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ORIGINAL ARTICLE

Economic evaluation of hormonal therapies for postmenopausal women with estrogen receptor–positive early breast cancer in Canada

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ABSTRACT

Background

Aromatase inhibitor (AI) therapy has been subjected to numerous cost-effectiveness analyses. However, with most AIs having reached the end of patent protection and with maturation of the clinical trials data, a re-analysis of AI cost-effectiveness and a consideration of AI use as part of sequential therapy is desirable. Our objective was to assess the cost-effectiveness of the 5-year upfront and sequential tamoxifen (TAM) and AI hormonal strategies currently used for treating patients with estrogen receptor (ER)–positive early breast cancer.

Methods

The cost-effectiveness analysis used a Markov model that took a Canadian health system perspective with a lifetime time horizon. The base case involved 65-year-old women with ER-positive early breast cancer. Probabilistic sensitivity analyses were used to incorporate parameter uncertainties. An expected-value-of-perfect-information test was performed to identify future research directions. Outcomes were quality-adjusted life-years (QALYS) and costs.

Results

The sequential TAM–AI strategy was less costly than the other strategies, but less effective than upfront AI and more effective than upfront TAM. Upfront AI was more effective and less costly than upfront TAM because of less breast cancer recurrence and differences in adverse events. In an exploratory analysis that included a sequential AI–TAM strategy, AI–TAM dominated based on small numerical differences unlikely to be clinically significant; that strategy was thus not used in the base-case analysis.

Conclusions

In postmenopausal women with ER-positive early breast cancer, strategies using AIs appear to provide more benefit than strategies using TAM alone. Among the AI-containing strategies, sequential strategies using TAM and an AI appear to provide benefits similar to those provided by upfront AI, but at a lower cost.

KEY WORDS

Breast cancer, cost-effectiveness, tamoxifen, aromatase inhibitors

1. INTRODUCTION

About 75% of all incident breast cancers occur in postmenopausal women, and approximately 80% of those breast cancers express the estrogen receptor (that is, they are ER-positive)[1]. Recurrence and death from ER-positive breast cancer can be effectively reduced through estrogen suppression or antagonism. It is estimated that each year in Canada, 7320 ER-positive breast cancers will occur in women 65 years of age or older[2].

A number of large randomized controlled trials have shown that, in postmenopausal women with ER-positive breast cancer, the use of aromatase inhibitors (AI) either upfront or after initial treatment with tamoxifen is associated with a statistically significant reduction in the risk of recurrence and, in some cases, an improvement in overall survival[3,4]. A recently published meta-analysis[5] of breast cancer outcomes in adjuvant trials of AI versus tamoxifen (TAM) considered two cohorts: specifically, trials comparing 5 years of an AI with 5 years of TAM, both starting soon after surgery[4,6]; or trials comparing 5 years of upfront TAM with TAM therapy switched after 2–3 years to 2–3 years of an AI (for a total of 5 years of hormonal therapy in both groups)[7–9]. The first cohort comprised 9856 patients with a mean 5.8 years of follow-up. At

5 years, AI therapy was associated with an absolute 2.9% [standard error (SE): 0.7%] decrease in recurrence (9.6% for AI vs. 12.6% for TAM, $2p < 0.001$) and a nonsignificant absolute 1.1% (SE: 0.5%) decrease in breast cancer mortality (4.8% for AI vs. 5.9% for TAM, $2p = 0.1$). The second cohort comprised 9015 patients with a mean 3.9 years of follow-up. At 3 years from treatment divergence (that is, approximately 5 years after starting hormonal treatment), sequential therapy with an AI was associated with an absolute 3.1% (SE: 0.6%) decrease in recurrence (5.0% for AI vs. 8.1% for TAM from divergence, $2p < 0.001$) and an absolute 0.7% (SE: 0.3%) decrease in breast cancer mortality (1.7% for AI vs. 2.4% for TAM from divergence, $2p = 0.02$). The meta-analysis concluded that recurrence rates are significantly lower with AIs than with TAM, either as initial upfront therapy or after 2–3 years of TAM[5]. Consequently, practice guidelines recommend that all such women receive AI at some point in their adjuvant therapy[10].

Therapy with AI has already been subjected to numerous cost-effectiveness analyses from the Canadian perspective[11–14]. However, many of the analyses used assumptions that the matured clinical data do not support, including the assumption that differences in disease-free survival will translate into improvements in overall survival. Furthermore, most AIs have now reached the end of patent protection and are available from generic manufacturers at substantially reduced cost. It is therefore desirable to repeat the cost-effectiveness analyses to identify the optimal strategy for postmenopausal women with ER-positive early breast cancer.

The latest guidelines include recommendations for extended treatment with TAM beyond 5 years, but no data for AIs beyond 5 years (either upfront or as part of sequential strategies) are currently available; trials are ongoing[10]. Here, we report the results of a cost-effectiveness analysis, from the Canadian health care perspective, of several 5-year hormonal therapy strategies (upfront and sequential TAM and AI therapies) currently being used in patients with ER-positive early breast cancer.

2. METHODS

2.1 Treatment Strategies

We compared three treatment strategies: two upfront therapies (5 years of TAM, 5 years of AI) and a sequential treatment [TAM for 2 years followed by AI for 3 years (TAM–AI)]. In an exploratory analysis, we also compared sequential AI for 2 years followed by TAM for 3 years (AI–TAM).

2.2 Model

We constructed a state-transition model to simulate lifetime health profiles and to compare treatment strategies in a cohort of 65-year-old postmenopausal women with ER-positive early breast cancer. During each yearly cycle, patients faced the possibility of progression to more advanced stages, of adverse events (AEs), or of death from other causes (Figure 1). Early breast cancer patients might develop a contralateral tumour, locoregional recurrence, or distant metastasis.

Hormonal therapies increase the risk of AEs, including stroke, cardiac events, endometrial cancer, thromboembolism, fractures, and arthralgia. The effects of each AE were considered separately. Transient AEs—such as thromboembolism, fractures, and arthralgia, which have a short-term cost–utility and mortality impact—were tracked in individual health states for 1 year and subsequently grouped into a post-short-term AE health state. Chronic AEs—such as stroke, cardiac events, and endometrial cancer—were tracked using separate health states to incorporate their long-term management costs, disutilities, and elevated risks of death over and above the breast cancer risks for recurrence or death. We used data from the medical literature (Table I) to assign cost and utility estimates ("QALY weights") to each health state over a lifetime time horizon. Costs and health effects were discounted at a common rate of 5%.

2.3 Assumptions

We made a few simplifying assumptions when building the Markov model. First, to make the sequential AI–TAM strategy from its single trial comparable with the meta-analysis data, we assumed that the sequential AI–TAM and upfront AI strategies have equal risks of recurrence. That assumption was based on results from the Breast International Group (BIG) 1-98 trial[3], which showed no difference in recurrence between the two strategies after 5 years. Second, we combined the contralateral tumour and locoregional recurrence health states into one health state. Third, we treated the AI drug class as a group without reference to a specific drug. The latter assumption took

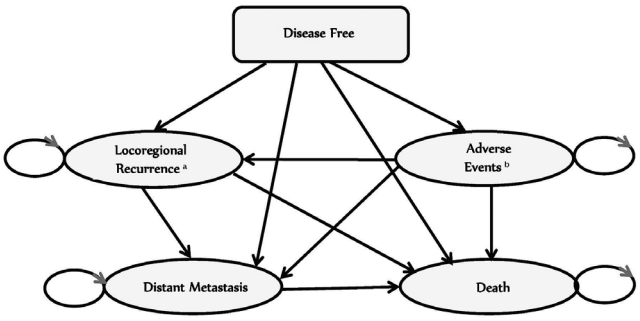

FIGURE 1 Markov model used in the analysis. [a] Includes contralateral tumour. [b] Adverse events of two types, with separate health states, are considered in the model: short-term events (thromboembolism, fractures, arthralgia) and chronic events (stroke, cardiac events, endometrial cancer).

TABLE I Mortality rates, costs, and utilities

Variable	*Base case*	*Low*	*High*	*Sources*
Mortality rates				
All hormone strategies	0.1797	0.138	0.196	Mouridsen, 2004[15]
Adverse events				
Thromboembolic event	0.200	0.173	0.360	Lee *et al.,* 2003[16], Anderson *et al.,* 1991[17]
Any cardiac event	0.1226	0.0912	0.0750	Askoxylakis *et al.,* 2010[18], Parkash *et al.,* 2007[19]
Fracture	0.217	0.166	0.232	Bentler *et al.,* 2009[20], Smektala *et al.,* 2008[21], Kannegaard *et al.,* 2010[22], Martinez *et al.,* 2003[23]
Endometrial cancer	0.032	0.010	0.062	Martinez *et al.,* 2003[23], Susini *et al.,* 2007[24], Cuzick *et al.,* 2010[25]
Stroke	0.129	0.074	0.167	Askoxylakis *et al.*, 2010[18]
Costs (2011 CA$)				
No events	693	478	716	Will *et al.,* 2000[26]
Breast cancer events				
Locoregional recurrence				
Year 1	10,840	7,489	13,657	Will *et al.,* 2000[26]
Year 2 onward	1,228	859	1,596	Will *et al.,* 2000[26]
Distant metastases, excluding palliative care				
Year 1	7,251	5,643	8,232	Will *et al.,* 2000[26]
Year 2 onward	6,699	4,689	8,709	
Breast cancer death	23,056	14,845	29,690	Will *et al.,* 2000[26]
Tamoxifen treatment	134	103	174	MOHLTC[27]
Aromatase inhibitor treatment	528	406	687	MOHLTC[27]
Adverse events				
Stroke				
Year 1	43,635	22,297	85,409	O'Brien *et al.,* 2003[28], Wagner *et al.,* 2009[29], Goeree *et al.,* 2005[30]
Year 2 onward	11,506	8,054	14,967	
Thromboembolic event	6,169	3,219	8,338	O'Brien *et al.,* 1999[31]
Any cardiac event				
Year 1	13,242	6,616	17,062	O'Brien *et al.,* 2003[28], Casciano *et al.,* 2004[32], Dhalla *et al.,* 2009[33]
Year 2 onward	1,386	970	1,802	
Fracture	7,993	651	18,125	Leslie *et al.,* 2011[34]
Arthralgia or myalgia	341	300	380	Thorne, 2007[35]
Endometrial cancer	7,835	5,828	10,943	Pinilla, 1998[36]
Utilities				
Disease-free state (no events)	0.85	0.79	0.91	Sullivan *et al.,* 2005[37], Mittmann *et al.,* 1999[38]
Breast cancer events				
Locoregional recurrence state, including contralateral tumour	0.725	0.663	0.802	Peasgood *et al.,* 2010[39]
Distant metastasis health state	0.614	0.488	0.75	Peasgood *et al.,* 2010[39]
Adverse events				
Stroke				
Year 1	0.553	0.497	0.609	Clarke *et al.,* 2002[40]
Year 2 onward	0.650	0.520	0.780	Clarke *et al.,* 2002[40]
Thromboembolic event				
Year 1	0.721	0.7	0.89	Sullivan *et al.,* 2005[37]
Year 2 onward	0.84	0.7	0.89	Sullivan *et al.,* 2005[37]
Any cardiac event				
Year 1	0.706	0.587	0.778	Clarke *et al.,* 2002[40]
Year 2 onward	0.683	0.587	0.778	Clarke *et al.,* 2002[40]
Fracture	0.70	0.64	0.96	Peasgood *et al.,* 2009[41]
Arthralgia or myalgia	0.85	0.8	0.9	Sullivan *et al.,* 2005[37], Mittmann *et al.,* 1999[38]
Endometrial cancer				
Year 1	0.68	0.6	0.85	Gold *et al.,* 1998[42]
Year 2 onward	0.82	0.6	0.85	Gold *et al.,* 1998[42]

account of the fact that adjuvant and neoadjuvant studies have both failed to show any differences between letrozole, anastrozole, and exemestane[43,44]. Fourth, we assumed that patients could experience non–breast cancer death from any health state, but that breast cancer–related death occurs only after distant metastasis.

2.4 Risk of Death

The annual risk of death among women with distant metastasis treated with hormonal therapy was obtained from a large phase III randomized trial, Protocol 025 (P025), which compared AI with TAM as first-line therapy in metastatic breast cancer[15] (Table I). We estimated mortality rates for breast cancer patients without distant metastasis by eliminating deaths from breast cancer, endometrial cancer, any cardiac event, thromboembolic events, and stroke from the age-specific annual mortality rates for Canadian women. Because long-term survival data for patients on sequential therapies beyond 5 years were unavailable, we assumed that the mortality rate from distant recurrence was similar for all four strategies over the expected life of each patient.

Risks of death from hormonal therapy–related AEs were obtained from various studies. The baseline mortality from stroke (13%) and any cardiac event (9%) were obtained from a systematic review that included twenty studies of long-term cancer survivors[18,19]. The base-case mortality from thromboembolic events (20%) was obtained from Canadian patients with solid tumours and acute venous thromboembolism participating in an open-label randomized controlled trial[16,17]. The risk of death from fracture in the 1 year after the fracture was estimated to be 22% based on a systematic review of prospective and retrospective studies of 64,316 patients after hip fracture surgery[20–22]. An endometrial cancer mortality rate of 3% was obtained from a 10-year prospective trial of patients with stages I–III endometrial carcinoma[23,24]. No excess mortality risk accrues to arthralgia or myalgia; age-specific mortality rates for Canadian females were therefore used for those AEs.

2.5 Transition Probabilities

Annual probabilities for first breast cancer events in years 1–5 for patients treated with upfront TAM and AI and sequential TAM–AI therapy were based on a meta-analysis[5] updated with the most recently published results from two large studies: BIG 1-98[3] and ATAC[25] (Table II). The ATAC trial data with 10-year follow-up were used to calculate the annual probabilities for 6 years onward, and we assumed that the probabilities of recurrence after 6 years were the same for the sequential strategies as for upfront AI. The annual probabilities of recurrence after contralateral tumour and locoregional recurrence were obtained from a previous cost-effectiveness study of early breast cancer treatment[11], which were calculated by pooling Kaplan–Meier estimates of disease progression in patients with locoregional recurrence from eight studies; we assumed that those probabilities were the same for all strategies. Probabilities of developing AEs (endometrial cancer, cardiac events, thromboembolic events, fractures, arthralgia, and stroke) while on treatment with each of the strategies were based on the number of grades 3–5 AEs reported in the BIG 1-98 study[3].

2.6 Costs

The cost of generic letrozole was used for AI. Costs for TAM and letrozole were based on Ontario Drug Benefit Formulary costs, including a 5% dispensing fee[27] (Table I). Costs for breast cancer events were based on a study that integrated data from Canada's Population Health Model and multiple other sources; it determined costs for breast cancer at diagnosis and for the management of local and distant recurrence[26]. Costs for locoregional recurrence, including contralateral tumour, were based on the average costs of local recurrence, including local treatment followed by systemic therapy. Costs for distant metastasis were based on the weighted average of metastatic sites and included diagnosis and treatment. Follow-up treatment for local recurrence included physician assessments, clinic costs, hematology, biochemistry, a bone scan, chest radiography, liver ultrasonography, and annual mammography, and were based on the average cost of locoregional recurrence (stage II). Breast cancer death was allocated costs for palliative care. Costs for treatment of stroke, thromboembolic events, any cardiac event (myocardial infarction, angina), fracture, and endometrial cancer were obtained from published Canadian studies[28–34,36,45]. The treatment cost for arthralgia was based on the annual cost of anti-inflammatory medication (celecoxib 100 mg daily)[35]. When necessary, all costs were inflated to 2011 Canadian dollars using the medical component of the Canadian Consumer Price Index[46].

2.7 Utilities

Utility weights for breast cancer health states were obtained from a meta-analysis of 476 utility values from forty-nine studies[39] (Table I). Data for metastatic and early breast cancer states were synthesized by meta-regression. Of the three models presented in the meta-analysis, we used the numbers from model 1, which were weighted by the inverse of the standard deviation for base-case parameters of locoregional recurrence (including contralateral tumour) and distant metastasis. To identify upper and lower bounds for sensitivity analyses, we used the model 2 values for "treatment type" and "response to treatment," which were weighted by sample size. The utility estimate

TABLE II Transition probabilities, by treatment strategy[a]

Variable	*Strategy*							
	Tamoxifen (TAM)		*Aromatase inhibitor (AI)*		*TAM→AI*		*AI→TAM*	
	Value	*Range*	*Value*	*Range*	*Value*	*Range*	*Value*	*Range*
Breast cancer events								
Locoregional recurrence								
0–5 Years	0.0094	0.0063–0.0123	0.0060	0.0041–0.0077			0.0060	0.0051–0.0700
0–2 Years					0.0088	0.0062–0.0102		
2–5 Years					0.0051	0.0041–0.0061		
6+ Years	0.0094	0.0063–0.0123	0.0060	0.0041–0.0077	0.0060	0.0041–0.0077	0.0060	0.0051–0.0700
Distant recurrence								
0–5 Years	0.0174	0.0161–0.0222	0.0141	0.0131–0.0202			0.0141	0.0051–0.0700
0–2 Years					0.0162	0.0142–0.0182		
2–5 Years					0.0120	0.011–0.013		
6+ Years	0.0169	0.0154–0.0182	0.0144	0.0070–0.0250	0.0148	0.0129–0.0174	0.0141	0.0131–0.0202
Adverse events								
Stroke	0.0035	0.0028–0.0042	0.0029	0.0023–0.0035	0.0039	0.0031–0.0047	0.0034	0.0027–0.0041
Thromboembolic event	0.0054	0.0043–0.0065	0.0022	0.0018–0.0027	0.0067	0.0054–0.0081	0.0048	0.0038–0.0057
Any cardiac event	0.0038	0.0024–0.0052	0.0067	0.0042–0.0080	0.0045	0.0030–0.0060	0.0046	0.0035–0.0055
Fracture	0.0042	0.0032–0.0054	0.0065	0.0055–0.0075	0.0047	0.0032–0.0060	0.0040	0.0028–0.0052
Arthralgia or myalgia	0.0050	0.0040–0.0060	0.0067	0.0054–0.0081	0.0058	0.0046–0.0069	0.0061	0.0049–0.0073
Endometrial cancer	0.0017	0.0014–0.0020	0.0003	0.0002–0.0003	0.0005	0.0004–0.0006	0.0006	0.0005–0.0007

[a] Includes the exploratory strategy of sequential aromatase inhibitor followed by tamoxifen.

for individuals without symptomatic breast cancer ("disease-free" health state) was based on the Medical Expenditure Panel Survey conducted in the United States during 2000–2002[37,38]. Preference-based scores were determined using the EQ-5D health questionnaire (EuroQoL, Rotterdam, Netherlands) which was administered within a group of 20,980 women with chronic conditions, of whom about 17% were more than 65 years of age. Utility estimates for thromboembolic events (n = 126) were obtained from the same study. Utilities for any cardiac events—including myocardial infarction, ischemic heart disease and heart failure (n = 456), and stroke (n = 69)—were also derived using the EQ-5D from U.K. patients who had previously experienced cardiac adverse events[40]. Because the latter study was conducted in patients with type 2 diabetes, we used the percentage utility decrement resulting from the event and subtracted it from the breast cancer disease-free health state utility. Utility values for fractures were obtained from a systematic review of twenty-seven studies for osteoporosis-related conditions[41]. We used EQ-5D utility values from hip fracture, because hip fractures represent the largest financial burden and the highest incidence[34]. Utility weights for endometrial cancer were based on representative data from the U.S. National Health Interview Survey and the Healthy People 2000 survey conducted in members of the U.S. population with chronic conditions[42].

2.8 Sensitivity Analyses

Plausible ranges of high and low values for the model variables were used to conduct deterministic and probabilistic sensitivity analyses examining the influence and uncertainty of all parameters. To identify parameters with influence on the optimal strategy, we used net benefit to conduct threshold analyses. Several scenarios explored the effects of assumptions about carryover benefits. Monte Carlo simulation was used to perform probabilistic sensitivity analyses. We used gamma distributions to represent uncertainty about cost parameters, because cost data are skewed and cannot be negative. We used beta distributions for the probabilities and utilities, because those estimates are confined to a 0–1 range.

All parameters were randomly sampled from their assigned distributions, and one thousand simulations were performed. We estimated the likelihood of each treatment strategy being optimal across a range of willingness-to-pay (WTP) thresholds and illustrated uncertainty in our results with a cost-effectiveness acceptability curve. To assess the value of additional information, we calculated the expected value of perfect information (EVPI) with a 10-year lifespan of the testing technology, and the partial EVPI for the input parameters at various WTP thresholds. The EVPI analyses inform decision-makers about the

expected value of conducting more research to support a decision. From the approximately 75% population prevalence estimates for ER-positive tumours in Canada[47], we estimated the number of patients with ER-positive breast cancers who were 65 years of age and older in Canada to be 14,160. Based on that population estimate, we estimated the population EVPI at various WTP thresholds.

Tables I and II list selected variables in the model.

3. RESULTS

3.1 Base-Case Results

Base-case results were based three strategies (upfront TAM, upfront AI, and sequential TAM–AI), with a calibrated sequential AI–TAM strategy included in an exploratory analysis. Total survival time was 2.4 months more per patient with the upfront AI and sequential TAM–AI strategies than with upfront TAM (Table III). Total cost per patient was $175 lower with upfront AI and $581 lower with sequential TAM–AI than with upfront TAM. Overall, compared with upfront TAM, AI-containing strategies were more effective and less costly as a result of less recurrence and differences in adverse events. Among the AI-containing strategies, sequential therapy provided similar benefits, but was less costly, mainly because of lower drug costs (sequential therapy strategies use some less costly TAM without a large impact on recurrence risk: AI–TAM, TAM–AI, and upfront AI involved 2, 3, and 5 years of AI respectively). In the exploratory analysis, the sequential AI–TAM strategy was the least costly and most effective, but only by very small, statistically nonsignificant differences. Per custom, we did not report incremental cost-effectiveness ratios for the dominant interventions. Figure 2 illustrates the costs and outcome trade-offs for all treatment strategies, including the exploratory sequential AI–TAM strategy.

3.2 Sensitivity Analyses

Table IV presents threshold values from one-way sensitivity analyses, listing the conditions under which a strategy other than sequential TAM–AI is optimal. The most sensitive parameters in the model were the probabilities of distant recurrence during treatment. If the probability of distance recurrence during 5 years of treatment were to be 3% lower with upfront AI or 4% higher with sequential TAM–AI, then upfront AI would become the optimal strategy. Upfront AI would also become optimal if the probability of locoregional recurrence during 5 years of treatment were to be 18% lower with upfront AI, or if the probability of stroke or any cardiac event were to be 18% lower with upfront AI. All of the foregoing cases are within the plausible range. The analysis was less sensitive to costing parameters, utilities, mortalities, and probabilities of AEs except for stroke, any cardiac event, and fractures (for the AI and TAM–AI strategies).

Scenario analyses to address uncertainty in the estimates of carryover benefit were also conducted. In a more conservative scenario (assuming no carryover benefit), if recurrence after 5 years for locoregional and distant metastasis were equal for all therapies, upfront AI monotherapy would become more expensive compared with the other strategies, upfront TAM would become the least costly, and compared with upfront TAM, all strategies would have very favourable incremental cost-effectiveness ratios. In a scenario in which the risks of recurrence in the first 5 years are maintained indefinitely for years 6 and beyond, a pattern of results similar to those for the base case are found, with slightly larger differences between the strategies. If the risks of recurrence for years 6 and beyond are used only for years 6–10, and no further differences are assumed for the remainder of the model, upfront AI would be more costly than upfront TAM, but the benefit of sequential therapies would remain similar to that of upfront AI, and sequential therapies would be less costly than either monotherapy. Finally, if the annual cost of treatment with AI were to be the same as the cost of TAM, upfront TAM becomes the most expensive strategy, and upfront AI becomes the least expensive.

3.3 Probabilistic Sensitivity Analysis

Multiple cost-effectiveness acceptability curves were created to illustrate the likelihood of each of the strategies being cost-effective at different WTP thresholds (Figure 3). At a threshold of CA$20,000 per QALY gained, the probabilities of being cost-effective were 41% for a sequential AI–TAM strategy, 33% for a sequential TAM–AI strategy, and 22% for an upfront AI strategy. Those probabilities remained stable at higher WTP thresholds.

3.4 EVPI

The overall EVPIs per patient for the strategies were, respectively, CA$1,877, CA$4,018, and CA$7,717 at WTP thresholds of CA$20,000, $50,000, and $100,000 per QALY gained. The population EVPI is lowest at CA$103 million if the WTP threshold is CA$1,000 per QALY gained, and it steadily increases as shown in Figure 4. The least decision uncertainty occurs at very low WTP thresholds; it increases as the WTP increases. The partial EVPI for the parameters varied with the WTP threshold (Figure 5). At the WTP threshold of CA$50,000 per QALY gained, additional information about the breast cancer event and the AE probabilities would be valuable. Should the corresponding partial EVPIs be quite low, additional research on breast cancer mortality, utilities, and treatment cost would be of little value.

TABLE III Base case results[a]

Variable	*Strategy*			
	TAM	*AI*	*TAM→AI*	*AI→TAM*
Breast cancer events (%)				
Locoregional recurrence including contralateral tumour	4.4	2.8	3.1	2.8
Distant metastasis	9.0	5.8	7.2	7.3
TOTAL	13.4	8.6	10.3	10.1
Adverse events (%)				
Stroke	1.6	1.3	1.8	1.5
Any cardiac event	1.7	3.0	2.0	2.1
Endometrial cancer	7.5	1.2	0.2	0.3
Thromboembolic event	2.4	1.0	3.0	2.1
Fracture	1.9	2.9	2.1	1.8
Arthralgia	2.2	3.0	2.6	2.8
Mortality (%)				
Breast cancer death	2.7	2.2	1.3	1.2
Other	5.6	5.8	5.9	5.7
TOTAL	8.3	7.9	7.2	6.9
Total life-years, per patient	17.93	18.33	18.32	18.38
QALYS, per patient	8.86	9.06	9.05	9.08
Costs (2011 CA$, discounted)				
Disease-free state	6,430	8,197	7,474	7,470
Breast cancer states	10,912	8,812	8,880	8,829
Adverse events				
Stroke	1,246	1,059	1,431	1,254
Any cardiac event	307	585	380	390
Endometrial cancer	54	9	18	19
Thromboembolic event	131	58	170	121
Fracture	132	216	153	129
Arthralgia	7	21	13	14
Post adverse-event state	316	402	434	353
TOTAL adverse events cost	2,193	2,350	2,599	2,280
TOTAL COST	19,534	19,359	18,953	18,579

Tamoxifen = TAM; AI = aromatase inhibitor; QALYS = quality-adjusted life-years.

4. DISCUSSION

In our base-case model, sequential TAM–AI was the most effective and least costly of the three main strategies. Upfront AI was more effective and less costly than upfront TAM because of a reduction in breast cancer recurrence and differences in AEs. Among the AI-containing strategies, sequential therapy appears to provide benefits similar to those with upfront AI at a lower cost. When the exploratory sequential AI–TAM strategy was included, it was numerically the least costly and most effective, but only by a very small margin that might not be clinically meaningful. Among the three AI-containing strategies, sequential AI–TAM was the least costly, involving the fewest years of AI therapy (2 years, compared with 3 and 5 years for TAM–AI and upfront AI respectively). The sequential AI–TAM strategy was included for exploratory purposes only. It assumed risks of recurrence equal to those with the upfront AI strategy because only one study (BIG 1-98) had considered the strategy, finding statistically nonsignificant numeric differences from upfront AI. The other strategies were based on a meta-analysis of eight trials, and thus in the estimates for the sequential AI–TAM strategy entail additional uncertainty. Overall, the findings suggest

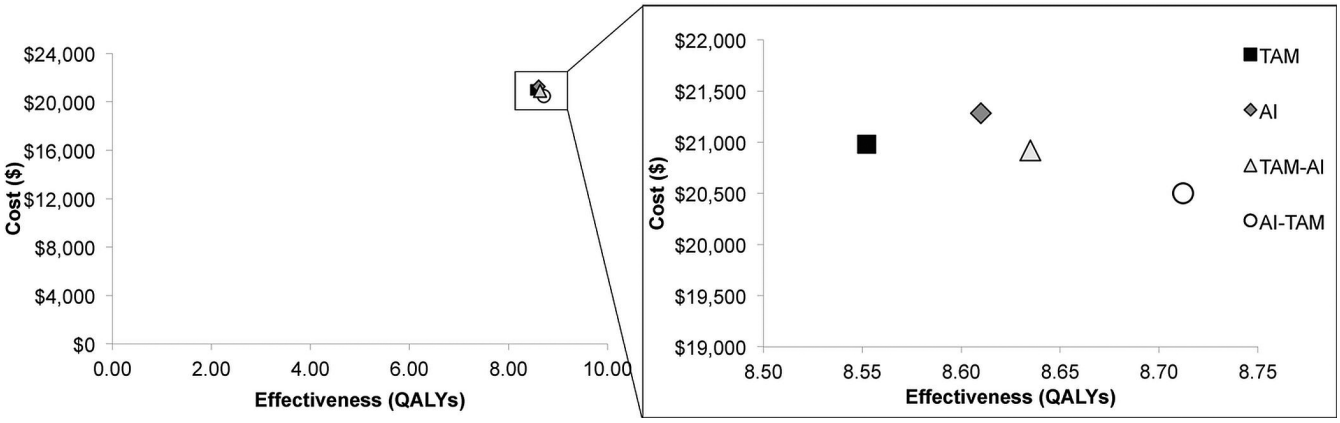

FIGURE 2 Base-case results on the cost-effectiveness plane for the breast cancer model. Includes the exploratory sequential strategy of aromatase inhibitor (AI) followed by tamoxifen (TAM). Inset illustrates the costs and effects of the four strategies in detail. QALY = quality-adjusted life-years.

TABLE IV Threshold values[a] for the conditions under which base case strategies other than tamoxifen (TAM) followed by aromatase inhibitor (AI) are optimal

Parameter[b]	*Base case value*	*Sensitivity analysis (range)*	*Condition in which optimal strategy changes*	*Threshold value*	*New optimal strategy*
Annual probability of					
locoregional recurrence (0–5 years) on upfront AI therapy	**0.0060**	**0.0041–0.0077**	**If lower by 18%**	**<0.0049**	**AI**
distant recurrence (0–5 years) on sequential TAM→AI therapy	**0.0148**	**0.0129–0.0174**	**If higher by 4%**	**>0.0154**	**AI**
distant recurrence (0–5 years) on upfront AI therapy	**0.0141**	**0.0131–0.0202**	**If lower by 3%**	**<0.0137**	**AI**
stroke for patients on upfront AI therapy	**0.0029**	**0.0023–0.0035**	**If lower by 18%**	**<0.0024**	**AI**
cardiac events for patients on upfront AI therapy	**0.0067**	**0.0042–0.0080**	**If lower by 18%**	**<0.0055**	**AI**
distant recurrence (0–5 years) on upfront TAM therapy	0.0174	0.0161–0.0222	If lower by 44%	<0.0097	TAM
distant recurrence (6+ years) on upfront TAM therapy	0.0169	0.0154–0.0182	If lower by 44%	<0.0095	TAM
fractures for patients on upfront AI therapy	0.0065	0.0055–0.0075	If lower by 32%	<0.0044	AI
Utility for disease-free state	0.85	0.79–0.91	If lower by 28%	<0.61	AI
			If lower by 46%	<0.45	TAM
Annual probability of death from metastatic breast cancer					
on AI (0–5 years)	0.1797	0.138–0.196	If lower by 42%	<0.1042	AI
on TAM→AI (0–5 years)	0.1797	0.138–0.196	If higher by 48%	>0.2660	AI

[a] Obtained from a one-way sensitivity analysis at a willingness-to-pay threshold of $50,000 per quality-adjusted life-year gained.
[b] Includes the calibrated exploratory strategy of sequential aromatase inhibitor followed by tamoxifen. Parameters within a plausible range appear in boldface type.

very small differences between the strategies, particularly between the three strategies using AI either upfront or sequentially. The results of the probabilistic sensitivity analyses confirm that finding, in that none of the four strategies (including the exploratory sequential AI–TAM strategy) is optimal in more than approximately 40% of the simulations across the WTP thresholds commonly accepted in Canada.

Earlier studies used results from the BIG 1-98[48], MA.17[43], and ATAC[49] clinical trials to analyze the cost-effectiveness of upfront AI and TAM[11,12,14] from the Canadian health care perspective. Another study[13] determined the cost-effectiveness of sequential TAM–AI compared with upfront AI and TAM, and found trends in costs and effects that are similar to those from our analysis. However, no studies have compared all four potential 5-year strategies in a single cost-effectiveness analysis. In addition, we used clinical data to derive breast cancer event probabilities from a meta-analysis of breast cancer outcomes in adjuvant trials of AI and TAM that included 18,871 patients[5]. The results have higher statistical power and are potentially less biased and more generalizable than results from individual studies. Finally, our study was based on longitudinal data, with longer patient follow-up and safety profiles.

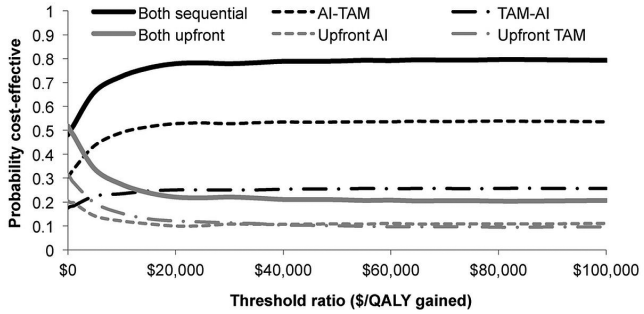

FIGURE 3 Cost-effectiveness acceptability curve for six treatment strategies in estrogen receptor–positive early breast cancer. Includes the exploratory sequential strategy of aromatase inhibitor (AI) followed by tamoxifen (TAM). QALY = quality-adjusted life-years.

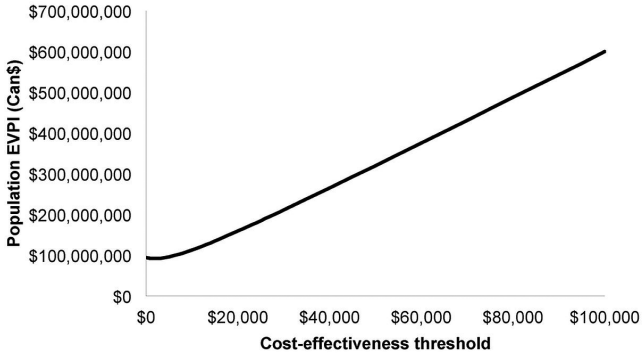

FIGURE 4 Plot of the expected value of perfect information (EVPI) for the analyzed population.

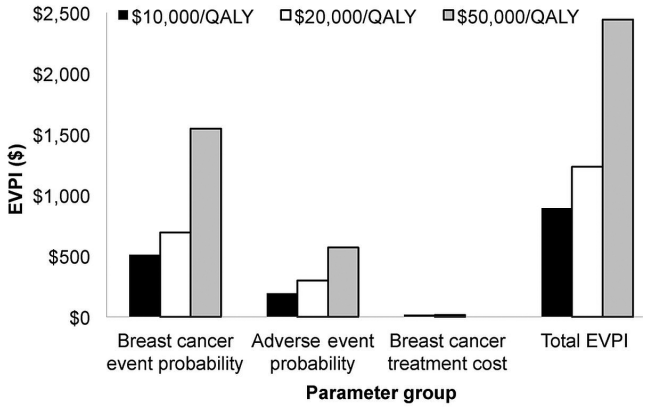

FIGURE 5 Plot of the partial and total expected value of perfect information (EVPI) per patient, by quality-adjusted life-year (QALY) cost threshold.

Our sensitivity analyses suggest several conditions under which the sequential TAM–AI strategy would no longer be optimal. If the risks of distant recurrence were to be lowered by 3% with upfront AI or increased by 4% with sequential TAM–AI, upfront AI would instead be optimal. Similarly, if disease-free survival were to be improved with upfront AI, that strategy would instead be optimal. Overall, the results are highly sensitive to the comparative effectiveness of sequential TAM–AI and the upfront AI strategies.

Our study has several limitations. First, although the results are potentially helpful for decision-makers in comparing a number of treatment strategies at one time, the use of heterogeneous patient characteristics from different studies in the model poses inherent difficulties, and inconsistencies in specific baseline estimates can arise. For instance, the reported mortality rate after recurrence in the Austrian Breast Cancer Study Group VIII trial (1807 patients) was significantly lower than that in the other six trials[5]. To keep the model parameters consistent, we excluded that trial from the analysis, and we also used a single consistent mortality rate from distant recurrence. Additionally, AE probabilities used in the model come from a single trial (BIG 1-98)[3], while the breast cancer event probabilities were derived from the meta-analysis of several studies. Considering that BIG 1-98[3] represents about one quarter of the meta-analysis data, uncertainty about side effects might affect the model results. However, any impact is likely to be small: according to BIG 1-98[3], no life-threatening AEs occurred in any group of treatment strategies, and the one-way sensitivity analysis indicated that AE probabilities are not the main drivers of the model. Finally, by assuming that the rates of breast cancer events are similar for all AI-containing strategies after 5 years of treatment and that the mortality rate from metastatic breast cancer is similar for all strategies, we could neglect potential differences in benefit and "carryover" effect among the therapies (unavoidable because of a lack of long-term data for upfront AI and both sequential therapies). We explored those assumptions about carryover benefit in scenario analyses and found that different assumptions would not affect the overall conclusions. It can be clinically reasonable to use equal breast cancer mortality rates because no available data suggest a post-progression benefit based on the adjuvant treatment received. In addition, there is currently little evidence to support any differences in overall survival between the treatments. Using the same mortality rates for all strategies (without stratification by therapy) caused differences in breast cancer event mortality between the model results and the meta-analysis (Table V).

To summarize, various adjuvant therapy strategies for breast cancer are currently in use. We examined 5-year strategies, but strategies of extended adjuvant therapy to 8 or 10 years are attracting increasing interest and are included in the latest American Society of Clinical Oncology guidelines[10]. However, the lack of comparative data for extended adjuvant therapy using either TAM or AI after upfront AI or sequencing makes formal comparisons difficult at the present time.

TABLE V Comparison of model[a] and meta-analysis results for four treatment strategies—including the exploratory calibrated aromatase inhibitor (AI) → tamoxifen (TAM) sequential strategy—at 5 years

Variable	*Model results (%)*				*Difference with TAM arm*			*Meta-analysis results (%)*				*Difference with TAM arm*		
	TAM	*AI*	*TAM→AI*	*AI→TAM*	*AI*	*TAM→AI*	*AI→TAM*	*TAM*	*AI*	*TAM→AI*	*AI→TAM*	*AI*	*TAM→AI*	*AI→TAM*
Breast cancer events														
Locoregional recurrence including contralateral tumour	4.4	2.8	1.9	2.8	1.6	2.5	1.6	4.5	2.9	2.0	2.6	1.6	2.4	1.9
Distant metastasis	9.0	7.3	7.4	7.3	1.8	1.6	1.8	8.1	6.7	5.7	7.2	1.4	2.4	0.9
TOTAL	13.4	10.1	9.3	10.1	3.3	4.1	3.3	12.6	9.6	7.8	9.8	3.0	4.8	2.8
Adverse events[b]														
Stroke	1.6	1.3	1.8	1.5	0.3	–0.2	0.0	1.7	1.4	1.9	0.9	0.3	–0.2	0.8
Any cardiac event	1.7	3.0	2.0	2.1	–1.3	–0.3	–0.4	3.3	5.7	3.8	3.7	–2.4	–0.5	–0.4
Endometrial cancer	0.8	0.1	0.2	0.3	0.6	0.5	0.5	0.8	0.1	0.3	0.1	0.7	0.5	0.7
Thromboembolic event	2.4	1.1	3.0	2.1	1.3	–0.6	0.3	2.6	1.1	3.3	0.7	1.5	–0.7	1.9
Fracture	1.9	2.9	2.1	1.8	–1.0	–0.2	0.1	7.2	9.7	9.4	6.3	–2.5	–2.2	0.9
Arthralgia	2.2	3.0	2.6	2.8	–0.8	–0.4	–0.5	2.5	3.3	2.8	2.1	–0.8	–0.3	0.4
Mortality														
Breast cancer death	2.7	2.2	1.3	1.2	0.5	1.4	1.5	6.4	5.5	9.9	7.1	0.9	–3.5	–0.7
Other	5.6	5.8	5.9	5.7	–0.1	–0.2	0.0	3.9	4	3.7	0.8	–0.1	0.2	3.1
TOTAL	8.3	7.9	7.1	6.9	0.4	1.2	1.5	10.4	9.5	13.6	8	0.9	–3.2	2.4

[a] Validity of the model was confirmed by comparing the outcomes after year 5 with our meta-analysis of outcomes from seven clinical trials. Breast cancer event rates produced by the model resemble the meta-analysis results except for the TAM→AI arm. Incidences of adverse events are consistent with those reported in meta-analysis, although some differences in fractures and arthralgia are observed. Overall mortality results are quite different for all the strategies.

[b] The AI→TAM and adverse event data are taken from the Breast International Group 1-98 trial.

5. CONCLUSIONS

Our study was prompted by the practical need to identify a cost-effective strategy among the various strategies currently used for hormonal therapy in postmenopausal women with ER-positive early breast cancer. We created a model to explore several 5-year hormonal strategies in the Canadian context: 5 years of upfront TAM, 5 years of upfront AI, sequential TAM (2 years) followed by AI (3 years), and an exploratory strategy with sequential AI (2 years) followed by TAM (3 years). The AI-containing strategies were more effective and less costly than upfront TAM. Of the three AI-containing strategies, those using sequential therapy were less expensive because of drug costs (that is, sequential therapies used some less costly TAM without a large effect on recurrence risk). Those results are sensitive to small changes in the parameters, and no individual strategy is optimal more than approximately 40% of the time. Moreover, the exploratory sequential AI–TAM strategy has not gained significant clinical support to date, and more evidence is required. Overall, in postmenopausal women with ER-positive early breast cancer, benefits accrue to strategies using AI compared with strategies using TAM alone. Among the AI-containing strategies, sequential therapy appears to provide benefits similar to those with upfront AI at a lower cost. Future research is required to address uncertainties about long-term breast cancer events and AE probabilities. As more evidence of clinical effectiveness becomes available, our model will address a current gap in the economic evidence.

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7. CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare the following interests: an honorarium was paid to EA's institution (Princess Margaret Hospital) by AstraZeneca. The remaining authors declare that they have no conflicts of interest.

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