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Cost-Effectiveness of the Addition of Rituximab to CHOP Chemotherapy in First-Line Treatment for Diffuse Large B-Cell Lymphoma in a Population-Based Observational Cohort in British Columbia, Canada

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ABSTRACT

Background: Diffuse large B-cell lymphoma (DLBCL) has primarily been treated with cyclophosphamide, doxorubicin, vincristine, and predisone (CHOP) chemotherapy since the 1970s. Recently, the addition of rituximab to CHOP (CHOP-R) has been found to improve survival and trial-based results have suggested that it is a cost-effective alternative to CHOP.
Objectives: The objective in this study was to evaluate the cost-effectiveness of CHOP-R relative to CHOP in first-line treatment of DLBCL in a population-based setting in British Columbia, Canada.
Methods: We created a patient-level simulation model describing potential pathways for DLBCL patients initiating treatment with either CHOP or CHOP-R. Model parameters were populated with statistical analyses of individual-level treatment and effectiveness data and published cost estimates. All results were stratified by age at treatment initiation (<60 years vs. ≥60 years). The base-case scenario was based on a 15-year time horizon and a 3% discount rate. Probabilistic sensitivity analysis was performed. All costs are reported as 2006 $CDN.
Results: For the base-case scenario, incremental cost-effectiveness ratios (ICERs) for younger individuals ranged from $11,965 per disease-free life-year gained to $19,144 per quality-adjusted life-year gained. For older individuals, estimated ICERs for all health outcomes were below $10,000 per unit outcome gained for a 15-year time horizon.
Conclusions: Using population-based data, CHOP-R was found to be a cost-effective alternative to CHOP, particularly for individuals aged 60 years and older. Results from this Canadian observational data source were consistent with international clinical trial-based studies. The use of CHOP-R as a first-line treatment for DLBCL is recommended, with respect to both clinical and cost-effectiveness.
Keywords: cost-effectiveness, lymphoma, patient simulation, rituximab.

Introduction

In 2008, there were approximately 7000 new cases of non-Hodgkin lymphoma diagnosed in Canada with 3100 deaths attributed to the disease [1]. Diffuse large B-cell lymphoma (DLBCL) is the most common form of non-Hodgkin lymphoma, representing approximately 30% of new cases [2].

DLBCL is an aggressive cancer, and before the introduction of modern treatments survival was typically less than 1 year [3]. Since the 1970s, the most common treatment for DLBCL has been cyclophosphamide, doxorubicin, vincristine, and predisone (CHOP) chemotherapy [4]. Approximately 60% of patients receiving CHOP achieve a complete response in the short term [5], and approximately 30% of individuals receiving CHOP achieve long-term cure [6]. Nevertheless, with more than half of individuals receiving CHOP not cured of their disease, 3-year progression-free survival is just 44% [7].

Rituximab is a chimeric anti-CD20 immunoglobulin G1 monoclonal antibody that was originally introduced in the mid-1990s for treating relapsed follicular lymphoma [8]. Since then, rituximab has been added to CHOP chemotherapy (CHOP-R) for individuals receiving initial treatment for DLBCL. The efficacy of CHOP-R in this setting has been established via the Groupe d'Etude des Lymphomes de l'Adulte (GELA) trial [9,10]. Further, an observational study has demonstrated the effectiveness of CHOP-R in routine practice in British Columbia (BC) where CHOP-R has been the standard of care for first-line treatment of DLBCL patients since 2001 [11]. Both the GELA trial and the observational study found a similar risk reduction for progression-free survival (risk ratios of 0.58 and 0.56, respectively).

Several theoretical assessments have also found CHOP-R to be a potentially cost-effective alternative to CHOP for treating DLBCL, extrapolating from the efficacy results of the GELA trial [12–15]. The objective in this study was to perform an economic evaluation of CHOP-R relative to CHOP using actual observational data describing routine practice in BC. The results of this study document the relative cost-effectiveness of CHOP-R when used in actual practice, as opposed to the idealized circumstances described by a randomized controlled trial.

Methods

Data Sources

Anonymized individual-level data were obtained from the British Columbia Cancer Agency (BCCA) Lymphoid Cancer Database which records routinely-collected treatment and outcomes information on patients with lymphoid cancer in the Canadian province of BC. The study sample included 266 HIV-negative adults (age > 15 years) initiating treatment with CHOP between

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September 1997 and June 2000 and 519 HIV-negative adults initiating treatment with CHOP-R between March 2003 and June 2007. Outcomes included relapse, death, or censoring, and were current to January 2010. All data were irreversibly anonymized after extraction from the Lymphoid Cancer Database before being supplied to study personnel. No study personnel had access to identifiable patient information.

These data were used in several time-to-event analyses to estimate the distributions associated with time spent in various health states. Time-to-event analyses included the time from initiating first-line therapy to relapse, and time from initiating second-line therapy to death. All analyses assumed a parametric Weibull form for the underlying hazard function.

Per-patient chemotherapy costs were derived from the BCCA Provincial Systemic Therapy Drug Database from 1995 to 2008, and these were used to calculate a mean and standard error associated with each regimen.

The cost of a single radiation fraction was estimated using a top-down approach, based on the total cost required to fund the BC radiation therapy program during 2006 to 2007 divided by the total number of fractions delivered during this time period. This unit cost was combined with individual-level data describing the number of fractions received by a patient within a given treatment regimen to obtain a distribution for radiotherapy costs for each regimen.

The cost of palliative care was estimated assuming a cost of $25,000 per year for palliative therapy [16]. This was combined with the estimated time spent receiving palliative care to obtain an overall cost distribution.

All other costs were based on a microcosting study of DLBCL performed in Alberta, Canada [17]. This included costs for assessment, treatment, and follow-up during first-line therapy, and oncologists, outpatient nursing, tests, hospitalization, and stem-cell transplantation (SCT) during subsequent regimens. All costs were stratified by receipt of rituximab during initial therapy. All costs are reported as 2006 $CDN.

Utilities were based on those reported by Knight et al. [15], and were categorized into complete responder (all individuals currently taking initial therapy and those who respond successfully), partial responder (all individuals receiving second-line therapy with curative intent), and progressive disease (all individuals receiving palliative care).

Model Structure

The model was structured as a microsimulation, comparing CHOP versus CHOP-R as first-line therapy over a maximum 15-year time horizon. The model was event-based, meaning that individuals moved forward in time in intervals based on the timing of certain prespecified events, rather than in uniform time cycles [18,19]. The structure of the model is shown in Figure 1. Potential pathways were determined based on expert opinion, treatment protocols and empirical data from the BCCA.

The model was evaluated separately for CHOP and CHOP-R regimens, and for individuals aged 60 years or older versus those

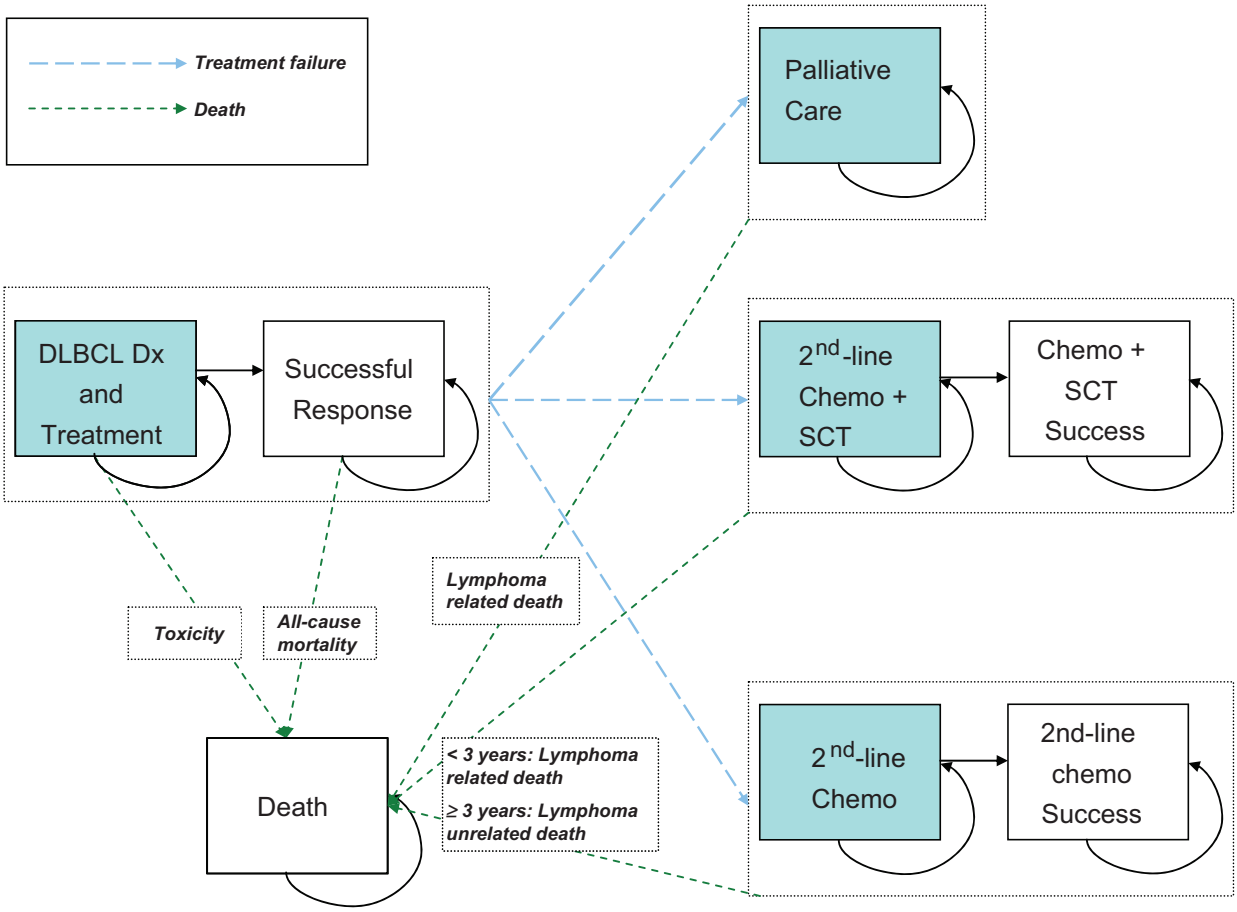

Figure 1 Microsimulation model structure. DLBCL, diffuse large B-cell lymphoma; SCT, stem-cell transplantation.

younger than 60. The time spent receiving a first-line regimen was randomly generated and treatment costs were accumulated throughout the treatment period. A small number of individuals were assumed to experience death from toxicity at some point during the treatment period.

Individuals surviving past the treatment period were then assigned to one of two outcomes: eventual DLBCL relapse or eventual mortality from non-DLBCL causes with no prior relapse. The probabilities associated with the respective outcomes were dependent on initial treatment regimen and age at diagnosis (<60 years vs. ≥60 years).

For individuals who relapsed, time until occurrence of relapse was randomly generated based on a Weibull survival model. Separate survival models were fit for the two age categories, so that the time until relapse was allowed to vary by age. Time between initial treatment completion and relapse was assumed to be spent in a "Successful Response" health state. After relapse, individuals were randomly assigned to one of three second-line treatment regimens: 1) second-line chemotherapy alone; 2) high-dose second-line chemotherapy plus SCT; or 3) palliative care. Each of the second-line treatment regimens was associated with a corresponding health state and Weibull survival model describing time between treatment initiation and death. The probability of receiving a particular second-line therapy was dependent on age, but for a given therapy the estimated time between therapy initiation and death was assumed to be independent of age. This framework was chosen based on empirical data which indicated an increased probability of palliative care and a decreased probability of high-dose chemotherapy plus SCT for individuals aged 60 years or older, but no significant effect of age within therapy options. Time until death was then randomly generated for each individual.

For individuals who were cured or who died of other causes before relapse, time until death was generated based on age- and sex-specific BC life tables [20]. All time between treatment completion and death was assumed to be spent in the "Successful Response" state.

Probabilistic sensitivity analysis was performed on all parameters of the survival analysis models, as well as the estimated costs and utilities associated with health states. During each iteration of the probabilistic sensitivity analysis, new sets of time-to-event parameters were generated based on the means and standard errors estimated within the respective Weibull models. The simulation proceeded based on these randomly generated model parameters. Costs were generated from gamma distributions, whereas utilities were estimated from beta distributions. The method of moments was used to estimate parameters for the respective gamma and beta distributions based on the mean and standard errors for costs and utilities.

The health outcomes considered were life-years, quality-adjusted life-years (QALYs), and disease-free (i.e., preprogression) life-years. Economic outcomes were defined as the incremental costs associated with a one-unit improvement in each of the health outcomes. All costs and outcomes were evaluated both undiscounted and discounted at 3% per year [21]. In addition, we performed a one-way sensitivity analysis using a maximum time horizon of 5 years, reflecting the period of empirical data availability.

Assumptions

In addition to high-level assumptions regarding model structure and appropriate parametric form for survival analyses, several assumptions were made regarding key model parameters in the base-case analysis.

Because of the limited period of availability of rituximab, only 6-year follow-up data were available for CHOP-R, and assumptions were required regarding long-term relapse and cure rates. As an *upper bound* for the cure rate after CHOP-R treatment, it was assumed that all the relapses after CHOP-R treatment were observed within the 6 years of follow-up data that were available. This is consistent with the cure rate after CHOP as the large majority (>80%) of relapses in the CHOP group occurred within 5 years. The *lower bound* for the CHOP-R cure rate was assumed to be equivalent to the CHOP cure rate. During the probabilistic sensitivity analysis, the CHOP-R relapse rate was varied between these two extremes using a uniform distribution.

After second-line therapy, no data were available describing date of further refractory or relapsed disease or receipt of palliative treatment. We therefore made the simplifying assumption that all deaths occurring within 3 years of relapse were due to lymphoma, whereas all deaths occurring more than 3 years after relapse were due to other causes. This assumption was based on empirical data showing that the Kaplan–Meier curve had reached a flat plateau within 3 years of relapse, and was verified by clinical experts in lymphoma. Deaths due to lymphoma were assumed to be associated with end-of-life costs equal to average palliative care costs, whereas deaths associated with other causes were not associated with palliative care costs.

Results

Of the 785 individuals included in the observational data source, 45.3% were younger than 60 years old at time of DLBCL diagnosis. This distribution was relatively constant over time, with 47.7% younger than age 60 during the pre–rituximab era and 44.1% younger than age 60 during the post–rituximab era.

The average costs associated with first- and second-line therapy are given in Table 1. The costs for first-line therapy reflect the costs associated with an entire course of therapy, including medications, assessment, follow-up, oncologists, nursing, laboratory tests, and hospitalizations. The probability of receiving radiotherapy was varied by treatment regimen and age category, but, conditional on receiving radiotherapy, the associated cost per radiotherapy course was assumed to follow a constant distribution across treatment regimens. In the BCCA data, the percentage of patients receiving radiotherapy was 37% for both CHOP and CHOP-R for individuals younger than age 60 and 25% for older individuals. Across age categories and options for second-line therapy, the percentage of individuals receiving radiotherapy varied between 21% and 41%.

The probabilities of all health state transitions and the time distributions associated with the various health states are summarized in Table 2. After initiating first-line therapy, the potential transitions were to: death from toxicity of first-line treatment, relapse/progression, or death from non-lymphoma-related causes. Therefore, all individuals who did not experience progressive disease or toxicity-related death were assumed to eventually die of other causes. After all of the second-line therapy options, the only subsequent health state considered was death so that 100% of individuals eventually transitioned to the death state. Nevertheless, there was variability across treatment options and individuals as to when this transition would occur and whether or not it would be due to lymphoma-related causes. It was assumed that survival after second-line therapy was independent of receipt of rituximab in initial therapy regimen.

Figure 2a,b shows the estimated time until relapse after first-line therapy for individuals younger than age 60 years and 60 or older, respectively. The available data provided approximately 6-year follow-up for patients receiving CHOP-R, at which point

Table 1 Input costs assumed for first- and second-line therapy in diffuse large B-cell lymphoma

Regimen	Estimated cost (standard error)	Probability of radiation <60 years	Probability of radiation ≥60 years	Radiation cost per course (standard error)*
First line				$5,773 ($166)
CHOP-R (per course)*	$33,968 ($1,979)	0.37	0.25	
CHOP (per course)*	$22,727 ($3,477)	0.37	0.25	
Second line				
Chemotherapy (per course)*	$20,920 ($4,164)	0.41	0.25	
Chemotherapy + SCT (per course)*	$31,957 ($6,590)	0.21	0.00	
Palliative (per year)†	$25,000 ($7,500)	0.33	0.28	

*Source(s): Lee et al. [17]; BC Cancer Agency. Includes treatment, assessment, and follow-up (medications, oncologists, nursing, tests, hospitalization).
†Source(s): Fassbender et al. [16].
CHOP, cyclophosphamide, doxorubicin, vincristine, and predisone; CHOP-R, CHOP with rituximab; SCT, stem-cell transplantation.

61% of younger CHOP-R patients and 68% of older CHOP-R patients are projected to remain free from relapse. More than 10 years of follow-up data were available for patients receiving CHOP, with 50% of younger CHOP patients and 29% of older CHOP patients projected to remain free from relapse at the end of follow-up. It was therefore assumed in the simulation model that the cure rate for CHOP was 50% for individuals younger than 60 and 29% for individuals aged 60 or older, whereas the cure rate for CHOP-R was varied uniformly between 50% and 61% for younger individuals and 29% and 68% for older individuals in the probabilistic sensitivity analysis.

The estimate of a 61% upper bound for cure rate for younger CHOP-R patients is based on an empirically observed sudden increase in relapse at 6 years (Fig. 2a). Nevertheless, this increase was heavily influenced by a single death because of the small number of patients providing follow-up to this point. The 95% CI for 6-year relapse-free survival was 42% to 89%, with the width reflecting the small remaining sample size. The estimated cure rate at 5 years was 74% with a substantially narrower 95% CI of 67% to 80%, and is likely a more reliable estimate of the actual cure rate. Nevertheless, our base-case analysis used a maximum cure rate of 61%, which provides a more conservative estimate of CHOP-R efficacy and will result in CHOP-R appearing less favorable. We also performed a sensitivity analysis in which we assumed that the maximum cure rate for younger individuals receiving CHOP-R was 74%.

For patients younger than 60 who relapsed, the second line of therapy was: chemotherapy with curative intent (no SCT) for 37% of patients; high-dose chemotherapy and SCT with curative intent for 19% of patients; and palliative care in the remaining 44% of patients. For older patients, second-line therapy consisted of: chemotherapy for 15%; high-dose chemotherapy with SCT for 3%; and palliative care for 82%. For the chemotherapy and high-dose chemotherapy with SCT regimens, the average cost reported reflects the cost for the entire course of therapy, including the same components as for first-line therapy. For the palliative therapy options, the average cost is the estimated cost per year spent receiving palliative therapy (16), and, for each patient receiving a palliative regimen, the cost per year was multiplied by the randomly-generated number of years that they spent in the palliative health state.

Figure 3 shows the estimated time until death after relapse for the three possible options of second-line therapy. These analyses were restricted to patients who relapsed after first-line therapy, and who initiated a second round of treatment. Time was measured relative to start date of second-line therapy. Based on empirical analyses, these curves were assumed to apply to individuals of all ages.

Health outcome and cost-effectiveness results are given in Table 3a,b. With a 15-year time horizon and a 3% discount rate, incremental cost-effectiveness ratios (ICERs) for younger individuals ranged from $11,965 per disease-free life-year gained to $19,144 per QALY gained. The corresponding range for undiscounted results was $10,632 per disease-free life-year gained to $15,948 per QALY gained. When the time horizon was restricted to 5 years, the estimated ICERs were $48,320 per life-year gained and per QALY gained, and $32,213 per disease-free life-year gained. This increase in ICERs approaching standard cost-

Table 2 Probabilities and mean times associated with health state transitions

Health state transition	CHOP-R	Probability of transition	Mean time (years) (95% CI)	CHOP	Probability of transition	Mean time (years) (95% CI)
First line						
First-line therapy	<60 years	0.008	0.36 (0.27–0.45)	<60 years	0.008	0.31 (0.21–0.40)
→ Toxicity death	≥60 years	0.026		≥60 years	0.026	
First-line therapy	<60 years	0.39–0.50*	0.93 (0.69–1.16)	<60 years	0.50	0.81 (0.60–1.02)
→ Relapse	≥60 years	0.32–0.71*	0.72 (0.55–0.90)	≥60 years	0.71	0.88 (0.66–1.10)
Second line						
Second-line chemotherapy → Death	1.00		1.94 (1.02–2.86)	As for CHOP-R patients		
High-dose chemotherapy + stem-cell transplantation → Death	1.00		5.49 (2.42–8.56)			
Palliative care → Death	1.00		0.43 (0.33–0.54)			

*Varied randomly across probabilistic sensitivity analysis.
CHOP, cyclophosphamide, doxorubicin, vincristine, and predisone; CHOP-R, CHOP with rituximab.

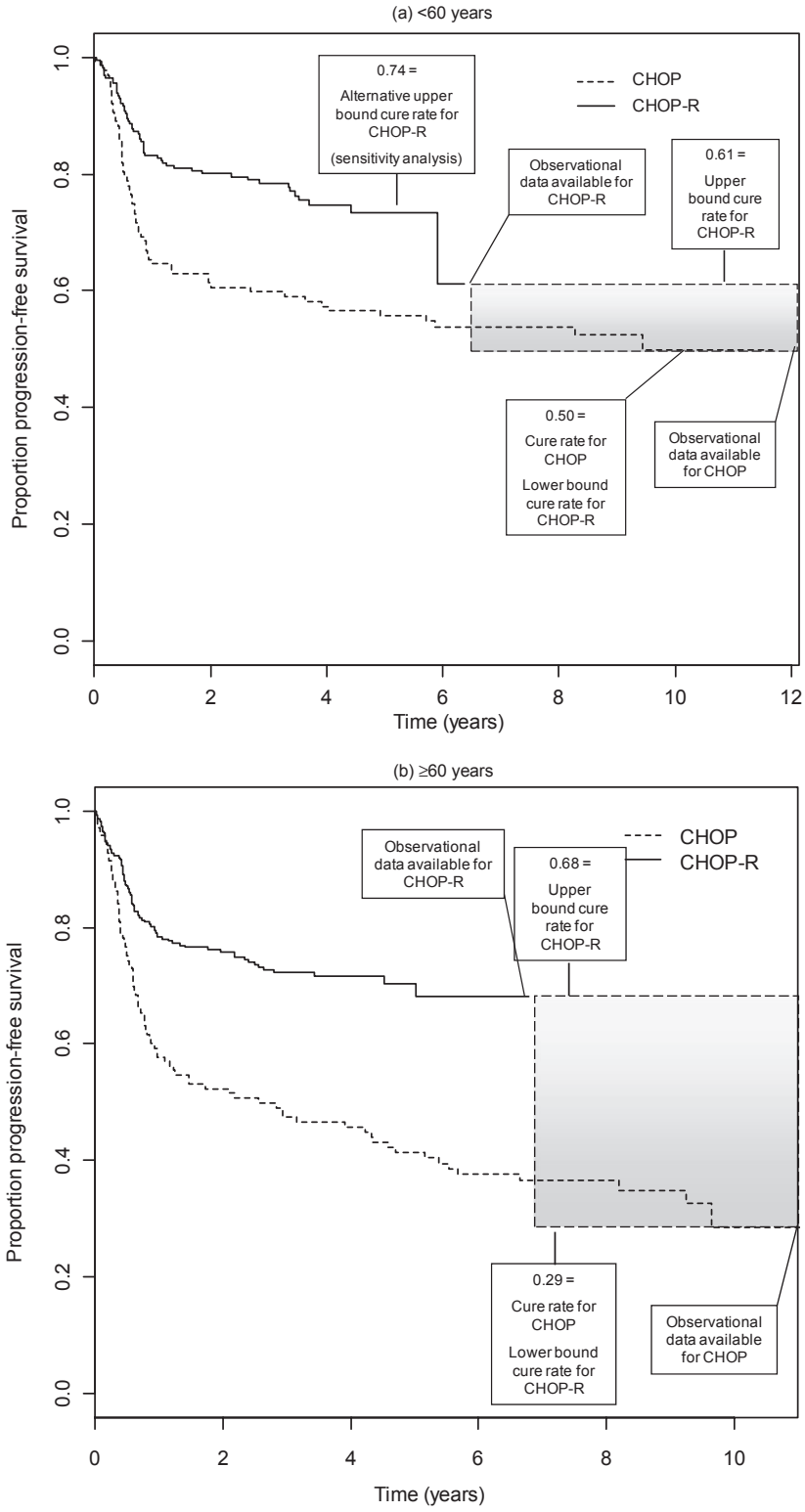

Figure 2 Time until relapse or cure after first-line therapy with cyclophosphamide, doxorubicin, vincristine, and predisone (CHOP) and CHOP with rituximab (CHOP-R) for diffuse large B-cell lymphoma, for patients (a) <60 years and (b) ≥60 years.

effectiveness thresholds [22] reflects the fact that the majority of costs occurs in the first 5 years, whereas benefits in outcome extend into subsequent years. For older individuals, ICERs were more favorable: estimated ICERs for all health outcomes were below $10,000 per unit outcome gained when using a 15-year time horizon. With a 5-year time horizon, estimated ICERs for all health outcomes remained below $20,000 per unit outcome gained.

When the upper bound of the cure rate for CHOP-R in younger individuals was increased to 0.74 from 0.61, all esti-

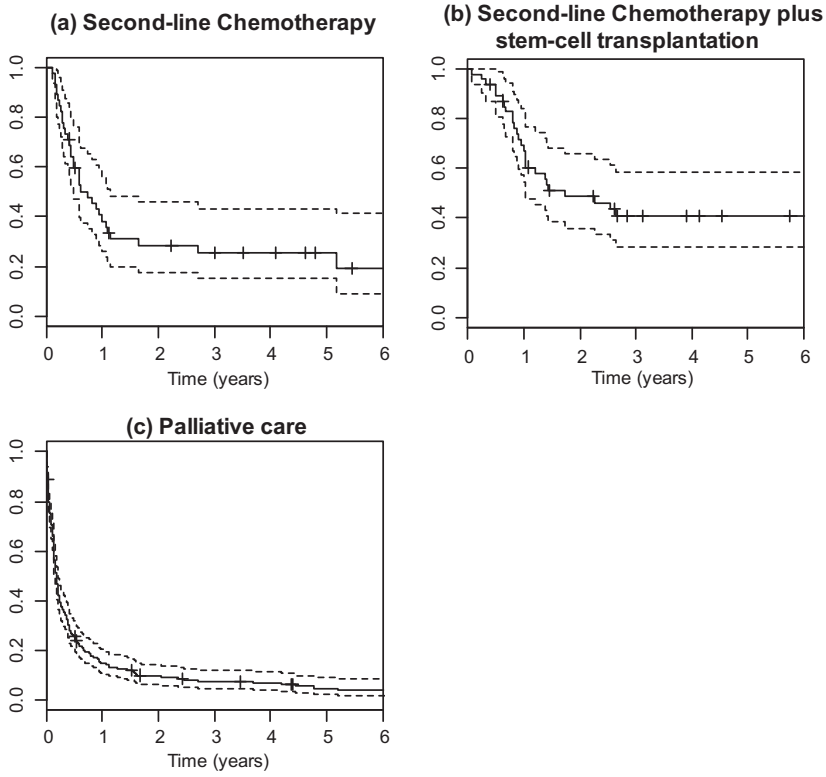

Figure 3 Time until death after relapse (with associated 95% CI), for three possible forms of second-line therapy: (a) chemotherapy; (b) high-dose chemotherapy with stem-cell transplantation; (c) palliative care.

mated ICERs dropped accordingly: $8325 per life-year gained, $10,174 per QALY gained, and $7044 per disease-free life-year gained. This sensitivity analysis was based on a time horizon of 15 years and a discount rate of 3%.

Results of the probabilistic sensitivity analysis are shown in Figure 4a,b for the base-case scenario of a 15-year time horizon and 3% discounting. Assuming a willingness-to-pay (WTP) threshold of $50,000 per QALY, CHOP-R was found to be cost-effective in 68% of iterations for younger individuals and 73% of iterations for older individuals.

Discussion

In this study, we found CHOP-R to be a cost-effective alternative to CHOP for first-line therapy in diffuse large B-cell lymphoma. The economic evaluation was based on "real-life" use of CHOP-R using data from a large observational cohort, thus confirming the results from other theoretical models. We applied a microsimulation model that generated individual life histories for hypothetical lymphoma patients receiving CHOP or CHOP-R as initial therapy.

One limitation to our study was the use of historical controls. Because CHOP-R was introduced as standard care for first-line DLBCL treatment in BC in 2001, there was no contemporary control group available for comparison, and DLBCL patients from 1997 to 2000, who received CHOP, formed the control group. Nevertheless, we expected minimal bias from the use of historical control data, as, with the exception of the addition of rituximab to initial therapy, all aspects of DLBCL diagnosis and treatment have remained consistent over the study period. These aspects include: diagnosis methods and criteria, disease staging, supportive care elements, and treatment retention. This is further supported by the fact that the results of observational studies using historical controls to compare CHOP and CHOP-R have produced results that are consistent with prospective randomized controlled trials [9,11].

Several other economic analyses comparing CHOP-R with CHOP have been performed in other countries [12–15]. Although all these studies found CHOP-R to be a cost-effective therapy based on standard WTP thresholds, there was variability between ICERs. Specifically, the base case cost per QALY gained was estimated to be $16,400 in France [12], $15,100 to $20,100 in The Netherlands [13], $23,500 in the United States [14], and $13,900 to $19,600 in the UK (all currencies converted to 2006 Canadian dollars using health-specific purchasing power parities [23]) [15]. Examination of cost and QALY results individually suggests that the variability in these results is driven almost entirely by differences in cost estimates, as the health outcomes were similar across all studies. Although this study is based on observational data compared to other published economic evaluations based on clinical trial data, differences in estimated life-years and QALYs tended to be minor enough to be likely explained by differences in study populations, specific treatment protocols, and assumptions regarding long-term survival. Conversely, total cost estimates varied more than threefold across studies for the CHOP arm and more than twofold for the CHOP-R arm [13,15]. The BC cost estimates presented here are within the range of those found in other studies for both arms, although incremental differences between arms tended to be smaller here compared with those reported in other studies, leading to generally smaller ICERs. Potential sources for cost differences include different acquisition costs for rituximab, different distributions among second-line therapy options, different costs associated with second-line therapy, or methodological dif-

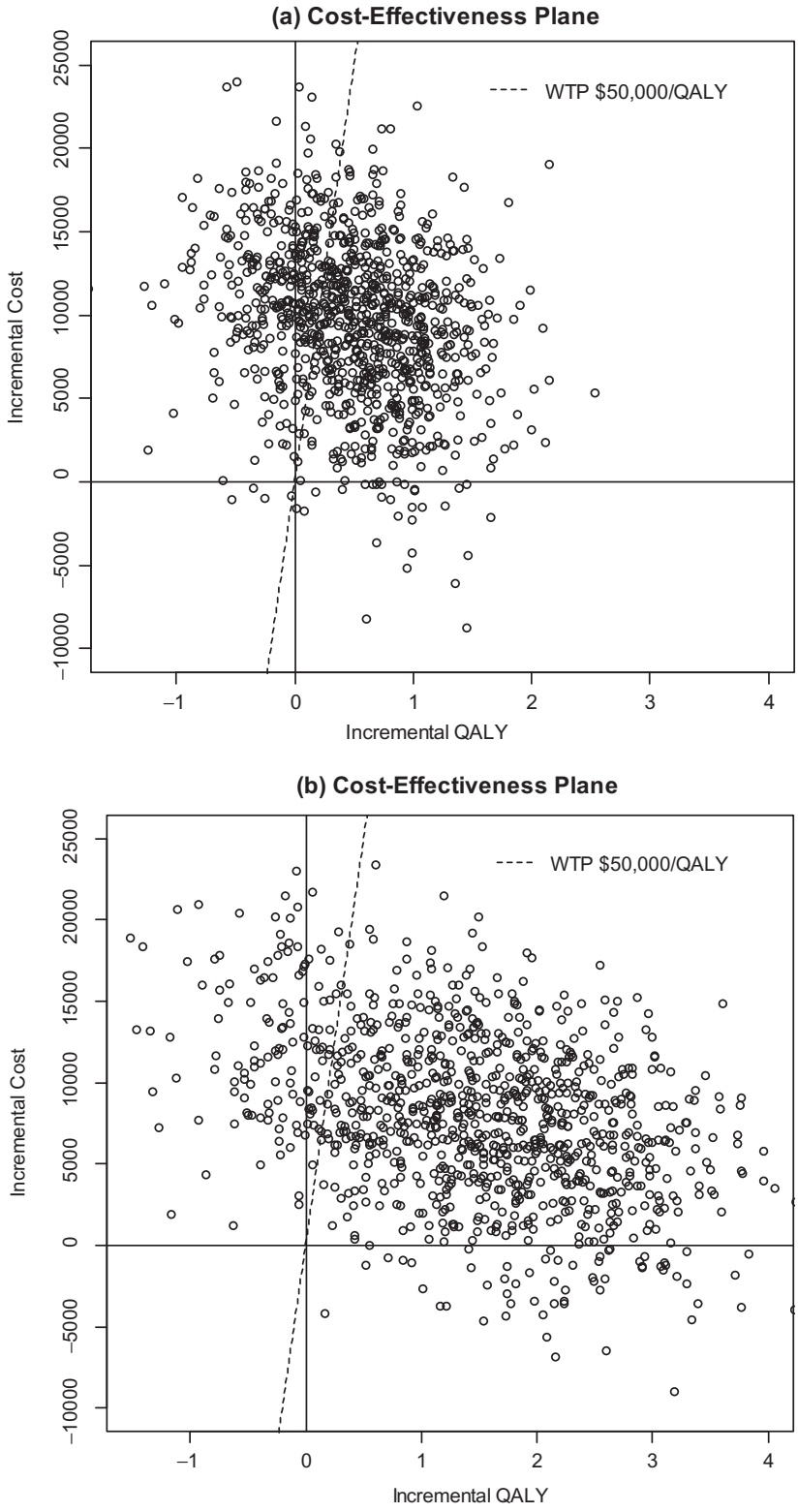

Figure 4 Scatterplot of incremental costs and benefits estimated using probabilistic sensitivity analysis for base-case scenario of 3% discount rate and 15-year time-horizon, for patients (a) <60 years and (b) ≥60 years. WTP, willingness to pay; QALY, quality-adjusted life-year.

ferences such as specific components of direct medical costs included. This variability highlights the importance of repeating economic evaluations for different health systems, as different funding structures could potentially lead to different conclusions in terms of cost-effectiveness.

Conclusion

Using a microsimulation built from observational Canadian data, CHOP-R was found to be a cost-effective alternative to CHOP chemotherapy alone for first-line treatment of DLBCL.

Table 3 Cost-effectiveness results for (a) patients <60 years and (b) patients ≥60 years

	CHOP-R	CHOP	Incremental	Incremental (cost per difference in outcome) ($)
(a)				
Discounted (3%)				
15-year time horizon				
Costs	$46,337	$36,765	$9572	—
Life-years	8.3	7.7	0.6	15,953
Quality-adjusted life-years	6.9	6.4	0.5	19,144
Disease-free life-years	6.8	6.0	0.8	11,965
Undiscounted				
15-year time horizon				
Costs	$46,783	$37,214	$9569	—
Life-years	10.1	9.3	0.8	11,961
Quality-adjusted life-years	8.3	7.7	0.6	15,948
Disease-free life-years	8.4	7.5	0.9	10,632
Discounted (3%)				
5-year time horizon				
Costs	$46,287	$36,623	$9664	—
Life-years	3.9	3.7	0.2	48,320
Quality-adjusted life-years	3.2	3.0	0.2	48,320
Disease-free life-years	2.6	2.3	0.3	32,213
Discounted (3%)				
15-year time horizon: Upper bound CHOP-R cure rate of 0.74				
Costs	$44,859	$36,494	$9157	—
Life-years	8.9	7.8	1.1	8,325
Quality-adjusted life-years	7.3	6.4	0.9	10,174
Disease-free life-years	7.4	6.1	1.3	7,044
(b)				
Discounted (3%)				
15-year time horizon				
Costs	$42,892	$34,968	$8194	—
Life-years	6.2	4.5	1.7	4,820
Quality-adjusted life-years	5.0	3.6	1.4	5,853
Disease-free life-years	5.3	3.4	1.9	4,313
Undiscounted				
15-year time horizon				
Costs	$43,139	$35, 373	$7946	—
Life-years	7.4	5.2	2.2	3,612
Quality-adjusted life-years	6.0	4.2	1.8	4,414
Disease-free life-years	6.5	4.1	2.4	3,311
Discounted (3%)				
5-year time horizon				
Costs	$42,881	$34,948	$7933	—
Life-years	3.0	2.6	0.4	19,833
Quality-adjusted life-years	2.4	2.0	0.4	19,833
Disease-free life-years	2.2	1.6	0.6	13,222

CHOP, cyclophosphamide, doxorubicin, vincristine, and predisone; CHOP-R, CHOP with rituximab.

The cost-effectiveness was most pronounced in individuals aged 60 and older because of improved effectiveness of CHOP-R observed in this age group. Results reported here are qualitatively consistent with studies performed in other jurisdictions using clinical trial data, in which CHOP-R was also found to be cost-effective based on standard WTP thresholds. Thus, all economic analyses performed to date support current practice guidelines in BC regarding the provision of CHOP-R as standard first-line therapy in DLBCL patients.

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