common presentation in HIV–lymphoma and should be managed according to the site-specific requirements for the non-HIV population.

Guidelines — Management for lymphomas associated with HIV	Level of evidence	Refs
Full-dose CHOP should be considered the current standard of care for HIV-related lymphoma, although new data are awaited.	IV	19, 23
Highly active anti-retroviral therapy (HAART) should be commenced or maximised in patients with HIV-related lymphoma.	III	22, 26
Hodgkin lymphoma should be managed as for non-HIV patients, with the addition of HAART.	III	30

Key point

Primary CNS lymphoma should be managed as for non-HIV patients with the addition of highly active anti-retroviral therapy (HAART).

16.4 Post-transplant lymphoproliferative disorder

16.4.1 Background

Post-transplant lymphoproliferative disorders (PTLDs) occur as a consequence of immunosuppression in the recipient of an allograft. They encompass a spectrum of specific pathologies well described in the WHO classification.³⁵ The incidence of PTLD varies considerably between 1% and 20% or more, depending on a number of variables that are discussed below. PTLD may be of early (within the first year after transplant) or late onset (any time thereafter). PTLD has been associated with solid organ transplants of all types and also in bone marrow or stem cell recipients. Recognition of patients at high risk for the development of PTLD is an important element of organ transplantation management.

16.4.2 WHO classification

The WHO categories are as follows:

- Early lesions
 - Reactive plasmacytic hyperplasia
 - Infectious mononucleosis-like
- Polymorphic PTLD
- Monomorphic PTLD (classified according to lymphoma classification)
 - B-cell neoplasms
 - Diffuse large B-cell lymphoma
 - Burkitt/Burkitt-like lymphoma

- Myeloma
- Plasmacytoma-like lesions
- T-cell neoplasms
 - Peripheral T-cell lymphoma unspecified
 - Other types
 - Hodgkin lymphoma

16.4.3 Clinical features

The clinical presentation is highly variable, correlating to some extent with the risk factors discussed below, as well as the specific morphologic subtype of PTL. Early-onset PTL commonly presents with an infectious mononucleosis-like syndrome, with cervical lymphadenopathy and tonsillar enlargement, or simply pyrexia of unknown origin. Late-onset PTL, like other immunodeficiency lymphomas, commonly present with extranodal disease that may manifest as organ dysfunction, often including the allograft.

Key point

Patients with post-transplant lymphoproliferative disorder (PTLD) should undergo standard diagnostic and staging procedures with special attention to extranodal sites including the allografted organ and/or gut, lung, central nervous system, kidney.

16.4.4 Risk factors

Nearly all the current knowledge pertaining to risk factors for PTL is derived from retrospective observational cohort studies. All of these studies suffer from one or more significant limitations, including small numbers, short follow-up times, recall bias, co-intervention bias, solid organ heterogeneity, non-uniformity of diagnosis, or inclusion of only early-onset PTL. Nonetheless, some consistent observations have been made.

Risk factors include:

- serological status for EBV and CMV of the donor and recipient
- immunosuppressive therapy
- recipient age
- underlying disease
- type of organ transplant
- miscellaneous factors

Serological status for EBV and CMV of the donor and recipient

EBV is implicated as an essential cofactor for the development of PTL. An EBV seronegative recipient (R-) may acquire EBV from a seropositive donor (D+). Pre-transplant EBV seronegativity increases the incidence of PTL 10- to 75-fold over that of EBV-seropositive recipients (R+) of organs from seropositive donors.³⁶ The majority of PTLs in this setting derive from donor EBV. In R+, EBV reactivation is usually the mechanism.

Cytomegalovirus (CMV) seromismatch (R-, D+) has been associated with up to a 7.3-fold risk of PTLD in several studies^{36,37}, although was not confirmed in a small study of paediatric lung transplants.³⁸ Reactivated CMV infection may play a role in PTLD, but is difficult to separate from its collinear relationship with higher levels of immunosuppression. CMV seromismatch exerts an important synergy with EBV seromismatch and OKT3 therapy in promoting PTLD.³⁶

Immunosuppressive therapy

The degree and duration of immunosuppression as well as the specific agents are important, recognised risk factors for PTLD.

Specific agents

OKT3

This has been associated with greatly increased risks of early onset, extensive-stage and fatal PTLD.^{36,39-43} Swinnen et al.³⁹ first reported the increased (nine-fold) prevalence of PTLDs in cardiac transplant recipients who received greater than a 10 mg cumulative dose of OKT3. Higher doses were associated with increased risk, with 6.2% of patients receiving ≤ 75 mg developing PTLD, and 35.7% receiving >75 mg developing the disorder ($p < 0.001$). The reported multivariate-adjusted relative risk of PTLD following OKT3 therapy has ranged between 1.8- and nine-fold.^{36,39,44,45} The relative risk of PTLD is synergistically increased four to six-fold by the combination of OKT3 therapy with other risk factors such as EBV and CMV seromismatch (D+, R-). All three risk factors together have been associated with over a 500-fold increased risk (95% CI 324–862) of PTLD compared with the absence of all three factors.³⁹ The median time to development of OKT3-associated PTLD has been reported between four and seven months after transplant but generally occurs within the first year.^{36,39,44,46} Two studies^{47,48} have not been able to confirm a high incidence and early onset of PTLDs in OKT3-treated transplant recipients, but insufficient statistical power and high baseline immunosuppression confound the interpretation of these.

Calcineurin inhibitors (cyclosporin and tacrolimus)

These have been associated with a one to five-fold risk of PTLD. Multivariate analysis of the large Collaborative Transplant Study database (45,141 kidney and 7634 heart transplant recipients) suggested that triple therapy containing a calcineurin inhibitor was associated with a 1.5-fold relative risk of PTLD compared to dual therapy or cyclosporin alone.⁴⁵ This finding was confirmed in a single centre Australian study of 2030 renal transplant patients.⁴⁶ The relationship between cyclosporin levels and PTLD has not been fully established.^{47,49} The incidence of PTLD associated with cyclosporin appears to be comparable to that associated with tacrolimus therapy in adults.^{46,50}

In paediatric patients, tacrolimus therapy increased the risk of PTLD up to 11-fold (absolute risk 11–20%) relative to non-contemporaneous patients treated with cyclosporin.^{47,51,52} Higher tacrolimus levels were a significant risk factor for lymphoma on multivariate logistic regression in a paediatric liver transplant population.⁵¹ There are insufficient data, however, for specific recommendations.

Mycophenolate mofetil

This has not been shown to be associated with a statistically significant increased risk of PTLD in several short-term, multicentre, randomised control trials.⁵³⁻⁵⁵ They were not adequately powered, however, to reliably assess the effect.

Interleukin-2 receptor antibody (basiliximab, daclizumab)

Induction with this agent⁵⁶⁻⁵⁹ does not appear to be associated with an enhanced risk of early PTLD in short-term (one-year) randomised controlled trials. Pooled data from two randomised, placebo-controlled trials of daclizumab (n=535) showed no increased risk of PTLD over placebo after three years.⁵⁸

Sirolimus and RAD

Sample sizes and follow-up times have been too small to determine precisely the risk of PTLD from these agents.^{60,61} The macrolide immunosuppressant, RAD (everolimus, an analogue of rapamycin/sirolimus), has been shown to inhibit the growth of human EBV-transformed B lymphocytes *in vitro* and *in vivo*⁶², indicating that it may be effective in the prevention and treatment of PTLDs. However, there has been insufficient clinical experience with this agent to test this possibility.

Antithymocyte globulin (ATG)

This has been reported to increase^{45,51,60,63} or have no effect^{38,46,64} on the occurrence of PTLD in small observational cohort studies. All of the studies reporting a deleterious effect of anti-lymphocyte antibodies on PTLD risk have lumped patients receiving ATG with those receiving OKT3 and have not analysed ATG administration as a separate covariate. Thus the risk of ATG may have been overestimated. On the other hand, the negative studies had a relatively small number of cases (up to 29) and may have been inadequately powered.

Duration and intensity of immunosuppression

PTLD can present as early as less than a month to as late as many years after transplantation. The incidence of PTLD is highest in the first year, which is the time of most intense immunosuppression (approximately 100 cases/10⁵ patient-years), and falls by about 60% thereafter (approximately 40 cases/10⁵ patient-years).^{36,45,46,65}

More intensive immunosuppression is associated with an earlier onset of PTLD. Penn⁴⁴ reported mean lag times between solid organ transplantation and PTLD diagnosis of seven months for OKT3, 15 months for cyclosporin, and 48 months for patients treated with azathioprine/cyclophosphamide. In a large renal transplant cohort, median lag times were six months for OKT3, 48 months for triple therapy calcineurin inhibitor/prednisolone/azathioprine or mycophenolate, and 168 months for dual therapy (prednisone + azathioprine).⁴²

Early onset PTLDs are much more likely to be EBV-related than late onset PTLDs. In one series, 50% of EBV-positive PTLDs had arisen within six months of transplantation, whereas 50% of EBV-negative PTLDs had not occurred until five years after transplantation.⁶⁶

Late-onset (several years) PTLD is less strongly associated with potent immunosuppression.^{46,67,68} Some of this association, however, may represent a bias of the shorter follow-up periods of studies involving newer, more potent, immunosuppressive therapies. PTLDs of T-cell origin are uncommon and may also arise later in the post-transplantation course.⁶⁹

Recipient age

Paediatric patients have higher frequency of PTLD than adult recipients of similar allografts. Contributing to this is a higher percentage of EBV- and CMV- seronegative recipients. Zangwill et al. reported an overall PTLD occurrence rate of 26% among 50 paediatric heart transplant recipients (mean follow up 3.3 years), with risk related to EBV status: 0% in persistently R-, 5% in R+, and 63% in patients who seroconverted after transplantation.⁷⁰

Ho reported similar findings in a series of paediatric kidney transplant recipients.⁷¹ Rates in seronegative adults are comparatively much lower.^{71,72}

Older recipient age appears to be a risk factor for the development of late-onset (>1 year) PTLD. The Collaborative Transplant Study observed that the incidence of late-onset PTLD in 7634 cardiac transplant recipients was significantly higher in individuals over the age of 49 years compared with those less than 20 years (480 versus 99 cases/10⁵ patient-years respectively).⁴⁵ A similar, non-significant trend was observed in 45,141 renal transplant recipients.

Underlying disease

Hepatitis C infection has been implicated as a risk factor for PTLD to complicate liver transplantation in two small retrospective studies using either contemporaneous or historical controls (11% versus 2% and 7% versus 1%, $p < 0.05$).^{73,74} However, these studies performed univariate analyses, which did not adjust for potential confounders, such as background immunosuppression. A similar finding has been reported for PTLD in cardiac transplant recipients (HCV positive 8% versus HCV-negative 2%, $p = 0.01$).⁷⁵

A striking association was reported in one series of patients who underwent liver transplantation for treatment of Langerhans cell histiocytosis. Two thirds of patients developed PTLD.⁷⁶

Children with cystic fibrosis receiving lung allografts have been reported to have a higher frequency of PTLD (23% versus 4% for other indications, adjusted odds ratio 11.0, 95% CI 2.7–55.7) in one ($n = 128$) retrospective, single-centre cohort analysis.³⁸

Type of organ transplant

The risk of PTLD appears to be strongly influenced by the type of organ transplanted. The risk is lowest in bone marrow transplant and renal and pancreatic transplant recipients (1–2%)^{45,46}; intermediate in liver and cardiac transplants (2–4%)^{45,77}; and highest in lung and intestinal transplants.^{74,78–81} The incremental risk may be partly due to variations in immunosuppressive burden (where lower immunosuppression is employed in renal and pancreatic transplants because rejection and graft loss is not generally immediately life-threatening). Moreover, the large lymphoid populations transferred with lung or intestinal transplants facilitate EBV transmission.^{67,82}

The allografted organ is at specific risk of involvement in patients with PTLD. The Collaborative Transplant Study demonstrated that renal lymphoma developed in 14.2% of renal transplant recipients versus 0.7% of heart transplant recipients. Allograft involvement is particularly common ($\geq 80\%$) in lung and intestinal transplant patients with PTLD.^{38,67,79–81,83}

In HLA-matched sibling bone marrow transplants, the incidence of PTLD is generally less than 1%.^{84–86} Several risk factors are associated with a much higher incidence.^{87–89} These include non-HLA identical transplants, T-cell depletion of the graft, severe graft versus host disease (GVHD), and in common with solid organ transplant recipients, EBV seronegativity and the use of antithymocyte globulin.

Miscellaneous risk factors

- Immunologic profile: a small, prospective, single-centre, nested case-control study found that a high absolute count of activated NK cells (CD56+ DR+) at baseline was a significant, independent predictor of PTLD development.⁹⁰
- Cytokine gene polymorphisms: preliminary data suggest that the development of PTLD is linked with low-producing polymorphisms of interferon- γ (80% versus 12%)⁹¹ and tumour necrosis factor- α .⁹²
- Caucasian race, cadaveric donor⁴⁷ and adenotonsillar hypertrophy⁹³ have each been implicated as PTLD risk factors in small, single studies of paediatric transplant populations.
- The degree of HLA mismatching does not appear to influence the risk of PTLD in recipients of solid organ transplants, in contrast to bone marrow transplantation.⁶⁷

What do other guidelines say?

ASTS/ASTP EBV-PTLD Task Force and Mayo Clinic Organized International Consensus Development Meeting

The three identified epidemiological risk factors for PTLD are EBV seronegativity pretransplantation (R-), CMV disease in a CMV mismatch (D⁺/R⁻) patient, and high doses of antilymphocyte antibodies or over immunosuppression.

Guidelines — Post-transplant lymphoproliferative disorder (PTLD) — risk factors	Level of evidence	Refs
Two of the major known risk factors for the development of PTLD are Epstein-Barr virus (EBV) sero-mismatch and cytomegalovirus (CMV) sero-mismatch (R-, D+).	III-2	36, 37

Key point

Before transplant, the Epstein-Barr virus (EBV) and cytomegalovirus (CMV) status of recipient and donor should be determined to identify patients at high risk of developing post-transplant lymphoproliferative disorder (PTLD).

Guidelines — Post-transplant lymphoproliferative disorder (PTLD) — risk factors	Level of evidence	Refs
Use of OKT3 is the third powerful known risk factor for PTLD.	III-2	39

Key point

Post transplant use of OKT3 should be minimised and recipients should be identified as patients at high risk for the development of post-transplant lymphoproliferative disorder (PTLD).

Recommendations for future research

- National registries (such as ANZDATA) should prospectively collect detailed clinical data, including demographics, immunosuppression, EBV and CMV status, and other potential risk factors in all transplant recipients and identify PTLD cases.
- Uniform practices of testing EBV and CMV serologies in both donors and recipients prior to transplantation should be promoted. This would help to identify at-risk patients and may influence subsequent decisions regarding maintenance and anti-rejection immunosuppression.
- Trials of newer immunosuppressive agents and subsequent post-marketing surveillance should specifically evaluate whether or not PTLD risk is modified.

16.4.5 Surveillance

Monitoring the EBV viral load

Measuring the EBV viral load in plasma and peripheral blood mononuclear cells has been used to identify patients at risk of developing PTLD. Studies are hard to compare because study design as well as EBV detection methods and analysis are highly variable. In the majority of cases, however,

EBV viral load is increased in patients with PTLD compared to patients without disease. There is overlap, however, with evidence that two-thirds of transplant recipients become persistent viral load carriers without evidence of PTLD. More recent studies utilising quantitative real-time PCR show the potential to identify threshold EBV levels above which patients are at greatly increased risk of developing PTLD.⁹⁴⁻⁹⁶

Viral load monitoring can be used to follow patients with PTLD and, along with other parameters, to provide an assessment of the effectiveness of therapeutic protocols.

CMV monitoring

There is no evidence pertaining to the usefulness or otherwise of CMV monitoring (e.g. PP65 antigenaemia, serology, polymerase chain reaction) in a PTLD surveillance program.

Monoclonal gammopathies

The best available evidence addressing the value of gammopathy monitoring by serum protein electrophoresis for PTLD surveillance is a prospective cohort study by Lemoine et al.⁹⁷ Nine hundred and eleven (911) consecutive liver transplant recipients underwent serum protein electrophoresis prior to transplantation, twice in the first post-transplant year and then annually thereafter. Gammopathy was observed in 114 patients overall, and in 18 out of 21 PTLD patients before the development of PTLD (therefore, positive predictive value = 16%). The adjusted relative risk of gammopathy for PTLD was 65.3. For diagnosis of PTLD remission, the positive and negative predictive values of gammopathy disappearance (on monthly serum electrophoresis monitoring) were 91% and 100% respectively. Gammopathy disappearance preceded the radiologic diagnosis of complete remission by a mean of four months.

Badley et al⁹⁸ observed the presence of monoclonal gammopathy in 5 of 7 (71%) patients with PTLD and 52 of 194 (27%) patients without PTLD (positive predictive value 9%, negative predictive value 99%) in a small (n=201), single-centre, retrospective cohort analysis. Numbers were too small to permit a multivariate analysis.

What do the other guidelines say?

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Quantitative EBV polymerase chain reaction technology is a promising innovation that may allow for an earlier diagnosis of PTLD and identification of those patients likely to develop PTLD. However, additional study is required before recommending it for routine clinical use.

Guidelines — Surveillance of post-transplant lymphoproliferative disorder (PTLD) patients	Level of evidence	Refs
Monitor EBV viral load serially by quantitative real-time PCR in plasma (preferably in the context of ongoing research).	IV	94-96
Monitor for the development of monoclonal gammopathy.	IV	98

Recommendations for future research

- The major future goal will be to standardise EBV-DNA quantitation using real-time PCR in order to generate comparable data and to establish threshold values to identify patients at high risk of developing PTLD.
- Concurrent evaluation of EBV-DNA load and gammopathy monitoring in prospective studies is needed, particularly in high-risk groups (e.g. EBV and CMV seromismatch, OKT3 therapy).

16.4.6 Therapy of PTLD

There is no standard approach. Early diagnosis and use of appropriate therapies is essential to the successful treatment and management of PTLDs. Treatment should be tailored to the specific form of disease in the individual patient. Most centres follow a step-wise approach, with the initial intervention influenced by the extent of disease and the degree of acute illness of the patient. This results in a diversity of modifications and makes it difficult to compare therapies.

Therapy for PTLD includes:

- reduction of immunosuppression
- antiviral therapy
- cytokine therapy, for example, interferon
- conventional chemotherapy
- monoclonal antibody
- surgical excision
- radiotherapy
- cellular immunotherapy

Reduction of immunosuppression

There are no randomised controlled trials evaluating this well-established approach. The available studies are all retrospective and often limited by recall, co-intervention and selection biases. The infrequent reporting of standardised prognostic markers, such as the International Prognostic Index, make it difficult to generalise results to clinical practice.

Reduction or cessation of immunosuppression is almost universally reported in the therapy of PTLD. However, there has been no standardised approach to immunosuppression management, and treatment has often been combined with other therapies in an *ad hoc* fashion. Thus it is not possible to make evidence-based recommendations regarding the extent to which immunosuppression should be curtailed, or for how long. Most studies have suggested major reductions with cessation of azathioprine or mycophenolate mofetil and reduction of calcineurin inhibitors by at least 50%.^{67–89} Prednisone dosage is usually reduced to 10 mg or below. Patients with kidney or pancreas transplants (where loss of the organ is not immediately fatal) may have all immunosuppressive agents ceased except for a maintenance dose of steroids to avoid Addisonian crisis.^{46,99}

Regression of PTLD after immunosuppressant dose reduction ranges from 23% to 63%.^{68,99} Reported subsequent allograft rejection rates have ranged between 0% and 74%.^{46,68,99,100}

Risk factors for non-response to reduction of immunosuppression have been analysed in a retrospective study of 42 PTLD patients. These were elevated lactate dehydrogenase, organ dysfunction and involvement of at least two organs.⁹⁹ The respective complete or partial response rates for 0, 1 or >1 risk factors present were 89%, 60% and 0%. The median time to documented radiologic complete or partial remission was 3.6 weeks (range 1.7–14.6 weeks). Other retrospective studies have suggested that patients with late-onset (>1 year post-transplantation) PTLD are unlikely to respond to immunosuppression reduction alone.^{46,78}

Systemic antiviral therapy

The efficacy of antiviral therapy for treating PTLD has not been firmly established. Transformed B cells have a circular viral DNA that is not very susceptible to inhibition with thymidine kinase

inhibitors such as acyclovir and ganciclovir.¹⁰¹ However, there are anecdotal reports of PTLD regression with both acyclovir and ganciclovir therapy.^{102–108} Other authors have documented poor clinical outcomes with acyclovir.^{101,103,109} There are no randomised controlled trials. The limited data available are all retrospective.

Cytokine therapy

There are no randomised trials. All studies are retrospective and most are small.^{110–113} Interferon alpha may succeed when no response has been seen with reduction of immunosuppression.^{112,113} However, the risk of rejection is also present with the use of this agent. Ten of the 34 cases in the published literature had rejection of the allograft.¹¹³ Complete response rates of up to 40% have been reported with interferon alpha.^{111,113} Recombinant interferon-alpha has been given with IV immunoglobulin and induced remission in five patients, with three durable responses.¹¹¹

Chemotherapy

Reported results of treatment of PTLD with conventional chemotherapeutic agents are conflicting.^{102,103} Early attempts to use anti-lymphoma chemotherapy resulted in high mortality rates and response rates were highly variable. This may be related to the heterogeneity of PTLD, different chemotherapy regimens, the type of organ transplant, the variable degrees of immunosuppression, the timing of treatments, and concomitant therapies. Infectious and other complications of chemotherapy were less well managed and may also have contributed to the poor outcomes. Nonetheless, observed cure rates of 20%, 11% and 23% were documented.^{41,103,114}

Davis et al.¹¹³ reviewed the more recent literature (1994–2000) and found 67 of 202 patients were treated with chemotherapy. The patients were heterogenous and were treated with different cytotoxic regimens. Forty-six patients (22%) achieved CR, with a mortality of 11% during chemotherapy.

More encouraging results have been obtained in cardiac transplant recipients mainly treated with ProMACE-CytaBOM. CR was obtained in 75%, with mortality of 25%. No relapses were observed at a median follow up of 64 months.¹¹⁵ An overall response rate of 80% (30 PR and 50% CR) was reported in ten selected patients with late onset (>1 year) PTLD post-renal transplant treated with CHOP chemotherapy.¹¹⁶ Modified approaches with regimens used to both treat the tumour and maintain an immunosuppressed state to preserve the allograft have also been reported.^{117–119} A case series from a single Australian centre with a treatment approach of initial reduction and eventual discontinuation of immunosuppression once established on CHOP chemotherapy reported an excellent outcome. Overall response rate was 100%, with CR in 93% and PR in 7%.¹²⁰

Advances in supportive care (G-CSF, blood product support, antimicrobials, etc) for patients with haematological malignancies, have contributed to reduced morbidity and mortality from chemotherapy in more recent studies.

Monoclonal antibody therapy

Anti-B-cell antibodies have demonstrated efficacy in the treatment of PTLD. Early experience was with murine anti-CD21 and anti-CD24. Fifty-eight patients were treated, with CR of 61% and low relapse rate of 8%.¹²¹ More recent experience has been with the humanised anti-CD20 monoclonal antibody, rituximab. Efficacy has been reported in a number of case reports and small case series.^{122–125} In the largest cohort to date, Milpied reported a 69% response rate, with 73% projected survival at one year.¹²³ Similar response rates (66%) were reported in twelve children with PTLD post stem cell transplantation treated with rituximab.¹²⁴ Rituximab has been included in the European Best Practice Guidelines for the management of PTLD based on the growing evidence of efficacy and minimal toxicity.¹²⁶ The growing body of evidence supporting the use of rituximab in combination with chemotherapy in de novo aggressive lymphoma will influence the approach to patients with PTLD, although no data specific to this population are yet available.

Surgery

Data are anecdotal or retrospective case series. Surgical resection has been used and may be curable in the early limited stage, particularly in relatively slowly growing PTLD. In one series, 74% of patients survived.¹¹⁵ However, another study reported a complete remission rate of only 31% in PTLD treated by surgery or radiotherapy.¹⁰³ Surgery has been used for resection of residual disease persisting after reduced immunosuppression or interferon therapy.^{78,110}

Radiotherapy

There are no randomised trials. Most of the reports are retrospective studies with small number of patients, often citing combined therapy with surgery or chemotherapy. Survival rates of around 20% for radiotherapy have been documented in PTLD.¹¹⁵ Radiotherapy has also been used in the treatment of CNS tumours and for control of localised disease elsewhere.¹⁰⁹

Cell therapy

Expression of the full complement of EBV latent antigens in PTLD provides an ideal target for T-cell-based immunotherapy. There are two distinct categories of PTLD — those arising in bone marrow transplant patients where the proliferating B cells are exclusively of donor origin, and those arising in solid organ transplant patients where the proliferating B cells are generally of recipient origin. The importance of cytotoxic T cells (CTL) in controlling these B-cell expansions was first demonstrated in the case of PTLD in bone-marrow transplant patients transfused with EBV-specific CTLs.¹²⁷ In this case, adoptive transfer of EBV-specific CTLs from the bone marrow donors was successfully used to resolve PTLD in the recipient. To date, more than 60 bone marrow transplant patients have been infused with EBV-specific CTL lines as a prophylactic treatment. None of these patients has shown any symptoms of PTLD. Interestingly, many of these adoptively-transferred EBV-specific T cells can be detected 18 months after the infusion.

Although applying a similar rationale of adoptively transferring EBV-specific CTLs to resolve PTLD arising in solid organ recipients is an attractive idea, there are fundamental differences between bone marrow and solid-organ transplantation that pose a major challenge. These include:

- activating a CTL response *in vitro* in cells from patients receiving high levels of immunosuppressive drugs
- the risk of expanding allospecific CTLs that will threaten the integrity of the transplanted organ when adoptively transferred; and the efficacy of adoptively-transferred CTLs in the face of high levels of immunosuppression *in vivo*.

One possible way to overcome these limitations is to use allogeneic CTL lines grown from healthy virus carriers who share MHC class I alleles with the patient.¹²⁸ Adaptation of this approach for wider clinical use has to proceed with some caution, however, because adoptive transfer of allogeneic T cells can be associated with allograft rejection. Ideally, the best strategy would be to expand autologous EBV-specific T cells from the patient. Such methodology is evolving. Indeed, a novel protocol has recently been developed for activating autologous EBV-specific CTL lines from solid-organ transplant patients.¹²⁹ This activation protocol involves co-cultivation of peripheral-blood mononuclear cells with autologous EBV-infected B-cell lines under conditions that favour expansion of virus-specific CTLs and hinder the proliferation of allospecific T-cells.

These CTLs consistently showed:

- strong EBV specificity, including reactivity through defined epitopes despite concurrent immunosuppressive therapy
- no alloreactivity towards donor alloantigens.

More importantly, adoptive transfer of these autologous CTLs into a single patient with active PTLD was coincidental, with a very significant regression of the PTLD. These results demonstrate that a potent EBV-specific memory response can be expanded from solid-organ recipients who have acquired their primary EBV infection under high levels of immunosuppressive therapy, and that these T-cells might have therapeutic potential against PTLD.

What do other guidelines say?

ASTS/ASTP EBV-PTLD Task Force and Mayo Clinic Organized International Consensus Development Meeting

The initial intervention in all patients should be a reduction in immunosuppression. However, how much reduction, for how long, and how to predict the response, is unknown.

Staged approach is recommended as follows:

1. reduce immunosuppression
2. IFN alpha
3. if no response to 1 and 2, proceed to chemotherapy.

The European Best Practice Guidelines for Renal Transplantation (Part 2)

Reduction of basal immunosuppression in all cases.¹²⁶

In the case of EBV-positive B-cell lymphoma, antiviral treatment with acyclovir, valacyclovir or ganciclovir may be initiated for at least one month or according to the level of EBV replication

In the case of CD20-positive lymphomas, treatment with rituximab, a chimeric monoclonal antibody directed against CD20, should be carried out.

Recommendations for future research

- National registries (such as cancer registries and/or ANZDATA) should prospectively collect detailed information on identified PTLD cases regarding IPI, treatment and outcome.
- Pooled registry data (e.g. pooled Collaborative Transplant Study database) should be analysed to determine the extent and duration of immunosuppression reduction associated with the most favourable risk:benefit ratios in the therapy of PTLD.
- A randomised controlled trial of immunosuppression reduction in monitored, high-risk patients is needed to confirm the effectiveness of such a pre-emptive strategy, with clearly defined triggers for pre-emptive treatment (such as a defined EBV load).
- A large, multicentre, randomised controlled trial of antiviral therapy in high-risk patients is needed.
- The role of rituximab, both as a single agent and in combination with chemotherapy, needs to be systematically evaluated in randomised international studies, .
- The role of surgery and radiation therapy needs to be prospectively evaluated in international trials of patients with localised PTLD.
- Setting up a transplant-related lymphoma task force under the auspices of the ALLG may be a useful starting point to generate some of the clinical trial work needed.

Guidelines — Management of post-transplant lymphoproliferative disorder (PTLD) patients	Level of evidence	Refs
Management of PTLD patients All patients with PTLD should have baseline immunosuppression substantially reduced or ceased as the initial therapeutic strategy	IV	67, 68, 99
Consider early additional therapy in patients with risk factors for non-response to reduced immunosuppression (elevated LDH, end organ dysfunction, multi-organ involvement, late onset PTLD, rapidly progressive disease).	IV	46, 78, 99
Additional therapies that should be considered but the roles of which have not been clearly defined include systemic antivirals (ganciclovir, acyclovir) ^{102–105} and alpha interferon. ^{110–113}	IV	102–105, 110–113
Standard combination chemotherapy for aggressive lymphoma should not be delayed in patients who are not responding to initial strategies (see Chapter 13 — Aggressive lymphoma).	IV	115, 116

Key point

Standard chemotherapy should be considered as initial therapy in patients with extensive systemic or rapidly progressive disease, particularly with IPI >1.

Guidelines — Management of post-transplant lymphoproliferative disorder (PTLD) patients	Level of evidence	Refs
Rituximab is an active agent and should be considered as an additional therapeutic modality.	IV	122–125
Radiation may contribute to the management of PTLD and should be considered in the same settings as non-PTLD lymphomas.	IV	109, 115
Adoptive immunotherapy with allogeneic EBV-specific CTL should be considered in post-BMT PTLD.	IV	127
Adoptive immunotherapy with autologous EBV-specific CTL should be considered for solid organ PTLD patients in the context of continuing clinical research.	IV	128, 129

16.5 Methotrexate-associated lymphoproliferative disorders

16.5.1 Background

Lymphomas and LPDs may occur in patients immunosuppressed with methotrexate, most commonly in the setting of treatment for rheumatoid arthritis, psoriasis or dermatomyositis. More than 100 cases have been reported in the literature, over 85% in association with rheumatoid arthritis, which is itself associated with an increased risk of lymphoma.^{130–135} There is no definitive epidemiological evidence, however, of the extent to which methotrexate increases the risk of lymphoma in such patients, if at all.^{136–139} Important clinical observations regarding lymphoma in this setting justify its inclusion as a

separate entity, however. The histologies observed are variable and include DLBCL, Hodgkin lymphoma, follicular lymphoma, lymphoplasmacytic lymphoma and polymorphous PTL. EBV has been implicated in the pathogenesis in approximately 50% of cases. Extranodal presentations are common. There are no other discernibly different features from lymphoma in non-methotrexate treated patients.

16.5.2 Therapeutic considerations

The most important clinical observation with respect to these lymphomas has been regression on withdrawal of methotrexate in approximately 60% of cases.^{140–142} The majority of these have been EBV positive. All evidence for this is in the form of case reports, but the observation is made repeatedly and consistently. The reported incidence of regression varies with the specific histology involved, with fewer Hodgkin and diffuse large B-cell lymphomas regressing than lymphoplasmacytic lymphomas.¹⁴² While the majority of those reported in the literature regressed, non-reporting of those that did not regress may bias this literature.

Guidelines — Methotrexate and lymphoproliferative disorders	Level of evidence	Refs
Patients being treated with methotrexate should be monitored for the development of a lymphoproliferative disorder.	IV	130–135,
Methotrexate should be ceased in patients who develop lymphoma and observed for regression before administration of the appropriate lymphoma therapy, if clinically feasible. Methotrexate should not be reintroduced in such patients.	IV	140–142

16.5.3 Recommendations for future research

- National registries should record whether lymphoma patients were being treated with methotrexate.
- Registries of rheumatoid arthritis patients should identify those who develop lymphoma, and determine the relative risk associated with methotrexate therapy.
- The role of EBV should be explored in all patients with methotrexate-associated lymphoma, with a view to the potential for therapeutic intervention with EBV-specific adoptive immunotherapy.

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