The cost–utility of adjuvant chemotherapy using docetaxel and cyclophosphamide compared with doxorubicin and cyclophosphamide in breast cancer

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ABSTRACT

Purpose

The adoption of a chemotherapeutic regimen in oncologic practice is a function of both its clinical and its economic impacts on cancer management. For breast cancer, U.S. Oncology trial 9735 reported significant improvements in disease-free and overall survival favoring adjuvant TC (docetaxel 75 mg/m² and cyclophosphamide 600 mg/m² every 3 weeks for 4 cycles) compared with AC (doxorubicin 60 mg/m² and cyclophosphamide 600 mg/m² every 3 weeks for 4 cycles). We conducted an economic evaluation to examine the cost–utility of adjuvant TC relative to AC, in terms of cost per quality-adjusted life year (QALY) gained, given the improved breast cancer outcomes and higher costs associated with the TC regimen.

Methods

A Markov model was developed to calculate the cumulative costs and QALYS gained over a 10-year horizon for hypothetical cohorts of women with breast cancer treated with AC or with TC. Event rates, costs, and utilities were derived from the literature and local resources. Efficacy and adverse events were based on results reported from U.S. Oncology trial 9735. The model takes a third-party payer perspective and reports its results in 2008 Canadian dollars. Costs and benefits were both discounted at 3%.

Results

At a 10-year horizon, TC was associated with $3,960 incremental costs and a 0.24 QALY gain compared with AC, for a favorable cost–utility of $16,753 per QALY gained. Results were robust to model assumptions and input parameters.

Conclusions

Relative to AC, TC is a cost-effective adjuvant chemotherapy regimen, with a cost-effectiveness ratio well below commonly applied thresholds.

KEY WORDS

Breast cancer, adjuvant therapy, chemotherapy, TC chemotherapy, AC chemotherapy, cost–utility analysis

1. INTRODUCTION

The adoption of a chemotherapeutic regimen in oncologic practice is a function of both its clinical and its economic impacts on cancer management. Randomized clinical trials examine potential improvements in cancer-related endpoints such as disease-free survival (DFS) and overall survival (OS), or toxicity differences between two equally effective therapies. From an economic perspective, the costs associated with the delivery of different regimens can vary considerably as a function of the systemic agents involved and the costs of toxicity management. Through cost-effectiveness or cost–utility analyses, those incremental costs should be considered in the context of the observed clinical benefits demonstrated in clinical trials.

Anthracycline- and taxane-based regimens are the backbones of most adjuvant chemotherapy strategies for breast cancer. The AC regimen (doxorubicin 60 mg/m² and cyclophosphamide 600 mg/m² every 3 weeks for 4 cycles) has been a standard chemotherapy option since 1975, and it has often been considered for those with low- to moderate-risk disease who could potentially benefit from adjuvant chemotherapy and for whom more intense regimens may not be appropriate. The U.S. Oncology trial 9735 recently reported significant improvements in DFS and OS favoring adjuvant TC (docetaxel 75 mg/m² and cyclophosphamide 600 mg/m² every 3 weeks for 4 cycles) compared with...
AC for breast cancer\textsuperscript{7,8}. However, the TC regimen is more costly than AC because of the incremental costs of docetaxel (Taxotere: Sanofi–Aventis, Laval, QC). We therefore undertook an economic evaluation to examine the cost–utility of adjuvant chemotherapy with TC relative to AC in terms of cost per quality-adjusted life year (QALY) gained.

2. METHODS

We developed a Markov model\textsuperscript{9–11} to evaluate the cost–utility of TC relative to AC based on two hypothetical cohorts of 1000 women of median age 51 years undergoing adjuvant chemotherapy for breast cancer. The model incorporated transition probabilities, costs, and utility values to estimate the cumulative costs and QALYSs associated with each chemotherapy strategy. The efficacy outcomes were based on the reported results of U.S. Oncology trial 9735\textsuperscript{7,8}.

2.1 U.S. Oncology Trial 9735

Between June 1997 and December 1999, Jones \textit{et al.}\textsuperscript{7,8} randomized 1016 patients with node-negative and -positive breast cancer to 4 cycles of adjuvant AC or TC administered every 3 weeks. The patients (median age: 51 years) in both treatment arms were well balanced with respect to major prognostic factors. Compared with AC, TC was associated with a statistically significant improvement in DFS at a median follow up of 5.5 years [86\% vs. 80\%; hazard ratio (HR): 0.67; 95\% confidence interval (CI): 0.50 to 0.94; \(p = 0.015\)] and 7 years (81\% vs. 75\%; HR = 0.74; 95\% CI: 0.56 to 0.98; \(p = 0.033\)), and also improved OS at the 7-year median follow up (87\% vs. 82\%; HR: 0.69; 95\% CI: 0.50 to 0.97, \(p = 0.032\)). Both regimens were reasonably well tolerated. More febrile neutropenic (FN) episodes (5\% vs. 2.5\%, \(p = 0.07\)) and fewer grade 3 or 4 chemotherapy-induced nausea and vomiting (CINV) episodes (8\% vs. 3\%, \(p\) value not reported) were associated with TC than with AC. A few treatment-related deaths were observed in the AC arm, including 1 case of congestive heart failure (CHF) and 3 cases of myelodysplasia (MDS) or acute myeloid leukemia (AML).

2.2 Markov Model

Our analysis took a Markov approach, defining a fixed number of possible health states\textsuperscript{9–11} (Figure 1). Each health state was assigned a utility value\textsuperscript{12–18} and cost\textsuperscript{14,19–22} (Table 1). All patients entered the model in the Chemotherapy state and transitioned to the Disease-Free state after completion of chemotherapy treatment. Patients could move to other states according to event rates derived from the literature\textsuperscript{23–26,28–30} and the relevant study\textsuperscript{7,8}

2.3 Event Rates

For the AC strategy, the baseline DFS rates used in the model were derived by combining two rates:

- the general mortality rate (death without recurrence) for women with a median age of 51 years, as derived from Canadian life tables\textsuperscript{30}, and
- the breast cancer recurrence rate for patients treated with AC.
TABLE I Costs and utilities used in the model

<table>
<thead>
<tr>
<th>Health states</th>
<th>Cost (CAS)³</th>
<th>Utility</th>
<th>Duration (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease-Free</td>
<td>42/month²⁰²³</td>
<td>0.90¹²¹³</td>
<td></td>
</tr>
<tr>
<td>Life on Chemotherapy</td>
<td>Δ5,299/patient⁶</td>
<td>0.74¹²¹³¹⁸</td>
<td></td>
</tr>
<tr>
<td>Local Relapse</td>
<td>11,535/event²⁰²³</td>
<td>0.70¹²¹³</td>
<td>4³</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.50¹²¹³</td>
<td>4³</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.90¹²¹³</td>
<td>Life</td>
</tr>
<tr>
<td>Distant Relapse</td>
<td>35,230/event²⁰²³</td>
<td>0.60¹²¹³</td>
<td>21²³</td>
</tr>
<tr>
<td>Early adverse events⁴</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CINV</td>
<td>61/event¹⁶</td>
<td>0.85¹⁶</td>
<td>3³</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>17,236/event¹⁹²³</td>
<td>0.47¹⁵</td>
<td>1³</td>
</tr>
<tr>
<td>Late adverse events⁴</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AML/mds</td>
<td>66,015/event²²</td>
<td>0.26¹⁴</td>
<td>9²⁴</td>
</tr>
<tr>
<td>CHF</td>
<td>19,008/event²¹</td>
<td>0.64¹⁷</td>
<td>12²⁵²⁶</td>
</tr>
<tr>
<td>Death</td>
<td></td>
<td>0.00¹²¹³</td>
<td></td>
</tr>
</tbody>
</table>

³ Inflated to 2008 Canadian dollars using the Consumer Price Index²⁷.
⁴ Including costs of managing febrile neutropenia and growth factor support for subsequent cycles: $6,597 for docetaxel–cyclophosphamide; $1,298 for doxorubicin–cyclophosphamide.
⁵ Assumptions.
⁶ Febrile neutropenia or CINV might develop during the 3 months of chemotherapy; AML/mds and CHF might develop any time during the 7 years after chemotherapy.

The recurrence rate was derived by applying the expected relative benefits of first-generation anthracycline-based regimens such as AC to a range of baseline 10-year recurrence risks of 25%–75% in the absence of adjuvant chemotherapy according to menopausal status²⁸, representing the risks posed by nodal status (that is, from node-negative to high-burden node-positive disease). The model structure therefore allows for an assessment of various baseline relapse risks and nodal status for patients treated with adjuvant chemotherapy. In the base case scenario, the 10-year recurrence rates for the AC strategy were based on a hypothetical cohort with a 52% node-positive rate (that is, a 10-year relapse risk of 38% in the absence of adjuvant chemotherapy), as observed in U.S. Oncology trial 9735.⁷,⁸ The sensitivity analysis also examined cohorts with lower and higher relapse risks (25%–75%).

The corresponding recurrence rates for the TC strategy were derived by applying the relative risk for DFS at 7 years’ median follow-up from U.S. Oncology trial 9735 (HR: 0.74; 95% CI: 0.56 to 0.98; p = 0.033) to the recurrence rates used in the AC arm for the initial 7 years after chemotherapy. No carryover benefit for TC relative to AC (that is, HR: 1) beyond the reported median follow-up period was assumed in the base case scenario. Table II lists other event rates and assumptions used in the model.

We incorporated a number of early and delayed chemotherapy-related adverse events based on reported toxicities from U.S. Oncology trial 9735.⁷,⁸
The analysis considered the greater risk of grade 3 or 4 cINV associated with AC (8.0% vs. 3.0%; relative risk: 2.6; range in sensitivity analyses: 1–4) and the greater risk of FN associated with TC (5.0% vs. 2.5%; relative risk: 2.0; range in sensitivity analyses: 1–4).7,8 The base case scenario incorporated secondary prophylaxis with granulocyte colony-stimulating factor (G-CSF) after FN events and assumed no chemotherapy dose adjustments. However, outside of clinical trials, use of TC appears to be associated with higher FN rates of approximately 26% (range: 10%–46%) without and 6% (range: 0%–7%) with primary G-CSF prophylaxis.7,31,32,33 Primary prophylaxis with G-CSF is also sometimes used with the TC regimen in clinical practice, because it is recommended for chemotherapeutic regimens associated with a FN risk greater than 20%.34 We therefore examined two additional scenarios:

- 20% FN rate, with secondary G-CSF prophylaxis after FN events, and
- primary G-CSF prophylaxis for all patients, with a 6% breakthrough FN rate despite the prophylaxis.

The analysis also assumed that AC is associated with an increased risk of AML or MDS (0.4%; range in sensitivity analyses: 0.0%–1.0%)24,29 and CHF (0.4%; range in sensitivity analyses: 0.0%–1.0%)21,25,26 over the 7-year median follow-up.

### 2.4 Utilities and Costs

Each health state was assigned a utility weight derived from the literature to permit an estimation of the QALY gains12–18 (Table 1). A utility weight of 1 represents perfect health; lower utilities denote worse quality of life. A utility of 0 represents death. During treatment, the base case scenario assumed comparable utilities between TC and AC (0.74 vs. 0.74) in the absence of the adverse events modelled. However, in the sensitivity analyses, we also examined the effect of varying the utilities (+20%) between TC and AC.

The upfront costs associated with adjuvant chemotherapy and the downstream costs associated with adverse events (cINV, FN, CHF, and AML or MDS), follow-up, and relapses (Table 1) were all considered14,19,20–22. Upfront costs were derived from local unit costs at the QEII Health Sciences Centre, Halifax, Nova Scotia, Canada, as per our previous work.23 Included were the costs associated with

- chemotherapy drug (AC or TC) acquisition per the recommended dose and schedule for an average person with a body surface area of 1.7 m²;
- supportive care medications;
- diagnostics, including laboratory tests and pre-chemotherapy cardiac evaluations; and
- health resource utilization.

All costs were converted into monthly costs or one-time event-driven costs. We also examined the effects of varying the costs after relapse (±20%) for the AC and TC regimens. For example, the costs of treating relapses may be lower after TC than after AC because palliative chemotherapy treatment with taxanes may not be indicated after adjuvant TC. A third-party direct payer perspective was considered. Using the Consumer Price Index–Health Care Component35, costs were adjusted to 2008 Canadian dollars. Costs and benefits were both discounted at 3% annually.9,11

### 2.5 Validation and Sensitivity Analyses

The DFS and OS rates generated by the model in the base case analysis (with a 52% node-positive rate) were compared with those reported by U.S. Oncology trial 9735.7,8 To test the plausibility of the cost–utility results over a reasonable range of uncertainty, the robustness of the model to changes in key parameters was examined primarily in a series of one-way sensitivity analyses and alternative scenarios. We examined a number of scenarios that are more aligned with clinical practice than with the clinical trial setting: for example, node-negative status (that is, lower relapse risk), older age (60 years), lower utility during TC treatment compared with AC (−20%), a high FN rate after TC treatment (+10% or +20%), and primary G-CSF prophylaxis for the TC regimen. A probabilistic sensitivity analysis with a cost-effectiveness acceptability curve9–11 based on plausible arbitrary ranges for input parameters was also conducted. The impact of the analysis horizon on the cost–utility estimate was examined for comparison with other studies that considered a longer horizon.

### 3. RESULTS

Adjuvant TC was associated with an estimated upfront cost of $6,597 compared with $1,298 for AC, for an incremental cost difference of $5,299 per patient. This incremental cost reflects primarily the higher drug acquisition cost associated with TC ($5,850 vs. $269), because the costs of supportive care medications ($76 vs. $192), diagnostic investigations ($223 vs. $417), and human resources utilization ($448 vs. $421) were not substantially different for the treatments. At a 10-year horizon, the net incremental cost was $3,960 per patient when the effects of recurrences avoided and the various adverse event profiles and rates associated with the two strategies had been accounted for.

At a 10-year horizon, TC was associated, relative to AC, with an incremental gain of 0.24 QALYS per patient. Survival outcomes estimated by the model were consistent with the results of U.S. Oncology trial 9735.7,8. The model predicted incremental absolute DFS and OS benefits of 6% and 4% for TC compared with AC.
with AC (82% vs. 76% and 88% vs. 84% respectively) compared with the 6% and 5% differences observed in the clinical trial (81% vs. 75% and 87% vs. 82% respectively). The slightly more conservative survival estimates from the model partly reflect assumptions in base case recurrence risk and background mortality that differed slightly from those in the actual clinical trial.

At a 10-year horizon, the cost–utility of TC relative to AC was $16,753 per QALY gained. These cost–utility results were robust to the key assumptions and input data used in the model (Figure 2). A lower upfront cost for TC (that is, a lower acquisition cost for docetaxel) resulted in increasingly favorable cost–utility estimates. Conversely, a lower base case recurrence risk (that is, node-negative disease) was associated with higher cost–utility of $26,047 per QALY gained. The higher FN rates associated with the TC regimen resulted in less favorable cost–utility estimates, although still within commonly acceptable cost–utility thresholds. Those cost–utilities were $21,333 and $33,510 per QALY gained at FN rates of 10% (that is, 4 times the FN risk with AC) and 20% (that is, the recommended FN threshold for primary G-CSF prophylaxis) respectively, and $43,693 per QALY if primary G-CSF was administered in all patients, assuming a 6% breakthrough FN rate. Other chemotherapy-related adverse events and variations in the utilities for TC and AC during treatment had little impact on the cost–utility results.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>Range tested</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline recurrence risk at 10 years</td>
<td>38%</td>
<td>75% 25%</td>
</tr>
<tr>
<td>Costs, relapse based on chemotherapy</td>
<td>TC&lt;AC</td>
<td>TC&lt;AC TC&gt;AC</td>
</tr>
<tr>
<td>Costs, chemotherapy (TC and AC)</td>
<td>Table i</td>
<td>-20% +20%</td>
</tr>
<tr>
<td>Carry over benefit (years 8–10)</td>
<td>No</td>
<td>Yes Lost</td>
</tr>
<tr>
<td>Discounting</td>
<td>3%</td>
<td>0% 5%</td>
</tr>
<tr>
<td>Costs, all</td>
<td>Table i</td>
<td>-20% +20%</td>
</tr>
<tr>
<td>Costs, chemotherapy (Δ TC–AC)</td>
<td>$5,299</td>
<td>Δ20% Δ20%</td>
</tr>
<tr>
<td>Febrile neutropenia (TC:AC risk ratio)</td>
<td>2</td>
<td>1 4</td>
</tr>
<tr>
<td>Relapse distribution (years 1–5:1–10)</td>
<td>75%</td>
<td>85% 65%</td>
</tr>
<tr>
<td>Chemotherapy utilities</td>
<td>TC&lt;AC</td>
<td>TC&gt;AC TC&lt;AC</td>
</tr>
<tr>
<td>AML/MDS (AC absolute risk)</td>
<td>0.4%</td>
<td>1.0% 0%</td>
</tr>
<tr>
<td>CHF (AC absolute risk)</td>
<td>0.4%</td>
<td>1.0% 0%</td>
</tr>
<tr>
<td>Utilities</td>
<td>Table i</td>
<td>+10% -10%</td>
</tr>
<tr>
<td>Costs, relapse</td>
<td>Table i</td>
<td>+20% -20%</td>
</tr>
<tr>
<td>Survival after Distant Relapse</td>
<td>1.75 Year</td>
<td>3 Year 1 Year</td>
</tr>
<tr>
<td>Relapse proportion (Local: All)</td>
<td>20%</td>
<td>10% 30%</td>
</tr>
<tr>
<td>Recurrence risk after Local Relapse</td>
<td>X 2</td>
<td>X 4 X 1</td>
</tr>
<tr>
<td>CINV (AC:TC risk ratio)</td>
<td>2.6</td>
<td>4 1</td>
</tr>
<tr>
<td>Synchronous Distant and Local Relapse</td>
<td>20%</td>
<td>30% 10%</td>
</tr>
<tr>
<td>Costs, follow-up</td>
<td>Table i</td>
<td>-20% +20%</td>
</tr>
<tr>
<td>Age</td>
<td>50 Years</td>
<td>40 Years 60 Years</td>
</tr>
<tr>
<td>Costs, adverse events</td>
<td>Table i</td>
<td>-20% +20%</td>
</tr>
</tbody>
</table>

**Figure 2** Sensitivity analysis. The y axis shows the parameters and the ranges tested in the sensitivity analysis; the x axis reflects the resulting cost–utility value in thousands of Canadian dollars per quality-adjusted life year (QALY) gained. The dashed vertical line represents the mean cost–utility result (C$16,753/QALY gained), and each bar shows the range of the cost–utility estimate for each parameter tested. For each parameter tested, the lower and higher cost–utility values in the bar respectively reflect the cost–utility estimates for the first and second columns of the range tested. The order of variables from top to bottom, with corresponding longer-to-shorter bars in the tornado plot, reflects the variables with more-to-less impact on the cost–utility results. TC = docetaxel–cyclophosphamide; AC = doxorubicin–cyclophosphamide; AML/MDS = acute myeloid leukemia or myelodysplastic syndrome; CHF = congestive heart failure; CINV = chemotherapy-induced nausea and vomiting.
The cost–utility results were also more favorable at longer horizons, with a cost–utility of $6,352 per qaly gained at a 25-year horizon (Figure 3). Limited probabilistic sensitivity analysis suggested that the likelihoods of TC being cost-effective relative to AC at the commonly used $50,000 and $100,000 per qaly gained willingness-to-pay thresholds were 91% and 97% respectively (Figure 4).

4. DISCUSSION AND CONCLUSIONS

Economic analyses—including cost-effectiveness and cost–utility studies—have become an integral component in the evaluation of new interventions or treatments, including adjuvant chemotherapy for breast cancer. The World Health Organization defines favorable cost-effectiveness based on the Gross Domestic Product (GDP) per capita in various jurisdictions:

- Highly cost effective: <GDP/capita
- Cost-effective: 1–3 times GDP/capita
- Not cost effective: >3 times GDP/capita

The cost–utility of $16,753 estimated in this analysis per qaly gained for TC relative to AC compares favorably with other oncology interventions and falls well below the Canadian GDP-per-capita threshold of $38,975 and the commonly reported thresholds of $50,000–100,000 per qaly in the United States and Canada, and of £20,000–£30,000 per qaly in the United Kingdom.

The cost–utility of TC relative to AC has been examined in two other studies, although neither examined the effects of primary G-CSF prophylaxis or of high FN rates for the TC regimen. Verma et al. in an abstract presentation also from a Canadian perspective, reported a 0.516 qaly gain and a $4,260 higher cost for TC relative to AC for a cost–utility of $8,251 per qaly gained at a lifetime horizon, compared with our estimate of $6,352 per qaly gained at a 25-year horizon. As in our study, their results were sensitive to the horizon examined, with a cost–utility of $43,248 per qaly gained at a 7-year horizon. In a recent publication from a Chinese perspective, Liubao et al. reported an incremental gain of 0.41 QALYS and 10,116 Chinese yuan (approximately CAS$1,547) in higher costs associated with TC relative to AC at a lifetime horizon (40 years), with an incremental cost-effectiveness ratio of 24,305 yuan (approximately CAS$3,716) per qaly gained. At a willingness-to-pay threshold of 86,514 yuan (approximately CAS$13,173) per qaly, the probability of TC being cost-effective was 90%. The most sensitive parameter in the model was the cost of primary chemotherapy treatment in the TC arm. However, comparisons to international results must be made cautiously, given the potential for substantial structural differences between health care systems.

Economic evaluations for other docetaxel-based adjuvant chemotherapy regimens for breast cancer have also been conducted. Compared with FAC (5-fluorouracil–doxorubicin–cyclophosphamide), TAC (docetaxel–doxorubicin–cyclophosphamide) administered with and without prophylactic G-CSF was found to be a cost-effective strategy in a number of jurisdictions. From a Canadian health care system perspective, Au et al. reported cost–utility ratios of $46,003 and $18,506 per qaly gained with and without prophylactic G-CSF at a 10-year horizon, and Mittmann et al. reported cost–utility ratios of $13,044 and $6,848 per qaly gained at a lifetime horizon. From a U.K. National Health Service perspective, Wolowacz et al. reported cost–utilities...
of £20,432 and £18,188 per QALY gained, with and without prophylactic filgrastim, at a 10-year horizon. From a Korean perspective, Lee et al. \cite{45} reported cost–utilities of 12,119,561 Korean won (approximately €9,926) and 8,885,794 won (approximately €7,277) per QALY gained, with and without prophylactic G-CSF, at a lifetime horizon.

Compared with FEC100 (5-fluorouracil–epirubicin–cyclophosphamide), FEC-D (5-fluorouracil–epirubicin–cyclophosphamide–docetaxel) was also found to be a cost-effective strategy \cite{23,46}. From a Canadian health care perspective, Younis et al. \cite{23} reported a cost–utility of $14,612 per QALY at a 10-year horizon, and from a French hospital perspective, Marino et al. \cite{46} reported a cost–utility of €9,665 per QALY at a 5-year horizon.

Collectively, the consistent favorable results observed in the foregoing economic evaluations from various health care jurisdictions provide compelling evidence that adjuvant chemotherapy regimens incorporating docetaxel—FEC-D, TAC, TC—are cost-effective strategies for women with breast cancer.

The cost–utility estimate for TC relative to AC depends on the incremental upfront cost difference between the two chemotherapeutic regimes. In our evaluation, TC was associated with higher estimated upfront costs relative to AC ($6,597 vs. $1,298), with an incremental cost difference of $5,299 per patient, primarily reflecting higher drug acquisition costs ($5,850 vs. $269). Should docetaxel become generic, lower upfront TC costs would result in an even more favorable cost–utility estimate, as observed in our study and the study by Liubao et al. \cite{41}. The cost–utility estimate of TC relative to AC is also affected by the horizon examined (that is, the analysis timeframe). Economic analyses attempt to capture all clinical benefits by modeling clinical outcomes beyond the relatively short duration of follow-up in most clinical trials. Although cost–utility estimates generally improve with a longer analytic horizon as the cumulative benefits (that is, the QALY gains) accrue for patients without recurrences, longer horizons also involve more uncertainty with regard to the magnitude of clinical benefit. In our study, and in the study by Verma et al. \cite{40}, the cost–utility estimate for TC was within commonly accepted thresholds \cite{36,37} at a 7-year horizon (corresponding to the median follow-up reported in U.S. Oncology trial 9735 \cite{7,8}).

In our primary scenario, the cost–utility estimate of $16,753 per QALY gained was based primarily on outcomes from U.S. Oncology trial 9735. We examined cohorts with 52% node-positive rates and a median age of 51 years. We assumed twice the FN risk with TC than with AC and comparable base case utilities for both regimes during the treatment period. However, in clinical practice, TC chemotherapy is perhaps more commonly used in older patients and in those with node-negative disease, and it is associated with higher FN rates and possibly with lower treatment-related utility \cite{27,31–33}. Our cost–utility estimates in those practical scenarios, and in circumstances in which primary G-CSF prophylaxis is considered for all patients, were less favorable than those in the primary analysis based on clinical trial data, although they remained within commonly used cost–utility thresholds \cite{36,37}.

Our study has limitations. As with all economic analyses, the results may not be generalizable to all other health care jurisdictions because of variation in upfront or downstream costs (or both) for chemotherapeutic drugs and cancer management. However, the very favorable cost–utility estimates observed in our study and in the study by Liubao et al. \cite{41} from the perspectives of the Canadian and the Chinese health care systems respectively, make it unlikely that TC would not be a cost-effective strategy in other jurisdictions. To test the robustness of our model, we performed mainly one-way sensitivity analyses (as opposed to probabilistic sensitivity analyses) because of a lack of evidence-based probability distributions for many of the parameters and because of the difficulties arising from defining arbitrary distributions \cite{9–11}. Our results were nevertheless robust to a wide range of uncertainty around the point estimates for key parameters examined in the model.

To summarize, adjuvant chemotherapy with TC is both more effective and more costly than AC, with favorable cost–utility estimates relative to commonly applied cost-effectiveness thresholds. For women with breast cancer, TC is an acceptable standard adjuvant chemotherapy option based on its favourable clinical and economic evaluations.

5. ACKNOWLEDGMENTS

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6. CONFLICT OF INTEREST DISCLOSURES

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