Cost-effectiveness of Switching to Exemestane Versus Continued Tamoxifen as Adjuvant Therapy for Postmenopausal Women With Primary Breast Cancer

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BACKGROUND. Sequential tamoxifen/exemestane therapy reportedly improves disease-free survival in women with primary breast cancer compared with continued tamoxifen therapy. The objective of the current study was to assess the cost-effectiveness of switching to exemestane after 2 to 3 years of tamoxifen versus continued tamoxifen in postmenopausal women with primary breast cancer for a total of 5 years of adjuvant therapy.

METHODS. A Markov model based on the Intergroup Exemestane Study (IES) population compared switching to exemestane versus continued tamoxifen for 2.5 years of therapy and 5 years of postadjuvant therapy follow-up. Disease progression and hazards ratios (HR) for recurrence and survival were determined from datasets (IES and the Surveillance, Epidemiology, and End Results program of the National Cancer Institute) and from the published literature. An expert panel validated treatment patterns, outcomes, and resource utilization. Direct medical costs were included based on published sources. Cost-effectiveness ratios were determined, and extensive sensitivity analyses were conducted.

RESULTS. Exemestane was found to be more effective than tamoxifen alone with regard to disease-free survival (2.6% absolute improvement), life-years gained (0.1028 LY), and quality-adjusted life-years gained (0.1195 QALY), at an additional cost of Can$2889 per person over 7.5 years. Incremental cost-effectiveness ratios were Can$28,119/LY gained and Can$24,185/QALY gained. The model was most sensitive to distant recurrence HR but was robust to variations in clinical, cost, and utility parameters.

CONCLUSIONS. Switching to adjuvant exemestane after 2 to 3 years of tamoxifen is cost-effective in postmenopausal women with primary breast cancer. ***Cancer* 2007;110:499–508.** © *2007 American Cancer Society.*

KEYWORDS: exemestane, tamoxifen, primary breast cancer, adjuvant therapy, cost-effectiveness, cost-utility.

Breast cancer is the most common type of cancer in women worldwide, with more than 1 million new cases diagnosed every year.[1] Evidence from phase 3 clinical trials suggests that aromatase inhibitors (AI) improve disease-free survival in patients with breast cancer and reduce the occurrence of thromboembolic and gynecologic events compared with tamoxifen in patients with primary breast cancer.[2–7] In postmenopausal women with primary breast cancer, a consistent improvement in clinical outcome has been observed when AIs are used as adjuvant treatment.[8] However, AIs

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may increase the occurrence of musculoskeletal events, including arthralgia, osteoporosis, and fractures.[8]

The Intergroup Exemestane Study (IES)[6] demonstrated that switching to the AI exemestane after 2 to 3 years of tamoxifen significantly improved disease-free survival compared with continuing tamoxifen for a total of 5 years (hazards ratio [HR] of 0.68, 95% confidence interval [95% CI], 0.56–0.82 [$P < .001$]) in postmenopausal women with resected unilateral invasive breast cancer with estrogen receptor (ER)-positive or unknown ER status. Based on these results, Canadian treatment guidelines have recommended exemestane as a standard of care after 2 to 3 years of tamoxifen for a total of 5 years of hormone therapy in postmenopausal women with hormone receptor-positive breast cancer.[9] Due to the higher cost of exemestane, a cost-effectiveness study was required to evaluate costs versus benefits and potential risks. The objective of the current study was to determine the incremental cost-effectiveness and cost-utility, from a government payer perspective, of switching to exemestane after tamoxifen therapy versus continuing tamoxifen in postmenopausal women with primary hormone receptor-positive breast cancer.

MATERIALS AND METHODS

Study Design

Incremental cost-effectiveness (cost per life-years [LY] gained) and cost-utility (cost per quality-adjusted life-years [QALY] gained) analyses were conducted to compare switching to exemestane therapy after 2.5 years of tamoxifen versus continued tamoxifen for a total of 5 years of hormonal therapy from a Canadian provincial payer perspective. As recommended by economic evaluation guidelines,[10] the treatment comparator was the current standard of care (adjuvant tamoxifen). Because women remain at a high risk of cancer recurrence for up to 10 years after initial diagnosis,[11] outcomes were evaluated to 10 years after the initial diagnosis but excluded the first 2.5 years of tamoxifen treatment that were common to both treatment comparators (total analysis of 7.5 years). The study was conducted from a Canadian public healthcare perspective. Costs and outcomes beyond 1 year were discounted at 5%.[10]

Population

The analysis used a hypothetical cohort of postmenopausal women from the IES population.[6] Women were assumed to be age 64 years at the time of model entry, and diagnosed with completely resected unilateral invasive breast cancer with ER-positive disease or unknown ER status. At the time of cohort entry, all women had received tamoxifen therapy (mean of 2.5 years) and had no evidence of breast cancer recurrence. The model cohort was representative of a typical cohort of postmenopausal women receiving tamoxifen for primary breast cancer in the Canadian setting with respect to age, lymph node status, histologic type, hormone receptor status, and the typical tamoxifen dose of 20 mg/day, according to an expert panel. However, compared with the IES population, fewer patients in Canada generally undergo a mastectomy (30% vs 50% in IES),[12] whereas more patients would have received adjuvant chemotherapy in Canada (approximately 50–60% of patients vs 32% in IES).

Model Overview and Assumptions

A Markov model with 6-month cycles (Fig. 1) was created in TreeAge Pro 2005 (TreeAge, Williamson, MA). The total time horizon was 7.5 years. Transition states were disease free; discontinuation due to adverse events (AEs); local, contralateral, and distant recurrence; and death (from breast cancer or not related to breast cancer [intercurrent death]). Disease progression was assumed to occur at an average of 6 months after the diagnosis of distant recurrence. Other clinical events including second primary non-breast cancer, osteoporosis, fracture, hypercholesterolemia, thromboembolism, and cardiac ischemic events were included in the model but were not considered as health states because they were assumed to have no impact on AI therapy or subsequent breast cancer-related treatments. For both treatment strategies, after a treated local or contralateral recur-

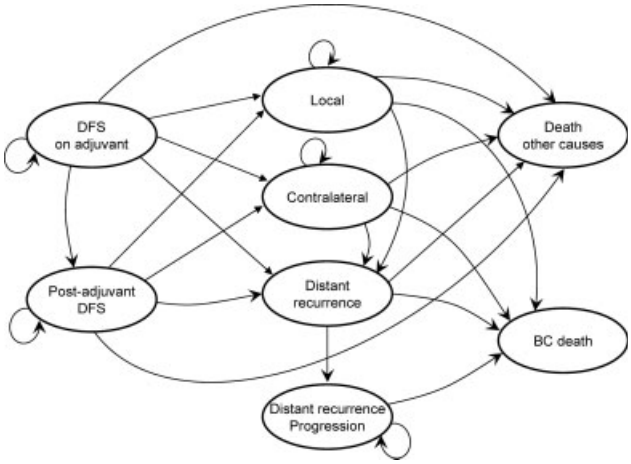

FIGURE 1. Markov model. DFS indicates disease-free survival; BC, breast cancer.

rence, therapy was switched to another AI, letrozole, although other scenarios were considered in the sensitivity analysis. It was assumed that AI therapy continued after the emergence of a second primary nonbreast cancer, but was discontinued after distant recurrence and the patient was treated appropriately for the metastases (systemic chemotherapy/letrozole hormonal therapy/palliative care). It was conservatively assumed that there was no additional recurrence benefit (no carryover effect) associated with exemestane within 5 years after the completion of the adjuvant therapy.

An expert panel of 4 Canadian oncologists validated the treatment patterns, outcomes, and resource utilization used in this model.

Transition Probabilities

Discontinuation due to AEs

Probabilities for discontinuation due to AEs were derived from an updated analysis of IES trial data after a median follow-up of 40 months.[13] The dropout rate due to AEs was 6.3% for exemestane treatment over 40.4 months, and was 5.2% for tamoxifen treatment over 39.1 months (6-month probabilities of .0094 and .0080, respectively).

Cancer recurrence

For the first 48 months, transition probabilities for local, contralateral, and distant recurrence were derived from an updated analysis of the published IES data demonstrating fewer recurrences with exemestane than tamoxifen over a median follow-up of 32.8 months (local: 34 vs 43; contralateral: 8 vs 25; and distant: 137 vs 197).[6] Tamoxifen probabilities were derived by determining event rates within each 6-month timeframe (Table 1). Exemestane recurrence probabilities were obtained by multiplying tamoxifen probabilities (Table 1) by HRs derived from Kaplan-Meier analyses over the duration of therapy in the IES study (local HR of 0.76 [95% CI, 0.49–1.19]; contralateral HR of 0.32 [95% CI, 0.15–0.72]; and distant HR of 0.70 [95% CI, 0.56–0.86]). Based on expert opinion, it was assumed that the rate of developing distant recurrence after a local or contralateral recurrence was twice the rate reported in the IES for those without a previous recurrence.

After 48 months, probabilities were extrapolated from Kaplan-Meier curves of the IES data using linear regression based on historic data. To reflect lower recurrence rates found by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) trial[14] in the 5 years after the completion of adjuvant therapy, recurrence rates were reduced by 40% in that timeframe, and were assumed to be identical for tamoxifen and exemestane (HR of 1.0).[14]

Surgery and chemotherapy costs associated with an invasive and a noninvasive recurrence are different. Because local and contralateral recurrences reported in the IES were not classified as invasive or noninvasive, the proportions of invasive recurrences found in the Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial[7] were applied to this analysis. As a consequence, 36.5% of local recurrences were estimated to be invasive for both treatments, 90% of contralateral recurrences were estimated to be invasive for tamoxifen, and 64% of local recurrences were estimated to be invasive for exemestane.

Intercurrent death

Intercurrent death was defined as death not related to breast cancer. In the first 48 months, probabilities for intercurrent death (Table 1) were derived from the IES dataset (59 deaths for exemestane vs 52 deaths for tamoxifen). The exemestane rate was determined by multiplying the tamoxifen rate by the HR for exemestane (HR of 0.93; 95% CI, 0.64–1.34). After 48 months, age-adjusted, 6-month mortality

TABLE 1
Tamoxifen Transition Probabilities Derived From the Intergroup Exemestane Study[6]

	No. of events/No. at risk (%)			
Months	Local recurrence	Contralateral recurrence	Distant recurrence	Intercurrent death
6	6/2354 (0.255)	1/2351 (0.043)	21/2345 (0.896)	6/2355 (0.255)
12	7/2289 (0.306)	6/2283 (0.263)	34/2276 (1.494)	6/2300 (0.261)
18	7/2191 (0.319)	5/2178 (0.230)	42/2171 (1.935)	8/2209 (0.362)
24	6/1968 (0.305)	3/1950 (0.154)	30/1932 (1.553)	14/1991 (0.703)
30	7/1588 (0.441)	7/1578 (0.444)	26/1556 (1.671)	9/1610 (0.559)
36	4/1125 (0.356)	1/1115 (0.090)	25/1100 (2.273)	7/1143 (0.612)
42	3/646 (0.155)	0/636 (0.000)	9/626 (1.439)	5/657 (0.761)
48	3/329 (0.912)	2/321 (0.623)	10/321 (3.120)	4/336 (1.192)

rates were based on age-standardized, all-cause mortality excluding breast cancer obtained from Statistics Canada for women ages 68–71.5 years. This age group was selected assuming that the age of women starting the cohort was similar to those in the IES trial (age 64 years), with death rates for ages 64 to 67 years taken from the IES trial.

Death related to breast cancer

Annual breast cancer-related mortality rates were not available from the IES trial. Rates were based on mortality data after local, contralateral, and distant breast cancer recurrence from the Surveillance, Epidemiology, and End Results (SEER)[15] registry database, a breast cancer database covering 26% of the U.S. population (1991–2002), with the assumption that mortality rates after recurrence are similar in Canada and the U.S. (Table 2).

Adverse Events

AEs were extracted from the Canadian exemestane product monograph[13] and IES trial publication.[6] Criteria for including an AE in the model were based on the following: a cumulative incidence >1%, a significant difference between exemestane and tamoxifen ($P \leq .05$)[6] or clinically important differences determined from the product monograph,[13] and a suspected significant impact on treatment costs. Based on these criteria, osteoporosis, fractures, hypercholesterolemia, thromboembolism, and cardiac events were included. All thromboembolic events were considered to be deep vein thromboses. Other AEs were excluded from the model unless symptoms were severe enough to require discontinuation and were captured in the discontinuation due to AE health state.

Compared with tamoxifen, exemestane was associated with a higher rate of osteoporosis (5.2% vs 2.9%), fractures (4.2% vs 3.1%), hypercholesterolemia (3.5% vs 1.9%), and cardiac events, including myocardial infarction, angina, and myocardial ischemia (2.1% vs 1.2%).[13] Tamoxifen was associated with a higher rate of thromboembolism (2.4% vs 1.0%).[13] The 6-month AE rates were obtained by dividing the overall proportion of patients with the event by the median follow-up time per drug (40.4 months for exemestane and 39.1 months for tamoxifen) and multiplying by 6 months.

Breast Cancer Utilities

Utilities for recurrences, terminal-stage cancer, and second primary nonbreast cancer were obtained from a number of published sources. Assumptions were made for missing data (Table 2). Recurrence-related utility inputs were based on a study using a standard gamble technique with U.S. and U.K. women ages 55 to 70 years with breast cancer.[16] Disease-free survival had a utility of 0.959, regardless of therapy and remission time after recurrence. Utility of distant recurrence was 0.432, assuming that most patients received chemotherapy. Terminal-stage utility (0.288) was based on a study using a time trade-off technique.[17] Disutility of second primary nonbreast cancer (−0.109) was obtained from Weinstein and Schiff.[18]

Resource Utilization and Cost

Resource utilization was based on IES data[6] and expert panel (Table 2). Only direct medical costs were included, in 2004 Canadian dollars (Can$1 = U.S.$0.85 for the week of January 15–19 2007). Non-2004 costs were inflated to 2004 using the medical component of the Canadian Consumer Price Index.[19]

The frequency of recurrence events was determined from the IES trial and the costs of the recurrences were determined from published sources.[20–26] In those patients without a recurrence (disease-free survival) costs included follow-up visit, medical tests, and bone mineral density scan based on expert panel. To monitor bone density loss, we assumed that the bone mineral density scan was conducted every 2 years with tamoxifen treatment and yearly with exemestane treatment based on expert opinion. Costs for AI-related AEs, breast cancer recurrence, second primary nonbreast cancer, and death are summarized in Table 2.

For AEs, the costs were those of alendronate treatment for osteoporosis (intermediate cost compared with etidronate and residronate),[27] atorvastatin treatment for hypercholesterolemia (the most commonly prescribed 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor in Canada),[27] outpatient low-molecular-weight heparin for deep vein thrombosis (thromboembolism),[28] acute myocardial infarction as a proxy for cardiac ischemic events,[29] and published estimates for fractures.[24] It was assumed that patients discontinuing therapy due to AEs had 1 extra physician visit to monitor AEs at an additional cost of Can$89.

Analyses

The incremental cost per LY gained and cost per QALY gained were determined for tamoxifen versus exemestane. One-way sensitivity analyses for clinical inputs, utilities, and costs were varied from their base case value over clinically relevant ranges. HRs were varied over their 95% CIs. Costs were varied by 50% to 150% of base case values, except for the cost

TABLE 2
Model Inputs

Parameter	Input	Source
Mortality rates		
Local recurrence, mo		National Cancer Institute[15]
≤30	0.0861	
>30	0.0226	
Contralateral recurrence, mo		
≤30	0.0107	
>30	0.0107	
Distant recurrence, mo		
6	0.4491	
7–30	0.1966	
31–60	0.0792	
>60	0.0138	
Breast cancer utilities		
Disease-free survival	0.959	Sorensen et al., 2004[16]
Local or contralateral BC (<1 y)	0.816	Sorensen et al., 2004[16]
Remission/stable disease after local or contralateral BC (>1 y)	0.959	Assumption
Distant recurrence (prior to progression)	0.432	Assumption
Distant cancer (after progression)	0.432	Sorensen et al., 2004[16]
Terminal stage (last 3 mo of life)	0.288	de Haes et al., 1991[17]
Disutility of second primary non-BC	−0.109	Weinstein and Schiff, 1983[18]
Death	0	
Cost estimates (2004 Can$)		
Disease-free survival/stable disease		
Physician visit* (once/6 mo)	89	OHIP[25,26]
Bone mineral density scan	183	OHIP[26]
Local recurrence (first 6 mo) (per episode)		
Noninvasive	4672	
Diagnostic and staging	263	Will et al., 2000[21]
2 physician visits†	177	OHIP[25,26]
Surgery and treatment‡	4232	Will et al., 1999[23]; CIHI[24]; and OHIP[26]
Invasive	12,644	
Diagnostic and staging	263	Will et al., 2000[21]
Physician visits†	177	OHIP[25,26]
Surgery and treatment‡	4232	Will et al., 1999[23]; CIHI[24]; and OHIP[26]
Chemotherapy§	7972	Trudeau et al., 2005[22]
Contralateral recurrence (first 6 mo) (per episode)		
Noninvasive	8404	
Diagnostic and staging	263	Will et al., 2000[21]
2 physician visits†	177	OHIP[25,26]
Surgery and treatment‖	7965	Will et al., 1999[23]; CIHI[24]; and OHIP[26]
Invasive	16,792	
Diagnostic and staging	263	Will et al., 2000[21]
Physician visits†	177	OHIP[25,26]
Surgery and treatment¶	8380	Will et al., 1999[23]; CIHI[24]; and OHIP[26]
Chemotherapy§	7972	Trudeau et al., 2005[22]
Distant recurrence (for 6 mo) (per episode)		
First 6 mo after recurrence	11,994	
Diagnostic and restaging	1054	Will et al., 2000[21]
Monthly physician visits†	531	OHIP[26]
Pharmacologic therapy (chemotherapy or letrozole therapy) until disease progression (for 6 mo)#	10,409	Verma and Rocchi 2003[20]
More than 6 mo after recurrence	14,928	
Chemotherapy**	9363	Verma and Rocchi 2003[20]
Diagnostic and restaging (progression)	721	Verma and Rocchi 2003[20]
Palliative care (for 6 mo)	4844	Verma and Rocchi 2003[20]
Second primary non-BC (per 6 mo)	20,487	
Initial diagnosis and treatment	18,060	Evans et al., 1995[42]; Maroun et al., 2003[43]; Pinilla, 1998[44]
Per 6-mo follow-up	2427	Evans et al., 1995[42]; Maroun et al., 2003[43]; Pinilla, 1998[44]
Death from BC (terminal care for last 3 mo of life)	20,139	Verma and Rocchi 2003[20]

(*continued*)

Table 2
(Continued)

Parameter	Input	Source
Death from other causes (intercurrent death)	5743	Verma and Rocchi 2003[20]
Adverse events		
Osteoporosis (alendronate 10 mg/day at Can$1.1057/day for 6 mo)††	231	ODBF[27]
Hypercholesterolemia (atorvastatin 20 mg/day at Can$2.20/day for 6 mo)††	402	ODBF[27]
Cardiac event (acute myocardial infarction) (per episode)	8303	Mittmann et al., 2005[29]
Thromboembolism (deep vein thrombosis) (per episode)	263	Boucher et al., 2003[28]
Fracture (per episode)	1450	CIHI[24]
Discontinuation due to an adverse event (per episode)	89	OHIP[25,26]
Monthly drug cost		
Tamoxifen (20 mg/day, Can$0.35/day)††	11.71	ODBF[27]
Exemestane (25 mg/day, Can$4.95/day)††	165.62	ODBF[27]
Lezotrole/anastrozole (once daily, Can$4.95/day)††[i]	165.62	ODBF[27]

BC indicates breast cancer, OHIP, Ontario Health Insurance Plan; CIHI, Canadian Institute for Health Information; ODBF, Ontario Drug Benefit Formulary.

* Each routine follow-up oncologist visit (Can$49.25) is associated with a liver function test, a serum calcium assessment, and a complete blood count (Can$39.33).

† Physician visit in oncology clinic for surgery (Can$88.58 each).

‡ Weighted average based on 90% of patients undergoing modified radical mastectomy (Can$3824), 10% undergoing partial mastectomy with lymph node dissection (Can$3514). An additional 10% of patients undergoing surgery also received radiation (Can$4388).

§ Average of current cost for chemotherapy after surgery (range, Can$4428–Can$14,618, including costs of supportive therapy, adverse events, and administration).

‖ Weighted average based on 25% of patients undergoing modified radical mastectomy (Can$3824), and 75% undergoing lumpectomy (Can$3495). All patients underwent radiation treatment (Can$4388).

¶ Same as above, plus axillary lymph node dissection (Can$415).

Weighted average based on 75% of patients receiving chemotherapy for metastatic breast cancer at Can$13,376 and 25% of patients receiving hormonal therapy with letrozole (Can$1509).

** Approximately 70% of patients receiving chemotherapy at Can$13,376.

†† Includes 10% markup and 1 professional fee per 3-month dispensing period.

of discontinuation due to AEs (which varied between Can$0 and the cost of a 3.5-day hospitalization for breast cancer [Can$4162])[24]; bisphosphonate treatment (ranged from least [Can$63] to most expensive [Can$341])[27,30]; atorvastatin treatment (between minimum recommended daily dose [10 mg; Can$323] and maximum dose [80 mg; Can$423])[27,31]; and thromboembolism treated on an inpatient basis (Can$7563).[24,32] Utility values were varied by ±20% of base case values. Two-way analyses were performed on parameters with the largest impact on cost-effectiveness ratios as determined by 1-way sensitivity analyses.

RESULTS

Base Case Results

Five years after the completion of adjuvant therapy (total of 7.5 years), the model predicted that switching to exemestane increased the disease-free survival by an absolute 2.6% over continuing treatment with tamoxifen (80.9% vs 78.3%). Discounted LYs gained were found to be greater with exemestane (Table 3), with an increment of 0.1028 years over tamoxifen. Exemestane therapy increased the total discounted medical costs by Can$2889 per patient over 7.5 years. Discounted incremental costs per patient included Can$4099 for medication, Can$565 for medical care associated with disease-free survival, and Can$126 for AEs. Cost savings were generated for reduced cancer recurrences (Can$1680) and other cancers (Can$221) per person in the exemestane group. The incremental cost-effectiveness ratio (ICER) for exemestane was Can$28,119 per LY gained.

Exemestane increased QALYs by 0.1195, resulting in an incremental cost-utility ratio (ICUR) of Can$24,185 per QALY (Table 3).

Sensitivity Analyses

Varying the probabilities for different outcomes resulted in a range of ICERs from Can$13,081 to Can$55,606 per LY gained, and a range of ICURs from Can$10,774 to Can$49,089 per QALY gained. No threshold values were found. Variations of >10% of the base case are reported in Figure 2. Incremental ratios demonstrated the greatest range with variations in HR for distant recurrence (Can$16,574–55,606 per LY and Can$14,102–49,089 per QALY), followed by HR intercurrent death (Can$22,195–45,853 per LY and Can$19,919–35,065 per QALY), disease recurrence after treatment (Can$13,081–28,119 per LY and Can$10,774–24,185 per QALY), and local recurrence (Can$25,525–33,066 per LY and Can$22,111–28,059 per QALY). Varying the cost of exemestane also was found to have considerable impact on the ICER and ICUR (Can$4723–43,716 per LY and Can$4063–37,600 per QALY). Incremental results also demonstrated a 10% change from the base case when varying the cost for

TABLE 3
Base Case Results for a Breast Cancer Patient Switching to Exemestane Versus Continued Tamoxifen

	Discounted base cse analysis (Undiscounted)		
Parameter	**Exemestane**	**Tamoxifen**	**Incremental (Exemestane-Tamoxifen)**
Clinical outcomes per patient			
LYs	6.2559 (6.8462)	6.1531 (6.7291)	0.1028 (0.1171)
QALYs	5.8989 (6.4523)	5.7794 (6.3171)	0.1195 (0.1352)
Average medical cost per patient (Can$)			
Drug cost	$4630 (4736)	$531 (544)	$4099 (4192)
Disease-free survival	$2134 (2343)	$1569 (1719)	$565 (624)
Recurrence	$9515 (10,634)	$11,195 (12,430)	−$1680 (−1796)
Adverse events	$319 (338)	$193 (204)	$126 (134)
Other cancers	$238 (245)	$459 (471)	−$221 (−226)
Total cost	$16,836 (18,296)	$13,947 (15,368)	$2889 (2928)
Discounted incremental ratios			
ICER			Can$28,119/LY
ICUR			Can$24,185/QALY

LY indicates life-year gained; QALY: quality-adjusted life-year gained; ICER, incremental cost-effectiveness ratio; ICUR, incremental cost-utility ratio.

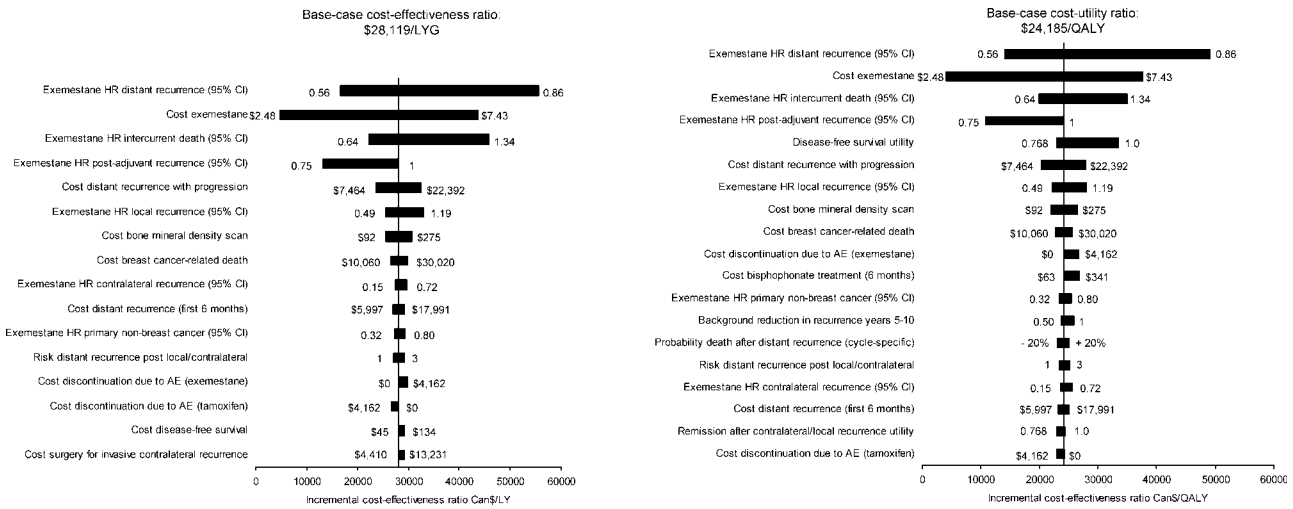

FIGURE 2. One-way sensitivity analyses for the incremental cost-effectiveness and cost-utility of switching to exemestane in breast cancer patients receiving tamoxifen. LYG indicates life-year gained; HR, hazards ratio; 95% CI, 95% confidence interval; AE, adverse event; LY, life-year; QALY, quality-adjusted life-years.

distant recurrence (Can$23,677–32,543 per LY and Can$20,364–27,990 per QALY) and disease-free survival utility (Can$22,850–$33,580 per QALY). The model was robust to variations with regard to other clinical, cost, and utility parameters.

Two-way sensitivity analyses for selected parameters resulted in ICUR variations between Can$9925 and Can$71,137 per QALY. When both the cost of distant recurrence with disease progression (95% CI, 50–150%) and the probability of distant recurrence (95% CI, 0.56–0.86) were varied, ICURs ranged from Can$9925 to Can$52,016 per QALY. Varying the disease-free survival utility with exemestane probabilities for posttreatment disease recurrence, distant recurrence, or intercurrent death produced ICURs of Can$9973 to Can$33,579 per QALY, Can$13,358 to Can$71,137 per QALY, and Can$18,882 to Can$51,631 per QALY, respectively.

DISCUSSION

The results of the current study demonstrated that switching from tamoxifen to exemestane was more effective than continued tamoxifen treatment with regard to disease-free survival (+2.6%), LYs gained (+0.1028 years), and QALYs gained (+0.1195 years),

at an additional cost of Can$2889 per person over 7.5 years. Incremental cost-effectiveness ratios for the base case were Can$28,119 per LY gained and Can$24,185 per QALY, indicating that switching to exemestane after 2.5 years of tamoxifen treatment is cost-effective, all by conservatively assuming there was no carryover effect of exemestane in the 5 years after the discontinuation of adjuvant therapy.

The type, timing, and sequencing of hormonal therapy are critical decisions to be made by oncologists when treating patients with breast cancer. The clinical benefits of switching to exemestane observed in the IES[6] and modeled over 7.5 years translated into partial cost offset of the higher cost of exemestane. Exemestane prevented breast cancer and other cancer recurrences, resulting in savings of Can$1901 over 7.5 years compared with continued tamoxifen treatment. Despite the increased risk of osteoporosis with exemestane, all AEs resulted in a modest cost increment of Can$126. The ICUR generated for exemestane was well below the commonly accepted thresholds of Can$50,000 per QALY in Canada.[33]

Other economic evaluations in Canada, the U.S., and the U.K. have consistently reported that AI strategies are cost-effective in the adjuvant treatment of early breast cancer, with ICURs below the widely accepted country-specific cost-effectiveness thresholds (<U.S.$50,000 per QALY, and <U.K.£20,000).[8,34–40] A recent Canadian analysis of the ATAC trial over a lifetime horizon reported that 5 years of anastrozole monotherapy compared with 5 years of tamoxifen resulted in an ICUR of Can$28,000 per QALY, assuming a constant reduction of recurrences with anastrozole for up to 10 years.[38] Another Canadian study that compared anastrozole with sequential tamoxifen/exemestane therapy assuming a carryover benefit of 5 years found that switching to exemestane was more cost-effective than continuing treatment with anastrozole (ICUR of Can$7683).[39] Based on the ATAC, MA-17, and IES trials, a European analysis concluded that sequential tamoxifen/exemestane therapy provided a significantly lower ICUR compared with anastrozole monotherapy or extended letrozole therapy (<U.S.$40,000 for a patients aged 65 years).[36] Finally, exemestane was associated with an ICER of U.K.£19,170 per QALY in a British analysis assuming no carryover benefit.[37] After this study, the National Institute for Health and Clinical Excellence (NICE) recommended sequential tamoxifen/exemestane as an alternative treatment of postmenopausal women with primary ER-positive invasive breast cancer.[37] Consistent with previous findings, the results of the current study support the cost-effectiveness of exemestane (ICUR of Can$24,185 per QALY), with the conservative assumption of a 2.5-year treatment effect with no carryover benefit, suggesting that the benefits of exemestane may have been underestimated. Our alternate analysis including this carryover effect (25% reduction in disease recurrence in the 5 years after adjuvant therapy based on extrapolation of the IES dataset) resulted in an ICER and ICUR of Can$13,081 per LY and Can$10,774 per QALY gained, respectively.

It is interesting to note that the daily cost disparity between tamoxifen and exemestane used in the current analysis is wider than it appears to be in the U.S. In Canada, the daily cost of exemestane is approximately 14 times higher than generic tamoxifen, whereas in the U.S., the cost disparity is 3 times higher than brandname tamoxifen and 6 times higher than generic tamoxifen. Therefore, in the U.S., the incremental treatment cost per person may be less than in Canada, making treatment with exemestane even more favorable.

Most cost-effective models included endometrial cancer, thromboembolism, and fractures,[37–39] in addition to ischemic cerebrovascular disorders[37,38] and vaginal bleeding.[37,39] A number of drug-related AEs were included in the current study based on incidence, clinical significance, potential cost impact, and the availability of data.[13] They translated into only modest cost increments (Can$126) for exemestane over tamoxifen. Due to the absence of sufficient resource utilization data in the IES trial, costs for gynecologic symptoms for tamoxifen were not included. Their exclusion, despite an increased number of gynecologic interventions reported in patients who were treated with tamoxifen in the ATAC trial,[41] biases the analysis against exemestane.

The results of the current study should be considered in light of the possible limitations of the model. The current analysis was based on data from a clinical trial, which may not reflect real-world practice. However, modeled treatment patterns and resource utilization were validated by an expert panel. The hypothetical model cohort, based on the IES population,[6] may differ from the Canadian population. It is estimated that approximately 50% to 60% of patients would have received adjuvant chemotherapy in Canada, compared with 32% reported in the IES population; fewer patients (30%) in Canada generally undergo a mastectomy, compared with 50% reported in the IES.[12] Data from beyond the duration of the clinical trial were extrapolated in the model. There were limited data regarding specific parameters such as distant recurrence rates after local invasive recurrences or treating patients after disease recurrence while they were receiving an AI. Assumptions

were made (which generally were conservative and in favor of the least expensive treatment, tamoxifen), and sensitivity analyses revealed that sequential tamoxifen/exemestane therapy continued to be cost-effective (<Can$50,000 per QALY) under most conditions.

The current study model, based on a conservative approach, suggests that sequential tamoxifen/exemestane therapy is a cost-effective treatment for postmenopausal women with primary breast cancer. This study reinforces the recent recommendations in Canada to fund the sequential use of tamoxifen/exemestane as a standard of care for postmenopausal women with ER-positive breast cancer or breast cancer of unknown ER status.

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