Pharmacoeconomic Analysis of Prophylactic Treatments for Emesis Secondary to Breast Cancer Chemotherapy

George Dranitsaris, Carlo De Angelis, David Warr and Lutchmie Narine

ABSTRACT

The objectives of this study were to perform a cost effectiveness analysis of ondansetron plus dexamethasone against standard metoclopramide antiemetic combinations in the prevention of acute and delayed emesis following breast cancer chemotherapy protocols administered within the institutional setting. A retrospective chart review was conducted on 163 inpatients who received 5-fluorouracil, cyclophosphamide and epirubicin (FEC) or doxorubicin (FAC). The proportion of patients with complete control of emesis within the first 24 hours (acute) and between 24-72 hours after the completion of chemotherapy (delayed) were determined. A comparative cost model was applied from a hospital perspective. Costs of primary therapy, rescue therapy, nursing costs for breakthrough emesis, extended hospitalization for uncontrolled emesis, and side effects were included in this calculation. The percentage of patients in the ondansetron group who experienced complete emesis control in the acute period was 69.4% compared to 49.2% in the metoclopramide group (p=0.015). The incremental cost in the ondansetron group was $26.83 per additional episode of emesis avoided. In the delayed emetic time frame, patients on ondansetron and those on the metoclopramide regimen had comparable rates of complete control of emesis, 58.2% vs. 47.7% (p=0.25), respectively. The incremental ondansetron cost was $80.19 per episode of emesis avoided. The results of this analysis suggest that ondansetron in combination with dexamethasone is an economically attractive treatment strategy in the hospital setting for the prevention of acute emesis. The use of ondansetron beyond the first 24 hours following moderately emetogenic chemotherapy becomes a more expensive treatment. .

Key words: *cost-effectiveness, dexamethasone, emesis, metoclopramide, ondansetron*

RÉSUMÉ

Le but de cette étude était de comparer le rapport coût/efficacité de l'association ondansétron-dexaméthasone à celui des associations standard d'antiémétiques avec métoclopramide, dans la prévention des vomissements immédiats et tardifs consécutifs aux séances de chimiothérapie contre le cancer du sein données en milieu hospitalier. Les chercheurs ont mené une analyse rétrospective des dossiers thérapeutiques de 163 patients hospitalisés auxquels on a administré l'association 5-fluorouracil-cyclophosphamide-épirubicine (FEC) ou doxorubicine (FAC). Ils ont évalué le pourcentage de patients qui ont obtenu une parfaite maîtrise de leurs vomissements dans les 24 heures suivant la chimiothérapie (vomissements immédiats) et dans les 24 à 72 heures après la chimiothérapie (vomissements tardifs). Un modèle de coûts comparés a été utilisé pour évaluer divers aspects des soins hospitaliers, notamment les coûts en terme de traitement principal, de traitement de secours, de soins infirmiers pour les vomissements perthérapeutiques, de séjour prolongé dû aux vomissements non maîtrisés et d'effets indésirables. Le taux de patients du groupe ondansétron ayant obtenu une parfaite maîtrise de leurs vomissements immédiats a été de 69,4 %, comparativement à 49,2 % pour les patients du groupe métoclopramide (p = 0,015). Le coût additionnel par épisode émétique évité était de 26,83 $ dans le groupe ondansétron. De plus, le taux de patients ayant obtenu une maîtrise parfaite de leurs vomissements tardifs était semblable pour le groupe ondansétron, 58,2 % et le groupe métoclopramide, 47,7 % (p = 0,25). Le coût additionnel par épisode émétique évité dans ce cas-ci était de 80,19 $ pour le groupe ondansétron. Les résultats de cette analyse portent à croire que l'ondansétron associé au dexaméthasone constitue une stratégie thérapeutique économique et intéressante pour le milieu hospitalier dans la prévention des vomissements immédiats. En revanche, l'utilisation de l'ondansétron après les 24 premières heures suivant une chimiothérapie modérément émétogène s'avère plus dispendieux.

Mots clés : *coût/efficacité, dexaméthasone, métoclopramide, ondansétron, vomissements*

Can J Hosp Pharm 1995; 48:266-275

George Dranitsaris, MSc.Phm., is the Coordinator of Pharmacoeconomic Research in the Department of Pharmacy at the Ontario Cancer Institute/Princess Margaret Hospital, Toronto, Ontario.

Carlo De Angelis, Pharm.D., is the Coordinator, Oncology in the Department of Pharmacy, Toronto-Sunnybrook Regional Cancer Clinic and Division of Clinical Pharmacology, Sunnybrook Health Science Centre, North York, Ontario.

David Warr, M.D., is a staff Medical Oncologist at the Ontario Cancer Institute/Princess Margaret Hospital.

Lutchmie Narine, PhD., is an Assistant Professor in the Department of Health Administration at the University of Toronto.

Address correspondence to: George Dranitsaris, MSc.Phm., Coordinator of Pharmacoeconomic Research, Department of Pharmacy, Ontario Cancer Institute/Princess Margaret Hospital, 610 University Avenue, Toronto, Ontario. M5G 2M9.

Acknowledgments: The authors would like to thank Laurie Dunn for the data collection. This study was supported by a grant from Glaxo Canada Inc.

INTRODUCTION

The development of new and often more expensive drug therapies with increased clinical effectiveness has placed a tremendous financial burden on health-care decision makers. Difficult questions often arise. Should the new drug entity replace the existing treatment? If yes, at what dose and frequency should the new drug product be administered to ensure cost-effectiveness? The available tools of pharmacoeconomics can facilitate the decision making process.

Although pharmacoeconomic research will play a major role in the use of new pharmaceuticals, it is not without limitations. A major drawback of many studies is that optimal clinical outcome data are required from Multi-Centre Phase III clinical trials. Often such trials are difficult and costly to conduct.[1] Another limitation of pharmacoeconomic studies relates to the applicability of the data towards centres not participating in the original Phase III trial.[2] The costs used in the original trial may not reflect the costs incurred by other institutions using the new agent, and often the choice of the alternative product for comparison may not be the standard therapy across all centres. Published literature is another data source for pharmacoeconomic analyses but because of space limitations in most journals, important clinical and toxicity data may not be described in detail. Both of these two sources measure efficacy.

Hospital patient records are an alternative to the two former methods.[1] This source is rich in patient information which can be used to estimate effectiveness as opposed to the efficacy of therapy. It has been suggested that an approach which estimates clinical effectiveness may be preferred over one that measures efficacy (i.e., randomized comparative trials) because the former method estimates the benefit of treatment in the everyday clinical setting in a wide variety of patients.[3]

Ondansetron has been shown to be effective in the prevention of emesis during cisplatin-chemotherapy,[5,6] and it has become the treatment standard for many cisplatin protocols. Although ondansetron has demonstrated greater efficacy than many metoclopramide containing combinations, it is more expensive. In the face of decreased government funding, pharmacy departments are increasingly required to justify the use of ondansetron in non-cisplatin containing regimens. In order for ondansetron to be cost effective, its higher cost must be offset by its superior efficacy. Buxton and O'Brien[7] demonstrated that, relative to high dose metoclopramide, the higher cost of ondansetron was offset by its superior efficacy in patients receiving cisplatin chemotherapy. They reported the two drugs would be equally cost effective even if ondansetron were priced five times more than metoclopramide[7].

FAC (5-fluorouracil, doxorubicin, cyclophosphamide) and FEC (5-fluorouracil, epirubicin, cyclophosphamide) are considered moderately emetogenic,[8] and as yet no formal pharmacoeconomic studies involving ondansetron have been published. Therefore, it was the objective of this study to evaluate the cost-effectiveness of ondansetron, compared to metoclopramide based antiemetic therapies, in patients with breast cancer receiving FAC and FEC chemotherapy. This retrospective study utilized the records of patients treated at the Princess Margaret Hospital (PMH) and Sunnybrook Health Science Centre (SHSC), two of the largest cancer treatment centres in the province of Ontario, Canada.

METHODS

A retrospective chart review was undertaken to determine the effectiveness of therapy and resources consumed in the everyday hospital setting. FAC and FEC are usually administered in an out-patient setting. Nausea and vomiting data in this population are limited since patients leave the clinic following administration of chemotherapy. Therefore, an analysis was undertaken of patients who were admitted to hospital for other reasons, and while in the hospital received FAC or FEC chemotherapy.

Retrospective Chart Review

A comprehensive patient search was conducted from 1985 to 1993 for patients with a histologic diagnosis of breast cancer who received FAC or FEC in-hospital. Patients with marked hepatic dysfunction (liver function tests greater than four times the upper limit of normal) were excluded from the study. As well, patients who had any nausea and/or vomiting 48 hours prior to chemotherapy were also rejected.

Approximately 60% of the charts were from patients who were treated with ondansetron plus dexamethasone. The remainder were from patients treated with "standard" non-ondansetron containing antiemetic regimens consisting of combinations of metoclopramide, dexamethasone, diphenhydramine, or lorazepam administered according to institutional guidelines. Charts of patients were reviewed and the dose, route and number of doses of the preventative antiemetic therapy administered was recorded as were the course number and type of chemotherapy administered. The administration of rescue medication when preventive antiemetic therapy failed was also documented. The distribution of antiemetic dose was sufficiently skewed in some cases to warrant the use of median values as opposed to mean. As a result, the median dose of individual drugs administered in each of the treatment arms as well as those administered for rescue therapy was used for the economic analyses.

Response to preventive antiemetic therapy was based on the number of episodes of either nausea or vomiting

following administration of chemotherapy. An episode of nausea was defined as the need for rescue medication without actual vomiting. This information, obtained from nursing notes, was compared to medication administration records to indicate the use of rescue medication. Unless indicated otherwise in the nursing notes, it was assumed that the administration of "rescue/breakthrough" medication was for controlling nausea. This was a conservative approach to the interpretation of the data but was deemed appropriate due to the retrospective nature of the study. The onset of an event (emesis or nausea) was characterized as acute when occurring within the first 24 hours, and delayed when it occurred between 24 and 72 hours following administration of chemotherapy. Complete control of emesis after primary therapy was defined as no episodes of nausea or vomiting.

In addition, the total number of vomiting episodes requiring a nursing intervention (i.e., clean-up, supplies, etc.) and the total number of hospital days required to treat uncontrollable emesis due to therapeutic failure were recorded for each treatment group. A hospital day for uncontrollable emesis was recorded if it was explicitly stated in the physician's notes that the patient was to remain in hospital because of poor emesis control. The above data were used to quantify the economic impact of managing a patient who had vomited. The cost of hospitalization was applied towards the delayed emesis time period only.

The final treatment related outcome obtained from the retrospective chart review was the occurrence of antiemetic related side effects. The type of medical intervention if any, was also recorded. The occurrence of side effects was incorporated into the outcome branches in the decision-analytic model (vide infra). The gathering of this information was facilitated by the development and use of a standardized data collection sheet.

Decision Analysis Costing Model

The prophylactic treatment of nausea and vomiting induced by FAC or FEC breast cancer chemotherapy was modeled using the principles of decision analysis.[9] The time frame for the study was the first 24 hours post-chemotherapy (acute phase) and between 24 and 72 hours post-chemotherapy (delayed phase). A decision-based analytic model was developed to measure the cost effectiveness of antiemetic therapies currently in use at both PMH and SHSC (Figure 1).

The model initially began with the primary treatment which consisted of ondansetron with dexamethasone in one group, versus a combination containing metoclopramide, dexamethasone, diphenhydramine or lorazepam in the other. Patients who failed to respond to primary therapy were subsequently followed-up for treatment with rescue medication. According to the model, success was defined as a state of complete emesis control. This state could have been achieved after primary therapy or if the patient responded to rescue medication (up to three doses). Patients who received more than three doses of rescue therapy were classified as complete therapeutic failures. The results of the chart review provided probability estimates for each of the nodes in Figure 1. All subjects were used to estimate the primary response rates but only those patients who received rescue medication were used to measure the response rates secondary to rescue treatment.

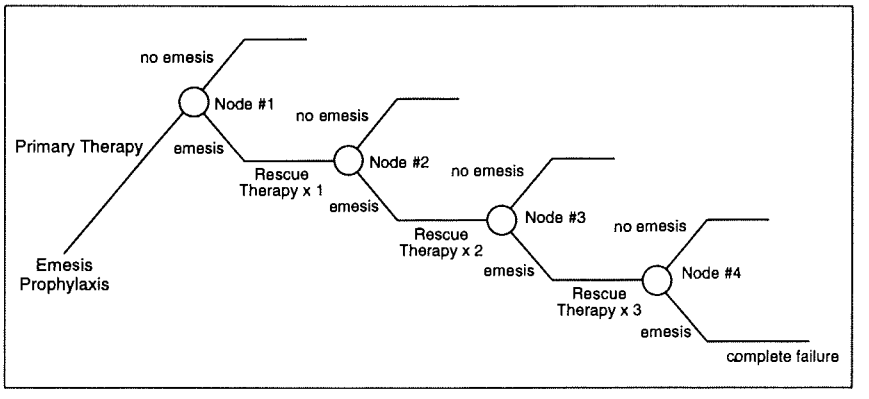

Figure 1. Prevention of emesis in patients receiving FEC or FAC chemotherapy.
Primary therapy was either ondansetron and dexamethasone or metoclopramide based therapy which may also have included dexamethasone, lorazepam or diphenhydramine. Rescue therapy consisted of prochlorperazine. The cost of therapy at each node or branch was calculated according to the following formulae and the resources consumed (see text):

Cost of no emesis at node 1 = Primary Therapy Cost (PTC) + Side Effect Management cost (SEMC) probability of primary response at node #1.

Cost of no emesis after one rescue dose (node 2) = (PTC + Cost of Rescue Therapy (CRT) + SEMC) x [(1-prob node #1)x(prob node #2)]

Cost of no emesis after two rescue doses (node 3) = (PTC + 2xCRT + SEMC) x [(1-prob node #1)x(1-prob node #2)x(prob node #3)]

Cost no emesis after three rescue doses (node 4) = (PTC + 3xCRT + SEMC) x [(1-prob node #1)x(1-prob node #2)x(1-prob node #3)x(prob node #4)]

Cost of continued emesis after three rescue doses (complete failure - node 4) = (PTC + 3xCRT + total Failure Cost (TFC) + SEMC) x [(1-prob node #1)x(1- prob node #2)x(1-prob node #3)x(1-prob node #4)]

Total cost = sum of costs encountered at each branch

Overall probability of success = [1-(1-prob node #1)x(1- prob node #2)x (1-prob node #3)x(1-prob node #4)]

Cost effectiveness ratio = Total cost / Overall probability of success

Cost Effectiveness Analyses (CEA)
The decision model (Figure 1) was used to measure the cost-effectiveness of each therapy for a given patient in terms of the ratio of cost per successful control of emesis using the following direct costs:

1. Primary therapy cost (PTC) = (cost of drug(s) + cost of preparation + cost of administration)
2. Cost of rescue therapy (CRT) = (cost of drug(s) + cost of preparation + cost of administration + nursing cost (e.g., clean up time, supplies, etc.) of managing a patient who has vomited).
3. Total failure cost (TFC) = (hospitalization due to uncontrolled emesis).
4. Side effects management costs (SEMC) refers to the costs associated with treating antiemetic induced side effects. The required treatment (if any), cost of treatment, and the incidence rate for a given side effect was obtained from the chart review and was calculated as:
   SEMC = cost of treatment x (% incidence x % treated).

Cost Effectiveness Calculations
The cost of successful therapy was the sum of all direct costs for each branch of the model shown in Figure 1 and was calculated according to each of the formula found in the legend of Figure 1. Each equation corresponds to one of the possible treat outcomes.

The hospital costs used in this study were from PMH as the majority of patients evaluated were from that centre. These hospital costs were within 5% of those incurred at SHSC. The cost of dose preparation and administration, including personnel and supplies, were obtained from 1993 pharmacy catalogues along with pharmacy and nursing workload measurement statistics. The cost of daily hospitalization (average operating cost) used was $532/day as reported by the Ontario Hospital Association (OHA). Other costs were obtained from PMH cost statistics (Appendix A).

The Yates-Corrected Chi-square statistic was used to test the significance of the difference between groups in the proportion of patients achieving complete emesis control. The cut off for significance was $p<0.05$. Discounting was not applied in this study because of the short time periods involved. However, sensitivity and incremental analyses were conducted as described by Jolicoeur et al.[4] These were characterized by varying the rates of complete emesis control while keeping all of the other variables in the analysis constant. As well, the dose, route, and duration of ondansetron therapy was varied to measure their impact on the cost effectiveness.

RESULTS

Retrospective Chart Review
Data from 163 in-patient charts from both centres, 129 from PMH and 34 from SHSC were the basis of this report. Ninety-eight patients received ondansetron containing therapy and 65 received "standard" non-ondansetron antiemetics for the prevention of acute and delayed emesis. Patients in the ondansetron group received chemotherapy after 1990 when the antiemetic became available for clinical use. The majority of subjects in the comparator group received chemotherapy before 1990 when metoclopramide containing regimens were the treatment standard. The FAC and FEC protocols did not substantially change during these two time periods. However, when ondansetron became commercially available there was a change in prescribing practice away from metoclopramide-based antiemetics.

The patient records were sufficiently detailed to allow a reasonably good estimation of clinical and resource consumption data. Patients were similar with respect to age, weight, height, and body surface area (Table I). Of the 98 patients in the ondansetron group, 44 were administered FAC and the other 54 received FEC. In the non-ondansetron group, 20 patients received FAC and 45 were dosed with FEC. As illustrated in Table I, the mean single day FAC and FEC doses administered to each of the study groups were similar.

The median pre-chemo dose in the ondansetron group was 8 mg of ondansetron IV combined with 10 mg dexamethasone IV. The post-chemo median dose was 8 mg of ondansetron orally every 12 hours for three doses. This was combined with

Table I. Patient demographic and chemotherapy data.

Summary Data[a]	Ondansetron Group	Comparator Group
Sample Size	98	65
Mean Age (yrs)	51.3 ± 11.3	49.2 ± 9.9
Mean Wt (kg)	67.1 ± 14.6	65.7 ± 12.8
Mean Ht (cm)	159.8 ± 8.7	160.5 ± 9.7
Mean BSA (m^2)	1.7 ± 0.2	1.7 ± 0.2
Total FEC Patients	54	45
Total FAC Patients	44	20
Mean 5-FU Dose (mg/m^2)	455.7 ± 78.9[b]	455.2 ± 81.1[b]
Mean Cyclophosphamide Dose (mg/m^2)	IV: 468.9 ± 77.8[b] PO: 69.5 ± 13.5[c]	IV: 468.5 ± 94.9[b] PO: 69.7 ± 6.41[c]
Mean Epirubicin Dose (mg/m^2)	48.5 ± 9.41[b]	50.3 ± 7.59[b]
Mean Doxorubicin Dose (mg/m^2)	46.2 ± 9.29[b]	39.2 ± 11.6[b]

[a] ±SD.
[b] Single day IV administration.
[c] As an alternative to single day IV dosing. Cyclophosphamide was administered as a daily oral dose for 14 consecutive days in some patients.

a median dose of 4 mg of dexamethasone orally every 12 hours for three doses. This treatment strategy was typical for both oncology centres. However, it was noted that physicians began using oral ondansetron pre-chemo with greater frequency in the latter part of 1993. Twenty such occurrences were noted in the 98 patients who received ondansetron pre-chemo. For the purpose of the economic analysis, these twenty doses were costed as IV doses (Table II).

Table II. Antiemetic[a] administration data.

Summary Data	Ondansetron Group	Metoclopramide Group
Median Pre-Chemo Dose in mg (range)	OND IV: 8.0[b] DEX IV: 10.0 (0-20)	MET IV: 30.0 (0-120) DEX IV: 10.0 (0-20) LOR SL: 1.0 (0-2) DIPH IV: 25.0 (0-50)
Median Post-Chemo Dose in mg (range)	OND PO: 24.0 (0-136) DEX PO: 12.0 (0-180)	MET IV: 30.0 (0-360) MET PO: 50.0 (0-320) DEX PO: 8.0 (0-54) DIPH PO: 50.0 (0-300)

[a] OND represents ondasetron; DEX represents dexamethasone, MET represents metoclopramide, LOR represents lorazepam and DIPH represents diphenhydramine.
[b] 20 of the 98 patients in this group received an oral pre-chemo dose of ondansetron. For the purpose of this study, this was costed as an intravenous dose.

The "standard" non-ondansetron containing antiemetic pre-chemo regimens consisted of drug combinations which included metoclopramide IV, dexamethasone IV, diphenhydramine IV and lorazepam SL (Table II). In the post-chemo non-ondansetron regimens, the majority of the drugs were given via the oral route except for a single dose of metoclopramide IV administered after the completion of chemotherapy (Table II).

Table III. Clinical and economic outcomes of antiemetic therapy.

Patient Outcome	Ondansetron Group (n=98)		Comparator Group (n=65)		Significance
ACUTE PHASE					
Complete primary control	68 (69.4%)		32 (49.2%)		0.015
Primary treatment cost		$32.80		$15.77	
Total emetic episodes	58		74		
Failure but no rescue[a]	6		7		
Rescue dose x 1	11		11		
Rescue dose x 2	6		3		
Rescue dose x 3	3		3		
Total rescue cost		$17.91		$16.95	
Rescue dose > 3	4		9		0.049
Complete failure[b]	5.1%		17.6%		
Total failure cost		$6.02		$18.59	
Total cost[c]		$56.73		$51.31	
Overall success[d]	94.9%		82.4%		0.039
Cost effectiveness ratio[e]		**$59.77**		**$62.26**	
DELAYED PHASE					
Complete primary control	57 (58.2%)		31 (47.7%)		0.25
Primary treatment cost		$37.13		$13.03	
Total emetic episodes	83		61		
Extended hospitalization (Patients)	8		7		0.77
Failure but no rescue[a]	4		7		
Rescue dose x 1	15		6		
Rescue dose x 2	6		4		
Rescue dose x 3	4		6		
Total rescue cost		$45.16		$14.90	
Rescue dose > 3	12		11		0.54
Complete failure[b]	13.6%		21.3%		
Total failure cost		$37.27		$83.21	
Total cost[c]		$119.56		$111.14	
Overall success[d]	86.4%		78.7%		0.31
Cost effectiveness ratio[e]		**$138.32**		**$141.26**	

[a] Not used to estimate cumulative probability of treatment success.
[b] Cumulative probability of reaching branch five of the decision tree.
[c] Sum of primary, rescue and total failure costs.
[d] Overall success = [1-(1-prob node #1)x(1- prob node #2)x(1-prob node #3)x(1-prob node #4)].
[e] Total cost divided by probability of overall successful control of emesis.

In the acute time period, complete emesis control was attained in 68 of 98 (69.4%) patients receiving ondansetron compared to 32 of 65 (49.2%) patients receiving metoclopramide based therapy ($p = 0.015$; Table III). Thirty patients in the ondansetron group (30.6%) and 33 in the comparator protocol (50.8%) experienced an emetic event. The total number of emetic episodes requiring a nursing intervention was 74 in the comparator group, compared to 58 in the patients treated with ondansetron.

In the delayed emesis time frame, complete primary control was achieved in 58.2%

of patients in the ondansetron group and 47.7% in the non-ondansetron group (Table III). Forty-one of 98 patients (41.8%) in the ondansetron group and 34 of 65 (52.3%) in the comparator protocol failed initial therapy (p=0.25; Table III). The total number of emetic episodes requiring a nursing intervention was 61 in the metoclopramide containing arm compared to 83 in the patients treated with ondansetron. Eight of the 98 patients in the ondansetron group had an extended hospitalization due to uncontrolled emesis compared to 7 of 65 patients in the metoclopramide based therapy group (p = 0.77; Table III). Unlike the results from the acute phase of the study, the sample size was not sufficient to detect a statistically significant difference between groups for the control of delayed emesis (p=0.25). A subsequent sample size estimate revealed that approximately 390 patients would be required in each group to detect a 10% difference in the control of delayed emesis. Alternatively, with the current sample size, a difference of approximately 17% would have had to be present in the proportion of patients with complete control of delayed emesis for the difference to be statistically significant. This is with consideration of a two-sided test, a significance level of 5% and an 80% power to detect significant differences. Therefore, the cost-effectiveness of ondansetron in the control of delayed emesis cannot be reliably demonstrated in this study.

Rescue Therapy

Patients who had an emetic episode after the use of ondansetron or metoclopramide containing combinations were then followed up with respect to rescue medication, typically prochlorperazine or dimenhydrinate. The drug, dose, route, and number of doses administered were recorded. These subjects were placed into one of the outcome branches of the decision model depending on the number of rescue doses administered and success of rescue therapy (Figure 1). There were a total of 30 patients in the ondansetron group during the initial 24 hours who had at least one episode of nausea or vomiting. Of these, 24 patients were treated with rescue medication. In the metoclopramide containing group, 33 patients had at least one emetic episode. Of these patients, 26 received rescue therapy (Table III).

A similar approach was used for delayed emesis after the initial 24 hours and up to 72 hours post chemotherapy. A total of 41 patients in the ondansetron group had at least one emetic episode (Table III). Of these, 37 patients received rescue medication. In the metoclopramide containing group, 34 patients had at least one emetic episode during the same time period. Of these patients, 27 received rescue therapy (Table III). Only those patients who received rescue medication were used to estimate the probabilities of successful rescue therapy required for the CEA (Figure 1).

The final treatment related outcome recorded from the retrospective chart review was the occurrence of anti-emetic related side effects. A summary of the side effects reported for each of the treatment groups is presented in Table IV. The overall incidence of side effects was higher in the metoclopramide containing group, with restlessness in the acute phase being reported (13%) significantly more often in the first 24 hours than any ondansetron related side effect (p = 0.023). Restlessness in the delayed phase was not reported more frequently than any ondansetron related side effect (p = 0.41). All reported side effects were easily treated and no patient required hospitalization for the management of an adverse effect.

Pharmacoeconomic Analyses

When considering only resource inputs and not therapeutic outcomes of therapy, the ondansetron group was approximately twice as expensive than the comparator group ($111 vs. $59). The lower acquisition cost of metoclopramide was the principal driving force that resulted in a lower overall cost of primary therapy. However, due to the significantly higher frequency of successful acute therapy and a difference in the number of patients hospitalized for uncon-

Table IV. Side effect incidence rates reported in each of the study groups.

Ondansetron Group[a]	% Incidence	Metoclopramide Group[a]	% Incidence
Acute Phase		**Acute Phase**	
Headache	2.5	Restlessness	13.8[b]
Fatigue	1.3	Hallucinations	6.2
Dry Mouth	1.3	Insomnia	6.2
Numb Extremities	1.3	Fatigue	3.1
Swollen Tongue	1.3	Headache	3.1
Diarrhea	1.3		
Facial Redness	1.3		
Delayed Phase		**Delayed Phase**	
Headache	3.9	Restlessness	7.8[c]
Lethargy	1.3	Insomnia	6.2
Constipation	1.3	Blurred Vision	6.2
Depression	1.3	Hallucinations	6.2
Diarrhea	1.3	Steroid Withdrawal	1.5

[a] Treatments for side effects consisted of acetaminophen for headache, anxiolytics for restlessness and insomnia, and laxatives for constipation. The rest of the adverse events where of short duration and did not require medical intervention.

[b] Restlessness in the metoclopramide group was reported significantly more often than headache in the ondansetron group during the acute phase (p = 0.023).

[c] Restlessness in the metoclopramide group was not reported more often than headache in the ondansetron group during the delayed phase (p = 0.41).

trolled emesis, ondansetron treatment was a marginally more cost effective treatment for the prevention of emesis associated with FAC or FEC chemotherapy (Table III). The single most relevant factor that contributed towards cost effective ondansetron therapy in the prevention of delayed emesis was the lower incidence of hospitalization required for the treatment of uncontrolled nausea and vomiting. Although the rate of hospitalization was not significantly different from the metoclopramide group (p=0.77), the difference in point estimates and the large costs involved, produced lower total costs of failure for ondansetron (Table III).

Sensitivity Analysis

A sensitivity analysis was conducted to test the stability of the findings. The probability of complete initial control of acute emesis in the ondansetron group after primary therapy was varied from 40-85% while keeping all of the other variables in the analysis constant. The baseline ratio of the metoclopramide comparator was used to determine the minimum response rate required in the ondansetron group for cost-effectiveness. As illustrated in Figure 2, a minimum response rate of approximately 63% would be required for cost effective ondansetron therapy. The work of Bonnetere et al,[10] Dicato [11] and the current study resulted in primary response rates of 66%, 73%, and 69%, respectively, all of which support the use of ondansetron for the prevention of acute emesis.

In the current study, the pre-chemo dose of ondansetron was 8 mg IV. A sensitivity analysis was conducted based on a variety of dosing alternatives. Recently it has become common practice to prescribe an oral dose of ondansetron pre-chemo, rather than an IV dose. This scenario was tested in the model. The results of changing the route improved the cost-effectiveness of ondansetron relative to the metoclopramide comparator by over 25% (Table V). Other analyses included the costing of administration of a 32 mg pre-chemo IV dose, a 16 mg IV pre-chemo dose, an 8 mg oral dose every eight hours for one day, and an 8 mg oral dose every 12 hours for one day (Table V). As shown in Table V, only the administration of a single 8 mg oral dose of ondansetron pre-chemo enhanced ondansetron cost-effectiveness, given the $62.26 cost per effective treatment for the metoclopramide based therapy.

A similar series of analyses were conducted for the prevention of delayed emesis. While keeping all of the other parameters constant, the probability of complete primary control in the ondansetron group was varied from 40-85%. The observed response to metoclopramide therapy (47.7%) was used to determine the minimum primary response rate required in the ondansetron group for cost effectiveness. As illustrated in Figure 3, a response rate of approximately 57% was required for ondansetron to be cost effective relative the metoclopramide treatment group. This was based on the administration of a median of three oral doses used in our study. The work of Bonnetere et al,[10] Dicato[11] and the current study resulted in initial response rates of 58%, 65%, and 58%, respectively, all of which suggest that the use of ondansetron in the

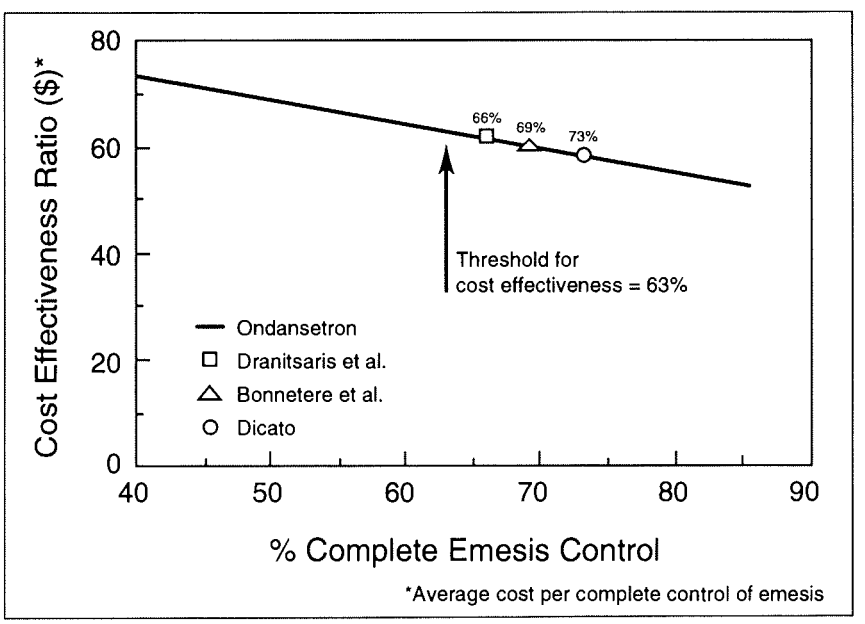

Figure 2. Sensitivity analysis: Variation in control of acute emesis. The cost effectiveness ratio is the average cost per effective treatment for complete emesis control.

Table V. Sensitivity analyses in acute emesis prophylaxis.

Parameter Adjustment[a]	Ondansetron Cost Effectiveness Ratio ($)	% Change[b] (+/-)	% Change[c] (+/-)
8 mg PO pre-chemo	45.32	+ 24.2	+ 27.7
32 mg IV pre-chemo	168.60	- 182	- 169
16 mg IV pre-chemo	96.11	- 60.8	- 53.4
8 mg PO q8h x 3 doses	84.52	- 41.4	- 34.9
8 mg PO q12h x 2 doses	64.92	- 8.62	- 3.60

[a] With the assumption that all of the other parameters in the model remain constant.
[b] The change in the cost effectiveness ratio relative to the observed initial ratio for ondansetron therapy of $59.77.
[c] The change in the cost effectiveness ratio relative to the observed initial ratio for metoclopramide therapy of $62.26. Positive (+) values indicate an advantage with ondansetron.

prevention of delayed emesis may also be economically attractive (Figure 3). However, as was indicated previously, a sample size of approximately 390 patients per group would be required to demonstrate that differences in response of this magnitude (47.7% vs. 58%) did not occur by chance alone.

The number of ondansetron post-chemo oral doses were then varied and the cost effectiveness ratio was determined with the following assumptions: primary and secondary response rates remained constant; no change in metoclopramide containing regimens. A range of post-chemo oral doses from 0-15 were analyzed in the model (Figure 4). The initial data point (zero ondansetron doses) was determined by combining the cost effectiveness ratios of an 8 mg IV ondansetron pre-chemo dose and metoclopramide-based antiemetics following chemotherapy. The combined acute and delayed metoclopramide cost effectiveness ratios were used for comparison. Ondansetron doses below the metoclopramide baseline estimate would be cost effective. As illustrated in Figure 4, the results from the model suggest that ondansetron was economically rational for up to three post-chemo oral doses. Beyond this, the question of "willingness to pay" comes into play where clinicians and patients must consider the cost or additional benefit.[13]

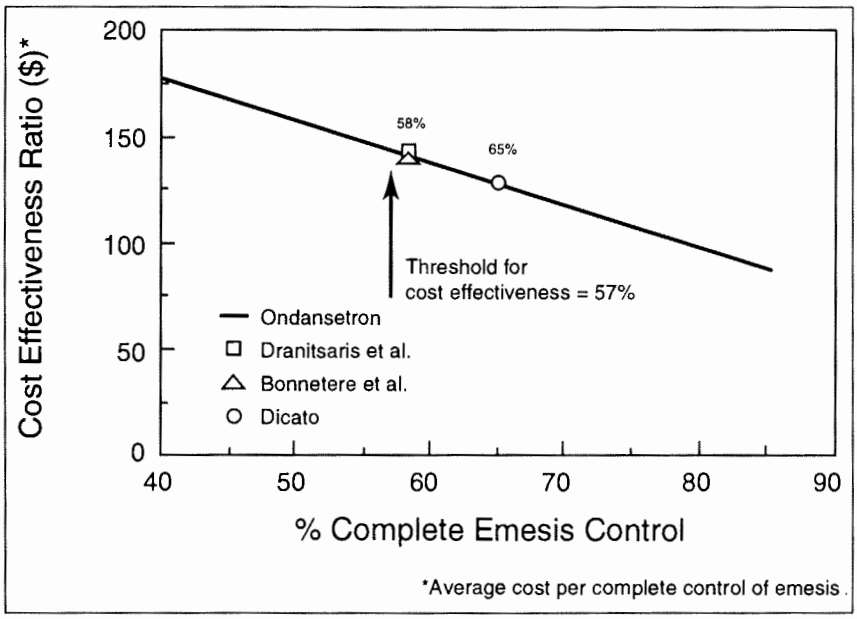

Figure 3. Sensitivity analysis: Variation in control of delayed emesis. The cost effectiveness ratio is the average cost per effective treatment for complete emesis control.

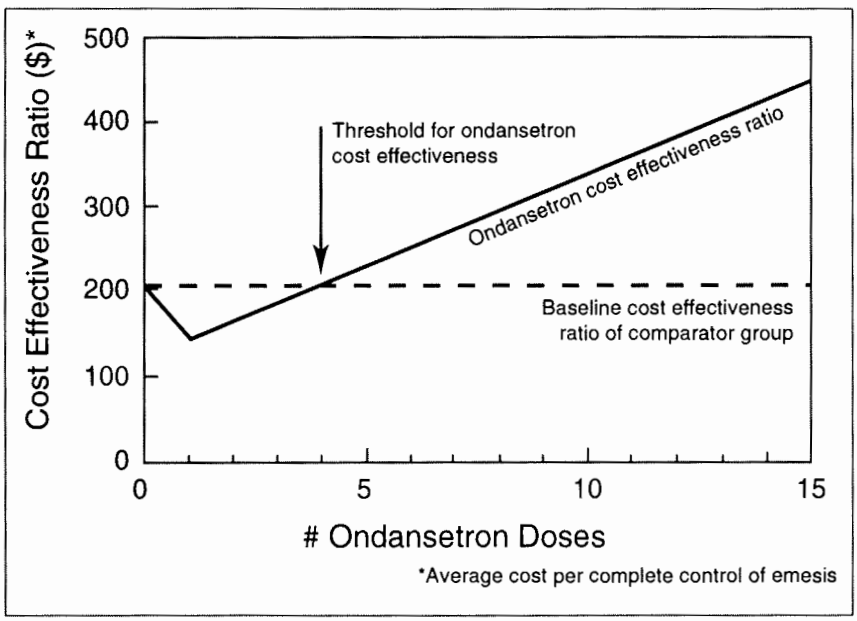

Figure 4. Sensitivity analysis: Variation in the number of ondansetron post-chemo doses. The cost effectiveness ratio is the average cost per effective treatment for complete emesis control.

Incremental Analysis

An incremental analysis was conducted to measure the cost of the additional benefits achieved by using the ondansetron protocol as opposed to the comparator therapy. Such an analysis was conducted for the acute and delayed time periods using the data in Table III. In the acute phase the difference in total cost between ondansetron and the metoclopramide group was $5.42 ($56.73-$51.31) and the difference in primary response rates was 20.2% (69.4% - 49.2%). This resulted in an incremental cost of $26.83 (5.42/0.202) per episode of emesis avoided during the first 24 hours after the completion of chemotherapy. Using the same procedure for the delayed period, where the difference in control was not significantly different, the incremental cost of ondansetron was $80.19 per episode of emesis avoided.

DISCUSSION

The development of new and often more expensive drug therapies has placed a tremendous stress on institutional drug budgets. Caregivers as well as patients may be demanding these new treatments

without clear evidence of incurred benefit at a reasonable cost. In order for these new agents to be successfully incorporated into a hospital formulary, cost effectiveness studies must be completed for each subgroup of patients who are potential candidates for the new therapy.

The results of this study support the use of ondansetron in breast cancer patients receiving moderately emetogenic chemotherapy in-hospital. This is especially relevant in light of the fact that breast cancer is the most common neoplasm affecting women in Western Europe and North America.[14] The prevention of emesis is a major concern to this group and clinicians, as it has a large impact on the patient's quality of life and economic resources required to manage uncontrolled nausea and vomiting.[15,16] When considering only costs of primary therapy, the ondansetron regimen was twice as expensive relative to the comparator regimen. However, an economic analysis which only measures the cost of primary therapy is complete when there is definitive evidence that the therapeutic outcomes of treatments are equivalent. [17] Since this was not the case with FAC or FEC chemotherapy induced emesis,[10,11,18] a cost effectiveness approach was therefore adopted. The results of the analyses demonstrated the ondansetron combination to be economically attractive for the prevention of acute and delayed emesis. Even though ondansetron had a higher initial acquisition cost, its higher overall clinical effectiveness resulted in reduced rescue treatment and consumption of hospital resources.

The results of the sensitivity analysis suggest that the model for acute emesis was sensitive towards the route of pre-chemo ondansetron administration, and most importantly the initial response rate of emesis prophylaxis. Administration of all ondansetron doses via the oral route improved its cost effectiveness relative to the metoclopramide-based comparator regimen. Finally, for ondansetron to be cost effective in the acute care setting, a minimum response rate of 63% was required. Response rates greater than 63% have been demonstrated in the current study as well as others.[10,11] A trend was seen during the chart review in that physicians started to prescribe oral ondansetron pre-chemo in the latter part of 1993. The lower acquisition cost of oral therapy would enhance the cost-effectiveness of ondansetron in the breast cancer clinical setting. However, an official change in prescribing practice should be delayed until the results of randomized trials demonstrate comparative efficacy of IV and oral ondansetron for moderately emetogenic chemotherapy.

The sensitivity analysis for the prevention of delayed emesis illustrated that an ondansetron response rate of approximately 57% must be achieved for cost effectiveness. The sensitivity analysis also demonstrated that in the prevention of nausea and vomiting, the administration of oral ondansetron for three doses following chemotherapy was cost effective. It is important to keep in mind that the frequency of control achieved with ondansetron was not significantly different than that obtained with metoclopramide based therapy.

An incremental analysis was also conducted. The results demonstrated that the incremental cost for improved effectiveness gained by using ondansetron was $26.83 in the acute phase compared to $80.19 in the delayed time period. These results are interesting because they suggest the use of ondansetron beyond the first 24 hours becomes progressively more expensive, which is consistent with reports from the literature[10,11] suggesting that 5-HT3 receptors are not as prominent in the mechanisms of delayed emesis as they are during the first 24 hours after chemotherapy.

The use of patient records to estimate clinical endpoints such as complete control of emesis is a weak data source epidemiologically because of the possibility of sampling and measurement bias. The ability to conduct sensitivity analyses may minimize this limitation by allowing the investigator to test for unknown or controversial parameters.[17] The response rates of ondansetron were varied to determine the threshold where the results of the model changed in favour of the comparator (Figures 2, 3, 4). This approach allowed us to present conservative recommendations for ondansetron use in our patient cohort (vide infra).

From this study, the antiemetic combination consisting of ondansetron and dexamethasone was determined to be economically rational for the prevention of emesis in breast cancer patients receiving anthracycline containing protocols in a hospital setting. For cost effective drug use, the results of our model promote the use of 8 mg of ondansetron IV with 10 mg of dexamethasone IV pre-chemo, followed by oral doses of 8 mg ondansetron and 4 mg dexamethasone every 12 hours for three doses of each drug. The substitution of the ondansetron IV by the oral formulation may further enhance cost effectiveness but further research is required to establish equivalent efficacy between the IV and oral dosage forms in moderately emetogenic chemotherapy. The results generated from this study may be of value to Pharmacy & Therapeutics Committees and government health care agencies for establishing guidelines for the use of ondansetron.

REFERENCES

1. Kozma CM, Kirchdoerfer LJ. Obtaining pharmacoeconomic data in health care organizations. *Top Hosp Pharm Manage* 1994; 13:23-30.
2. Drummond MF, Davies L. Economic analysis alongside clinical trials. *Intl J of Technology Assessment in Health Care* 1991; 7:561-73.
3. Detsky AS. Guidelines for economic analysis of pharmaceutical products.

PharmacoEconomics 1993; 3:354-61.
4. Jolicoeur LM, Jones-Grizzle AJ, Boyer G. Guidelines for performing a pharmacoeconomic analysis. *Am J Hosp Pharm* 1992; 49:1741-50.
5. Marty M. Ondansetron in the prophylaxis of acute cisplatin-induced nausea and vomiting. *Eur J Cancer Clin Oncol* 1989 (supp); 25:S41-5.
6. Marty M, Pouillart P, Scholl S, et al. Comparison of the 5-hydroxytryptamine3 (serotonin) antagonist-ondansetron (GR38032F) with high dose metoclopramide in the control of cisplatin-induced emesis. *N Engl J Med* 1990; 322:816-21.
7. Buxton MJ, O'Brien BJ. Economic evaluation of ondansetron: preliminary analysis using clinical trial data prior to price setting. *Br J Cancer* 1992; 66:S64-7.
8. Bakowski MT. Advances in anti-emetic therapy. *Cancer Treat Rev* 1984; 11:237-56.
9. Weinstein MC, Fineberg HV. *Clinical decision analysis.* Philadelphia, Pa: W.B. Sanders Co; 1980.
10. Bonneterre J, Chevallier B, Metz R, et al. A randomized double-blind comparison of ondansetron and metoclopramide in the prophylaxis of emesis induced by cyclophosphamide, fluorouracil, and doxorubicin or epirubicin chemotherapy. *J Clin Oncol* 1990; 8:1063-9.
11. Dicato MA. Oral treatment with ondansetron in an outpatient setting. *Eur J Cancer* 1991; 27:S18-9.
12. Johnson NE, Nash DB, Carpenter CE, et al. Ondansetron: cost and resource utilization in a US teaching hospital setting. *PharmacoEconomics* 1993; 3:471-81.
13. Gafni A. Using willingness-to-pay as a measure of benefits. What is the relevant question to ask in the context of public decision making about health care problems? *Med Care* 1991; 29:1246-52.
14. Silverberg E, Lunera J: Cancer Statistics 1987. CA-*A Journal for Clinicians* 1987; 37:2-19.
15. O'Brien BJ, Rusthoven J, Rocchi A, et al. Impact of chemotherapy-associated nausea and vomiting on patients' functional status and on costs: survey of five Canadian centres. *Can Med Assoc J* 1993; 149:296-302.
16. Morran C, Smith DC, Anderson DA. Incidence of nausea and vomiting with cytotoxic chemotherapy: A prospective randomized trial of antiemetics. *Br Med J* 1979; 1:1323-4.
17. Drummond MF, Stoddart GL, Torrance GW. Methods for the economic evaluation of health care programmes. Oxford, England: *Oxford Univ. Press*; 1987.
18. Marschner N. Anti-emetic control with ondansetron in the chemotherapy of breast cancer: A review. *Eur J Cancer* 1991; 27:S15-7.

Appendix A. Summary of therapy costs.

Resource Breakdown		Cost ($)
Primary Therapy Costs:		
Drug Acquisition:	Ondansetron 8 mg IV	34.40
	Ondansetron 8 mg PO	17.40
	Metoclopramide 50 mg IV	1.98
	Metoclopramide 10 mg PO	0.06
	Dexamethasone 10 mg IV	3.03
	Dexamethasone 4 mg PO	0.13
	Lorazepam 2 mg SL	0.04
	Diphenhydramine 25 mg IV	1.75
	Diphenhydramine 50 mg PO	0.14
	Prochlorperazine 10 mg PO	0.05
IV Doses:		
Preparation time[a]		4.25/dose
Administration time[a]		3.30/dose
Cost of mini-bags		1.55 each
Cost of supplies (needles, syringes, etc)		0.73/dose
PO Doses:		
Preparation time[a]		2.00/dose
Administration time[a]		1.20/dose
Future Costs:		
	Daily hospitalization[b]	532/day
	Nursing time per emetic episode[c]	3.95
	Linen, disposables etc	10.00

[a] Obtained from nursing and pharmacy workload measurement statistics, Princess Margaret Hospital.
[b] Average daily operating cost for a teaching hospital reported by the Ontario Hospital Association.
[c] From Johnson et al (1993).