Post-transplant lymphoproliferative disease (PTLD) describes a heterogenous group of lymphoproliferative diseases, occurring as a result of uncontrolled B cell proliferation in the context of post-transplant immunosuppression. The incidence depends on the type of transplant and immunosuppression used; the median time to onset is shorter for recipients of stem cell transplants (2 months) than those of solid organ transplants (6 months). The associated mortality is high, therefore treatment optimisation is essential.

Conventionally, treatment 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. There has been interest in the use of monoclonal antibodies directed to B-cell antigens as a less toxic alternative to chemotherapy, including rituximab, a chimeric monoclonal antibody to CD20 antigen.

There have been three Phase II studies evaluating the efficacy of rituximab as monotherapy in the second-line treatment of PTLD, following failure of reduction in immunosuppression. All used rituximab at a dose of 375mg/m² weekly for four weeks; the complete response rates observed ranged from 44-64%. One paper described the longer-term outcome of 60 patients in two of the Phase II trials; the authors note that after a median follow-up of 16.3 months, the median progression-free survival was 6.0 months (95% CI 1.8-10.1 months); 2-year and 3-year overall survival was 72.5% and 51.8%, respectively. However as over half of patients (57%) who received rituximab treatment progressed within 12 months, the authors suggest that a more intensive intervention is required, especially for those at an increased risk.

The preliminary results of a Phase II trial assessing rituximab in combination with CHOP chemotherapy have been published in abstract (n=64); although the overall response rate looks very promising (90% after 19.6 months of follow-up), toxicity is significant, with a total of 16% suffering from WHO grade 3-4 infections (a complication associated with four early deaths).

Currently, the data for first-line use of rituximab in PTLD (i.e. no previous reduction in immunosuppression) are limited to small, retrospective studies. The role of rituximab in this setting requires further exploration in prospective, controlled trials. As rituximab has not been directly compared to an alternative second-line treatment for PTLD (e.g. chemotherapy, specific immunotherapy), the superior treatment option is currently unknown. Whether the best treatment option varies according to disease severity/ presence of certain prognostic factors is also unknown at present.
Rituximab for post-transplant lymphoproliferative disease

1) Introduction

Post-transplant lymphoproliferative disease (PTLD) is characterized by uncontrolled proliferation of B cells in the context of pharmacological immunosuppression following solid organ or bone marrow transplantation. It affects about 2% of transplant patients in the first year and 1% per year thereafter, but the frequency appears to vary depending on the type of transplant and level of immunosuppression. The median time to onset of PTLD is shorter for haematopoietic stem cell transplant (HSCT) recipients - around 2 months compared to 6 months in solid organ transplants (SOT). The overall mortality rate for this disorder is high, estimated at about 60% after SOT and 80% after HSCT (1-3).

PTLD describes a heterogenous group of lymphoproliferative diseases, ranging from something similar to primary EBV infection, to aggressive non-Hodgkin’s lymphomas. The 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. As with other post-transplantation infections, the disease is more common (up to 40%) if the infection is acquired as a primary infection from the donor organ (1-3).

Management

There have been no prospective randomised trials assessing treatments for PTLD and therefore there are no clear guidelines as to its optimum management. The principles of treatment are three-fold:

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

a) 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 first-line therapy in most cases. 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 (4). This may also be dependant on the presence of certain prognostic factors, for example elevated lactate dehydrogenase, multi-organ involvement and organ failure at the time of diagnosis (5). 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 (5). 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.

b) 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 (5). 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% 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 (5). Attempts have been made to reduce this toxicity by employing lower dose chemotherapy and by using G-CSF support (5).

Antiviral therapy (e.g. aciclovir, ganciclovir) has been attempted as both a treatment and prophylaxis of PTLD; this is however unlikely to be effective as a monotherapy and the data to support its use are sparse at present. Non-specific immunotherapy has also been employed by some; however its use is limited due to its adverse effects, including allograft rejection (5).

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.

2) Evidence for rituximab in PTLD

a) Rituximab monotherapy (second-line)

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% (4). This prompted its evaluation in prospective trials, and there have been three published Phase II studies to date (see Table 1).

All three of the Phase II studies have evaluated rituximab in the treatment of patients in whom reduction in immunosuppression has been 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) (6). 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...
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(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 (66%) 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 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 (7, 8). 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 (7). 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) (8). 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).

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 (9). 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 1. 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) (10). 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.

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.

b) Rituximab in combination with chemotherapy (second-line)

There are less data for rituximab in combination with chemotherapy than there are for monotherapy for 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 (11). 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 preliminary results of a phase II trial evaluating the combination of rituximab and CHOP chemotherapy (with G-CSF support) in the treatment of PTLD have been published in abstract form (12). At the time of the third interim analysis, a total of 64 patients had completed the protocol treatment (all SOT apart from one bone marrow transplant recipient). The median age of the patients was 53 years (range 16-74), 79% patients had late PTLD (>1 year after transplantation) and 48% of tumours were EBV-positive. Participants were treated with four weekly doses of rituximab (375mg/m² on days 1, 8, 15 and 22), followed by CHOP chemotherapy (days 50, 72, 94 and 116) and G-CSF. After a median of 19.6 months of follow-up, the overall response rate was 90% (65% CR and 25% PR). At two years, PFS was 71.4% and DFS was 81.2%. A total of 16% suffered from WHO grade 3-4 infections, a complication associated with four early deaths (7%).

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 (13). 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:

- 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.

c) First-line rituximab

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 (4).
# Table 1 – Prospective studies of rituximab in the second-line treatment of PTLD

<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>
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<tbody>
<tr>
<td><strong>Monotherapy</strong></td>
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<tr>
<td>Choquet et al, 2006 (6)</td>
<td>Phase II</td>
<td>43</td>
<td>48 (13-73)</td>
<td>51.8 months</td>
<td>375mg/m² weekly for 4 wk</td>
<td>RI</td>
<td>ORR 44.2% (29-60%) Median survival – 15 mo (454 days) 67% survival at 1yr</td>
<td>Normal LDH</td>
</tr>
<tr>
<td>Oertel et al, 2005 (7)</td>
<td>Phase II</td>
<td>17</td>
<td>51 (26-73)</td>
<td>65.3 months (3-177)</td>
<td>375mg/m² weekly for 4 wk</td>
<td>RI</td>
<td>ORR 59% (CR 52.9%) Median duration of CR – 35 mo 3-year OS – 56%</td>
<td>EBV-positivity Shorter time to diagnosis</td>
</tr>
<tr>
<td>Blaes AH et al, 2005 (8)</td>
<td>Phase II</td>
<td>11</td>
<td>56 (43-68)</td>
<td>9 months (1-122)</td>
<td>375mg/m² weekly for 4 wk (repeated in responders)</td>
<td>RI</td>
<td>ORR 64% (55% CR) Median duration of CR – 8 mo (2-25+) Median survival – 14 mo (&lt;1-32+)</td>
<td></td>
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<tr>
<td>Choquet et al, 2007 (9)</td>
<td>Long-term follow-up for two Phase II studies</td>
<td>60</td>
<td>49 (16-73)</td>
<td>Early – 4.7 months (2.9-8.6) Late – 82.7 months (14-186)</td>
<td>375mg/m² weekly for 4 wk</td>
<td>RI</td>
<td>ORR 59% (CR 42%) Median PFS 6.0 mo (95% CI 1.8-10.1) Median OS 34.5 mo</td>
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<td><strong>In combination with chemotherapy</strong></td>
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<tr>
<td>Orjuela M et al, 2003 (11)</td>
<td>Pilot study</td>
<td>6</td>
<td>4-23 years</td>
<td>10-144 months</td>
<td>Cy, prednisolone, rituximab</td>
<td>RI</td>
<td>ORR 100% (95% CI 54-100) Five CRs and one PR Median duration of response – 12.5 mo</td>
<td></td>
</tr>
<tr>
<td>Trappe et al, 2007 (12)</td>
<td>Preliminary Phase II (abstract)</td>
<td>75 (64 evaluable)</td>
<td>53 (16-74)</td>
<td>not stated; 79% had late PTLD (&gt;1 year)</td>
<td>Rituximab and CHOP</td>
<td>RI</td>
<td>ORR 90% (65% CR)</td>
<td></td>
</tr>
</tbody>
</table>
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References


The document reflects the views of LNDG and may not reflect those of the reviewers

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