A Canadian economic analysis of U.S. Oncology Adjuvant Trial 9735

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ABSTRACT

Objectives

Recent results of the U.S. Oncology Adjuvant Trial 9735 demonstrated significant disease-free survival and overall survival benefits for docetaxel and cyclophosphamide (TC) compared with doxorubicin and cyclophosphamide (AC) in the adjuvant treatment of operable invasive breast cancer. Based on clinical data from the 9735 study, we evaluated the lifetime cost-effectiveness of TC compared with AC from the perspective of the Canadian publicly funded health care system.

Methods

A Markov model was developed to estimate the incremental cost per quality-adjusted life-year gained and per life-year gained. Monthly survival and risk of disease recurrence up to 7 years were obtained directly from the overall survival and disease-free survival curves in the 9735 study; life-years beyond 7 years were estimated using the average life expectancy of age-matched women in the general Canadian population. Canadian-specific resource utilization and unit costs (in 2008 Canadian dollars) were applied to estimate costs for chemotherapy administration, chemotherapy-related toxicities, recurrence, and adverse events. Health-utility scores and decrements used in the calculation of quality-adjusted life-years were derived from the literature.

Results

The lifetime cost per quality-adjusted life-year gained was $8,251 for TC compared with AC, and the cost per life-year gained was $6,842. The results were robust across a range of sensitivity analyses.

Conclusions

Cost-effectiveness, combined with efficacy and an acceptable safety profile, support the adoption of TC as an alternative to AC in Canadian clinical practice for the adjuvant treatment of operable early breast cancer.

KEY WORDS

Cost-effectiveness, cost–utility, docetaxel, anthracycline, breast cancer, adjuvant chemotherapy

1. INTRODUCTION

Adjuvant chemotherapy with an anthracycline-based regimen is standard practice in Canada for the treatment of operable early breast cancer. However, given improvements in the survival of patients with early-stage breast cancer, concern over long-term side effects—especially anthracycline-associated cardiomyopathy [1–4]—is increasing, highlighting a clinical need for agents or combinations that are both efficacious and more acceptable in their toxicity profiles.

Taxanes such as docetaxel have been shown to be among the most active drugs in the treatment of metastatic breast cancer [5] and have since demonstrated efficacy and improved toxicity profiles in the adjuvant setting [6–10]. Recently, the U.S. Oncology Adjuvant Trial 9735 demonstrated significant improvements in 7-year disease-free survival (81% vs. 75%; hazard ratio: 0.74; $p = 0.033$) and overall survival (87% vs. 82%; hazard ratio: 0.69; $p = 0.032$) for docetaxel and cyclophosphamide (TC) compared with doxorubicin and cyclophosphamide (AC) as adjuvant chemotherapy in women with resected node-positive or high-risk node-negative breast cancer [6].

On the basis of the positive results from the 9735 study, the TC regimen was approved in Canada as an alternative to AC in the adjuvant treatment of operable early breast cancer. This approval has the potential to significantly alter current clinical practice. However, the adoption of TC will also have an incremental impact on health care budgets. Based on the results of the 9735 study, we undertook an economic evaluation to estimate the cost-effectiveness of adjuvant TC for early-stage breast cancer in comparison with standard

care using AC from the perspective of the Canadian publicly funded health care system.

2. METHODS

2.1 Model Design

An economic model developed in Excel (Microsoft Corporation, Redmond, WA, U.S.A.) estimated the incremental cost per quality-adjusted life-year gained and per life-year gained for TC compared with AC in a hypothetical cohort of 1000 women characteristic of those constituting the intention-to-treat population of the 9735 study. Details of the 9735 trial have been published previously [6,7]. Briefly, the study was a phase III prospective comparative randomized clinical trial of 1016 women with operable breast cancer and no evidence of metastatic disease who had undergone complete surgical excision of the primary tumour and were eligible for adjuvant chemotherapy. Patients were randomly assigned to four 3-week cycles of either AC (doxorubicin 60 mg/m^2, cyclophosphamide 600 mg/m^2) or TC (docetaxel 75 mg/m^2, cyclophosphamide 600 mg/m^2) administered by intravenous infusion over 30–60 minutes on day 1 of each 21-day cycle. Among enrolled patients (mean age: 51 years), most (71%) were estrogen receptor– or progesterone receptor–positive (or both), and approximately half (48%) were node-negative.

Our model (Figure 1) used a Markov approach by defining a finite number of mutually exclusive health states between which patients could move according to a set of pre-specified transition probabilities. The model cycle length, dictating the timing of movements between health states, was 1 month. The base-case analysis was conducted for a lifetime horizon. Costs and outcomes beyond 1 year were discounted at 5% annually [11] and are presented from the perspective of the Canadian publicly funded health care system. Costs are presented in 2008 Canadian dollars.

All patients started the model in the "alive on adjuvant chemotherapy" state, where patients in the TC arm of the model receive adjuvant chemotherapy with TC and patients in the AC arm of the model receive adjuvant AC. After 3 months of adjuvant chemotherapy, patients could transition to the "alive and disease-free" state. In each model cycle, patients in each of these alive states either remain there or transition to "dead." For the first 7 years, the proportion of patients dying is based on the disease-free survival curves from the 9735 study (Figure 2) [6]. Overall survival in the 9735 study was based on the intention-to-treat population and was measured from the date of first drug dose to date of death (from any cause) using the Kaplan–Meier method. The proportion of patients transitioning to death is dictated by the inverse of the overall survival curves. Although the survival advantage associated with TC may extend beyond the limited follow-up of clinical trials [12],

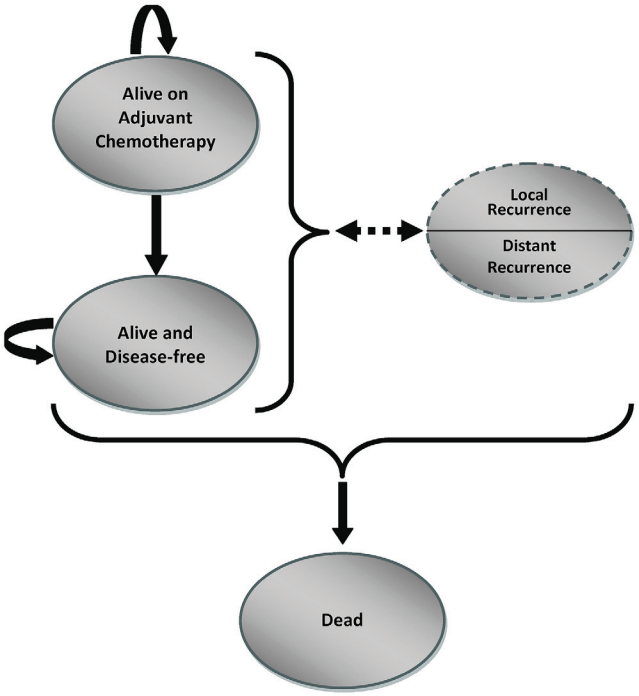

FIGURE 1 *Markov model states and transitions. Patients start in the "alive on adjuvant chemotherapy" state and can transition to "alive and disease-free" after treatment. Patients in either of the "alive" states can experience "local or distant recurrence" based on the disease-free survival curve from the 9735 study. Patients can progress from the "alive" states to the "dead" state each month based on the overall survival curve from the 9735 study.*

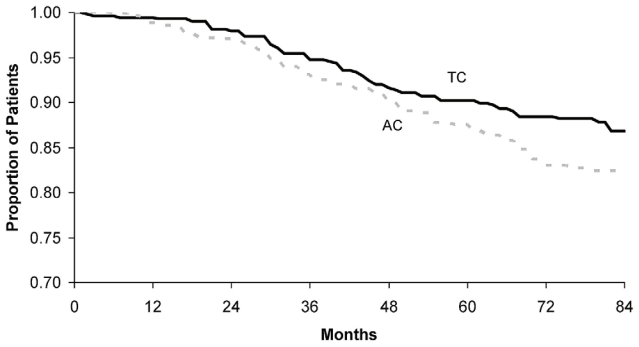

FIGURE 2 *Overall survival from U.S. Oncology Adjuvant Trial 9735 [6]. TC = docetaxel–cyclophosphamide; AC = doxorubicin–cyclophosphamide. Reproduced with permission.*

the analysis conservatively assumed no continued survival benefit for TC beyond 7 years. Rather, life expectancy for patients in both treatment arms was assumed to match that of the general population of Canadian women aged 58 years (that is, 26 years) [13]. Lower estimates of life expectancy were also tested in sensitivity analyses.

In each model cycle, all patients in the alive states are also at risk of disease recurrence or relapse. Because overall survival from the clinical trial aggregated

mortality from all causes (including recurrence), mortality associated with recurrence was not modeled as a health state. Rather, recurrence was incorporated into the model as an event that could occur during any cycle, from the point of treatment initiation to the end of year 7. Treatment-specific incidence of relapse for the first 7 years in the analysis is calculated as the inverse of the 7-year Kaplan–Meier disease-free survival curves from the 9735 study [6]. Because the composite measure of disease-free survival reported by Jones *et al.* included date of first dose until all-cause death, and because transition to "death" is considered separately in the model, the disease recurrence curves used in the analysis were adjusted to remove death. Figure 3 illustrates the disease-free survival curves for TC and AC from the 9735 trial, together with the estimated recurrence curves used in the economic analysis. Beyond 7 years, the analysis assumed no risk of recurrence for patients in either treatment arm. That assumption is conservative, given that additional 8-year data reported by Jones *et al.* suggest a low risk of death or recurrence for TC patients after year 7, with the risk of death or recurrence for AC patients persisting beyond 7 years. [6]

Costs and health consequences were assigned to all patients experiencing recurrence. For that purpose, recurrence was classified as either local or distant based on data from the 9735 study. As reported, recurrences experienced by TC patients were 13.6% local and 86.4% distant; recurrences experienced by AC patients were 18.8% local and 81.2% distant [7].

Utilities and utility decrements used in the calculation of quality-adjusted life-years were derived from the literature. Canadian resource utilization and unit costs were also derived from published literature to estimate the costs of chemotherapy, drug administration, toxicity management, and recurrence. Table I summarizes all input parameters, base-case values, and sources.

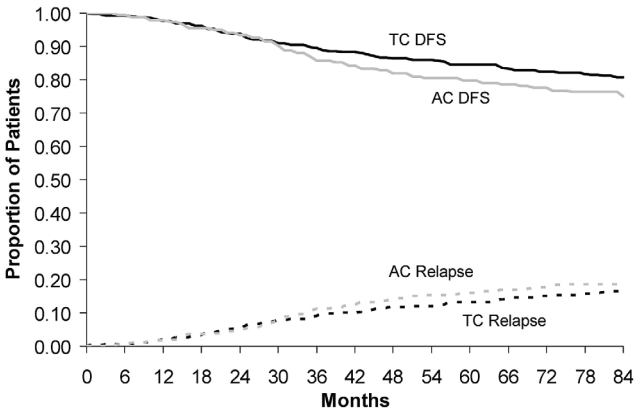

FIGURE 3 Disease-free survival from U.S. Oncology Adjuvant Trial 9735 [6], and estimated disease recurrence. TC = docetaxel–cyclophosphamide; AC = doxorubicin–cyclophosphamide; DFS = disease-free survival. Reproduced with permission.

2.2 Health Utility Assumptions

To simultaneously capture survival and quality of life, outcomes are summarized in terms of quality-adjusted life-years. Utility scores reflecting remission from early breast cancer and post 7-year survival of breast cancer, and utility decrements associated with local and distant recurrence are incorporated into the model based on estimates available in the literature.

A published utility score of 0.79 for patients with early breast cancer in remission was used [14]. That utility score was calculated from European Organisation for Research and Treatment of Cancer quality-of-life questionnaire (QLQ-C030) data for 929 patients in the BCIRG001 clinical trial who had completed chemotherapy and who had not experienced a relapse [10], using a published algorithm [21]. A lack of data for the utility associated with TC and AC chemotherapy precluded the inclusion of chemotherapy utility into the model. The same utility of 0.79 was assumed for the TC and AC groups alike, given that there is no evidence to suggest a difference in utility between the TC and AC regimens. Although utility may be lower during adjuvant chemotherapy, adjustment for lower utility during the adjuvant treatment period would not affect the incremental analysis, because similar decrements would be experienced in both arms.

Utility decrements for local (–0.09) and distant recurrence (–0.29) were calculated from Wolowacz *et al.* [14] by subtracting the respective utility scores reported for local and distant recurrence from the utility score reported for remission. These utility decrements are applied in the model according to the proportion of patients in each treatment arm experiencing local or distant recurrence respectively. Age-specific general population utility scores for patients surviving beyond 7 years were derived from Statistics Canada data [15].

2.3 Health Care Resource Costs

Canadian resource utilization and unit costs were used to estimate the cost of study chemotherapy (including drug and administration costs), treatment for disease monitoring during chemotherapy and afterwards, treatment associated with chemotherapy-related toxicities, and recurrence (Table I). The public payer perspective was taken in the analysis, which includes all direct costs to the health care system. Where applicable, costs were inflated to 2008 Canadian dollars (CA$1 = US$0.77) using the health care component of the consumer price index [18].

The costs for docetaxel, doxorubicin, and cyclophosphamide were derived from the Sunnybrook Health Sciences Centre Drug Formulary [16] and did not include any mark-ups or dispensing fees. No drug wastage was assumed, because excess drug is typically used to treat a subsequent patient.

Chemotherapy administration costs included physician assessment visits, chemotherapy unit visits

TABLE I Summary of key input parameters and assumptions

Parameter	*Base case value*		*References*
	TC	*AC*	
Age at start (median years)	51		Jones *et al.,* 2009 [6]
Monthly survival to 7 years	See Figure 2		Jones *et al.,* 2009 [6]
Life expectancy beyond 7 years (years)	26		Statistics Canada [13]
Monthly disease recurrence to 7 years	See Figure 3		Jones *et al.,* 2009 [6]
Site of recurrence (%)			Jones *et al.,* 2006 [7]
Local	13.6	18.8	
Distant	86.4	81.2	
Utilities and utility decrements			
Utility for disease-free survival			
Within 7 years of treatment	0.79		Wolowacz *et al.,* 2008 [14]
Post 7 years			Wolfson, 1996 [15]
Ages 50–64	0.86		
Ages 65–74	0.84		
Ages 75–84	0.79		
Ages 85–99	0.74		
Utility decrement for local recurrence	–0.09		Wolowacz *et al.,* 2008 [14]
Utility decrement for distant recurrence	–0.29		Wolowacz *et al.,* 2008 [14]
Costs (2008 CA$)			
Chemotherapy drug (per cycle)[a]			SHSC [16]
Docetaxel	1,499.33[b]	—	
Doxorubicin	—	79.80[c]	
Cyclophosphamide	9.66[d]	9.66[d]	
Chemotherapy drug administration (per cycle)			
Physician visits	96.08	96.08	OMHLTC [17]
Chemotherapy unit visit	156.86	79.47	SHSC [18], Cancer Care Ontario
Pharmacist	11.43	7.89	SHSC [18], Cancer Care Ontario

[a] Assumes a body surface area of 1.75 m^2 and no drug wastage.
[b] Assumes 75 mg/m^2 of docetaxel every 3 weeks for 4 cycles and a vial size of 80 mg at a cost of $913.88 ($11.4235 per milligram).
[c] Assumes 60 mg/m^2 of doxorubicin every 3 weeks for 4 cycles and a vial size of 50 mg at a cost of $38.00 ($0.7600 per milligram).
[d] Assumes 600 mg/m^2 of cyclophosphamide every 3 weeks for 4 cycles and a vial size of 1000 mg at a cost of $9.20 ($0.0092 per milligram).
SHSC = Sunnybrook Health Sciences Centre; OMHLTC = Ontario Ministry of Health and Long Term Care; ALT = alanine aminotransferase; ALP = alkaline phosphatase; AST = aspartate aminotransferase.

(nursing time, overhead), pharmacist time, pretreatment drugs for nausea and vomiting, and diagnostic tests. Estimates of chemotherapy unit, nursing, and pharmacist time for each regimen were derived from Cancer Care Ontario; estimates for chemotherapy unit overhead charges, oncology nursing wages, and pharmacist wages were derived from Sunnybrook Health Sciences Centre [16]. Physician costs were derived from the Ontario Schedule of Benefits for Physician Services [17]; the costs of diagnostic tests were derived from the Ontario Schedule of Benefits for Laboratory Services [19].

The base-case analysis included the costs of all grade 3 or 4 hematologic events. The proportions of patients experiencing those toxicities, which include neutropenia, febrile neutropenia, anemia, and thrombocytopenia, were derived for each treatment regimen from the 9735 study [6]. Three long-term fatal toxicities (coronary artery failure, myelodysplastic syndrome, and myelofibrosis) likely related to treatment with AC [6] were conservatively excluded from the base case, but were included in a sensitivity analysis. Inpatient costs associated with the treatment of hematologic and long-term toxicities were derived from Sunnybrook Health Sciences Centre [16].

A recent study by Risebrough *et al.* [20] provided the direct health care costs associated with diagnosis and management of local and distant recurrence in

TABLE I *(Continued)*

Parameter	*Base case value*		*References*
	TC	*AC*	
Pre-treatment medications			SHSC [16]
Oral dexamethasone[e]	6.00	1.40	
Ondansetron[f]	20.96	31.44	
Diagnostic tests (per cycle)			OMHLTC [19], Cancer Care Ontario
Complete blood count	23.28	23.28	
ALT, ALP, AST, bilirubin	10.36	10.36	
Serum creatinine, blood urea nitrogen	5.18	5.18	
Urinalysis	2.59	2.59	
Cardiac function test (per course)[g]		327.75	
Hematologic toxicities (per month)			Jones *et al.,* 2009 [6], OMHLTC [17]
Anemia	6.73	22.30	
Neutropenia	1,085.03	1,019.86	
Thrombocytopenia	14.58	31.96	
Febrile neutropenia	85.24	43.20	
Cost of diagnosing and treating relapse (per relapse)[i]			Risebrough *et al.*, 2007 [20]
Local recurrence	5,074.36	6,493.89	local expert opinion
Distant recurrence	15,649.20	17,352.64	

[e] Assumes 100% of docetaxel–cyclophosphamide patients received 8 mg twice daily for 3 days and 100% of doxorubicin–cyclophosphamide patients received 8 mg pre-chemotherapy and 20% of patients received 4 mg twice daily for 2 days, for a total of 11.2 mg per patient per cycle.

[f] Assumes 100% of docetaxel–cyclophosphamide patients received 2 doses of 8 mg and 100% of doxorubicin–cyclophosphamide patients received 3 doses of 8 mg.

[g] Assumes 1 multiple-gated acquisition scan at baseline for 100% of patients, and a 2nd scan during treatment for 50% of patients, according to Cancer Care Ontario chemotherapy regimen protocol and expert opinion.

[h] Calculated as the proportion of patients experiencing grade 3 or 4 hematologic toxicities for each treatment regimen from U.S. Oncology Adjuvant Trial 9735 multiplied by the unit cost for treating the toxicity, as derived from Sunnybrook Health Sciences Centre.

[i] Calculated from U.S. Oncology Adjuvant Trial 9735 as the proportion of patients experiencing local or distant relapse, multiplied by the unit cost for treating local and distant relapse, determined from Risebrough *et al.,* 2007 [20].

SHSC = Sunnybrook Health Sciences Centre; OMHLTC = Ontario Ministry of Health and Long Term Care; ALT = alanine aminotransferase; ALP = alkaline phosphatase; AST = aspartate aminotransferase.

Canada. The cost estimates reported by those authors were derived from a number of sources (Ontario Health Insurance Plan, Canadian Institute for Health Information [22–24]) and included costs associated with diagnosis, staging, physician visits, surgery, and chemotherapy. The estimates from Risebrough *et al.* were adjusted to reflect the increased costs associated with treating recurrence in patients who had previously received adjuvant treatment with TC and AC. Algorithms for post-adjuvant treatment were provided by an expert oncology and pharmacy panel at The Ottawa Hospital Cancer Centre.

As in Risebrough *et al.,* patients who experienced local noninvasive recurrence were assumed to be treated with surgery. For patients who experienced local invasive recurrence, the panel estimated that 50% of patients would receive an additional course of chemotherapy and that 50% would receive no chemotherapy. For adjuvant TC patients, it was estimated that 100% of patients would receive AC in post-adjuvant treatment of local recurrence; for adjuvant AC patients, it was estimated that 100% of patients would receive TC. For patients who received adjuvant chemotherapy with TC and who experienced distant recurrence, it was estimated that 50% of patients would receive a second course of TC and 50% would receive a course of AC. For patients who received adjuvant chemotherapy with AC and who experienced distant recurrence, it was estimated that 20% of patients would receive a second course of AC and that 80% would receive a course of TC. After progression, 100% of patients, regardless of adjuvant chemotherapy, were expected to receive approximately 6 cycles of chemotherapy with capecitabine. Because the cost of treating recurrences was estimated to be higher for AC patients than for patients in the adjuvant TC arm, the impact on that parameter of alternative assumptions was explored in sensitivity analyses.

2.4 Sensitivity Analyses

A series of one-way sensitivity analyses were performed to explore the effect of changes in key variables and assumptions, including the treatment benefit of TC with respect to overall survival and disease recurrence, life expectancy beyond 7 years, resource utilization and costs, and utility estimates.

Confidence limits for the overall survival curves were not reported in the 9735 study. Alternatively, a sensitivity analysis was conducted by applying a 50% reduction to the difference in overall survival observed between TC and AC at each month. For example, based on the 9735 study, the base case assumed that 87% of TC patients, compared with 82% of AC patients, remained alive at the end of 7 years, but the sensitivity analysis assumed that 84.5% of TC patients, compared with 82% of AC patients, remained alive at the end of 7 years—for example, 87 – [(87 – 82) * 0.5] = 84.5.

For the same reason, the same methodology was used to conduct a similar sensitivity analysis on the benefit of TC with respect to disease recurrence. That is, the sensitivity analysis assumed a 50% reduction in the difference in disease recurrence between TC and AC at each month.

Survival for patients alive at the end of year 7 was assumed to be equal to that of the general population because of a lack of survival data in this patient population. The impact of a shorter life expectancy (20 years vs. 26 years in the base case) was explored.

Several one-way sensitivity analyses were conducted with respect to costs:

- The costs of long-term fatal toxicities observed in the trial were included according to the event rates reported in the 9735 study [6].
- A body surface area of 1.6 m^2 was assumed in the calculation of chemotherapy drug costs. [The base case assumed 1.75 m^2 according to an analysis conducted in breast cancer patients treated with chemotherapy at The Ottawa Hospital Cancer Centre (Verma S. Personal communication. January 2008).]
- To address diversity in cancer centres with regard to the number of cardiac scans performed for patients receiving AC, one sensitivity analysis assumed 1 cardiac scan per patient per course of treatment, and a second assumed 2 scans per patient per course of treatment.
- Costs of local and distant relapse were increased and decreased by 20% from those used in the base case.
- Local and distant relapse costs were assumed to be equal between treatment arms.
- The cost of secondary prophylaxis with granulocyte colony-stimulating factor (G-CSF) was included in the cost of TC. (The base case assumed no prophylactic growth factors because none were used in the clinical trial.)
- A threshold analysis was also conducted to identify the acquisition cost of docetaxel at which the cost per quality-adjusted life-year gained exceeded the thresholds of $30,000 and $50,000, holding all other parameters constant.

Several sensitivity analyses explored the effects of alternative assumptions about utility. One sensitivity analysis used estimates reported by Mansel *et al.* [25] (who reported lower decrements for local and distant recurrence) to explore the utility decrement associated with recurrence; a second used estimates reported by Locker *et al.* [26] (who reported higher estimates for local and distant recurrence). Another sensitivity analysis assumed a utility score of 0.79 for disease-free patients surviving beyond 7 years.

Finally, to reflect the timeframe of the 9735 trial, and because lifetime analysis required assumptions and data from a number of difference sources, we also conducted a sensitivity analysis using a 7-year time horizon.

3. RESULTS

The average life expectancy was 14.64 years for adjuvant TC compared with 14.02 years for adjuvant AC, yielding a gain of 0.62 years of life for patients receiving TC. The TC regimen remained superior to AC after adjusting life-years for quality of life, with a total of 11.88 quality-adjusted life-years per patient for TC and 11.36 for AC—a gain of 0.52 quality-adjusted life-years for TC patients over their lifetime. Table II summarizes the total discounted life-years and quality-adjusted life-years.

Mean total lifetime disease-related costs were $12,840 with TC and $8,579 with AC; the difference in costs was driven primarily by higher drug acquisition costs for TC. Costs associated with chemotherapy accounted for approximately 84% of the total cost in the TC arm and 70% in the AC arm. The next largest contributor to total costs was the cost of relapse, which was 22% lower in the TC arm than in the AC arm. Treatment with TC resulted in a $4,260 increase in total costs per patient (discounted) compared with AC.

TABLE II Lifetime cost-effectiveness[a] of adjuvant docetaxel–cyclophosphamide (TC) versus doxorubicin–cyclophosphamide (AC) in early, operable breast cancer

Variable	*Total costs (CA$) per patient*	*Life-years*	*QALYS*
AC	8,579	14.022	11.359
TC	12,840	14.644	11.875
ICER (CA$)	—	6,842	8,251

[a] All values include 5% annual discounting.
QALYS = quality-adjusted life-years; ICER = incremental cost-effectiveness ratio.

Table II reports incremental cost-effectiveness ratios. In the life-time analysis, cost per quality-adjusted life-year gained was $8,251 (discounted) for those treated with adjuvant TC; cost per life-year gained was $6,842.

3.1 Sensitivity Analyses

Figure 4 reports the results of the one-way sensitivity analyses. With the exception of time horizon, the sensitivity analyses produced results similar to those in the base case, with cost per life-year gained remaining between $2,892 and $13,700, and cost per quality-adjusted life-year gained remaining between $3,600 and $16,356. In the analysis based on the 7-year timeframe of the clinical trial, the cost per quality-adjusted life-year gained was $43,248 for TC; the cost per life-year gained was $36,120 (not shown in Figure 4).

Threshold analyses on the acquisition cost of docetaxel indicated that a per-cycle cost more than 3 times that used in the base-case analysis ($4,498.00 versus $1,499.33) would be necessary to exceed the threshold of $30,000 per quality-adjusted life-year gained, and a cost nearly 5 times that used in the base-case analysis ($7,346.74) would be necessary to exceed a threshold of $50,000 per quality-adjusted life-year gained.

4. CONCLUSIONS

As a result of clinical study 9735, TC is becoming widely adopted in clinical practice as an alternative to AC for the adjuvant treatment of early breast cancer. However, replacement of AC with TC comes at an incremental cost to payers. We undertook an economic evaluation to determine the cost-effectiveness of TC compared with standard AC in the adjuvant treatment of operable early breast cancer. Since the development of this economic evaluation, the TC regimen has been funded across all Canadian provinces. Listing recommendations generally offer few details about the supportive cost-effectiveness analyses submitted for review. From the standpoints of health economics research and decision-making,

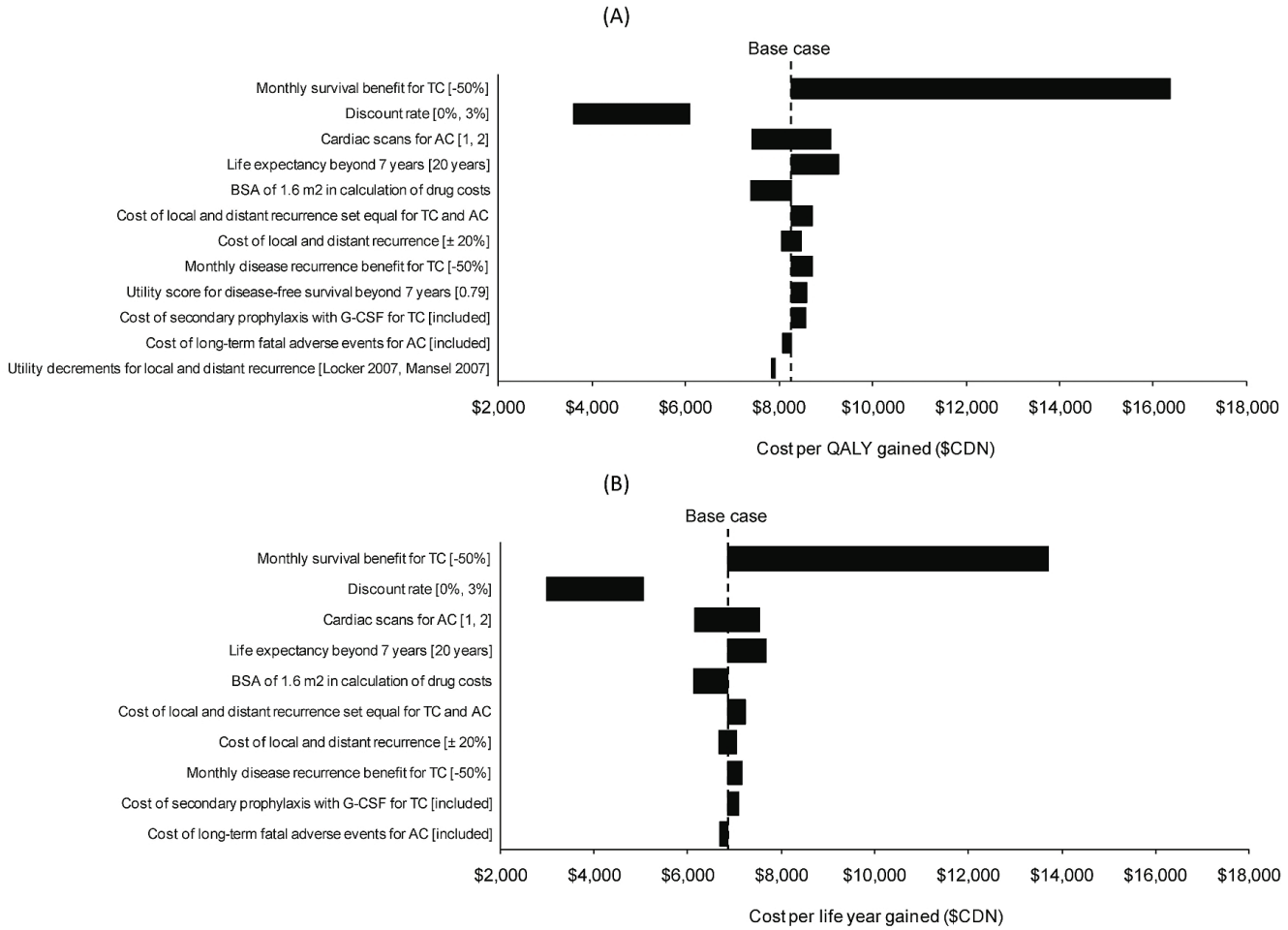

FIGURE 4 Tornado diagram displaying the results of one-way sensitivity analyses for (A) cost per quality-adjusted life-year (QALY) gained, TC (docetaxel–cyclophosphamide) versus AC (doxorubicin–cyclophosphamide), and (B) cost per life-year gained, TC versus AC. Numbers in brackets denote the ranges of values used. BSA = body surface area; G-CSF = granulocyte colony–stimulating factor.

it is important that pharmacoeconomic evaluations supporting the reimbursement of regimens be available in the public domain so that reviewers of cost-effectiveness analyses can compare methodologies used and so that researchers can benchmark for future agents coming onto the market.

In the base-case analysis, adjuvant treatment with TC, compared with that using AC, resulted in a cost per quality-adjusted life-year gained of $8,251 and a cost per life-year gained of $6,842.

Strengths of the present analysis include the use of a "gold standard" comparative randomized trial as a source for the primary outcomes and the use of conservative assumptions. For the base-case analysis, it was conservatively assumed that clinical benefits for TC in terms of overall survival did not extend beyond the 7-year timeframe of the clinical trial. Under scenarios of continued benefit for TC, incremental cost-effectiveness ratios would be expected to improve. In addition, given that the patients receiving TC in study 9735 experienced fewer recurrences than did the patients receiving AC, exclusion of the costs and quality-of-life consequences of subsequent recurrences resulted in lower total costs for AC and higher cost-effectiveness ratios for TC compared with AC than would be expected in actual practice.

There are some important limitations of our analysis. First, the clinical outcomes driving the cost-effectiveness analysis were derived from the 9735 study, which included only patients from the U.S. population, which raises a potential issue regarding the generalizability and applicability of the study results to Canada. For example, is there reason to believe that the overall and disease-free survivals observed in the trial would have been different had the trial been conducted in a Canadian population of patients? Unfortunately, few data in the published literature address this issue. A systematic review of studies comparing health outcomes among patients treated for similar underlying medical conditions in the United States and Canada suggests that there are no consistent differences in health outcomes between the two countries [27]. It may follow that the outcomes observed under the controlled conditions of a clinical trial would be even less heterogeneous, supporting the assumption in the analysis that the findings of the 9735 study are generalizable and relevant to the Canadian population. Nevertheless, clinical trial data specific to a Canadian population would have strengthened the analysis.

Secondly, as in most economic evaluations that combine clinical trial data with data from outside the trial, the lifetime analysis required key assumptions that may represent potential limitations. For example, the analysis relied on the literature and expert opinion to provide estimates of resource use and costs associated with disease recurrence. Although sensitivity analyses suggested that the results were robust to changes in that parameter, the inclusion of real-life data from retrospective analyses or prospective naturalistic studies would strengthen the analysis. Similarly, the availability of utility values for the calculation of quality-adjusted life-years was limited and demonstrated significant heterogeneity. However, we used the best available values, and the results of the sensitivity analyses suggest that the impact of this parameter on long-term results is modest.

Our conclusions are supported by a recent economic evaluation presented by Younis *et al.* at the 2008 San Antonio Breast Cancer Symposium, which found that, compared with AC, TC is cost-effective at a cost per quality-adjusted life-year gained of CA$16,753 over a 10-year time horizon [28]. The cost per quality-adjusted life-year decreased to $6,352 when the time horizon was extended to 25 years in a sensitivity analysis. Younis *et al.* used data from the 9735 trial and an alternative model structure to conduct their evaluation. The authors applied hazard ratios from the 9735 trial to model survival for TC and used data from several external sources to model risk of recurrence and death from recurrence. In contrast, our model was based on the best available evidence and required fewer assumptions, with probability transitions derived exclusively from the 9735 trial. However, the study by Younis *et al.* provides external validation for our model.

The results of the analysis of TC compared with AC as adjuvant chemotherapy in operable breast cancer demonstrate that TC represents a cost-effective use of resources and provide additional support for its use in the management of early-stage breast cancer.

5. ACKNOWLEDGMENTS

Cornerstone Research Group Inc. is an independent research organization and was contracted by Sanofi–Aventis Canada Inc. to develop the health economic model and to conduct the economic evaluation. Sanofi–Aventis was solely responsible for the funding of all components of the study. The authors acknowledge Christine Chin and Helena Koa of Sanofi–Aventis for their support during the study.

6. CONFLICT OF INTEREST DISCLOSURES

LMB and MFT are employees of and shareholders in Cornerstone Research Group Inc., which received funds as consultants to Sanofi–Aventis Canada Inc. SV and SEJ have received honoraria from Sanofi–Aventis Canada Inc. NM and BCFC have received unrestricted funding from Sanofi–Aventis Canada Inc.

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