Combined modality therapy versus chemotherapy alone as an induction regimen for primary central nervous system lymphoma: a cost-effectiveness analysis

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Background. In immunocompetent patients with primary central nervous system lymphoma (PCNSL), combined modality therapy (CMT) using high-dose methotrexate and radiotherapy (WBRT) has improved response rates compared with chemotherapy alone. The trade-off is delayed and potentially devastating treatment-related neurotoxicity (NT).

Methods. A cost-effectiveness analysis using a Markov model compared CMT with chemotherapy alone in age-stratified patients with PCNSL. Baseline probabilities were derived from a systematic literature review. Direct and lost productivity costs were collected from a Canadian perspective and presented in Can$ in 2011. Outcomes were life expectancy, quality-adjusted life years (QALYs), and incremental cost-effectiveness ratio.

Results. The quality-adjusted life expectancy was 1.55 QALYs for CMT and 1.53 QALYs for chemotherapy alone. In younger patients (aged <60 years), CMT yielded 2.44 QALYs, compared with 1.89 QALYs for chemotherapy alone, yielding an expected benefit with CMT of 0.55 QALYs or 6.6 quality-adjusted months. The CMT strategy dominated in younger patients, as it was Can$11 951 less expensive than chemotherapy alone. The chemotherapy-alone strategy dominated in older patients, as it was Can$11 244 less expensive than CMT, and there was no difference in QALYs between the strategies. The model was robust in sensitivity analyses of key variables tested through the plausible ranges obtained from costing sources and published literature.

Conclusion. The preferred induction strategy for younger patients with PCNSL appears to be CMT, which minimized cost while maximizing life expectancy and QALYs. This analysis confirms that the preferred strategy for older patients is chemotherapy alone.

Keywords: central nervous system lymphoma, chemotherapy, cost-effectiveness, quality of life, radiotherapy.
median survivals, with CMT leading to less relapse but higher mortality from NT. Analysis of a larger cohort of patients identified a difference in survival between older patients (aged ≥60 years) compared with younger patients (aged <60 years) that seemed to be primarily related to NT following WBRT (75% vs 26%) because relapse rates were similar. Thiel et al. conducted the only randomized controlled trial comparing consolidating WBRT with no further treatment in patients treated with high-dose MTX. There was no significant difference in median overall survival (32 vs 37 months); however, the trial failed to meet its stated endpoint demonstrating the noninferiority of WBRT. Definitive conclusions regarding the relative benefit of radiation could not be derived from the trial, and thus the ideal induction regimen for PCNSL and the role of WBRT remain unresolved.

Choosing a therapeutic strategy, particularly when there is no clear survival benefit between 2 treatments, can be difficult and should take into account patient preferences and the quality-of-life detriment associated with each approach. Some patients may want to decline radiotherapy due to the severe NT risk and its associated quality-of-life detriments. Thus, they would be willing to trade off some advantage in relapse rate for perceived lower toxicity risk and potential improvement in quality of life. It is important to understand these preferences when counseling patients about their treatment options. Quality-adjusted survival, using quality-adjusted life years (QALYs), adjusts the time spent in a particular health state by a utility value (on a scale of 0 [dead] to 1 [perfect health]) that patients place on that particular health status.

There have been no cost-effectiveness analyses to date comparing these 2 strategies. Both NT and relapsed disease are associated with significant costs from a direct health care system perspective, in addition to caregiver burden and lost productivity effects. In particular, there may be a differential impact of radiation therapy according to age; younger patients may experience lower rates of NT with radiation compared with older individuals but have the potential to suffer greater economic and employment consequences should this toxicity occur. We have previously presented a decision analysis comparing the life expectancy and quality-adjusted life expectancy of the 2 treatment strategies. This work is unique in that it evaluates the cost effectiveness of these strategies, taking into account quality-adjusted impact from a societal perspective, to determine the optimal age-stratified induction strategy for patients with newly diagnosed PCNSL.

**Methods**

**Structure of Model**

We developed a Markov decision-analytic model to compare CMT versus chemotherapy alone for a hypothetical cohort of patients aged 60 years and newly diagnosed with PCNSL over a 5-year time horizon. The probabilities of transitioning from one state to another were evaluated on a 3-month cycle. We also age-stratified the model to evaluate hypothetical cohorts of patients aged <60 years and patients aged ≥60 years of age. Patients were treated with a MTX-based regimen of at least 3.5 g/m², with the addition of WBRT in the CMT strategy; those who achieved a complete response (CR) were followed for the development of either mild or severe NT as defined by the individual study. Patients in the chemotherapy-alone group who did not achieve a CR with induction or who relapsed from a CR were treated with salvage radiotherapy. Patients treated with the CMT strategy who did not achieve a CR or relapsed were considered to be palliative. The structure of the model has been previously detailed (Figure 1). The primary outcome for the model was the incremental cost-effectiveness ratio (ICER) that compared the relative differential costs and benefits (QALYs) with CMT versus chemotherapy alone. Threshold and sensitivity analyses were performed using the quality-adjusted model. For both treatment-related variables and costs, the ranges used in the analysis were such that they were clinically plausible as derived from the literature and cost-collection sources. Probabilistic sensitivity analyses (n = 1000 simulations) were performed using distributions identified from the data. Gamma distributions were used to model cost variables, and beta distributions were used to model probability variables. TreeAge Pro 2009 Release 1 (TreeAge Software) was used to construct the model and perform the analyses.

**Key Assumptions**

Assumptions regarding treatment options and development of NT were made based on clinical experience and published data including: (i) all patients who received chemotherapy alone as induction therapy and received salvage radiotherapy upon relapse; (ii) once patients have reached the peak of their NT, they do not progress from mild to severe NT once in complete response (CR); (iii) if there was not enough evidence to derive age-stratified values for the model variables, the overall group values were used; and (iv) the cost of caring for someone with NT was assumed to be similar to caring for someone with Alzheimer’s dementia.

**Baseline Estimates**

The baseline estimates of the model variables were derived from a systematic review of published studies, as previously described. Age-stratified estimates are presented (Table 1). The

![Fig. 1. Markov decision model. CMT, combined modality therapy; CR, complete response; Cx, chemotherapy alone; NT, neurotoxicity; PCNSL, primary central nervous system lymphoma; \(\rightarrow\) Transition between health states; \(\rightarrow\) Transition only allowed once, in patient who has not had radiotherapy.](https://academic.oup.com/neuro-oncology/article-abstract/16/10/1384/1050010)
literature revealed that the CR rates were lower with chemotherapy alone compared with CMT (48% vs 71%), yielding an odds ratio (OR) of 0.38;4,13,17

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26 this range was explored further in sensitivity analyses. We modeled the hazard ratio (HR) for the probability of relapse with chemotherapy alone versus CMT of 1.56 based on the randomized controlled trial (RCT) by Thiel et al., 13 with the range from other studies having been further explored. We used the same relapse probability for the age-stratified analysis because we felt the RCT provided the strongest evidence and there has been no published evidence suggesting a difference between the aged ≤60 years and aged ≥60 years groups.12

The literature clearly suggests that patients who receive WBRT, particularly if older, have a much higher incidence of treatment-related delayed NT.8,9,12,13,19 We modeled a baseline NT estimate post-CMT at 1 year of 18% based on the Omuro et al. study published in 2005.8 In the aged <60 years and aged ≥60 years groups, we modeled a NT at 1 year of 4% and 22% at base case, respectively. However, a wide clinically plausible range was explored in sensitivity analyses. Competing causes of death were modeled: PCNSL, complications due to treatment (chemotherapy or WBRT), NT, or natural causes.

The utilities assigned to each health state were derived from a survey of expert physicians who treat patients with PCNSL.15 We used sensitivity analyses to determine the impact of health state preferences, particularly those related to NT, on the model.

Costs

Costs were derived from a societal perspective, combining the public health payer’s perspective, caregiver burden, and lost productivity (Table 2). The drug acquisition costs of high-dose MTX, vincristine, procarbazine, and cytarabine, as well as supportive drug costs, were based on Cancer Care Ontario unit costs. Unit costs for medical visits and laboratory and radiological tests were based on the Ontario Schedule of Benefits for Physician Services and for Laboratory Services.27,28 Pharmacy and nursing costs were obtained from hospital human resources departments. Resource utilization and overhead costs were based on published guidelines and statistics.29 – 31 The costs of adverse events were derived from the literature. The most significant side effect was febrile neutropenia, and a recent Canadian analysis by Lathia et al. placed the cost of a febrile neutropenic episode at Can$6324 in 2007 dollars.32

The cost of WBRT was calculated per fraction, assuming 30 fractions, based on the cost-analysis by Earle et al.13 On the assumption that the NT manifestations are similar to Alzheimer’s dementia, we used the analysis by Hux et al. to model a 3-month cost of Can$5283.71 for mild NT and Can$12 109.67 for severe NT.34 These costs incorporate both caregiver burden and costs of long-term care facility use. A number of the studies characterizing neurotoxicity in PCNSL used the mini-mental

Table 1 Age-stratified key model variables and baseline estimates

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline estimate</th>
<th>Low</th>
<th>High</th>
<th>Baseline estimate</th>
<th>Low</th>
<th>High</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;60 yrs of age</td>
<td></td>
<td></td>
<td></td>
<td>≥60 yrs of age</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>Induction</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Odds Ratio of complete response on chemo vs. CMT</td>
<td>0.2</td>
<td>0.09</td>
<td>0.7</td>
<td>0.32</td>
<td>0.06</td>
<td>0.16</td>
<td>4,13,17,26</td>
</tr>
<tr>
<td>Probability of death from chemotherapy</td>
<td>0.06</td>
<td>0</td>
<td>0.09</td>
<td>0.04</td>
<td>0</td>
<td>0.16</td>
<td>17,20</td>
</tr>
<tr>
<td>Probability of death during CMT</td>
<td>0.05</td>
<td>0</td>
<td>0.1</td>
<td>0.07</td>
<td>0</td>
<td>0.16</td>
<td>4,21,22,24,25,38</td>
</tr>
<tr>
<td>Probability of death in CR without neurotoxicity</td>
<td>0.008</td>
<td>0.002</td>
<td>0.02</td>
<td>0.003</td>
<td>0.001</td>
<td>0.01</td>
<td>4,24,39</td>
</tr>
<tr>
<td><strong>Refractory disease and relapse</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hazard Ratio of relapse on chemo vs CMT</td>
<td>1.56</td>
<td>1.00</td>
<td>2.40</td>
<td>1.56</td>
<td>1.00</td>
<td>2.4</td>
<td>13</td>
</tr>
<tr>
<td>Probability of CR from salvage RT</td>
<td>0.56</td>
<td>0.37</td>
<td>0.70</td>
<td>0.56</td>
<td>0.37</td>
<td>0.70</td>
<td>39–41</td>
</tr>
<tr>
<td>Probability of death post relapse</td>
<td>0.75</td>
<td>0.50</td>
<td>1.00</td>
<td>0.75</td>
<td>0.50</td>
<td>1.00</td>
<td>12,24,25,62,63</td>
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<tr>
<td>Probability of relapse post second CR</td>
<td>0.14</td>
<td>0.03</td>
<td>0.21</td>
<td>0.14</td>
<td>0.03</td>
<td>0.21</td>
<td>39–41</td>
</tr>
<tr>
<td><strong>Neurotoxicity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hazard Ratio of no neurotoxicity from chemo vs CMT</td>
<td>0.12</td>
<td>0.01</td>
<td>2.00</td>
<td>0.12</td>
<td>0.01</td>
<td>2.00</td>
<td>3,4,12,13,18,20</td>
</tr>
<tr>
<td>Probability of Neurotoxicity post CMT at 1 yr</td>
<td>0.04</td>
<td>0</td>
<td>0.4</td>
<td>0.22</td>
<td>0.10</td>
<td>0.90</td>
<td>8</td>
</tr>
<tr>
<td>Probability of death from neurotoxicity</td>
<td>0.02</td>
<td>0.01</td>
<td>0.07</td>
<td>0.07</td>
<td>0.05</td>
<td>0.09</td>
<td>4,8,12,21</td>
</tr>
<tr>
<td>Probability of developing severe NT given that NT occurs</td>
<td>0.02</td>
<td>0.01</td>
<td>0.07</td>
<td>0.06</td>
<td>0.02</td>
<td>0.07</td>
<td>8,9,21</td>
</tr>
<tr>
<td><strong>Quality-of-life adjustments</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Utility of patients with incurable PCNSL</td>
<td>0.14</td>
<td>0</td>
<td>0.60</td>
<td>0.14</td>
<td>0</td>
<td>0.60</td>
<td>4,12,13,18,20</td>
</tr>
<tr>
<td>Utility of mild neurotoxicity in CR</td>
<td>0.74</td>
<td>0.60</td>
<td>0.90</td>
<td>0.74</td>
<td>0.60</td>
<td>0.90</td>
<td>39–41</td>
</tr>
<tr>
<td>Utility of no neurotoxicity in CR</td>
<td>0.94</td>
<td>0.90</td>
<td>1.00</td>
<td>0.94</td>
<td>0.90</td>
<td>1.00</td>
<td>12,24,25,62,63</td>
</tr>
<tr>
<td>Utility of patients with PCNSL on therapy</td>
<td>0.14</td>
<td>0</td>
<td>0.40</td>
<td>0.14</td>
<td>0</td>
<td>0.40</td>
<td>39–41</td>
</tr>
<tr>
<td>Utility of severe neurotoxicity in CR</td>
<td>0.33</td>
<td>0.20</td>
<td>0.50</td>
<td>0.33</td>
<td>0.20</td>
<td>0.50</td>
<td>39–41</td>
</tr>
</tbody>
</table>

The baseline estimates for the probability variables used in the model were normalized to a 3 mo time unit. This was done as the cycle length of the Markov model was 3 months.

Utilities were derived from a survey of expert physicians. Abbreviations: CMT, combined modality therapy; CR, complete response; NT, neurotoxicity; PCNSL, primary central nervous system lymphoma; RT, radiotherapy.
status examination (MMSE) to capture mild and severe disease; by matching the same definitions in the Alzheimer’s dementia literature, we felt this assumption was reasonable. The cost of palliation per 6 months was Can$20,768 for the last 6 months of life based on a Canadian costing study. Costs of death were assumed to be Can$0.

Productivity for the younger patient (aged <60 years) was assumed to be 40 hours per week at the average wage of Can$23.69, as per Statistics Canada values in 2011. Younger patients in CR were assumed to resume productivity at 100%. Based on data by Harder et al., patients with mild NT were modeled as 40% productivity, and patients with severe NT or relapsed disease were modeled at 0%. Hurd et al. described the productivity/contribution of older patients as 83% of younger patients, thus we modeled this proportion for patients aged ≥60 years.

All costs were adjusted to 2011 Canadian dollars (Can$1 = US$0.96) using the Consumer Price Index (www.bankofcanada.ca).

## Results

### Baseline Analysis

The life expectancy was 2.48 years for patients receiving induction therapy with CMT and 2.56 years for those receiving chemotherapy alone, yielding a net expected benefit of 0.08 years or 1 month in favor of chemotherapy alone. With quality-of-life adjustment, the expected benefit from CMT as an induction therapy was a minimal 0.02 QALYs or 7 quality-adjusted days (1.55 QALYs for CMT and 1.53 QALYs for chemotherapy alone).

### Age-stratified Analysis

#### Aged <60 Years

The life expectancy was 3.44 years for younger patients receiving CMT and 3.14 years for those receiving chemotherapy alone, yielding a net expected benefit of 0.3 years or 3.6 months in favor of CMT. Quality-of-life adjustment yielded 2.44 QALYs with CMT versus 1.89 QALYs with chemotherapy alone. This yielded an expected benefit from CMT of 0.55 QALYs or 6.6 quality-adjusted months (Table 3).

#### Aged ≥60 Years

The life expectancy was 2.39 years for older patients receiving CMT and 2.47 years for those receiving chemotherapy alone, yielding a net expected benefit of 0.08 years or 1 month in favor of chemotherapy alone. With quality-of-life adjustment, both the CMT and chemotherapy alone strategies yielded a quality-adjusted life expectancy of 1.43 QALYs (Table 3).

## Cost-utility Analyses

The costs of health states are presented in Table 3, including both direct health care system costs, caregiver burden, and lost productivity as indirect costs. In the overall group, the cost of CMT was Can$140,735, and the cost of chemotherapy alone was Can$129,430, yielding an incremental cost-effectiveness ratio of Can$506,078 per QALY.

### Aged <60 Years

The cost of CMT was Can$146,259, and the cost of chemotherapy alone was Can$158,210. Thus, CMT was Can$11,951 less expensive and had an expected benefit of 0.55 QALYs; the CMT strategy dominates (Table 3).

### Aged ≥60 Years

The cost of CMT was Can$139,777, and the cost of chemotherapy alone was Can$128,533. Thus, chemotherapy was Can$11,244 less expensive; with no difference in QALYs; the chemotherapy alone strategy dominates (Table 3).
Sensitivity Analyses

Threshold analyses were performed to determine when the optimal decision would change to favor one strategy over the other, as the values of the probability estimates in the model were varied through the plausible ranges. Sensitivity analysis demonstrated that for the overall and the aged ≥60 years groups, the model was sensitive to the relapse HR and the odds ratio of CR with chemotherapy alone versus CMT as well as the probability of developing NT at 1 year. The chemotherapy alone strategy always remained less expensive, with CMT becoming minimally more effective at the extreme ends of the ranges used. The model was robust to sensitivity analyses of key variables in the aged <60 years group (Table 4). When the OR of CR with chemotherapy alone vs CMT was improved from our baseline estimate of 0.36 to 0.51, chemotherapy alone became the optimal approach. However, this is a higher OR than reported in the literature for studies directly comparing the 2 strategies, including that by Thiel et al. in which the OR was 0.40.13 For both the younger and older groups, the model was insensitive to changes in utilities or cost variables.

Probabilistic Sensitivity Analyses

Probabilistic sensitivity analyses (1000 simulations) were performed using the distributions described above by the age-stratified groups. The cost-effectiveness acceptability curves are presented for younger patients and older patients (Supplementary 1 and 2). For the commonly accepted willingness-to-pay threshold of Can$50,000 in younger patients, CMT is the more cost-effective strategy 97% of the time, and in older patients, chemotherapy alone is the more cost-effective strategy 82% of the time (Figure 2).

Discussion

Although CMT (HDMTX and WBRT) may improve disease control in PCNSL compared with chemotherapy alone, this approach may be associated with significant delayed NT, particularly in older patients. Clinical trials to date have failed to definitively establish a superior approach, and outcomes stratified by age are not readily available in the literature. This is in keeping with the efficacy results of our Markov decision-analytic model, suggesting that for all patients, receiving CMT for PCNSL resulted in a minimal gain of 7 days in quality-adjusted life expectancy, demonstrating that overall the 2 strategies are essentially equivalent.15 However, as we have previously demonstrated, the model indicates that CMT leads to higher life expectancy for younger patients, even when adjusted for quality, with a gain of more than 7 quality-adjusted months.15 However, in older individuals, we were not able to establish a difference in quality-adjusted outcomes between the approaches.

Our economic evaluation suggests a differential age-stratified approach to maximize cost-effectiveness from a societal benefit. In younger patients, CMT was less expensive by almost Can$12,000 and, coupled with the gain in quality-adjusted life expectancy, yielded a dominant strategy confirming the finding that CMT is the optimal induction strategy for newly diagnosed younger patients with PCNSL. The cost of CMT is likely lower due to the decreased chance of relapse, with its associated poor prognosis.

Table 3. Primary outcomes of life expectancy and quality-adjusted life expectancy for overall group and age-stratified groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Overall</th>
<th>&lt;Aged 60 years</th>
<th>&gt;Aged 60 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Base case</td>
<td>Threshold</td>
<td>Base case</td>
</tr>
<tr>
<td>HR of relapse chemo vs CMT</td>
<td>1.56</td>
<td>2.23</td>
<td>1.56</td>
</tr>
<tr>
<td>OR of CR with chemo vs CMT</td>
<td>0.38</td>
<td>0.25</td>
<td>0.20</td>
</tr>
<tr>
<td>Pr of NT at 1 year with CMT</td>
<td>0.18</td>
<td>0.05</td>
<td>0.04</td>
</tr>
<tr>
<td>Utility of severe NT in CR</td>
<td>0.33</td>
<td>None</td>
<td>0.33</td>
</tr>
<tr>
<td>Cost of palliation</td>
<td>21868.93</td>
<td>None</td>
<td>23328.68</td>
</tr>
<tr>
<td>Cost of NT when in CR</td>
<td>23860</td>
<td>None</td>
<td>25320</td>
</tr>
<tr>
<td>Discount rate</td>
<td>5%</td>
<td>None</td>
<td>5%</td>
</tr>
</tbody>
</table>

Abbreviations: CMT, combined modality therapy; CR, complete response; Cx, chemotherapy alone; HR, hazard ratio; NT, neurotoxicity; OR, odds ratio; Pr, probability.
and progression to palliation, which is a costly state. The converse was true of older patients, in whom chemotherapy alone was less expensive by Can$11,000 with no difference in QALYs, demonstrating a cost minimization in which chemotherapy alone is the dominant strategy.

Age-stratification is key in this disease, and the model is very robust to sensitivity analyses for the group aged <60 years. Although the older patient model was sensitive to relapse HR and OR of CR, chemotherapy alone continued to remain cheaper. Even at the end values for these variables as reasonable from the literature, the overall difference in either direction was minimal, demonstrating essentially equivalent quality-adjusted life expectancy. Although there was uncertainty around the baseline values, probabilistic sensitivity analyses confirmed the diverging conclusions for the 2 age groups. For the commonly accepted willingness-to-pay threshold of Can$50,000, CMT is the more cost-effective strategy for younger patients 97% of the time, while chemotherapy alone is the more cost-effective strategy for older patients 82% of the time.

There are several limitations to this cost-effectiveness analysis. The data used for certain variables, particularly those in the age-stratified models, were derived from smaller studies or inferred from the overall group data, which may not truly represent age-stratified outcomes. However, we feel that the estimates were conservative and that we were able to address this heterogeneity through sensitivity analyses. Although our analysis is unique with the inclusion of indirect costs (work productivity), these data were not collected prospectively but were instead

Fig. 2. Incremental effectiveness scatter plot for (A) patients aged <60 years and (B) patients aged ≥60 years.
modeled from Canadian employment statistics. However, sensitivity analyses did not suggest that a wide variability in indirect costs would affect our conclusions. We also assumed that mild NT did not progress to a more severe form, as the NT rate modeled was defined as severe at its peak. As most of the literature reported the rates cross-sectionally, it is difficult to capture the spectrum of progression. However, we were reassured by recent reports about cognitive function in treated PCNSL patients. Correa et al. (2012) evaluated 50 patients after a median of 42 months since treatment and demonstrated decreased cognitive function in patients treated with CMT compared with chemotherapy alone. However, a second evaluation 16 months later revealed no further significant cognitive changes, demonstrating that patients reach a stable plateau, whether it is mild or severe. Finally, we assumed the cost of caring for someone with radiation-induced NT was similar to Alzheimer’s dementia, which may not be completely identical. Several of the studies in PCNSL used clinical examination or MMSE to assess for NT, similar to Alzheimer’s dementia, and we attempted to match the different categories of NT with the costs described by Hux et al. for the different severities of Alzheimer’s dementia. Reassuringly, the model was very robust to sensitivity analyses of cost variables, and we feel the care needed for such a patient would be very similar.

In conclusion, our cost-effectiveness analysis is able to address a controversial treatment area in PCNSL, exploring the implications of the trade-offs between improved tumor control with CMT versus decreased NT with chemotherapy alone. This analysis confirms that chemotherapy alone is the most cost-effective strategy in older patients. However, in younger patients, the dominant strategy appears to be CMT, which significantly maximizes life expectancy and quality-adjusted life-expectancy while minimizing costs.

Supplementary Material
Supplementary material is available online at Neuro-Oncology (http://neuro-oncology.oxfordjournals.org/).

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Conflict of interest statement. None declared.

References


