

Population-Based Pharmacoeconomic Model for Adopting Capecitabine/Docetaxel Combination Treatment for Anthracycline-Pretreated Metastatic Breast Cancer

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Key Words. *Population based · Pharmacoeconomic · Capecitabine · Docetaxel · Metastatic breast cancer*

LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Evaluate the combination of docetaxel and capecitabine compared with docetaxel alone for cost effectiveness.
2. Categorize cost differences according to the costs of drugs, hospitalizations, consultations, and other expenditures.
3. Appreciate how combining efficacy quality of life and cost to effectiveness data can be used to support decisions on health care.

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ABSTRACT

Purpose. To model the cost-effectiveness of adopting capecitabine/docetaxel combination therapy in place of single-agent taxane therapy for women in the province of Ontario, Canada, receiving treatment for anthracycline-pretreated metastatic breast cancer.

Methods. Clinical effectiveness and economic data were combined in a population model, from the perspective of a universal health care system. Estimates of clinical effectiveness and medical resource utilization were derived prospectively during a phase III randomized controlled trial comparing single-agent docetaxel with capecitabine/docetaxel combination therapy. Population data were obtained from the Cancer Care Ontario Registry and provincial prescription claims data.

Results. During 1999-2000, 542 patients were eligible for taxane monotherapy. As capecitabine/docetaxel treatment confers a median 3-month survival benefit compared with docetaxel monotherapy, the projected survival gain in these patients was 136 life-years. The results of the cost-effectiveness analysis demonstrate that the survival benefit provided by the addition of capecitabine to single-agent docetaxel is afforded at a small incremental cost of Canadian \$3,691 per life-year gained. Hospitalization costs for treatment of adverse events were less for patients receiving capecitabine/docetaxel combination therapy than for those receiving docetaxel monotherapy. The results were robust for adjustments in treatment costs and adverse effects costs.

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Conclusion. Due to its 3-month survival gain and small incremental treatment cost, capecitabine/docetaxel is judged to be a highly cost-effective treatment in anthracycline-pretreated advanced breast cancer. From the per-

spective of the Ontario health care system, the addition of capecitabine to docetaxel in this patient population is a clinically appropriate and economically acceptable treatment strategy. *The Oncologist* 2003;8:232-240

INTRODUCTION

Single-agent docetaxel is recognized as one of the most active therapies for the treatment of anthracycline-pretreated metastatic breast cancer (MBC) [1, 2]. Recently, a large, randomized, phase III study in patients with anthracycline-pretreated MBC demonstrated that the addition of the novel, oral fluoropyrimidine capecitabine (Xeloda®; F. Hoffmann-La Roche; Basel, Switzerland) to docetaxel led to a significantly superior tumor response rate, time to disease progression (TTP), and overall survival (by 3 months at the median) compared with single-agent docetaxel [3]. Furthermore, the combination regimen demonstrated a manageable safety profile that was consistent with the known toxicities of the individual agents. Importantly, quality of life was maintained in patients receiving the combination versus those receiving single-agent docetaxel.

Capecitabine monotherapy has rapidly emerged as a reference treatment for patients with anthracycline- and taxane-pretreated MBC. Capecitabine is approved in this setting in more than 50 countries worldwide, including Canada and the U.S. Oral capecitabine is activated to 5-fluorouracil (5-FU) by a unique, thymidine phosphorylase (TP)-dependent process that generates 5-FU preferentially in tumor tissue, reducing systemic exposure to 5-FU and potentially improving efficacy [4-6]. Furthermore, oral capecitabine mimics continuous infusion 5-FU and avoids the inconvenience, complications, and additional costs associated with i.v. chemotherapy. The rationale for combining capecitabine with docetaxel is based on the particularly low rate of myelosuppression with capecitabine and preclinical studies showing taxane-mediated upregulation of TP and synergy between capecitabine and the taxanes [7].

The survival benefit achieved with capecitabine plus docetaxel compared with single-agent docetaxel has led to the approval of capecitabine/docetaxel combination therapy for treatment of anthracycline-pretreated MBC patients and precipitated a reevaluation of 'best practice' in this setting. Ontario, as a province of Canada, has a public health care system that aims to provide universally accessible health care. In order to fulfill this mandate effectively, health care resources must be allocated appropriately to maximize benefit and cost-effectiveness. It is, therefore, important to determine not only the amount of health benefit a pharmaceutical yields to the population, but also the cost at which this result is achieved. Population-based pharmaco-economic analyses provide a means through which the costs

and outcomes of a therapy may be considered for the optimal allocation of health care resources. The aim of a cost-effectiveness analysis is not to save money, but rather to support decisions that optimize spending and greatest net benefit to the target population [8].

Direct health care costs associated with the lifetime management of breast cancer in Canada were estimated using Statistics Canada's Population Health Model [9]. This model integrated clinical data from a cohort of 17,700 women diagnosed with breast cancer in 1995. The total cost of treatment for this cohort was estimated to be over 454 million Canadian dollars, with hospitalization, mainly for initial treatment and terminal care, representing 63% of the lifetime costs of care delivery. In Ontario, the taxanes, paclitaxel and docetaxel, are the chemotherapeutic agents most commonly administered in patients with anthracycline-pretreated MBC. Taxane monotherapy is the treatment of choice for the majority of anthracycline-pretreated patients with human epidermal growth factor receptor 2 (HER2)-tumors. Patients with HER2+ tumors are generally offered a taxane plus trastuzumab, owing to the results of a phase III study showing that the addition of trastuzumab to paclitaxel achieved a significantly greater response rate and TTP, with a 40% greater median survival in anthracycline-pretreated patients with strongly HER2+ tumors [10, 11]. Currently, in Ontario, capecitabine monotherapy is generally offered to patients with taxane-pretreated MBC.

The objectives of the current study were to model, in terms of expected survival benefit and hospital costs, the overall cost implication and cost-effectiveness of adopting capecitabine/docetaxel combination therapy in place of single-agent taxane therapy for women receiving treatment for anthracycline-pretreated MBC within the province of Ontario.

METHODS

Model Design

Measures of clinical effectiveness and economic data were combined in a population model for Ontario using the Canadian public health care system as the base case to perform a cost-effectiveness analysis. Estimates of clinical effectiveness and medical resource utilization were derived from data collected during a randomized, controlled clinical trial comparing single-agent docetaxel with capecitabine/docetaxel combination therapy in anthracycline-pretreated patients with MBC [3].

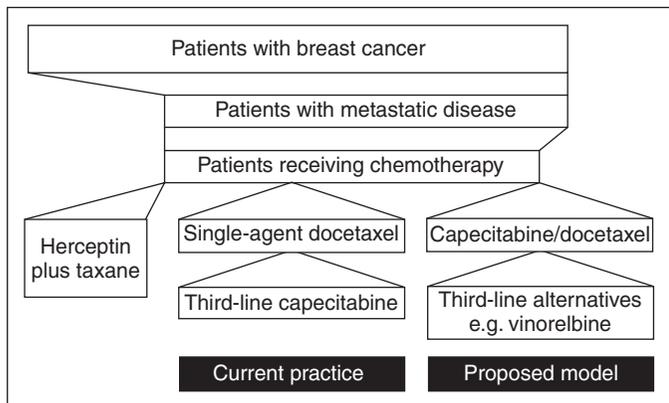


Figure 1. Population model.

Population data were derived from the Cancer Care Ontario Registry of taxane-eligible patients' drug use and Ontario public and private prescription claims data. Practice policy was assumed to follow the evidence-based 'best practice' and reimbursement guidelines formulated by Cancer Care Ontario (Fig. 1). For the purposes of the model, it was assumed that the size of the treatment population was unchanged between 1999 and 2000, with the same number of patients receiving taxane therapy for anthracycline-pretreated MBC ($n = 542$). It was also assumed that patients with HER2⁺ MBC receiving trastuzumab would not be eligible for capecitabine/docetaxel therapy and that all other anthracycline-pretreated patients would be eligible for capecitabine/docetaxel therapy. Patients with progressive disease following capecitabine/docetaxel therapy were assumed to be eligible for further salvage treatment with vinorelbine.

Clinical Outcomes

Clinical outcomes were estimated using data from the international, randomized, phase III trial comparing the capecitabine/docetaxel combination with single-agent docetaxel therapy in 511 anthracycline-pretreated patients with MBC [3]. In that study, efficacy, safety, and medical resource utilization data were collected prospectively as predefined in the trial protocol. In the study, patients were randomized to 3-week treatment cycles consisting of capecitabine 1,250 mg/m² twice daily (bid) on days 1-14 in combination with a lower dose of docetaxel (75 mg/m²) on day 1 ($n = 255$) or standard dose docetaxel (100 mg/m²) on day 1 ($n = 256$). Patients achieving a complete or partial response after 6 weeks of therapy continued on treatment until disease progression or development of unacceptable toxicities. Treatment-related adverse events (AEs) were managed with dose modification (including treatment interruptions and dose reductions) and standard pharmacologic

Table 1. Randomized phase III study comparing capecitabine/docetaxel combination therapy with docetaxel monotherapy: cumulative chemotherapy doses and clinic visits for infusion

	Capecitabine/docetaxel ($n = 251$)	Docetaxel ($n = 255$)
Mean cumulative docetaxel dose per patient (mg)	641	845
Mean cumulative capecitabine dose per patient (mg)	272,620	NA
Mean number of clinic visits for infusion per patient	4.7	4.6

NA = not applicable

interventions. Table 1 shows the mean cumulative doses of capecitabine and docetaxel and the mean number of infusions administered per patient during the study (safety population, $n = 506$). In the combination arm, the median delivered dose of capecitabine during the course of the study was 77% of the planned dose, and the corresponding value for docetaxel was 87%. In the single-agent docetaxel arm, the overall median delivered dose was 100% of the planned dose (interquartile range, 75%-100%).

After a minimum follow-up of 15 months, capecitabine/docetaxel combination therapy resulted in significantly superior efficacy, including a significantly higher tumor response rate (42% versus 30% with docetaxel, $p < 0.01$) and a significantly longer TTP (hazard ratio = 0.652, $p = 0.0001$; median, 6.1 versus 4.2 months with docetaxel). Notably, capecitabine/docetaxel therapy was associated with a significant survival benefit compared with docetaxel monotherapy (hazard ratio = 0.777, $p < 0.01$), with a 3-month advantage in median survival (14.5 months and 11.5 months, respectively) (Fig. 2). The 12-month survival rates were

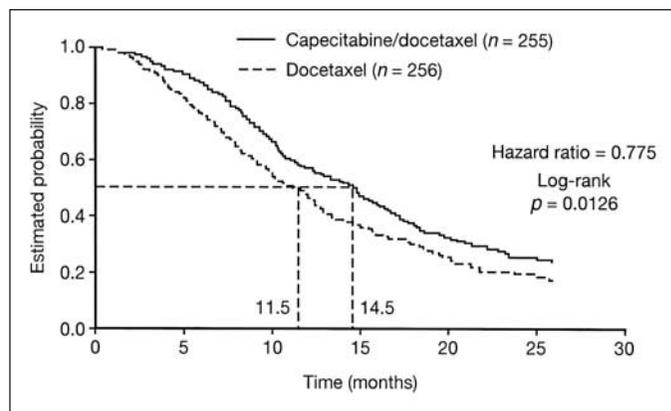


Figure 2. Overall survival in randomized phase III trial comparing capecitabine/docetaxel combination therapy with single-agent docetaxel therapy in patients with anthracycline-pretreated MBC [3].

57% in the combination arm and 47% in the single-agent docetaxel arm.

There was a higher incidence of gastrointestinal side effects and hand-foot syndrome in patients receiving the capecitabine/docetaxel combination, while myalgia, arthralgia, and neutropenic fever/sepsis were more common with single-agent docetaxel. Table 2 lists the frequency of treatment-related AEs (all grades and serious), unscheduled consultations, and hospitalizations for treatment of AEs recorded in the safety population ($n = 506$) during the study.

Medical Costs

In Ontario, the costs of hospital and cancer clinic care and i.v. chemotherapy are funded by the provincial Ministry of Health, with medications provided outside of hospitals funded by a combination of public and private insurance programs. The model considered all medical costs during treatment and treatment costs after subsequent disease progression. For the purposes of the model, it was assumed that current single-agent taxane costs were equivalent to single-agent docetaxel costs, and that capecitabine costs for capecitabine/docetaxel treatment were equivalent to single-agent capecitabine costs for salvage treatment of taxane-pretreated MBC. It was also assumed that patients with progressive disease following capecitabine/docetaxel therapy would be considered eligible for further salvage treatment with vinorelbine.

All costs are shown as Canadian dollars (CA\$). The cost of capecitabine was derived from the current list price of CA\$732 per bottle of 120 tablets (500 mg), and the cost of docetaxel was based on the actual acquisition cost of CA\$11.46 per mg. The most current pharmacy-order catalogs were used to determine the costs of additional pharmacotherapies. The model included one clinic visit for each treatment cycle at a cost of CA\$117, based on a recent cost estimate for a clinic visit for chemotherapy administration [12]. The estimated cost of daily hospitalization (CA\$416) was derived from a recent Statistics Canada study of Ottawa-area hospitals [9]. Unscheduled consultation costs were derived from published Canadian cost analyses [9] and fee schedules. It was assumed that the additional dispensing fee for capecitabine (estimated value CA\$4.47) would be paid by the Ontario Drug Benefit Program.

The model considered costs incurred during a period extending up to 1 year, and it was assumed that discounting was not required for this period [13]. The perspective of the analysis was restricted to the costs that would be accumulated at the hospital level and, in the case of oral therapy, at the drug benefit program level. Indirect costs and direct nonmedical costs were not included.

Table 2. Randomized phase III study comparing capecitabine/docetaxel combination therapy with docetaxel monotherapy: treatment-related AEs and hospitalizations (safety population)

	Capecitabine/docetaxel ($n = 251$)	Docetaxel ($n = 255$)
Treatment-related AEs	98%	94%
Treatment-related serious AEs	32%	33%
Treatment-related AEs requiring treatment discontinuation	25%	18%
AE-related hospitalizations	29%	26%
Mean duration of AE-related hospitalizations per patient (days)	4.8	5.5
Mean number of unscheduled consultations		
General practitioner	0.37	0.58
Nurse/other	4.07	2.87
Specialist	5.09	3.19

Sensitivity Analyses

Some potential disparities between the trial setting and current clinical practice in Ontario were addressed by sensitivity analyses. First, it was considered that the single-agent docetaxel dose was more likely to be 75 mg/m² in clinical practice, rather than the 100 mg/m² dose used in the clinical trial. In this setting, the use of capecitabine would not, therefore, be offset against the lower docetaxel dose for combination therapy. Accordingly, a sensitivity analysis was performed to test the influence of this lower dose, in which the docetaxel costs were reduced by 25%. Correspondingly, it was assumed that either reducing the dose or reducing the cost had no impact on the clinical benefit of the single-agent therapy. Clinically, we assert that a lower dose may be less efficacious than the full doses used in the study, and the clinical differences in favor of the combination would be greater in that scenario.

Second, the costs associated with the management of AEs in a closely monitored clinical trial may be higher than those encountered in routine clinical practice, and a sensitivity analysis was performed with the costs associated with AEs removed from the standard therapy arm and retained for the combination arm. Again, clinically, it may be expected that, if AE costs were less frequent in practice, then they would be lower in both arms of the analysis. However, since this is the first study of the combination, it should not be assumed that the rate of AEs would be lower in practice. The sensitivity analysis is designed to answer the question: "If the AE costs for standard therapy were zero, would the inclusion of AE costs in the combination arm still make it cost-effective?"

Table 3. Estimated costs per patient for second-line treatment with capecitabine/docetaxel or single-agent docetaxel therapy: model population ($n = 542$)

	Cost per patient (CA\$)		
	Capecitabine/docetaxel	Docetaxel	Incremental cost of capecitabine/docetaxel
Chemotherapy	10,645	9,653	+992
Infusion	545	550	-5
Hospitalization for AEs	2,013	2,284	-271
Consultations	392	281	+111
Treatment for AEs	64	65	-1
Total	13,659	12,833	+826

RESULTS

Population

During the 12-month period from 1999 to 2000, a total of 741 patients received taxane therapy funded by Cancer Care Ontario. This patient population included 199 patients with HER2⁺ tumors who received paclitaxel/trastuzumab therapy and were considered ineligible for taxane monotherapy in the model. The remaining 542 patients were assumed to be eligible for taxane monotherapy. During the 2000 calendar year, 227 documented claimants (public and private insurance) received single-agent capecitabine as salvage therapy for taxane-pretreated MBC.

Clinical Effectiveness

Capecitabine/docetaxel therapy has been shown to confer a median 3-month survival benefit over single-agent docetaxel therapy [3]. The projected survival gain of capecitabine/docetaxel therapy compared with single-agent docetaxel therapy in the 542 taxane-monotherapy-eligible patients treated annually in Ontario is, therefore, 136 life-years gained.

Costs

The estimated total incremental cost per patient for capecitabine/docetaxel combination therapy compared with single-agent docetaxel therapy was CA\$826 (Table 3). This small incremental cost for capecitabine/docetaxel combination therapy was mainly attributable to greater chemotherapy and consultation costs for the combination regimen compared with single-agent docetaxel. Notably, hospitalization costs for treatment of AEs were lower with capecitabine/docetaxel therapy compared with single-agent therapy, perhaps attributable to the lower docetaxel dose.

The Cancer Care Ontario Registry and Ontario Claims Data suggest that approximately 30% of patients treated with taxane therapy elect to receive subsequent capecitabine therapy. Accordingly, in the current model,

costs for third-line therapy were included for 166 patients. The costs per patient for subsequent salvage therapy with vinorelbine (for capecitabine/docetaxel combination-treated patients) and capecitabine (for single-agent docetaxel-treated patients) were estimated to be CA\$4,129 and CA\$3,805, respectively. The overall annual expenditure for patients receiving third-line salvage therapy in Ontario were calculated to be CA\$693,672 for vinorelbine and CA\$639,240 for capecitabine, meaning third-line therapy would likely be more costly if the capecitabine-docetaxel combination was used as a second-line treatment.

Budget Impact

The estimated incremental costs for adopting capecitabine/docetaxel combination therapy to replace the current practice of single-agent docetaxel therapy for the treatment of anthracycline-pretreated patients with MBC are listed in Table 4. During the treatment phase, the incremental cost for capecitabine/docetaxel therapy was estimated to be CA\$447,692 per annum, with a further incremental cost of CA\$54,432 per annum estimated for vinorelbine salvage therapy after disease progression.

Cost-Effectiveness

The total incremental cost for capecitabine/docetaxel combination therapy compared with single-agent docetaxel therapy for the Cancer Care Ontario population was estimated to be CA\$502,030 per annum, or CA\$3,691 per life-year gained (Table 5).

Sensitivity Analyses

Since the dose of docetaxel monotherapy used in clinical practice is likely to be 75 mg/m², reduction of the single-agent docetaxel dose in this model by 25% reduced docetaxel costs from CA\$12,833 to CA\$10,419, with a subsequent increase in the incremental cost of capecitabine/docetaxel combination therapy from CA\$827 to CA\$3,240 per patient, or CA\$12,961 per life-year gained.

Table 4. Annual budgetary impact of adopting capecitabine/docetaxel combination therapy for the treatment of patients with anthracycline-pretreated MBC in Ontario: model population ($n = 542$)

	Current model Docetaxel	New model Capecitabine/docetaxel Vinorelbine	Incremental cost of adopting new model
Second-line therapy			
Third-line therapy			
Second-line therapy			
Cost per patient	12,833	13,659	826
Cost per year: model population	6,955,486	7,403,178	+447,692
Third-line therapy*	(sequential capecitabine)	(sequential vinorelbine)	
Cost per patient	3,805	4,129	+324
Cost per year: model population ($n = 168$)	639,240	693,672	+54,432
Total cost per year: model population	7,594,726	8,096,850	+502,124

*Estimates based on 166 patients (31%). Costs shown in CAS

Table 5. Cost-effectiveness: capecitabine/docetaxel versus single-agent docetaxel in patients with anthracycline-pretreated MBC

	Docetaxel	Capecitabine/docetaxel	Difference
Patients projected to be alive at 1 year (%)*	251	309	59
Total life-months gained	6,016	7,425	+1,409
Incremental annual cost-model population			+502,030
Cost per life year gained			+3,691

*Derived by % alive in each arm in randomized trial at 1 year \times Ontario population ($n = 542$). Costs shown in CAS

When costs for managing AEs with single-agent docetaxel were discarded, the incremental cost of capecitabine/docetaxel combination therapy was estimated to be CA\$3,111 per patient, with a cost-effectiveness ratio of CA\$12,444 per life-year gained.

Both of these ratios would be considered cost-effective based on the proposed cutoffs for cost-effectiveness of oncology treatments of US\$50,000 per life-year gained [14] and GB£20,000 per life-year gained [15]. These ratios also compare favorably with the majority of cost-effectiveness ratios reported in a recent meta-analysis of oncology cost-utility (CU) publications [16].

DISCUSSION

Cytotoxic chemotherapy is the mainstay of treatment for MBC that is unresponsive to hormonal therapy or is rapidly progressive and life threatening [17]. Anthracyclines, usually administered in combination regimens, are well-established agents in first-line treatment of MBC and adjuvant treatment of primary breast cancer. Paclitaxel and docetaxel are commonly used for treatment of anthracycline-pretreated MBC, with the efficacy of docetaxel most clearly established in this setting. A phase III trial showed that docetaxel was more effective than methotrexate plus 5-FU, resulting in a significantly ($p < 0.001$) higher response rate

(42% versus 21%) and longer TTP (median 6.3 months versus 3.0 months) in patients with anthracycline-pretreated MBC [2]. Docetaxel is the only agent to have demonstrated a superior survival benefit compared with another recognized salvage regimen, mitomycin-C plus vinblastine. In a randomized, phase III trial comparing those therapies in patients with anthracycline-pretreated MBC, docetaxel achieved a significantly greater tumor response rate (30% versus 12%, $p < 0.0001$), significantly longer TTP ($p = 0.001$, median 4.4 versus 2.5 months), and significantly longer overall survival ($p = 0.0097$, median 11.4 versus 8.7 months) compared with mitomycin-C plus vinblastine [1]. While paclitaxel is also used in patients with anthracycline-pretreated MBC, no phase III trials comparing paclitaxel with other commonly used regimens have been conducted. Overall survival is typically less than 1 year with paclitaxel, and response rates are generally variable in anthracycline-pretreated patients [18, 19]. In addition, uncertainty remains about the optimal paclitaxel dose and administration schedule.

Many of the strategies aimed at increasing the efficacy of chemotherapy for MBC are associated with a substantial economic impact through higher drug acquisition costs, greater toxicities, and more frequent or prolonged i.v. infusions. The majority of pharmacoeconomic studies of second-line therapy for MBC have used Markov modeling and demonstrated

incremental CU benefits for the use of docetaxel compared with paclitaxel [20-22]. In general, these studies show that docetaxel is associated with lower overall treatment costs and provides superior quality-adjusted life benefits compared with paclitaxel. These studies were limited in that they were not based on comparative trials, but used disparate data derived from heterogeneous patient populations.

Recently, two studies have demonstrated that novel combination regimens incorporating the taxanes can improve outcomes compared with single-agent taxane therapy in patients with anthracycline-pretreated MBC. A recent trial has shown that the addition of trastuzumab to paclitaxel significantly ($p < 0.001$) improved response rates and TTP compared with paclitaxel monotherapy in patients with anthracycline-pretreated, HER2⁺ MBC [10]. In the same trial, overall survival was significantly better ($p < 0.05$) in patients with HER2⁺ tumors treated with the paclitaxel/trastuzumab combination [11]. Based on those results, trastuzumab plus a taxane is now considered the standard of care for patients with MBC who have HER2⁺ tumors. Prior to the evaluation of the capecitabine/docetaxel combination, no cytotoxic combination had achieved superior survival compared with docetaxel monotherapy in a general population of patients with anthracycline-pretreated MBC. The significantly superior efficacy, with a median 3-month survival benefit, achieved with the capecitabine/docetaxel combination compared with docetaxel monotherapy [3] is unsurpassed in the context of anthracycline-pretreated MBC and has led to regulatory approval of the capecitabine/docetaxel combination in this setting.

Based on clinical data from the randomized, phase III trial and population registry data, the current model enabled an effective estimate of the potential economic impact of adopting capecitabine/docetaxel therapy in place of single-agent docetaxel for the treatment of anthracycline-pretreated MBC in the province of Ontario. The results of the cost-effectiveness analysis demonstrate that the survival benefit provided by the addition of capecitabine to single-agent docetaxel therapy is afforded at a small incremental cost of CA\$3,691 per life-year gained. This favorable cost-effectiveness ratio is largely attributable to the fact that the additional cost of capecitabine is largely offset by the lower dose of docetaxel in capecitabine/docetaxel combination therapy compared with single-agent docetaxel therapy. It is also notable that the two sensitivity analyses, which omitted both the drug-cost offset in the combination arm and the costs incurred in the management of AEs in the monotherapy arm, yield cost-effectiveness ratios that are considered favorable for medical intervention [8, 14, 15]. As observed in the phase III trial, the dose of capecitabine (1,250 mg/m² bid) was noted to be quite toxic when used in combination

with docetaxel, leading to dose reductions in close to half of the patients assigned this treatment. This has prompted the evaluation of a lower dose of capecitabine (950 mg/m² bid) in combination with docetaxel in several ongoing or planned studies. In this model, we have elected not to conduct a sensitivity analysis substituting a lower initial dose of capecitabine (i.e., 950 mg/m² bid) as a 25% reduction in the cost of capecitabine, coupled with the assumption that there would be no decrease in survival gain, would bias the cost-effectiveness ratio further in favor of that combination.

The current model does not include a patient utility element. However, the manageability of toxicities uniquely associated with capecitabine (hand-foot syndrome and diarrhea) and the magnitude of the survival benefit observed in the trial suggest that there would likely be a positive CU outcome with combination capecitabine/docetaxel therapy. This may be further supported by quality-of-life data from the phase III, randomized trial, which indicate that quality of life is maintained with capecitabine/docetaxel combination therapy compared with single-agent docetaxel therapy [23]. Further limitations of the model are that it assumes that 100% of the anthracycline-pretreated patients with HER2⁻ MBC would receive taxane monotherapy and, therefore, be eligible for capecitabine/docetaxel therapy. However, this is unlikely at present in Ontario as a substantial number of anthracycline-pretreated patients receive vinorelbine instead of a taxane. The model also fails to account for any potential prolonged sequential use of capecitabine or its use in patients who have not previously received taxane treatment.

Unfortunately, due to the absence of a crossover design, the relative merits of sequential versus combination therapy could not be addressed in the randomized trial. The authors of the trial have asserted that the early separation of the survival curves suggests that combination therapy may confer particular benefits in the prevention of early deaths in a subset of heavily pretreated patients who had a heavy tumor burden. Nonetheless, the issue of sequencing treatments (i.e., docetaxel → capecitabine) versus choosing an effective (but toxic) combination (i.e., docetaxel + capecitabine) earlier on has generated much debate and may be the subject of future scientific inquiry.

Importantly, this model does not assume that the survival benefit observed for the combination therapy would hold in the setting of single-agent docetaxel therapy followed by single-agent capecitabine therapy. Notwithstanding this, the sequence of treatments does have relevance when third-line therapies are considered in the model. Based on Cancer Care Ontario registry and Ontario prescription claims data, it is clear that 30% of patients treated with a taxane are subsequently treated with capecitabine, an observation upheld in the randomized trial where 44/163 (27%) patients who

received single-agent docetaxel therapy subsequently received capecitabine therapy post-study. In our model, we applied these observations to the costing of third-line (post-taxane) treatments, but assumed that, for patients initially treated with the combination treatment, single-agent vinorelbine therapy would be the likely choice for those eligible for salvage treatment on progression. Although this conferred a higher cost for third-line therapy in docetaxel/capecitabine-treated patients, it is important to note that, for the model population, the cost-effectiveness remained well within acceptable ranges.

In summary, from the perspective of the Canadian provincial health care system, the cost of the addition of capecitabine to docetaxel for treatment of anthracycline-pretreated MBC is well within an acceptable range for health care intervention [8, 14, 15] and supports the allocation of health care resources to this treatment strategy. In a recent meta-analysis of oncology CU publications, the median value for cost-effectiveness among 89 assessments in 40 studies was US\$20,000 per quality-adjusted life year (QALY) gained [16]. Although our model does not use utility to approximate quality of life, it appears that the cost-effectiveness ratio for capecitabine/docetaxel therapy in the Cancer Care Ontario population is more favorable than the majority of oncology cost-effectiveness ratios reported in the meta-analysis.

This model can be adapted to enable an assessment of costs in other countries, using appropriate currencies, health

care perspectives, and resources. Extrapolation of the analysis to a U.S. model may be complicated by the higher U.S. cost of care for these patients. However, the oral administration of capecitabine, together with the lower hospitalization costs for capecitabine/docetaxel therapy compared with single-agent docetaxel therapy revealed by the current analysis, indicate that the impact of the higher overall cost of medical care would be minimal.

Cost and CU analyses of capecitabine/docetaxel therapy versus single-agent docetaxel therapy in patients with anthracycline-pretreated MBC performed in the U.S. support the results of the current study [24]. In that study, measures of clinical effectiveness and economic data were combined in an analytical model using the U.S. health care system as the base case and, as in the current study, data relating to clinical effectiveness and medical resource utilization collected prospectively during the phase III clinical trial. The cost per life-year gained for capecitabine/docetaxel therapy compared with docetaxel alone was US\$3,954 in the U.S. study, supporting the cost-effectiveness ratio obtained in the current study. Following adjustment of TTP and survival to account for the different utility of these two health states, the cost per QALY gained for the combination therapy over docetaxel alone in the U.S. study was calculated as US\$5,850. Clearly, capecitabine/docetaxel therapy is a highly active and cost-effective new treatment option for women with anthracycline-pretreated MBC.

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