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Cost estimate

Cost-utility analysis of second-line hormonal therapy in advanced breast cancer: a comparison of two aromatase inhibitors to megestrol acetate

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Randomized trials comparing the aromatase inhibitors, anastrozole and letrozole, to megestrol acetate (MA) in postmenopausal women with advanced breast cancer demonstrated that both agents are better tolerated than MA with comparable efficacy. In addition, one trial revealed that tumor response and time to treatment failure were significantly better with letrozole. Since oncologists are faced with a choice between three agents with at least comparable efficacy but different toxicity profiles and cost, a cost-utility analysis was conducted to quantify these differences and to determine if the new agents are more cost-effective than MA. In the absence of a randomized three-arm trial, a decision model was developed to simulate the most common therapeutic outcomes. The clinical data were obtained from an overview analysis of randomized trials. Total hospital resource consumption was collected from 87 patients with advanced disease that had failed second-line hormonal therapy. Utility estimates were obtained from interviewing a random sample of 25 women from the general public and 25 female health care professionals using the Time Trade-Off technique. The model suggested a similar duration of quality-adjusted progression-free survival between drugs (letrozole 150 days, anastrozole 153 days and MA 146 days). Letrozole had an overall cost of Can$2949 per patient which was comparable to MA at Can$2966 per patient. In contrast, anastrozole was slightly more costly than MA at $Can3149 per patient, respectively. The analysis revealed that letrozole has comparable overall costs relative to MA while providing at least equivalent quality-adjusted progression-free survival. These outcomes were largely related to its higher tumor response rate, which translated to a lower proportion of patients requiring chemotherapy. Anastrozole was slightly more costly than MA and did not demonstrate superiority in quality-adjusted progression-free survival in this palliative setting. [© 2000 Lippincott Williams & Wilkins.]

Key words: Anastrozole, breast cancer, cost analysis, letrozole, megestrol acetate.

Introduction

At the close of the last century, Beatson suggested that some forms of human breast cancer are hormone dependent.[1] This concept was later confirmed by the identification of estrogen and progesterone receptors. Estrogen receptor-positive (ER+) tumors are typically more common in older women and play an important stimulatory role, especially in metastatic ER+ breast cancer. Hence, the sequential use of pharmacologic interventions that interfere, directly or indirectly, with the affects of estrogen can be highly effective in suppressing the growth of the tumor.[2]

Research into the mechanisms of hormonal action has identified two important targets for anticancer therapy. The first is direct ER blockade with agents such as tamoxifen and the second is inhibition of aromatase, an enzyme critical in estrogen synthesis. Currently, tamoxifen is considered to be the first-line hormonal agent in the treatment of breast cancer in both the adjuvant and palliative settings.[3] In patients with hormone-sensitive tumors who progress after tamoxifen, second-line hormonal therapy is an option. The non-specific aromatase inhibitor aminoglutethamide was shown to be clinically effective in ER+ postmenopausal women with breast cancer.[2] However, the poor toxicity profile of this agent relegated it to the third-line setting. The second-line agent of choice subsequently became the progrestin, megestrol acetate (MA).

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Research efforts into the search for better aromatase inhibitors with increased specificity and reduced toxicity led to the development of several new compounds: anastrozole (Arimidex®, AstraZeneca), vorazole (Rivizor®, Janssen) and letrozole (Femara®, Novartis). Anastrozole was the first such agent to receive approval in second-line therapy following the publication of two large randomized trials which demonstrated similar efficacy and reduced toxicity relative to MA.[4,5] In contrast, the clinical development of vorozole was terminated following a rejection to approve the drug by the US Food and Drug Administration (FDA).[6]

Hence, letrozole was the second such agent to receive approval after the publication of two large randomized trials comparing letrozole to MA in one study and to aminoglutethamide in the other.[7,8] What was particularly interesting in these trials was that the response rate with letrozole 2.5 mg daily was superior to MA (24 versus 16%, p=0.04) as was the time to treatment failure against both comparators.[7,8] As with anastrozole, letrozole was also better tolerated than MA and aminoglutethamide. Even though these results are impressive, it is important to be aware that a second confirmatory trial to establish the superiority of letrozole over MA (as required by the FDA) has recently been completed and the results should be available in early 2001. In addition, a head-to-head comparison against anastrozole in the second-line setting is currently underway. Therefore, the comparison between anastrozole and letrozole should be approached with some care until the results of these additional trials are available.

Given the available clinical information, there are three second-line hormonal agents currently available to the oncologists (aminoglutethamide has recently been discontinued by the manufacturer): MA, anastrozole and letrozole. Both anastrozole and letrozole are better tolerated and at least as efficacious as MA in the second-line setting. However, in Canada, anastrozole and letrozole are approximately 40% more expensive on an acquisition cost basis than MA. Therefore, the issues that formulary committees have to consider are 2-fold. Do the aromatase inhibitors provide better value than MA when all of the clinical and economic factors are quantified? Furthermore, is one aromatase inhibitor more cost-effective than another as an alternative to MA.

In the absence of a well-designed three-arm randomized trial, the application of decision-analytic techniques is one method that can be used to shed light on these important questions. The advantage of decision analysis is that it combines the best available clinical, economic and quality of life data, and expresses it into a single quantitative outcome, the incremental cost per quality-adjusted progression-free year. Such an outcome can then be used for health policy decision making. In this study, a cost-utility analysis was conducted to determine which second-line hormonal option provides the greatest benefit to patients at the most reasonable cost to the Canadian health care system.

Methods

Development of decision model

In the absence of a randomized three-arm trial comparing the aromatase inhibitors to MA in postmenopausal women, a decision model was developed to simulate the most likely therapeutic outcomes. The baseline analysis considered postmenopausal women with advanced breast cancer who are ER/PR+, anthracycline naive and have failed first-line hormonal therapy with tamoxifen. The primary clinical outcome for measuring successful therapy in the current analysis was quality-adjusted progression-free survival benefit. The face and content validity of the model was verified by two oncologists involved in the management of breast cancer patients in Canada's two largest provinces, Ontario and Quebec.

The model began at the decision node (square) where a choice would have to be made between letrozole, anastrozole and MA (Figure 1). Patients would receive letrozole 2.5 mg, anastrozole 1 mg or MA 160 mg on a daily basis. After a 3 month treatment period, the probability of response (circle) would be assessed for each of the three agents. Patients who responded to second-line hormonal therapy would continue treatment until disease progression. In contrast, patients with disease progression at the 3 month interval would be offered standard chemotherapy consisting of a combination of 5-fluorouracil, doxorubicin and cyclophosphamide (FAC). As an alternative to the baseline analysis, patients who had previously received an anthracycline-based regimen in the adjuvant setting and had experienced disease progression, single-agent paclitaxel or docetaxel were considered in the model.

Following three cycles of chemotherapy, non-responders would then be offered best supportive care while responders would continue to receive an additional three cycles (Figure 1). For patients with non-life threatening disease, a third-line hormonal agent may be an option prior to chemotherapy (e.g. tamoxifen→aromatase inhibitors→MA). Since there was no randomized trial data available for these sequences, they were not considered in the model.

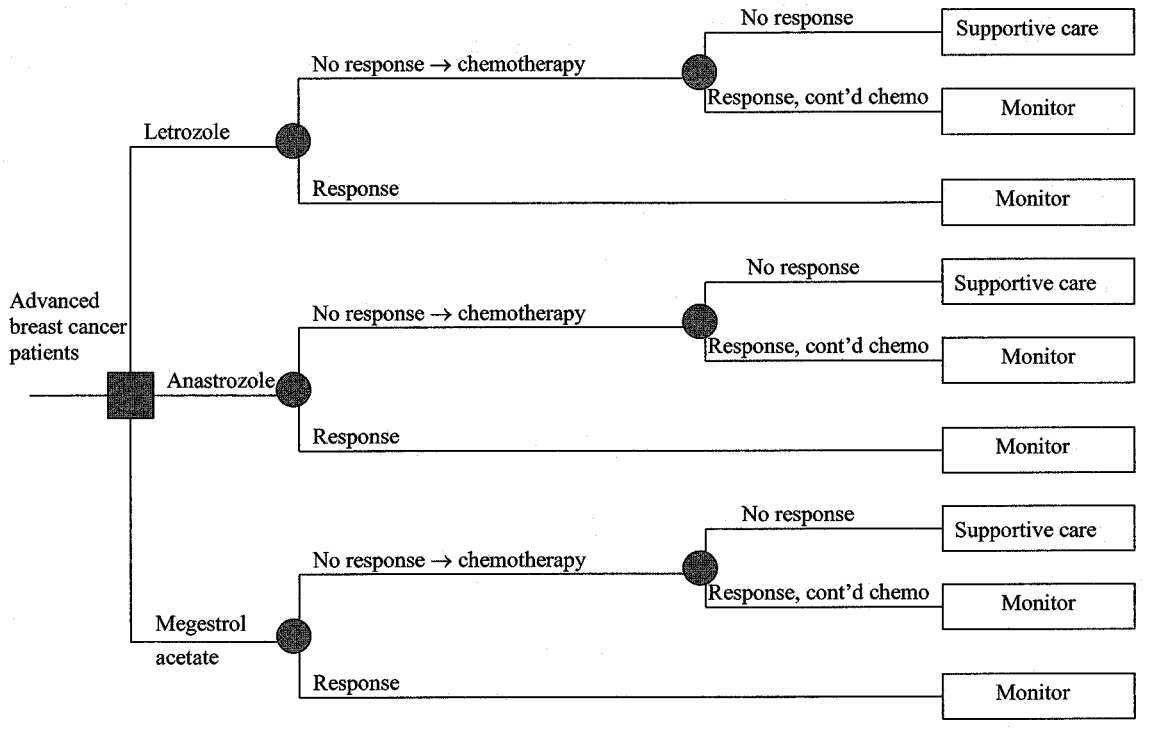

Figure 1. Decision analytic model of second-line hormonal therapy in advanced breast cancer.

Clinical data

The clinical data required for the model, which consisted of disease response, side effect rates and progression-free survival estimates for each of the three hormonal alternatives, were obtained from an overview analysis of the literature. A computer literature search of *Medline* and *Cancer Lit* was performed from 1984 through 1998 for human clinical studies involving letrozole, anastrozole and MA. Eligibility criteria relative to validity of trial design and analysis were used to identify potential studies. To be eligible, studies must have used a randomized design with letrozole, anastrozole or MA in one of the treatment arms, and subjects must have been postmenopausal women with either positive or unknown estrogen/progesterone receptor status and had failed tamoxifen. A similar set of study inclusion criteria were used to identify randomized trials for FAC and taxane chemotherapy. During the literature review, effort was given to avoid the inclusion of duplicate publications.

Studies were selected on the basis of the inclusion criteria and agreed upon by two evaluators. The following data were abstracted from accepted studies: drugs, dose, frequency of administration, definition of response, study design (e.g. blinded versus non-blinded), eligibility criteria, study populations, incidence of drug-related toxicity, number of withdrawals caused by adverse drug reactions and all clinical outcomes.

Response and adverse effect rates from the different studies were combined using Bayesian probabilities to calculate a point estimate and 95% confidence intervals for each outcome.[9] This technique was based on a modification of the method presented by DerSimonian and Laird,[10] which incorporates both between and within study variances to yield superior resultant estimates. In the case of the reported estimates for median progression-free survival, equal weighting was used with studies of similar sample sizes.

Estimation of treatment costs

The analytic time period for this investigation was from the start of second-line hormonal therapy until disease progression and a Canadian health care system perspective was taken. In order to measure chemotherapy treatment costs in patients who failed second-line hormonal therapy, a retrospective chart review was undertaken from 1997 to 1999. Such an approach to economic data collection has the advantage of representing 'real life' hospital resource utilization as opposed to the controlled situation

created by a randomized trial. The inclusion criteria for the chart review included patients who were hormone receptor positive or status unknown and had progressed despite second line therapy with either MA or one of the aromatase inhibitors.

Patient data obtained from the charts included demographic information, hormone receptor status, radiation history and previous anticancer therapy. Hospital resource consumption associated with anticancer therapy was then collected. This consisted of costs for hospitalization, outpatient clinic visits, antiemetics (e.g. ondansetron), chemotherapy (including preparation and administration), laboratory tests, patient monitoring, adverse effect management and all related physicians fees. All patient costs were captured from the first cycle up to 3 weeks after the last cycle of chemotherapy. Resource utilization during the progression-free survival interval included costs for physician visits and monitoring.

The cost of drugs, personnel and supplies were obtained from current pharmacy ordering catalogues along with pharmacy and nursing workload measurement statistics, Princess Margaret Hospital (PMH), 1999. Monthly costs for letrozole, anastrozole and MA with the associated dispensing fee were obtained from the Outpatient Pharmacy. The average operating cost of hospitalization was Can$521/day as reported by the Ontario Hospital Association (1998) for a teaching hospital. Laboratory and diagnostic costs were obtained from the Departments of Biochemistry, Microbiology and Diagnostic Imaging, PMH. The oncologist's fees for service were obtained from the Schedule of Benefits: Physician Services under the Health Insurance Act, Ontario Ministry of Health. The costs quoted in the study were in Canadian dollars (Can$1=US$0.68 as of December 1999).

Quality of life data

The health-related quality of life values measured in the analysis were patient preferences for alternative health outcomes, as depicted in the decision-analytic model. In the current study, quality-adjusted progression-free periods were measured as 'healthy months equivalent' for the time spent in each outcome of the decision model using the Time Trade-Off technique.[11] The scores in months were then converted to utility measures between 0 and 1, where 0 represented death and 1 was a state of perfect health or optimal quality of life.

It has been recommended in the Canadian Guidelines for Economic Evaluations[12] and by the Panel on Cost-Effectiveness in Health and Medicine of the US[13] that treatment preferences be measured from members of the general public who are potential candidates of the new medical intervention. Therefore, the sample population for the baseline analysis consisted of 25 Canadian women living in Ontario. With a sample of 25 subjects, health state preferences were measured with a precision that extended to ± 1.5 months, with a 95% probability.

Potential subjects were initially screened via a random telephone dialing strategy. To be eligible for the survey, participants had to be 18 years of age or older, have permanent residence status in Ontario, indirectly supported the Canadian health care system through tax contributions and gave informed consent to participate in the interview. Once subjects were identified by telephone, a trained field surveyor interviewed them face-to-face.

After informed consent was obtained, each participant was interviewed for 15–20 min. Respondents were presented with information about the natural history of metastatic breast cancer, followed by a description of the methods of administration and the side effect profile of each of the three hormonal agents. Since there was an absence of data from a head-to-head comparison between letrozole and anastrozole, an identical side effect profile was assumed. The interview continued with a description of the nine health states (Figure 1) and the length of time lived within each health state.

Subjects were then asked how many months of 'perfect health' they considered being equivalent to the time spent in each of the less than optimal health states described. These measures were then used to weigh each branch of the model by the quality of life experienced by a patient living through that event. An identical process was administered for each of the nine outcomes in the decision model (Figure 1).

Participants provided responses to each health outcome. The utility value for each branch of the model was based on scores from the interviews. It was defined as the ratio of the equivalent time in perfect health to the months receiving treatment (e.g. 3 healthy months equivalent to 6 treatment months=0.50). This provided a utility value in the range of 0–1, where 0 represented death and 1 was a state of perfect health. The mean utility value for each outcome was then multiplied by the time spent in each pathway (progression free survival plus the time to receive treatment) to estimate the associated quality-adjusted progression-free survival benefit.

Graphic interview tools were used to facilitate the participant's understanding of the Time Trade-off technique. To minimize the framing effect, all pathways were presented in a consistent manner pictorially. Demographic data were also collected from each

participant, and consisted of age, marital status, education, household income, number of children and history of anticancer treatment. A non-random sample of 25 female health care professionals (e.g. oncology pharmacists and nurses) was also interviewed for comparison.

Cost-utility analysis

The clinical, economic and respondent preference data were then combined into a cost-utility analysis comparing the two aromatase inhibitors to MA. The primary outcome determined in the study was the incremental cost per quality-adjusted progression-free year gained, which was calculated by dividing the difference in cost relative to MA (numerator) by the difference in quality-adjusted progression-free survival benefit (denominator). Future costs and benefits were not discounted because of the short time periods involved. However, the stability of the baseline results were tested by a comprehensive sensitivity analysis. This procedure included substituting preferences derived from healthy women in the general public with those measured in female health care professionals. The data were also reanalyzed using the upper and lower 95% confidence limits of response, costs for chemotherapy and health state utilities.

Statistical analysis

Demographic data and utility estimates were presented as descriptive statistics as means, medians or proportions. Costs for chemotherapy were presented as means with 95% confidence intervals (CI).

Results

Overview analysis of randomized trials

A total of 13 published randomized trials with second-line anastrozole, letrozole or MA in one of the treatment arms met the study inclusion criteria. Similarly, there were seven comparative studies with FAC chemotherapy, and one trial each for single-agent pacltaxel and docetaxel accepted for review (Table 1).

The outcomes of the statistical pooling of clinical data with second-line hormonal therapy generated an overall objective response of 10.3% for anastrozole, 18.4% for letrozole and 11.0% for MA, respectively (Figure 1). The associated progression-free survival was approximately 5 months for anastrozole compared to 4.5 months for both letrozole and MA (Table 1). These data were subsequently used in the model. For FAC chemotherapy, the pooled response was 52.1%, while rates for paclitaxel and docetaxel were 26 and 30%, respectively (Table 1).

Economic data from the chart review

Over the previous 2-year period (1997 to mid-1999), 87 charts met the inclusion criteria for review. Twenty-four patients received first-line FAC chemotherapy, and second-line taxane administration consisted of 34 receiving paclitaxel and 29 being treated with docetaxel (Table 2). Most patients were

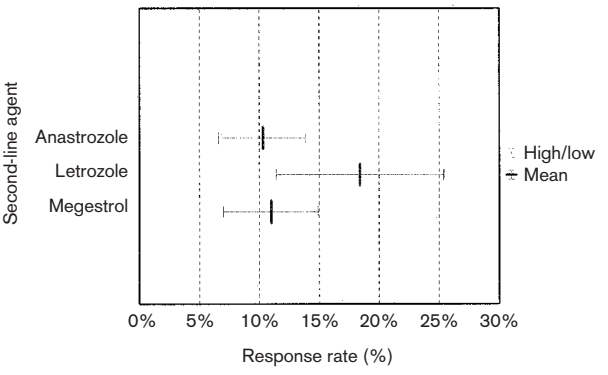

Figure 2. Pooled response rate of second-line hormonal agents.

Table 1. Clinical outcomes derived from overview analysis of published randomized trials

Treatment	No. trials	No. patients evaluated	Pooled response rate (95% CI)	Median PFS (days)	Reference
Anastrozole	2	263	10.3% (6.6–13.9)	147	4,5
Letrozole	3	383	18.4% (11.4–25.4)	135	7,8,14
MA	8	744	11.0% (7.0–14.9)	135	4,5,7,15–19
FAC	7	907	52.1% (46.7–57.5)	236.5	20–26
Doxetaxel	1	203	30% (23.7–36.4)	133	27
Paclitaxel	1	73	26% (12.0–40.0)	126	28

PFS, progression-free survival.

Table 2. Demographic and chemotherapy administration data derived from the chart audit

Parameters	FAC ($n=24$)	Paclitaxel ($n=34$)	Doxetaxel ($n=29$)
At the start of chemotherapy (range)			
median age	63 (43–75)	51 (31–69)	54 (31–69)
median ECOG score[a]	1 (0–3)	1 (1–3)	1 (0–2)
medium num of metastatic sites	2 (1–4)	2 (1–4)	2 (1–5)
median disease-free period (months)[b]	47 (1–174)	37 (1–164)	31 (0–137)
Receptor status			
ER+	23 (96%)	20 (59%)	18 (62%)
PR+	19 (79%)	17 (50%)	16 (55%)
unknown	0 (0%)	5 (15%)	2 (7%)
Radiation history			
radiation to primary site	19 (79%)	25 (74%)	20 (69%)
radiation to metastatic site(s)	14 (58%)	22 (65%)	13 (45%)
Adjuvant therapy			
none	6 (25%)	10 (29%)	9 (31%)
hormonal	12 (50%)	13 (38%)	13 (45%)
chemotherapy	6 (25%)	16 (47%)	11 (38%)
Prior treatment of advanced disease			
hormonal	24 (100%)	34 (100%)	29 (100%)
chemotherapy	0 (0%)	30 (88%)	25 (86%)
Current treatment for metastatic disease			
median dose (mg/m^2)		153 (92–215)	101 (73–109)
median num of cycle (range)	5 (1–10)	4 (1–10)	4 (1–12)
median num treatment days (range)	248 (19–1520)	84 (21–277)	105 (21–252)

[a]A measure of patient performance status on a scale from 0 to 4, where 0 represents no symptoms.
[b]From initial diagnosis to first metastases.

Table 3. Cost of chemotherapy in patients who progressed on hormonal treatment

Resource item	FAC ($n=127$ cycles)	Paclitaxel ($n=139$ cycles)	Doxetaxel ($n=138$ cycles)
Overall drug cost[a]	118	1075	1737
Patient monitoring[b]	112	101	150
Ambulatory day care visit[c]	112	112	41
Side effects management[d]	212	304	634
Physician fees	88	91	73
Total cost per cycle	$627	$1680	$2653
(95% CI)	(512–742)	(1574–1976)	(2363–3053)

[a]Consists of costs for drug acquisition, preparation, administration and supplies.
[b]Consists of cost for laboratory tests and all related radiological examinations.
[c]Cost of 'chair time' to receive chemotherapy.
[d]Includes costs for standard premedication and antiemetics.

ER/PR+ with a small proportion having an unknown receptor status. All patients had failed tamoxifen and had received second-line hormonal therapy prior to chemotherapy. MA (54%) and anastrozole (46%) were the two hormonal agents administered, and no patient had received letrozole. Patients received a median of five cycles of FAC and four cycles of paclitaxel or docetaxel at standard doses (Table 2). The total cost of FAC was approximately $627 per cycle, while second-line paclitaxel and docetaxel were $1680 and $2653 per cycle, respectively (Table 3).

Quality of life data for the model

The third component required for the cost-utility analysis was estimates of patient quality of life for the time period spent in each of the nine health states (Figure 1). Health state utilities for each outcome were estimated from a sample of 25 women from the general population. The median age of respondents was 50.5 years (range 20–81), 32% were married, 36% had received a post-secondary school education, 24% had a household income below $30 000, 52% did not have

children and 8% had received some form of anticancer therapy in the past. For comparison, preferences were also measured in a cohort of 25 health care professionals. Unlike the former group, health care workers were younger (median age 37; range 22–61), more educated (96% had received post secondary school education), had higher household incomes (100% had incomes above $30 000) and none had received any form of anticancer therapy in the past.

Utility values for the nine health states from public female volunteers and health care professionals are presented in Table 4. In both groups of respondents, utility scores were lowest under the scenarios where patients failed second-line hormonal therapy and subsequent chemotherapy. The health state with the highest utility score (i.e. highest quality of life) was when a response to second-line hormonal therapy was achieved. Both groups considered this health state to be equivalent to approximately 0.80 on a quality of life scale between 0 and 1 (Table 4).

There were also differences in how subjects responded to each of the three agents and the associated side effect profile. Public respondents gave the same score for each of the three comparators when a response was achieved, despite differences in side effects and frequency of administration. In contrast, health care professionals gave higher scores for the aromatase inhibitors relative to MA (Table 4). Hence, it appears that health care workers were more concerned about the side effects of MA and therefore had lower preferences for the drug. Healthy women from the general public may have been more willing to tolerate side effects in order to respond to therapy.

Using these data and the overview analysis results, the model was used to estimate the quality-adjusted progression-free survival for each strategy. When the public volunteers were the sources for utilities, the aromatase inhibitors provided a slight benefit over MA, but the differences between strategies were within 7 days of each other (Table 5). When the data were re-analyzed with the values provided by health care professionals, the additional benefit provided by the aromatase inhibitors was enhanced to approximately 14 days relative to MA (Table 5). Nonetheless, the differences between drugs were too small to conclude than one agent provided more quality-adjusted benefit than another.

Cost-utility analysis

The utilities in days were transformed to years and then combined with the clinical and economic data for the cost-utility analysis. The average cost per patient for anastrozole and letrozole was $3149 and $2966 compared to $2949 for MA, respectively (Table 6). Despite its higher drug acquisition cost, letrozole had overall costs that were similar to MA while providing comparable quality-adjusted survival benefits. This finding was primarily due to its higher overall tumor response rate (Table 1). Hence, the main economic

Table 5. Quality-adjusted progression-free survival benefit (days)

Strategy	Public volunteers ($n=25$)	Health care workers ($n=25$)
Anastrozole→chemotherapy[a]	153	142
Letrozole→chemotherapy[a]	150	139
MA→chemotherapy[a]	146	124

[a]FAC.

Table 4. Health state utilities derived using the Time Trade-Off technique

Health outcomes	Utility estimate [mean (95% CI)][a]	
	Public volunteers ($n=25$)	Health care workers ($n=25$)
Letrozole		
no response and progression during FAC	0.45 (0.37–0.55)	0.53 (0.45–0.92)
no response to letrozole but response to FAC	0.67 (0.55–0.79)	0.57 (0.49–0.65)
response to letrozole	0.80 (0.49–0.73)	0.78 (0.71–0.84)
Anastrozole		
no response and progression during FAC	0.45 (0.37–0.55)	0.53 (0.45–0.92)
no response to anatrozole but response to FAC	0.67 (0.55–0.79)	0.57 (0.49–0.65)
response to anatrozole	0.80 (0.70–0.92)	0.72 (0.66–0.78)
MA		
no response and progression during FAC	0.45 (0.35–0.55)	0.40 (0.30–0.48)
no response to MA but response to FAC	0.64 (0.52–0.76)	0.53 (0.44–0.61)
response to MA	0.80 (0.69–0.91)	0.67 (0.58–0.76)

driver behind this outcome was that a smaller number of patients treated with letrozole would require chemotherapy over the time period evaluated by the model. Anastrozole also provided comparable quality-adjusted benefits, but had an overall cost that was marginally higher than MA. When the utility values were divided by the overall cost of each drug, the average cost-effectiveness ratio (i.e. average cost per progression free year) indicated a slight economic advantage with letrozole (Table 6). These finding were stable even when the data were re-analyzed using the utilities derived from health care professionals.

In the original study protocol, the incremental cost per quality adjusted life year for each aromatase inhibitor relative to MA was suppose to be calculated. However, given the insignificant differences in quality-adjusted progression-free survival between the three drugs, such a calculation would generate costs per quality-adjusted progression-free years that would be difficult to interpret. Hence, they were omitted from the analysis. Notwithstanding, sufficient information is provided in Table 6 to allow the interested reviewer to calculate such outcomes.

Sensitivity analysis

A series of one-way sensitivity analyses were then conducted using the 95% CI for response rates, treatment costs and health state utilities. The comparisons were relative to MA only since the 'head-to-head' comparison trial between the aromatase inhibitors is still ongoing. In most of the scenarios evaluated, letrozole remained the preferred alternative to MA with modest but consistent economic advantages (Table 7). The economic outcomes for anastrozole ranged from $6400 per quality-adjusted progression-free year under the best case scenario (i.e. lower 95% CI for cost/cycle of FAC) to $29 000 in the worst case scenario where a patient would receive taxotere after progressive disease (Table 7).

Table 6. Baseline results of second-line hormonal therapy

Outcome	MA	Letrozole	Anastrozole
Women from the public			
average cost/patient ($)	2966	2949	3149
quality-adjusted progression-free benefit (years)[a]	0.40	0.41	0.42
average cost-effectiveness ratio ($)[b]	7400	7200	7500
Female health care providers			
average cost/patient ($)	2966	2949	3149
quality-adjusted progression-free benefits (years)	0.34	0.38	0.39
average cost-effectiveness ratio ($)[b]	8700	7800	8100

[a]Converted from days in Table 5 to years.
[b]Average cost divided by quality-adjusted progression-free benefit.
All estimates were rounded to the nearest hundred.

Table 7. One-way sensitivity analysis of averge cost-effectiveness ratios ($)

Sensitivity maneuver[a]	MA	Letrozole	Anastrozole
Women from the public (baseline)	7400	7200	7500
failure followed by paclitaxel chemotherapy	19000	18100	19000
failure followed by docetaxel chemotherapy	29200	26600	29000
95% CI of response letrozole (11.4–25.4%)	7400	7400–6900	7500
95% CI of response anastrozole (6.6–13.9%)	7400	7200	7700–7300
95% CI of response MA (7.0–14.9%)	7600–7200	7200	7500
95% CI cost/cycle FAC ($512–742)	6100–8600	6200–8200	6400–8600
95% CI of MA utilities (see Table 4)	9300–6200	7200	7500
Female health care providers (baseline)	8700	7800	8100
failure followed by paclitaxel chemotherapy	22500	17600	19000
failure followed by docetaxel chemotherapy	34400	27400	29000
95% CI of response letrozole (11.4–25.4%)	8700	8000–7700	8100
95% CI of response anastrozole (6.6–14.9%)	8700	7800	8300–7800
95% CI of response MA (7.0–14.9%)	9000–8600	7800	8100
95% CI cost/cycle FAC ($512–742)	6200–10100	6600–8900	6900–9300
95% CI of MA utilities (see Table 4)	9600–7600	7800	8100

[a]Outcome presented as the average cost per quality-adjusted progression-free year.

A similar reanalysis of the primary data was performed using the utility estimates derived from health care professionals. The conclusions were identical to the previous analysis where letrozole was the preferred alternative in most cases, while anastrozole continued to be slightly more costly than MA (Table 7). However, the most interesting difference between public volunteers and health care professionals was that the latter group perceived a lower overall quality of life with MA (Table 4). Hence, the economic outcomes imply that letrozole was an even better alternative to MA than anastrozole when the utility estimates from health care practitioners were used in the analysis (Table 7).

Discussion

Despite recent advances in its early detection and treatment, a significant proportion of patients diagnosed with an early breast malignancy eventually develop metastatic disease. Unfortunately, metastatic breast cancer remains incurable. As a result, an important objective for oncologists is to effectively palliate the patient and improve quality of life.

Chemotherapy is one of the most effective options for palliation in the metastatic setting. Studies with some of the newer agents such as docetaxel and Herceptin® have even reported an overall survival advantage in some patients.[29,30] Despite these benefits, the use of such agents has been associated with severe side effects characterized by anemia, febrile neutropenia, congestive heart failure and even treatment-related death.[29–31] Given these risks, the use of effective hormonal therapy that is well tolerated is an important option because it would maintain patient quality of life and delay the need to initiate chemotherapy.

The three hormonal agents approved for second-line use include anastrozole, letrozole and MA. All agents have advantages and disadvantages in terms of disease response, tolerability and cost. To quantify these differences and to provide evidence for informed formulary decision making, a cost-utility analysis was performed. Within the analytic time frame evaluated, the findings revealed modest but consistent economic advantages with letrozole, regardless of the source of health state utilities and variations in tumor response rates. The primary driver behind this finding was the higher response rate of letrozole relative to MA, which translated to fewer patients requiring chemotherapy for progressive disease. Additional cost savings with letrozole may also be realized if single-agent chemotherapy with expensive drugs such as paclitaxel or docetaxel were to be offered to non-responders instead of FAC. In contrast, the use of anastrozole as an alternative to MA would represent a slight incremental cost to the health care system.

As stated above, the main driver behind the letrozole results depended on the objective response rate of 18.4% derived from the overview analysis. It is possible that the higher response observed with letrozole could have been due to the selection of patients with more hormone-sensitive disease. However, as concluded by Hamilton and Piccart in their review of the data from all the studies,[6] there was no evidence to suggest that any of the trials had selected a population that was more hormone sensitive than either of the others. It is also important to point out that the pivotal trial comparing letrozole to MA was the only study to demonstrate superiority in terms of response rate, response duration, duration of clinical benefit and time to treatment failure.[7] Another feature of this study that adds considerable weight to the validity of the data is that unlike the two anastrozole trials,[4,5] it was double blinded. The pooled response rate with letrozole derived from the overview analysis is therefore from high quality clinical trials.

The findings of the current study have important implications with respect to drug use policy in the management of patients with hormone sensitive advanced breast cancer. Both of the aromatase inhibitors provide comparable quality-adjusted progression-free survival benefits relative to MA. In Canada, anastrozole and letrozole have the same drug acquisition cost, both 40% more than MA. However as was suggested by the cost-utility analysis, letrozole as a formulary alternative to MA would result in similar overall treatment costs. In contrast, the analysis implied that it may be slightly more costly to use anastrozole instead of MA. This study illustrates the importance of including all the available agents in a decision analysis (anastrozole and letrozole versus MA) in order to provide the most comprehensive picture for informed formulary decision making.

There are a number of limitations that have to be addressed. Even though the clinical data for the decision model was abstracted from randomized trials, none of the studies directly compared anastrozole to letrozole. Therefore, the comparisons should only be made against MA. Another drawback to the decision model was the failure to consider third-line hormonal therapy for non-responding patients without life-threatening metastases. However, it is unlikely that this would have altered the findings of the analysis because the use of third-line hormonal therapy would be an option after all three second-line agents. As reported in the randomized trials, the health state

utilities for MA were estimated using a 40 mg 4 times daily administration schedule as opposed to the once-daily option that is now available to patients. The presentation of the former dosing schedule to respondents was a bias against MA. The final limitation that should be acknowledged was that the cost of managing drug-related side effects was not included in the analysis. This was a bias against the aromatase inhibitors since MA was reported to have a higher incidence of serious side effects such as cardiovascular complications.[7]

In conclusion, the cost-utility analysis revealed that letrozole has comparable overall costs relative to MA while providing at least equivalent quality-adjusted progression-free survival benefits. These outcomes were largely related to its higher tumor response rate, which translated to a lower proportion of patients requiring chemotherapy. Anastrozole was slightly more costly than MA and did not demonstrate superiority in quality-adjusted progression-free survival in this palliative setting.

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