Cost-effectiveness analysis of rituximab re-treatment with salvage chemotherapy for relapsed/refractory aggressive histology CD20+ lymphoma with intent to proceed to autologous stem cell transplant

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Introduction
- Diffuse large B-cell lymphomas (DLBCL) are the most common form of aggressive non-Hodgkin’s lymphomas, with an estimated incidence of 2,400 cases in Canada in 2016

- Standard of care for first-line treatment of aggressive lymphoma is R-CHOP (rituximab and cyclophosphamide, doxorubicin, vincristine, and prednisone), which yields sustained remission in 60% of patients

- Patients whose disease progresses or relapses after primary treatment have poorer prognosis; these patients may be offered salvage chemotherapy followed by potentially curative autologous stem cell transplant (ASCT)

- In patients with relapsed/refractory aggressive B-cell lymphoma who had received first-line RCHOP, LY.12 trial cohorts (Baetz et al 2017) showed adding the anti-CD20 monoclonal antibody rituximab to salvage chemotherapy (rituximab re-treatment) improved rates of response and ASCT, particularly among those with response to prior rituximab

- The objective of this analysis was to assess the cost-effectiveness of rituximab re-treatment compared to salvage chemotherapy alone for treating patients with relapsed/refractory aggressive CD20+ lymphoma with intent to proceed to ASCT

Methods
Approach

Table 1. Model overview

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perspective</td>
<td>Publicly funded Canadian health care system</td>
</tr>
<tr>
<td>Time Horizon</td>
<td>20 years</td>
</tr>
<tr>
<td>Model Cycle Length</td>
<td>1 week</td>
</tr>
<tr>
<td>Discount Rate</td>
<td>1.5% per annum</td>
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</tbody>
</table>

Salvage chemotherapy +/- rituximab

- Patients who respond to salvage therapy may receive ASCT
- Patients whose disease progresses or relapses after salvage chemotherapy or ASCT may be considered for CAR T-cell therapy, another potentially curative but expensive treatment option. CAR T-cell therapy only recently became available, with capacity limits, in Ontario: scenarios (a) with and (b) without CAR T-cell therapy considered

Inputs
- Efficacy data were derived from two randomised phase 3 trials that evaluated rituximab +/- salvage chemotherapy and ASCT in relapsed/refractory DLBCL. Data for induction originated from a subgroup analysis of the LY.12 trial among patients with prior rituximab response. Efficacy according to ASCT receipt was derived from the CORAL study (Gisselbrecht et al 2017). Individual patient-level data were recreated using established methods and parametric curves fitted according to best practice. The combination of these datasets in the model validated well with the overall EFS data observed for each cohort

Cost-effectiveness analysis

Table 2. (a) Probabilistic Results

<table>
<thead>
<tr>
<th>Costs</th>
<th>R-GDP</th>
<th>GDP</th>
<th>Incremental</th>
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</thead>
<tbody>
<tr>
<td>$419,591</td>
<td>$343,918</td>
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Table 3. (b) Probabilistic Results

<table>
<thead>
<tr>
<th>Costs</th>
<th>R-GDP</th>
<th>GDP</th>
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</thead>
<tbody>
<tr>
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Discussion

- Cost savings were driven by the impact of potential cure, as less patients progressed to expensive CAR T-cell therapy as a result
- Without CAR T-cell therapy available, rituximab retreatment modestly increases costs and benefits due to higher rates of transplant; but there is no opportunity for avoidance of subsequent expensive therapy
- The effects of improved EFS during induction, improved transplant rates and avoidance of need for further therapy aligns with the benefits anticipated by clinical experts
- The model was most sensitive to transplant rates in each group and proportions of patients receiving CAR T-cell therapy

Limitations
- Unpublished EFS and OS subgroup data from LY.12 trial for patients who had previously responded to R-CHOP were needed; these outcomes were not statistically significantly improved in multivariable analyses. The uncertainty is incorporated in the model and all simulations support the use of the rituximab regimen in this population

Conclusions
- Available data appear to support superior transplant rates for rituximab retreatment compared to salvage chemotherapy alone in relapsed/refractory DLBCL
- While there is considerable uncertainty, the addition of rituximab to salvage therapy was cost-effective in all of the simulations at commonly accepted willingness-to-pay thresholds, due to improved transplant rates and avoidance of need for further therapy with CAR T-cell or additional salvage therapy as palliation
- Given limited access to CAR T-cell therapy in Ontario, when CAR T-cell therapy is not included as a downstream treatment option, rituximab retreatment still appears to be a cost-effective treatment strategy
- Thus, regardless of the availability of CAR-T cell therapy, the use of rituximab with salvage chemotherapy in this setting appears to be economically supported and cost-effective.