1. The drug and the review

Rituximab is a monoclonal antibody that binds specifically to CD20, an antigen expressed on the surface of mature and immature B lymphocytes. The binding of rituximab to CD20 results in cell lysis via the recruitment of immune effector functions; it has also been demonstrated to induce cell death via apoptosis. Rituximab (Mabthera®) is licensed in the UK for the treatment of Non-Hodgkin's lymphoma, chronic lymphocytic leukaemia and rheumatoid arthritis.

Post-transplant lymphoproliferative disease (PTLD) describes a heterogeneous group of lymphoproliferative diseases, occurring as a result of uncontrolled B cell proliferation in the context of post-transplant immunosuppression. There has been interest in the use of monoclonal antibodies directed to B cell antigens as a less toxic alternative to chemotherapy in the treatment of PTLD.

This review summarises the current best quality evidence available for rituximab in the treatment and pre-emptive therapy of PTLD (an unlicensed indication), both as monotherapy and in combination with chemotherapy.

2. Background

PTLD affects about 2% of transplant patients in the first year and 1% per year thereafter; this does however vary according to the type of transplant and immunosuppression used. The associated mortality is high, estimated at around 60% for disease occurring after solid organ transplantation and 80% after stem cell transplantation.

Conventionally, treatment of solid organ recipients has consisted of a reduction in the doses and/or number of immunosuppressants as first-line, followed by cytotoxic therapy if required (the latter may be used first line in aggressive cases). Although response rates of up to 70% have been seen, cytotoxic therapy is associated with severe toxicity and may result in treatment-related deaths. More recently there has been a move towards the use of rituximab in this indication. For patients who have had a stem cell transplant, and also for some solid organ recipients (depending on the type), reduction in immunosuppression may not be a feasible option.

Guidelines from the British Committee for Standards in Haematology and the British Transplantation Society on the surveillance, diagnosis and management of PTLD in solid organ transplant recipients were published recently. These acknowledge the lack of published randomised controlled trials (RCTs) evaluating treatments for PTLD on which to base treatment recommendations; much of the available evidence consists of single-arm studies, registry reviews or case series.
The guidelines recommend reduction of immunosuppression for all patients; those with clinically low risk disease without an adequate response should receive single-agent rituximab (375mg/m² weekly for four weeks). Patients with high risk disease and those with low-risk disease who fail to achieve an adequate remission or progress despite previous reduction of immunosuppression and single agent rituximab should receive rituximab in combination with anthracycline-based chemotherapy (e.g. R-CHOP).

Guidelines from the Second European Conference on Infections in Leukaemia on the management of EBV infections in patients with haematological malignancies and after stem cell transplantation were published in 2009. These recommend rituximab as first-line treatment of PTLD in such patients, despite the lack of randomised controlled trials. Other options include reduction of immunosuppression (if possible), adaptive immunotherapy with in vitro-generated donor EBV-cytotoxic T-cells (if available), or infusion of donor lymphocytes to restore T-cell reactivity. Chemotherapy is recommended as a second-line therapy.

3. Literature

A comprehensive search of the literature using MEDLINE (1950 onwards) and EMBASE (1980 onwards) was conducted (last searched 19/01/2010), and the retrieved references reviewed to identify any additional articles of relevance. A number of websites were accessed for information, including NICE, SMC, AWMSG, National electronic Library for Medicines (NeLM), National Library for Health (NLH), and Micromedex. Additionally an online search of ASH annual meeting abstracts was conducted.

Search strategy

EMBASE: exp *RITUXIMAB/ AND exp *LYMPHOPROLIFERATIVE DISEASE/dt [Limit to: Human and English Language]
MEDLINE: rituximab.ti,ab AND exp *LYMPHOPROLIFERATIVE DISORDERS/dt [Limit to: Humans and English Language]

Prospective, non-comparative studies have evaluated the pre-emptive use of rituximab monotherapy in the management of HSCT recipients whose EBV titres rise above a predefined threshold, with the aim of reducing the incidence of PTLD. No data for rituximab in this indication were located for solid organ recipients.

Three Phase II studies have evaluated the efficacy of rituximab (375mg/m² weekly for four weeks) as monotherapy in the second-line treatment of PTLD, following failure of reduction in immunosuppression. One additional paper described the longer-term outcome of 60 patients in two of the Phase II trials, with a median follow-up of 16.3 months. The results of a Phase II study assessing rituximab in combination with CHOP chemotherapy have been presented at conference and details of this are included. All of these studies have evaluated rituximab in solid organ transplant recipients; only retrospective data exist for the treatment of patients with PTLD following a stem cell transplant.

Although there have not been any prospective trials comparing rituximab monotherapy to an alternative second-line treatment for PTLD, the Phase II trial of rituximab + CHOP was amended so that patients received subsequent treatment according to their response to rituximab monotherapy. There are therefore some data comparing rituximab followed by CHOP to continued rituximab monotherapy in low-risk patients.

4. Efficacy studies

Pre-emptive therapy

The located non-comparative studies investigated rituximab in the prophylaxis of PTLD in patients with high EBV titres following HSCT. The largest series suggest a high complete response rate (above 90% of patients have clearance of EBV-DNA, with no signs of PTLD) but only indirect data give any insight as to how many of the patients would have actually gone on to develop PTLD without treatment. One author suggests that, using a threshold for pre-emptive therapy of 1000 copies/mL, around 6 patients would need to be treated with rituximab to prevent once case of PTLD.

No data on the pre-emptive use of rituximab to prevent PTLD in solid organ transplant recipients were located from a search of the published literature.
Monotherapy for treatment

The three Phase II trials for rituximab monotherapy (375mg/m² weekly for four weeks) in patients with PTLD following solid organ transplantation were of a similar design; all included patients in whom reduction in immunosuppression was unsuccessful (n=43, 17 and 11). The main endpoint in all three studies was overall response rate – this ranged from 44.2% (28% complete response) to 64% (55%). One author reporting long-term follow-up from two of these studies (median follow-up of 16.3 months) noted a median progression-free survival of 6 months and median overall survival of 34.5 months, with 51.8% alive at three years.

Findings from an ongoing Phase II study of combination therapy provide some data on the use of rituximab consolidation in patients who have a complete response to four doses of rituximab monotherapy (see below).

In combination with chemotherapy for treatment

An ongoing Phase II study is evaluating sequential treatment with rituximab and CHOP-21 chemotherapy (with G-CSF support) in the treatment of PTLD following solid organ transplant that is unresponsive to reduction of immunosuppression. Originally patients were treated with four weekly doses of rituximab, followed by four cycles of CHOP-21 starting 4 weeks after the last dose of rituximab (sequential treatment, ST; n=64). Following interim results, the protocol was however amended and patients received subsequent treatment depended on their initial response to the four doses of rituximab (risk stratified sequential treatment; RSST; n=40). In RSST, those achieving a complete remission following rituximab (low risk) received four further doses of rituximab monotherapy, and all others (high risk) were treated with four cycles of rituximab plus CHOP-21.

At the time of the most recent analysis (median follow-up of 34 months for those receiving ST and 9.1 months for those receiving RSST), the overall response rate following completion of treatment was 89% (CR 69%) for ST and 90% (CR 73%) for RSST (p<0.0001 compared to response to initial rituximab courses). The authors conclude that in low risk patients, subsequent consolidation with rituximab monotherapy (RSST) seems not to be inferior to consolidation with 4 cycles of CHOP (ST). In addition, there is a suggestion from their findings that the use of R-CHOP may be associated with improved survival compared to CHOP in high-risk patients (n=72).

5. Safety

Due to the absence of placebo controls, the data do not allow determination of adverse events occurring more often in those exposed to rituximab. Serious events attributed to treatment included intestinal perforation at the site of PTLD involvement; others included neutropenia, anaemia, and purpura with myalgia. Early treatment-related deaths due to infection were observed in six patients (9%) who received treatment with R-CHOP in a study of this combination treatment in SOT recipients.

6. Critical evaluation

Although there are limited studies evaluating the pre-emptive use of rituximab as a way of reducing the incidence of PTLD, none have provided any comparative evidence, and so its place in therapy remains to be defined. Alternative strategies include the early, prompt treatment of PTLD (where frequent monitoring of EBV-DNA aids fast diagnosis) – this would avoid ‘over-treatment’ (i.e. patients receiving pre-emptive therapy when they would not have actually gone on to develop PTLD). One author notes that a study comparing these two interventions is unlikely as large patient numbers would be required to demonstrate any statistically significant difference.

The efficacy data for rituximab in the treatment of PTLD are limited to Phase II studies in solid organ transplant recipients and to small retrospective studies in stem cell transplant recipients. This is representative of the general evidence base for treatments in this area, which consists mainly of single-arm studies, registry reviews and case series. Recent guidelines from the British Committee for Standards in Haematology/ British Transplantation Society recognise this lack of controlled data and their recommendations are therefore ‘a synthesis of expert opinion guided by published evidence’. It is recommended that in all cases, individual patient circumstances may dictate an alternative approach.

There are no studies that compare rituximab monotherapy with other treatments in the management of PTLD that has not responded to the reduction of immunosuppression. Due to the adjustments to the protocol, the ongoing Phase II study may provide some comparative data on the use of sequential rituximab and CHOP versus the use of risk-adjusted treatment.
The trial was not however originally designed to test this, so this may limit the statistical significance of any conclusions drawn. Data from this is also being used to make a comparison of overall survival between CHOP and R-CHOP in those not receiving a complete response following four doses of rituximab monotherapy. Again this comparison would not have been specified in the original protocol, and the study would not have been powered to detect statistically significant differences between these two groups. Further results from and full publication of the study are awaited.

Although no direct comparisons are available, rituximab treatment would be expected to have an improved safety profile compared to the use of chemotherapy, based on known safety profiles in other indications. Data from the ongoing Phase II study suggest that the use of risk-adjusted sequential treatment reduces toxicity by limiting chemotherapy to those with high-risk disease.

7. Health Economics

No health economic analyses are available for rituximab in this setting.

8. Estimated cost per 100,000 population

Costs of PTLD treatment:
- **Rituximab monotherapy (375mg/m² for four weeks)** - £636 per 100,000 for HSCT and £2934 per 100,000 for SOT
- **CHOP (four cycles)** - £115 and £530, respectively

This is based on an estimated 2959 HSCT carried out in 2008 (27), with a 3% incidence of PTLD (0.13 patients per 100,000) (5), and 3513 SOT carried out in 2008 (28), with a 10% incidence of PTLD (0.6 patients per 100,000 population) (1-4). This assumes that all patients go on to PTLD (in practice this would not necessarily be required in low risk patients responding to reduction in immunosuppression).

(Please see Table 3 in the full review for further details of other possible treatment regimens)

Costs of pre-emptive therapy of PTLD:

**Rituximab monotherapy (375mg/m² for 1-3 doses)** - £1711-£5132 per 100,000 for HSCT

This is based on an estimated 2959 HSCT carried out in 2008 (27), and 30% of these patients meeting the criteria for pre-emptive PTLD therapy based on a threshold of 1000 copies/mL EBV-DNA (1.4 patients per 100,000 population) (13)

9. Points for consideration

- Is rituximab superior to other options (e.g. chemotherapy; specific immunotherapy) for the treatment of PTLD after failure of reduction of immunosuppression? In practice CTLs may not be a realistic alternative option as they are not generally available and take time to manufacture.
- In which patients, if any, would the upfront use of rituximab in combination with chemotherapy be indicated?
- What is the most appropriate schedule of rituximab administration for pre-emptive treatment of PTLD, and at what threshold of EBV titre should treatment be initiated to be most cost-effective?
- Is pre-emptive treatment associated with improved outcome compared to prompt treatment upon clinical presentation?
- Does the pre-emptive use of rituximab have any effect on overall survival?
- How does rituximab compare to reduction of immunosuppression and the infusion of EBV-specific CTLs in the prophylactic treatment of patients at a high risk of developing PTLD (would these other options be a realistic alternative in practice)?
- What is an acceptable number of patients needed to treat with pre-emptive therapy to prevent a single case of PTLD?
- The risk of PTLD in stem cell transplant patients varies depending on the type of transplant. Could these patients therefore be considered separately and only those at a high risk monitored for EBV/ treated pre-emptively?
Rituximab for post-transplant lymphoproliferative disease (PTLD)

Background

Post-transplant lymphoproliferative disease (PTLD)

PTLD is characterised by uncontrolled proliferation of B cells (or in 15% of cases T cells and rarely other haemopoietic cells) in the context of pharmacological immunosuppression following solid organ or bone marrow transplantation. PTLD represents a heterogenous group of lymphoproliferative diseases, ranging from indolent lymphoproliferation resolving after reduction of immunosuppression, to aggressive lymphoma that is rapidly fatal without combination cytotoxic chemotherapy (1-4).

The frequency of PTLD appears to vary depending on the type of transplant and level of immunosuppression. For recipients of solid organ transplants (SOT), incidences as high 10% have been reported (1-4). Findings from the Collaborative Transplant Study database suggest that the risk of developing PTLD in this population appears to be greatest within the first year post-transplantation. The estimated incidence from this series was 224 per 100,000 in the first year, 54 per 100,000 in the second year and 31 per 100,000 in the sixth year post-transplantation (4). The overall cumulative incidence of PTLD after haematopoietic stem cell transplantation (HSCT) is approximately 1-3% (5). The median time to onset is shorter for HSCT recipients - around 2 months compared to 6 months in SOT. The overall mortality rate for this disorder is high, estimated at about 80% after HSCT and 60% after SOT (1-4).

Epstein-Barr virus (EBV) is the main, but not exclusive, causative factor in the pathogenesis of this disorder, and can be detected within the lymphoma cells of up to 90% of affected patients. EBV is a herpes virus, known to be a potent transforming agent that produces blastic transformation and uncontrolled proliferation in B cells. As with other post-transplantation infections, the disease is more common if the infection is acquired as a primary infection from the donor organ (1-4).

Current treatment of PTLD – SOT recipients

The principles of treatment of PTLD are three-fold:

- Restore T-cell function
- Reduce B-cell mass
- Target EBV infection

Guidelines from the British Committee for Standards in Haematology and the British Transplantation Society (BCSH/BTS) on the surveillance, diagnosis and management of PTLD in solid organ recipients were published recently. These acknowledge the lack of published randomised controlled trials (RCTs) evaluating treatments for PTLD on which to base treatment recommendations; much of the available evidence consists of single-arm studies, registry reviews or case series (4).

The following sections briefly summarise management options for PTLD, including recommendations from the BCSH/BTS guideline for solid organ recipients. Effective therapy should be instituted before progressive disease results in declining performance status and multi-organ dysfunction. The goal of treatment should be complete and durable remission with retention of transplanted organ function with minimal toxicity. There is no universally accepted prognostic scoring system for PTLD, but a number of groups have identified some poor risk factors including poor performance status, EBV-negative tumour and graft involvement (4).

i. Pre-transplant management

Transplant donors and recipients should be screened for prior exposure and infection with EBV using approved serological assays. A recombinant EBV vaccine is under development; although it has been shown to reduce the incidence of symptomatic primary EBV infections in healthy individuals, further study in immunocompromised hosts is needed before its potential as an agent to reduce or eliminate EBV+ PTLD can be assessed (4).

ii. Reduction of immunosuppression

If diagnosed early, then stepwise reduction of immunosuppression with careful monitoring of graft function can result in restoration of control and this is the frontline therapy in most cases. The BCSH/BTS guideline states that this is essential; in some patients this will be adequate therapy and in others it will facilitate further treatment. Reduction of immunosuppression should be conducted under the direction of the transplant team, and should be done in partnership with the patient and/or their guardian. Patients need to be monitored weekly for organ function as immunosuppression reduces (4). Reduction of immunosuppression may not be possible in some cases and depends on the organ transplanted.

A response to reduction in immunosuppression is usually seen within 2-4 weeks. The response rates seen with this method have varied widely (20-73%), probably due to the use of different immunosuppression regimens and the variable risk of rejection associated with different transplant types (3). This may also be dependant on the presence of certain prognostic factors, for example elevated lactate dehydrogenase (LDH), multi-organ involvement and organ failure at the time of diagnosis (6). For patients with a higher risk of rejection, or in those for whom the graft is indispensable for survival, it may only be possible to reduce the dose of or discontinue one medication out of the immunosuppression regimen (6). In HSCT recipients, the use of reduced immunosuppression does not significantly increase the speed at which the immune system recovers; therefore this strategy is not as effective as it is for SOT recipients.

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iii. Drug therapy

Conventional cytotoxic therapy should be used in cases where the condition worsens despite reduction in immunosuppression; it may also be used first-line in patients who have aggressive sub-types of PTLD (6). The majority of data on chemotherapy for treatment of PTLD come from retrospective studies employing various regimens (e.g. CHOP); although response rates of up to 70% and 5-year disease-free survival rates of around 62% have been seen, such therapy is associated with significant toxicity and may result in treatment-related deaths. This population may be at a higher risk of toxicity due to several factors, including baseline pharmacological suppression, graft dysfunction, and colonisation with resistant infectious organisms (7). Attempts have been made to reduce this toxicity by employing lower dose chemotherapy and by using G-CSF support (6).

Current treatment of PTLD - HSCT recipients

Guidelines from the Second European Conference on Infections in Leukaemia on the management of EBV infections in patients with haematological malignancies and after stem cell transplantation were published in 2009. These recommend the following first-line treatment of PTLD in such patients (10):

- anti-CD20 therapy (rituximab) – it is recognised that this recommendation is given despite a lack of randomised trials but is considered as ‘the highest priority’ (the other options should be taken into account, when available or as a second-line therapy)
- reduction of immunosuppression, if possible
- Adaptive immunotherapy with in vitro-generated donor EBV-cytotoxic T-cells, if available
- Infusion of donor lymphocytes to restore T-cell reactivity

Chemotherapy is recommended as a second-line therapy.

In practice reduction in immunosuppression may not be an option for patients who have had a stem cell transplant; they may require ongoing immune suppression early post-transplant to prevent graft-versus-host disease and graft rejection.

Rituximab

Rituximab is a monoclonal antibody that binds specifically to CD20, an antigen expressed on the surface of mature and immature B lymphocytes. The binding of rituximab to CD20 results in cell lysis via the recruitment of immune effector functions; it has also been demonstrated to induce cell death via apoptosis. Rituximab (Mabthera®) is licensed in the UK for the treatment of Non-Hodgkin’s lymphoma, chronic lymphocytic leukaemia and rheumatoid arthritis.

There has been interest in the use of monoclonal antibodies directed to B-cell antigens as a less toxic alternative to chemotherapy. This review summarises the current evidence for rituximab, an anti-CD20 monoclonal antibody, in the treatment of PTLD (currently an unlicensed indication).

PRE-EMPTIVE RITUXIMAB TO REDUCE THE INCIDENCE OF PTLD

HSCT recipients

Attention has been focused on assays for the early diagnosis of PTLD, as the clinical presentation can often be non-specific, and it is a reasonable assumption that early initiation of treatment would improve survival. Nearly all of the assays employed currently for the pre-emptive diagnosis of PTLD are based on PCR amplification of EBV DNA from the peripheral blood (9), as there is a direct correlation between EBV proliferation and progression to PTLD (4). The use of EBV PCR monitoring to determine risk of developing PTLD has become widespread in the HSCT community (4).

Various data are reported on a threshold level for diagnosing EBV reactivation, and these relate to local experience (10). In general, PCR assays have been around 50-80% sensitive when used for pre-emptive diagnosis of PTLD. Coupled with the fact that subclinical reactivation occurs in 20-60% of HSCT recipients without clinical signs of PTLD, the positive-predictive value of such assays remain highly variable (9). There are no clear demographic factors that can be used to delineate which patients with reactivation will go on to develop PTLD (9).

Patients who receive an unrelated or HLA-mismatched HSCT or T-cell depletion are at a higher risk of EBV re-activation and subsequent PTLD (10); other risk factors include the use of antithymocyte globulin (ATG) or anti-CD3 monoclonal antibodies for the prophylaxis or treatment of graft rejection or graft-versus-host disease (9). Prospective monitoring of EBV load is recommended after high-risk allogeneic SCT, with frequency and duration dependant on the clinical risk of the patient. These patients should also be closely monitored for symptoms and/or signs attributable to PTLD (10). The risk of PTLD in HLA-identical sibling transplant recipients not receiving T-cell depletion and in those undergoing autologous SCT is low and routine screening is not recommended in these patients (10).
Wagner et al concluded that assessment of EBV DNA may best be used to guide prompt rather than pre-emptive treatment of PTLD (11). They followed 85 patients who underwent HSCT (closely HLA-matched unrelated donors or HLA-mismatched family members) who had EBV monitored on at least four occasions. In 60 patients, the EBV load remained <4000 copies/microgram PBMC DNA, with no signs or symptoms of lymphoproliferation. The remaining 25 (29.4%) had an EBV load above this threshold on ≥1 occasion; in 9 of these the load was elevated only once, was not accompanied by symptoms, and normalised over time without intervention. Of the 16 patients with levels >4000 copies/microgram on ≥2 occasions; eight developed symptoms or imaging findings consistent with PTLD. Hence the detection of 2 or more levels of EBV DNA >4000 copies/microgram had a sensitivity of 100% for the prediction of early PTLD but a specificity of 50% in this study (11).

In this study, the authors did not institute pre-emptive therapy in the 16 patients with EBV loads above the threshold on ≥2 occasions, but waited until clinical symptoms (e.g. adenopathy; fever) appeared before treatment ('prompt treatment'; n=8). Five were treated with rituximab, two with CTL infusions, and one with a combination of the two. Clinical symptoms disappeared in all patients, and in 7 the EBV loads decreased to normal (one had persistent elevated loads for 14 months). They note that the specificity of 50% seen in this study indicates that pre-emptive treatment with the chosen threshold would have exposed half the recipients to unnecessary therapy. They suggest that the most effective way to prevent morbidity and mortality from EBV PTLD after HSCT is to maintain a high index of suspicion for the disease and to confirm a clinical assessment with measurement of EBV DNA; this avoids unnecessary treatment (11).

The authors of a review article describe their experience of using an EBV assay at their centre (MSKCC). Of the 28 patients who had viral loads above the previously defined threshold (1000 gEq/mL), five developed PTLD after HSCT. They note that based on their results, 5.6 patients needed to receive pre-emptive rituximab (assuming 100% efficacy) to prevent one case of PTLD (9). They say that the sensitivity of the PCR assay used was better for diagnosing patients who presented with a syndrome consistent with PTLD than for pre-emptive diagnosis.

There are to date a limited number of published studies evaluating the pre-emptive treatment of PTLD based on elevated EBV loads. All of those including rituximab have involved patients who have had a HSCT, and none directly compare pre-emptive rituximab with other potential management strategies (including prompt treatment upon clinical presentation). Locasted studies evaluating rituximab in >5 patients are summarised in Table 1 (there are additional case reports described in the literature) (12-15).

The trial most commonly cited in support of the pre-emptive use of rituximab is that by van Esser and colleagues – this prospective trial included 49 consecutively treated patients receiving a partial T-cell depleted allo-genic SCT either from a matched sibling donor or a matched unrelated donor (13). Those who experienced an EBV reactivation ≥1000 gEq/mL within 180 days of transplantation received a single infusion of rituximab (n=15); two additional patients reaching this threshold also had signs/symptoms of PTLD and so were treated with a therapeutic protocol. Of those given pre-emptive rituximab, 14 of 15 had a sustained response, and EBV DNA became undetectable in plasma after a median of 8 days. After 12 months of follow-up, no further reactivations were observed. The two patients who required treatment were given two infusions of rituximab – both had a complete response and were alive at the last follow-up (338 days and 415 days). The authors note that frequent monitoring allowed early diagnosis and treatment for these patients. They compare their results to a historical control of 85 recipients of T-cell depleted SCT, of which 26 patients had EBV DNA above threshold levels and 10 (49%) developed EBV PTLD. This compares to the current cohort in which three of 17 patients (18%) with EBV DNA >1000 copies/mL developed PTLD.

Citing the van Esser study, guidelines from the European Conference on Infections in Leukaemia recommend rituximab (375mg/m² weekly) as a pre-emptive strategy for PTLD after high-risk allo-SCT, with the number of doses assessed locally on the basis of changes in EBV DNA load. Other strategies recommended include reduction in immunosuppression (where possible) and donor EBV-specific CTL infusion (10).

Definitive conclusions about the efficacy (and cost-effectiveness) of EBV PCR screening and use of rituximab in the pre-emptive treatment of PTLD in HSCT recipients cannot be made on the basis of current published evidence, due to the small patient numbers and the lack of any randomised, direct comparisons. Despite this, it is becoming a common approach at a number of transplant centres (9).

A review article notes that the advantages and disadvantages of pre-emptive and prompt treatment need to be weighed, as comparative studies of the two approaches are lacking. Both approaches involve the identification of high-risk patients based on pre-transplant characteristics as well as on post-transplant monitoring of EBV DNA. Although pre-emptive treatment may be associated with the disadvantage of over-treatment, waiting for the signs and symptoms of PTLD may necessitate multiple infusions of rituximab and possibly the use of donor lymphocyte infusions.
Rituximab for post-transplant lymphoproliferative disease (PTLD)

The authors note that a prospective comparative study of the two is unlikely as large patient numbers would be required to demonstrate any statistically significant difference. In the absence of such data, they favour the pre-emptive approach, but reduction in immunosuppression may be tried prior to rituximab to add ‘another step and refinement to the pre-emptive strategy’. (5)

SOT recipients

No data on the pre-emptive use of rituximab to prevent PTLD were located from a search of the published literature. In adults there is little evidence to support the routine use of EBV PCR outside the allogeneic HSCT setting. The BCSH guideline does not recommend the routine surveillance of adult SOT populations using this method as a means of identifying patients at high risk of PTLD or initiating therapy (4).

RITUXIMAB IN THE TREATMENT OF PTLD

<table>
<thead>
<tr>
<th>Study; pt group</th>
<th>PCR assay</th>
<th>Threshold</th>
<th>Median time to EBV reactivation</th>
<th>Pre-emptive rituximab (N)</th>
<th>Complete response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ahmad (retrospective) Mix of haplo-identical, Sib and MUD (n=115)</td>
<td>Plasma real-time</td>
<td>&gt;40,000 gCop/mL or 2 x rising loads &gt;10,000 gCop/mL</td>
<td>86 days (range 29-304)</td>
<td>Weekly until negative PCR (median of 3) (n=19)</td>
<td>17/19 (7 viral load clearance after one dose)</td>
</tr>
<tr>
<td>Van Esser (prospective) Partial T-cell depleted, Sib or MUD (n=49)</td>
<td>Plasma real-time</td>
<td>1000 copies/mL</td>
<td>112 days (range 39-189)</td>
<td>Single infusion 375mg/m² (n=15)</td>
<td>14/15 (93%)</td>
</tr>
<tr>
<td>Dominietto HLA-matched or mismatched unrelated donor (n=77)</td>
<td>Plasma real-time</td>
<td>1000 copies/mL</td>
<td>86 days (range 20-248)</td>
<td>Two doses of 375mg/m² one wk apart (n=8)</td>
<td>4/8 (50%) *</td>
</tr>
<tr>
<td>Comoli (prospective) T-cell depleted, Sib (paediatric) (n=27)</td>
<td>Quantitative</td>
<td>&gt;1000 copies/10⁵ PBMC in 2 consecutive samples</td>
<td></td>
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</tr>
</tbody>
</table>

Sib: HLA-matched sibling donor; MUD: HLA-matched unrelated donor

* The authors comment their results are likely due to poor reconstitution of the T-cell compartment in their pts

Complete response was defined as clearance of EBV-DNA <50gEq/mL from plasma and absence of signs and symptoms of PTLD

The authors note that a prospective comparative study of the two is unlikely as large patient numbers would be required to demonstrate any statistically significant difference. In the absence of such data, they favour the pre-emptive approach, but reduction in immunosuppression may be tried prior to rituximab to add ‘another step and refinement to the pre-emptive strategy’. (5)

SOT recipients

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Rituximab monotherapy – SOT recipients

The first reported case of rituximab use in the treatment of PTLD was in 1998; since then there have been a number of case reports, case series and retrospective studies, with observed response rates ranging from 44% to 65% (6). This prompted its evaluation in prospective trials, and there have been four published Phase II studies to date (see Table 2) (7, 16-19).
### Table 2 – Prospective studies of rituximab in the second-line treatment of PTLD (all solid organ transplants)

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study type</th>
<th>No. of patients</th>
<th>Median age (years)</th>
<th>Median time to PTLD onset</th>
<th>Treatment regimen</th>
<th>Prior treatment</th>
<th>Outcome</th>
<th>Predictors of response</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Monotherapy</strong></td>
<td></td>
<td></td>
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</table>
| Choquet et al, 2006 (7) | Phase II   | 43              | 48 (13-73)         | 51.8 months                | 375mg/m² weekly for 4 wk | RI              | • ORR 44.2% (CR or CRu: 28%)  
                         |            |                 |                    |                            |                   |                 |  • Median survival - 15 mo (454 days)  
                         |            |                 |                    |                            |                   |                 |  • 67% survival at 1yr  
 | Oertel et al, 2005 (16) | Phase II   | 17              | 51 (26-73)         | 65.3 months (3-177)       | 375mg/m² weekly for 4 wk | RI              | • ORR 59% (CR 52.9%)  
                         |            |                 |                    |                            |                   |                 |  • Median duration of CR – 8 mo (2-25+)  
                         |            |                 |                    |                            |                   |                 |  • Median survival – 14 mo (<1-32+)  
 | Blaes AH et al, 2005 (17) | Phase II   | 11              | 56 (43-68)         | 9 months (1-122)          | 375mg/m² weekly for 4 wk (repeated in responders) | RI              | • ORR 64% (55% CR)  
                         |            |                 |                    |                            |                   |                 |  • Median duration of CR – 6 mo (1-12)  
                         |            |                 |                    |                            |                   |                 |  • Median survival – 14 mo (<1-32+)  
 | Gonzalez-Barca et al (18) | Phase II   | 38              | 55 (19-69)         | 66.2 months (2.2-202)     | 375mg/m² weekly for 4 wk; repeated in those with PR | RI              | • 34% CR after first course  
                         |            |                 |                    |                            |                   |                 |  • 12/17 with PR had 2nd course – 83% CR  
                         |            |                 |                    |                            |                   |                 |  • Overall ITT CR 60%  
 | Choquet et al, 2007 (19) | Long-term  | 60              | 49 (16-73)         | Early – 4.7 months (2.9-8.6) Late – 82.7 months (14-186) | 375mg/m² weekly for 4 wk | RI              | • ORR 59% (CR 42%)  
                         | follow-up for two Phase II studies | | | | | | |  • Median PFS 6.0 mo (95% CI 1.8-10.1)  
                         |            |                 |                    |                            |                   |                 |  • Median OS 34.5 mo  
 | **In combination with chemotherapy** | Pilot study | 6               | 4-23               | 10-144 months             | Cy, prednisolone, rituximab | RI          | • ORR 100% (95% CI 94-100)  
                         |            |                 |                    |                            |                   |                 |  • Five CRs and one PR  
                         |            |                 |                    |                            |                   |                 |  • Median duration of response – 12.5 mo  
 | Orjuela M et al, 2003 (22) | Preliminary | 104 (64 ST and 40 RSST)* | 53 for ST and 60 for RSST (>1 year) | not stated; 75% had late PTLD | Extended rituximab or CHOP-R* | RI              | • ST*: ORR 89% (69% CR)  
                         | Phase II (abstract) | | | | | | |  • RSST*: ORR 90% (73%CR)  
 | Trappe et al, 2009 (23) | Preliminary | 104 (64 ST and 40 RSST)* | 53 for ST and 60 for RSST (>1 year) | not stated; 75% had late PTLD | CHOP-R* | RI              |                          |                        |

*ST*: Standard therapy; *RSST*: Rituximab-based salvage therapy

**Note:** Table adapted for presentation.
Rituximab for post-transplant lymphoproliferative disease (PTLD)

All of the Phase II studies have evaluated rituximab in the treatment of PTLD following SOT, in patients where reduction in immunosuppression was unsuccessful (i.e. second-line). In the largest, a total of 46 patients (43 evaluable) with CD20+ PTLD following SOT that was not responding despite reduction in immunosuppression for at least two weeks were treated with rituximab (375mg/m² weekly for four weeks) (7). Inclusion criteria included ECOG performance status (PS) of 0-3, a tumour of greater than 2cm and/or bone marrow involvement. Graft types included kidney (n=18), heart (n=11), liver (n=7), lung (n=4) and heart and lung (n=3). All immunosuppressive drugs were reduced by at least 50% in dose and/or reduced to a maximum of two drugs. The immunosuppressive regimen was kept stable throughout the study duration, except in the case of rejection. Treatment response was classified as complete (CR), complete unconfirmed (Cru), partial (PR), stable disease (SD) or progressive disease (PD). The majority (74%) of patients had advanced stage disease (Ann Arbor stages III and IV).

The primary endpoint of the study was overall response rate (CR+Cru+PR) at day 80; this occurred in 19 patients (44.2%) – including 9 CRs, 3 CRus and 7 PRs. Response was maintained in 13 of the 19 patients (68%) at day 360. Estimated overall survival (OS) at one year was 67%, with a median survival of 454 days. One patient died due to chemotherapy toxicity (given following relapse) and nine patients developed graft rejection (one fatal). A total of 23 patients were retreated for PTLD progression or relapse, five with rituximab monotherapy (one CR, one SD and three progressions), and 18 with chemotherapy (mainly CHOP; five CR, two PR, three stable disease and six progressions). Cellular EBV load was determined in 39 patients and was high (>600 copies/ microgram DNA) in 46%; this was not found to be predictive of response at 80 days (OR 0.400; 95% CI 0.109-1.466). A total of 57% of patients reported grade 3 or 4 adverse events, but only two serious events were considered to be related to rituximab (intestinal perforation at the lymphoma site and purpura with myalgia).

Two smaller Phase II trials with a similar design and using an identical regimen of rituximab have also been published (16, 17). In both cases the response was slightly higher, but they included a slightly lower proportion of patients with severe disease. One involved 17 patients with CD20+ PTLD (8 had localised stage I or II disease), of which 9 (52.9%) achieved a CR, for a median duration of 35 months. There was additionally one PR, two cases of minor remission, and four with stable disease (16). In ten patients there was evidence of EBV positivity – this was found to be a predictive factor for response to rituximab (p<0.0001). The authors note that patients with EBV-negative disease (who also had an increased interval between grafting and diagnosis) had a poor response to rituximab in this study, and therefore suggest that such cases should perhaps be treated from the outset with a combination of rituximab and chemotherapy.

The second smaller trial involved 11 patients with CD20+ PTLD (stage I or II disease in 5 cases), with a shorter median time from SOT to diagnosis than the other two (9 months versus 65 and 52 months) (17). In this, patients who responded to rituximab treatment were retreated every six months for up to two years (maximum of four cycles). With a median follow-up of 10 months (range 1-32 months), the ORR was 64% (55% CR and 9% PR). Three patients went on to receive chemotherapy, including CHOP (n=1) and CHOPE (n=2).

Gonzalez-Barca et al evaluated the efficacy of four doses of rituximab in the treatment of PTLD, with a repeated course in those who achieved only a partial remission (18). Their study included 38 adults who were treated with four doses of rituximab 375mg/m². They were evaluated for response 4-8 weeks after the last infusion – those with CR received no further treatment and those with PR were eligible for a further treatment course. After the first course of rituximab, 13 (34%) patients achieved CR, 17 a PR, and 8 did not respond (including 5 did not complete the course due to disease progression). Twelve of the 17 who achieved PR were treated with additional rituximab; this was not possible in the other five as they progressed before this could be administered. Of these 12, ten (83%) achieved a CR – therefore the overall intention-to-treat CR for 1-2 courses of rituximab was 60% (n=23 of 38). Overall survival was 47% at 27.5 months (14 patients died, ten due to progression of PTLD).

Finally, the long-term outcomes of 60 patients with CD20+ PTLD treated with single-agent rituximab in two of the Phase II studies are described (19). Stage I or II disease was present in 37% and the remainder had more advanced (stage III or IV) disease. A total of 55% had elevated serum LDH and 52% of tumours were EBV-positive. Response rates are summarised in Table 2. Overall, 57% experienced disease progression within twelve months of therapy; only nine of the 35 patients (26%) who responded to treatment progressed within this time period. After a median follow-up of 16.3 months, the median PFS was 6.0 months (95% CI 1.8-10.1 months); 2-year and 3-year survival was 72.5% and 51.8%, respectively. According to the authors, the fact that half of all patients receiving rituximab progressed within six months of treatment lends ‘considerable support’ to a more intensive intervention, especially for those at an increased risk.

The results of a pooled analysis of the available data on rituximab monotherapy in the second-line treatment (following reduction of immunosuppression) of adults with PTLD were presented at the 2007 ASH Annual Meeting, (literature search up until June 30th 2007) (20). Studies involving children (<18 years of age) and those with less than 5 patients were excluded.
A total of 308 patients (17 reports) were included in the analysis; the majority (n=284) were recipients of solid organ transplants. The mean age of the patients was 57 years and the PTLD was late-onset (>1 year) in most patients (around 70%). Patients were initially treated with four weekly doses of rituximab (375mg/m²) and it was continued as a maintenance therapy in responding patients in a few studies. The complete response rate was 58% (29-78%) among SOT patients and 70% among HSCT recipients. Long-term follow-up from two prospective trials demonstrate a durable remission in 30-37% of SOT patients at five years.

In order to refine patient selection for the different modalities of therapy some groups have tried to identify patients more likely to have a poor response to rituximab monotherapy – those with late PTLD and EBV-negative disease may be less responsive. From the findings of their Phase II study, Choquet et al proposed a prognostic score taking into account the following:

- Age > 60 years,
- Performance status ECOG 2-4
- Raised LDH

Those in the low risk (0 risk factors), intermediate risk (1 risk factor) and high risk group (>1 risk factor) had 1- and 2-year survival rates of 100%, 79%, 36% and 88%, 50% and 0% respectively. They suggest rituximab monotherapy is inadequate for intermediate and high risk groups and recommend its use in combination with chemotherapy as initial treatment for such patients (4).

So far there have been no prospective trials comparing rituximab monotherapy to an alternative second-line treatment for PTLD (e.g. chemotherapy, specific immunotherapy), therefore the superior treatment option is currently unknown (3). Whether the best treatment option varies according to disease severity/ presence of certain prognostic factors is also unknown at present.

There are no Phase II trials evaluating rituximab in patients with PTLD that has relapsed following chemotherapy. Trappe et al have reported on seven adults who received rituximab monotherapy for relapsed/refractory PTLD after first-line CHOP chemotherapy (with or without rituximab). The majority had late PTLD (minimum onset of disease 120 months after transplantation) and association with EBV was shown in 63% of cases. Four patients had elevated LDH and three had an ECOG performance status of ≥2). There was a CR in 3 patients (43%); one remained in CR at a follow up of 69 months and two relapsed but were successfully re-treated. One patient had a PR and one stable disease (both 14%). At a median follow-up of 69 months, median PFS was 9 months (21).

Rituximab in combination with chemotherapy – SOT recipients

There are less data for rituximab in combination with chemotherapy than there are for its use as monotherapy in the treatment of PTLD.

The use of a low dose regimen of cyclophosphamide and prednisolone in combination with rituximab for the treatment of PTLD was assessed in a small pilot study (22). A total of six patients with CD-20+ PTLD after SOT who had disease progression despite reduction in immunosuppression were treated with 2-6 courses (each for 21 days) of cyclophosphamide (600mg/m² on day 1) and prednisolone (2mg/kg/day for five days). Rituximab was administered at a dose of 375mg/m² weekly for the first six weeks. Three patients (50%) were aged under 18 (two aged 4 and one aged 16), and the organs transplanted were the heart (n=2), liver (n=2) and kidney (n=2). The onset of PTLD post-transplant ranged from 10-144 months; patients had received immunosuppression for a median of 39 months (range 10-144 months). The overall response rate was 100% (95% CI 54-100%), with five CRs and one PR; the median duration of response was 12.5 months. At the time of publication, all patients with a CR remained without evidence of disease. According to the report the treatment was well tolerated, with no grade 3 or 4 infectious toxicities and no requirement for RBC or platelet transfusions, or G-CSF support.

The results of an ongoing phase II trial evaluating sequential treatment with rituximab and CHOP-21 chemotherapy (with G-CSF support) in the treatment of PTLD unresponsive to reduction of immunosuppression have been published in abstract form (23). Initially patients were treated with a fixed sequence of rituximab at days 1, 8, 15 and 22, followed by four cycles of CHOP-21 combined with G-CSF support starting 4 weeks after the last dose of rituximab (sequential treatment, ST; n=64). The trial was amended in 2007 following the results of an interim analysis, whereby subsequent treatment depended on initial response to the four doses of rituximab (risk stratified sequential treatment; RSST; n=40). In RSST, those achieving a complete remission following rituximab (low risk) continued with four 3-weekly courses of rituximab monotherapy (i.e. extended rituximab), while patients in PR, SD or PD (high risk) were treated with four cycles of R-CHOP-21 combined with G-CSF.

At the time of the most recent analysis, a total of 104 patients had completed the protocol treatment, with a median follow-up of 34 months for those receiving ST and 9.1 months for those receiving RSST. Almost half of patients had EBV-positive tumours and just over half had advanced disease (Ann Arbor III/IV); 75% had late PTLD. The main findings were as follows (23):
Rituximab for post-transplant lymphoproliferative disease (PTLD)

- Overall response rate was 54% (CR 32%) to the four initial courses of rituximab chemotherapy in all patients.
- The final ORR following completion of treatment was 89% (CR 69%) for ST and 90% (CR 73%) for RSST (p<0.0001 compared to initial rituximab courses).
- 86% of patients receiving ST and 90% of those receiving RSST were without disease progression at one year. Respective values for ST at two and three years were 75% and 75%, respectively (not available for RSST).

The authors conclude at this stage that in patients with a complete response following four doses of rituximab, subsequent consolidation with rituximab monotherapy (RSST) seems not to be inferior to consolidation with 4 cycles of CHOP (ST). For those not achieving a CR following four doses of rituximab monotherapy (n=72), the results suggest that use of R-CHOP may be associated with improved survival compared to CHOP. There was no difference in toxicity between these two treatments at the time of this analysis (23).

In a retrospective study, the authors describe the outcomes of 35 patients with PTLD treated at a single centre with rituximab and/or chemotherapy following failure of reduction in immunosuppression (24). All were SOT recipients apart from one patient, who had undergone a bone marrow transplant. The median time from transplantation to development of PTLD was 4 years (range 3 months to 23 years) and over half (57%) presented with advanced stage disease (stage III or IV). A total of 22 patients received single-agent rituximab (19 following reduction in immunosuppression and three following progression/relapse after chemotherapy). Twenty three patients received chemotherapy as part of their treatment (ten CHOP, nine R-CHOP and four other regimens); 16 of these received it as first-line following reduction in immunosuppression and seven received it following treatment with rituximab. The main findings were as follows (24):

- The ORR was 68% (59% CR) for rituximab and 74% (57% CR) for chemotherapy.
- Median OS was 31 months (range 1.5-51) for rituximab and 42 months (0.4-70) for chemotherapy.
- Median TTF was not reached in the rituximab group and was 10.5 months (0.4-54) for the chemotherapy group.
- In this small group of patients, the addition of rituximab to CHOP did not significantly affect response to treatment, TTF or OS.
- Treatment-related toxicity was significant only for patients receiving chemotherapy, with 52% of patients hospitalised (mainly for infections) and six (26%) treatment-related deaths.
- Addition of rituximab to CHOP was not associated with any increase in toxicity compared to CHOP alone.

No prospective studies comparing chemotherapy plus rituximab to chemotherapy alone have been published, therefore the value (if any) of the addition of rituximab has yet to be determined. The results of the retrospective study suggest that it may not improve response rates, but this needs to be confirmed in controlled trials.

Rituximab prior to reduction of immunosuppression (first-line)

Most data for rituximab in PTLD concern its second-line use, after reduction of immunosuppression has been tried. Patients with more aggressive PTLD may however require prompt therapy; the use of rituximab in this setting (i.e. no previous reduction in immunosuppression) has only been evaluated retrospectively and in a small number of patients. The role of rituximab in this setting requires further exploration in prospective, controlled trials. For details of the retrospective data, please refer to a recent review (3).

Rituximab for the treatment of PTLD in HSCT recipients

A review article notes that several reports have shown efficacy of multiple infusions (mainly four) of rituximab in established EBV-PTLD after SCT, with complete response rates ranging from 66-100% (5). An article reviewing all published literature and meeting abstracts notes that 146 patients with PTLD following SCT have been treated with rituximab and 92 of these (63%) had cure or improvement (24). The data are however limited to retrospective studies. Although the Phase II studies discussed above for SOT recipients support these results, they cannot be directly extrapolated to this setting (5).

SAFETY OF RITUXIMAB IN PTLD

Below is a summary of the most common and any serious adverse events experienced by participants during the Phase II studies. Due to the lack of a placebo control in any of the studies, it cannot be determined whether rituximab was associated with a significant increase in adverse effects compared to placebo.

Choquet et al

The most commonly reported adverse events (irrespective of attributability) included transplant rejection (22%), abdominal pain (20%), and dyspnoea (17%). Although 52 serious adverse events were reported by 29 patients, only two were considered to be related to rituximab (intestinal perforation at the site of PTLD involvement, and purpura with myalgia). There were two deaths due to infections (septic shock). Neutropenia was reported by two patients after the completion of treatment; one of these patients had a tacrolimus overdose, and in the other case the neutro-
penia was asymptomatic and resolved spontaneously. Two patients withdrew from treatment due to adverse events, between day 1 and 50 (7).

Oertel et al

In 17 patients there were four episodes of toxicity – three grade 1 non-haematological and one grade 2 haematological (anaemia). No grade 3 or 4 toxicities were reported during a mean follow-up of 24.2 months (16).

Blaes et al

There is a lack of detail on reported side effects; the authors say that rituximab was generally well tolerated, over a median follow-up of 10 months (range 1-32 months). There were mild blood pressure changes in two of the eleven patients – one had brief infusion-related hypotension (resolved with fluids) and the other developed mild hypertension during infusion that was controlled with medication (17).

Trappe et al

In those receiving sequential treatment (rituximab then CHOP), there were six (9%) early treatment-associated deaths due to infection (1 from CMV-colitis, 1 from PCP-pneumonia, 1 from fulminant hepatitis, 3 from sepsis). Two further patients died due to haemorrhage during treatment (21).

In those receiving RSST, there was one (2.5%) early treatment related death due to infection (sepsis secondary to intestinal perforation in response to R-CHOP treatment). The authors suggest from these findings that the use of risk stratification according to the response to 4 courses of rituximab monotherapy may therefore improve outcomes by restricting che-

At the time of the analysis, there was no difference in toxicity between CHOP and R-CHOP in ST/RSST

There have been case reports describing the association of rituximab with gastrointestinal perforation in patients with PTLD (26). The SPC states that this adverse effect (fatal in some cases) has been seen in patients receiving rituximab for the treatment of non Hodgkin's lymphoma, most often in combination with chemotherapy.

The SPC states that infusion-related reactions (including tumour lysis syndrome) are among the most frequently reported or observed serious adverse drug reactions. A case report describes tumour lysis syndrome occurring in a heart transplant patient with PTLD following a single dose of rituximab. The diagnosis was made based on the presence of hypocalcaemia, hyperphosphataemia, increased uric acid, acute renal failure, and markedly elevated LDH. The patient was not resuscitated as per his family’s wishes, and no post-mortem was performed (27).

HEALTH ECONOMICS

No cost-effectiveness data for rituximab in the treatment of PTLD could be located. The costs of the various treatment options (including CHOP as the standard chemotherapy option) are summarised below. These represent average estimates of drug costs only. The cost of PTLD as pre-emptive therapy is also included – please bear in mind that this does not take into account any possible cost savings that would result, for example from a reduction in need for treatment of PTLD.

Table 3: Estimated drug costs of rituximab in the prophylaxis or treatment of PTLD

<table>
<thead>
<tr>
<th>Schedule</th>
<th>Dose</th>
<th>Cost per person</th>
<th>Cost per 100,000/yr</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>HSCT</td>
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<td></td>
<td></td>
<td></td>
<td>SOT</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rituximab monotherapy</td>
<td>Rituximab 375mg/m² for four weeks</td>
<td>£4,890</td>
<td>£636</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>£2934</td>
</tr>
<tr>
<td>Rituximab monotherapy with</td>
<td>Rituximab 375mg/m² for eight doses</td>
<td>£9,780</td>
<td>£1271</td>
</tr>
<tr>
<td>further rituximab consolidation</td>
<td></td>
<td></td>
<td>£5868</td>
</tr>
<tr>
<td>CHOP</td>
<td>Four cycles of CHOP (see regimen below)</td>
<td>£884</td>
<td>£115</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>£530</td>
</tr>
<tr>
<td>Rituximab followed by CHOP</td>
<td>Rituximab 375mg/m² for 4 wks then CHOP (four cycles)</td>
<td>£5,774</td>
<td>£751</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>£3464</td>
</tr>
<tr>
<td>Rituximab followed by R-CHOP</td>
<td>Rituximab 375mg/m² for 4 wks then R-CHOP (four cycles), with rituximab 375mg/m² on day 1 of each cycle</td>
<td>£10,664</td>
<td>£1386</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>£6398</td>
</tr>
<tr>
<td>Pre-emptive therapy</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Rituximab monotherapy</td>
<td>Rituximab 375mg/m² for 1-3 doses**</td>
<td>£1,222-3,666</td>
<td>£1711-£5132</td>
</tr>
<tr>
<td></td>
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</tbody>
</table>

*based on a body surface area of 1.7m²

** most of the prospective studies used a single dose; Ahmad et al gave rituximab weekly until the EBV-PCR was negative (median of 3 doses)

CHOP: Cyclophosphamide (750mg/m² dy 1), doxorubicin (50mg/m² dy 1), vincristine (1.4 mg/m² up to max 2mg on dy 1), and prednisolone (40mg/m² per day for 5 dy) every 21 dy
Cost per 100,000 population
The figures in Table 3 represent very crude estimates based on drug costs alone. The following assumptions have been made:

Treatment of PTLD:
2959 HSCT carried out in 2008 (27), with a 3% incidence of PTLD (0.13 patients per 100,000) (5)
3513 SOT carried out in 2008 (28), with a 10% incidence of PTLD (0.6 patients per 100,000 population) (1-4)

Pre-emptive therapy of PTLD:
2959 HSCT carried out in 2008 (27), with 30% meeting the criteria for pre-emptive therapy based on a threshold of 1000 copies/mL (1.4 patients per 100,000 population) (13)

Please note that pre-emptive use of rituximab based on EBV titres may result in treatment of a certain number of patients who would not have gone on to develop PTLD if they had received no such treatment. As stated previously in this review, the authors of one paper say that based on their experience, 5.6 patients needed to receive pre-emptive rituximab (assuming 100% efficacy) to prevent one case of PTLD (based on a threshold of 1000 copies/mL).

Summary of gaps in the evidence
• Although rituximab has been evaluated prospectively in Phase II trials for the treatment of PTLD that has not responded to reduction of immunosuppression, there is no data available directly comparing this to alternative options (e.g. chemotherapy; specific immunotherapy).

• The data for pre-emptive therapy with rituximab for HSCT recipients is limited to non-comparative case series that do not allow direct comparison of pre-emptive rituximab to other potential strategies (including prompt therapy upon presentation).

• Only limited, retrospective data on rituximab for the treatment of PTLD in HSCT recipients have been published. It is not known whether the results from the Phase II studies of rituximab treatment in SOT recipients can be directly extrapolated to the HSCT setting.

• The use of rituximab in the first-line treatment of PTLD – i.e. before reduction in immunosuppression – has only been studied retrospectively and in a small number of patients.

• There are no data on the use of pre-emptive rituximab in the treatment of SOT recipients with high EBV titres.

Points for consideration
• Is rituximab superior to other options (e.g. chemotherapy; specific immunotherapy) for the treatment of PTLD after failure of reduction of immunosuppression? In practice CTLs may not be a realistic alternative option as they are not generally available and take time to manufacture
• In which patients, if any, would the upfront use of rituximab in combination with chemotherapy be indicated?
• What is the most appropriate schedule of rituximab administration for pre-emptive treatment of PTLD, and at what threshold of EBV titre should treatment be initiated to be most cost-effective?
• Is pre-emptive treatment associated with improved outcome compared to prompt treatment upon clinical presentation?
• Does the pre-emptive use of rituximab have any effect on overall survival?
• How does rituximab compare to reduction of immunosuppression and the infusion of EBV-specific CTLs in the prophylactic treatment of patients at a high risk of developing PTLD (would these other options be a realistic alternative in practice)?
• What is an acceptable number of patients needed to treat with pre-emptive therapy to prevent a single case of PTLD?
• The risk of PTLD in stem cell transplant patients varies depending on the type of transplant. Could these patients therefore be considered separately and only those at a high risk monitored for EBV/ treated pre-emptively?
Rituximab for post-transplant lymphoproliferative disease (PTLD)

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8. Matthera SPC; accessed on www.medicines.org.uk (last updated 23/03/2010)


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