Pergamon

European Journal of Cancer Vol. 31A, Nos 13/14, pp. 2174–2180, 1995
Elsevier Science Ltd
Printed in Great Britain
0959–8049/95 $9.50+0.00

0959-8049(95)00483-1

Original Paper

Economic Analyses of Toxicity Secondary to Anthracycline-based Breast Cancer Chemotherapy

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Doxorubicin (D) is one of the most active agents in the treatment of breast cancer but can be associated with cardiotoxicity (CT) and febrile neutropenia (FN). Epirubicin, a stereoisomer of doxorubicin, is reported to have similar efficacy but reduced toxicity. A retrospective chart audit was performed to estimate the incidence, average length of hospitalisation and resource consumption for the management of CT and FN in 200 patients breast cancer patients receiving equidoses of doxorubicin or epirubicin. Overall, there were three more episodes of CT in the doxorubicin group than in epirubicin patients (five versus two) at a cost of Canadian dollars C$4268/episode. With regard to FN, there were 11 more episodes in the doxorubicin arm (25 versus 14) at a cost of C$5419/episode. The results of the study support the substitution of equidose epirubicin for doxorubicin in women undergoing treatment for malignancies of the breast. Such a policy may result in reduced toxicity-related management costs.

Key words: cost, doxorubicin, epirubicin, cardiotoxicity, febrile neutropenia
Eur J Cancer, Vol. 31A, Nos 13/14, pp. 2174–2180, 1995

INTRODUCTION

BREAST CANCER is the most common neoplasm affecting women in Western Europe and North America [1]. In Canada alone, there were 12 307 new cases of breast cancer reported in 1987 and 4585 deaths from the disease [2]. The National Cancer Institute of Canada (NCIC) estimated that in 1992 the corresponding numbers were 15 700 and 5200, respectively, with an associated mortality rate of approximately 33% [3].

The anthracyclines (doxorubicin) alone or in combination are considered to be the most active single agents in the treatment of advanced breast cancer [4–6]. One drawback of doxorubicin is its potential for cardiotoxicity and dose-limiting myelosuppression [7–9]. Epirubicin, a stereoisomer of doxorubicin, is reported to be less toxic than doxorubicin, and yet has similar antitumour activity [9–11].

In a French study, 263 patients were randomised to either one of two regimens consisting of 5-fluorouracil and cyclophosphamide, both 500 mg/m^2 intravenously (i.v.), and either epirubicin (FEC) 50 mg/m^2 i.v. or doxorubicin (FAC) 50 mg/m^2 i.v. [12]. Both groups were balanced with regard to previous radiation therapy and adjuvant chemotherapy. Treatments were repeated every 3 weeks for up to six cycles. The overall response rates and survival were not significantly different between the two groups. A total of 8 patients in the FAC group had to discontinue therapy due to clinical congestive heart failure (CHF) in 3 subjects and 5 cases of cardiac arrhythmias. There were no such cardiac abnormalities in the FEC group. In addition, patients receiving FEC were reported to have less myelotoxicity, nausea and vomiting. Anthracycline-based breast cancer protocols commonly used at the Princess Margaret Hospital (PMH, Canada) are identical to those used in the French study [12] where the two therapies were dose equivalent.

The development of cardiotoxicity (CT) and febrile neutropenia (FN) can have a major impact on a patient's quality of life and may require costly hospitalisation, medication, and specialist consultations [13–15]. This is especially relevant to patients undergoing breast cancer chemotherapy who already have to cope with the tremendous psychological and physical burden of treatment. From an institutional perspective, reducing costs is an important objective, particularly in the current circumstances of severe fiscal restraint faced by many hospitals.

If a situation exists where two similar therapies with equivalent antineoplastic response rates are available, but one therapy is reported to have less costly side-effects than the other, it may be beneficial for the patient and the institution to adopt the less toxic protocol. What would make this therapy even more desirable would be if it were available at the same acquisition cost as the more toxic alternative.

The equidose FAC and FEC breast cancer protocols used at

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Revised 30 Jun. 1995; accepted 16 Aug. 1995.

PMH may fit the scenario described above. What has made the susbtitution of epirubicin for doxorubicin attractive from the perspective of PMH is the manufacturer's recently negotiated price adjustment making the acquisition cost of epirubicin identical to that of doxorubicin. Such a treatment policy may help avoid unnecessary hospitalisation and contribute to the efficient reallocation of limited hospital resources.

The primary therapy for many breast cancer patients at this institution was the FAC protocol until a recent recommendation by the Department of Pharmacy to the Medical Breast Group to use the FEC protocol exclusively. In order to support the Department of Pharmacy's initiative to make an official switch from FAC to FEC chemotherapy, we conducted an economic analysis on cardiotoxicity and myelosuppression secondary to FAC and FEC. The supportive care costs of epirubicin- and doxorubicin-induced cardiac abnormalities and FN incurred by the hospital for every 100 breast cancer patients were also calculated.

MATERIALS AND METHODS

Retrospective chart review

A comprehensive patient search which covered the period from 1985 to 1994 was conducted for patients who received FAC or FEC at PMH. Using a random number table, patients who were selected had to have a histological diagnosis of breast cancer and to have received at least one course of chemotherapy with either FAC or FEC exclusively. Patients with a previous cardiovascular accident (i.e. myocardial infarction, CHF) were excluded from the study. Patients with mild or moderate hypertension receiving standard medication were not excluded from the analysis. Information regarding chemotherapy administration included drug, dose, route and regimen for all courses, as well as the cumulative anthracycline dose.

Patient records were reviewed for the development of myelosuppression (absolute neutrophil count $< 1 \times 10^9$/l) and cardiotoxicity after each course of chemotherapy. Documentation of myelotoxicity included the number of therapy delays, the length of the delay and the number of subsequent chemotherapy cycles requiring dose reductions due to neutropenia.

The incidence of neutropenia requiring hospital admission was also recorded for both groups of patients. Also, the number of hospital days, the dose, duration and type of antibiotic therapy, the number of antibiotic levels ordered, the number of infectious disease (ID) consultations requested, and the number of routine laboratory tests performed were recorded. For patients who received treatment for FN or cardiac abnormalities in other hospitals, copies of the medical records were obtained.

Documentation of CT included the number of routine monitoring procedures ordered (left ventricular ejection fraction (LVEF%), chest X-ray, etc.), the occurrence of a cardiac event requiring a hospital admission, the number of hospital days, the dose, duration, and type of supportive therapy, and the number of cardiologist consultations which were recorded for both groups.

Economic analysis

An economic analysis from a hospital perspective was performed to determine the budgetary impact of managing cardiovascular abnormalities and FN episodes in patients after a course of FAC or FEC chemotherapy. The analysis included cost of hospitalisation, pharmaceutical support (including pharmacy preparation and nursing administration costs), therapeutic drug monitoring, laboratory tests for patient monitoring and specialist consultations. The data were presented as the overall cost of each type of toxicity per cycle of FAC or FEC.

The true cost of CT and FN was also determined using the incidence method as described by Hamilton [16, 17]. Briefly, this method combines the average hospital cost of an adverse event, the estimate of the true incidence rate determined from a study population as well as the population size. A sensitivity analysis was then conducted using the upper and lower limits of the 95% confidence interval (CI) for the difference in the incidence estimates.

The cost of supportive medication at PMH, including personnel and supplies, was obtained from current pharmacy ordering catalogues along with pharmacy and nursing workload measurement statistics. The cost of daily hospitalisation (average operating cost) used was C$521/day as reported by the Ontario Hospital Association for a teaching hospital [18] (the costs quoted in this study are in Canadian dollars ($1 C = $0.73 U.S.A. as of June 1995)). Laboratory and cardiac function tests, specialist consultations and therapeutic drug monitoring costs were obtained from the Departments of Biochemistry, Microbiology and Nuclear Medicine, PMH (Appendix). The acquisition costs of FAC and FEC chemotherapy were not included in the economic analysis because these two therapies are now cost equivalent in our institution.

Statistical analysis

A haematological toxicity ratio of 1 : 1.2 has been reported at equal doxorubicin/epirubicin doses [9]. Thus, the inclusion of approximately 100 patients in each group allowed the detection of a 20% difference in severe neutropenia requiring hospitalisation between the two treatment groups. This was with consideration of a two-sided test at a significant level of 5% and an 80% power to detect significant differences.

The Yates-corrected χ^2 statistic was used to test the significance of the difference between groups with respect to the incidence of CT and FN requiring a hospital admission. The non-parametric Mann–Whitney U-test was used to test the significance of the difference between groups with respect to the overall cost of toxicity per course of chemotherapy. The cut-off for significance for each of these procedures was $P < 0.05$. The 95% CI for the difference in the incidence estimates between FAC and FEC was determined using the method described by Gardner and Altman [19].

RESULTS

Cardiac toxicity

Between 1985 and 1994, 536 and 389 breast cancer patients received FAC and FEC chemotherapy at this institution, respectively. A total of 100 patients were randomly selected from each group. All patients had a diagnosis of breast cancer and were receiving FAC or FEC chemotherapy. 77 FAC and 75 FEC patients received their chemotherapy between 1990 and 1994, respectively. Prophylactic antibiotics were not routinely prescribed following the completion of a course of chemotherapy. Patients were similar with regard to physical characteristics, diagnoses and metastatic sites (Table 1).

An assessment of chemotherapy administration revealed that 21 patients did not receive any therapy prior to FAC compared with 23 subjects in the FEC group (Table 2). There was a perfect balance of patients in each group with regard to having received previous chemotherapy (27 in each group), and the majority of patients received at least one form of hormonal therapy before initiating anthracycline treatment. An interesting observation

Table 1. Patient data

Characteristic	FAC (n = 100)	FEC (n = 100)
Age, years	54.5	50.5
Median (range)	(36–79)	(27–84)
Weight, kg	67.0	63.5
Median (range)	(39–106)	(41–148)
Height, cm	161	161
Median (range)	(140.5–175)	(145–179)
Surface area, m^2	1.7	1.7
Median (range)	(1.3–2.2)	(1.4–2.2)
Case diagnosis		
Metastatic breast carcinoma	81	75
Inflammatory breast carcinoma	16	20
Ductal carcinoma	3	5
Metastatic sites		
Skin	1	0
Soft tissue	13	7
Nodes	20	25
Lung/pleura	28	24
Liver	35	30
Bone	45	52
Brain	8	11
Bladder	1	0
Eye/choroid	4	5
Pericardium	0	1

FAC, 5-fluorouracil, cyclophosphamide, doxorubicin; FEC, 5-fluorouracil, cyclophosphamide, epirubicin.

Table 2. Chemotherapy administration data

Characteristic	FAC (n = 100)	FEC (n = 100)
Patients with no previous therapy	21	23
Previous chemotherapy		
CMF	25	17
5FU/FA	1	0
5FU/mitomycin	0	1
Mitoxantrone	1	8
Actinomycin/vincristine	0	1
Irradiation to the mediastinum/thoracic spine	52	63
Hormonal manipulation		
Medroxyprogesterone	15	16
Tamoxifen	64	62
Aminoglutethamide	14	18
Progesterone	5	4
Oestrogen	3	0
Megesterone	10	8
Diagnosis to FAC/FEC treatment, months		
Median (range)	43 (1–216)	18 (1–292)
Cumulative dose of doxorubicin/epirubicin		
Median (range)	202 (23.5–513.5)	260 (38.9–860)
Duration of treatment, months		
Median (range)	4 (1–12)	4 (1–24)
Cycles administered		
Median (range)	6 (1–12)	6 (1–17)

See Table 1 for abbreviations of FAC and FEC. 5 FU, 5-fluorouracil; CMF, cyclophosphamide, methotrexate, 5FU; FA, folinic acid.

was noted; FEC patients began therapy within 18 months of the initial diagnosis compared to 43 months in patients who received FAC (Table 2). This may suggest that hormonal therapy was used for a shorter period of time in patients receiving FEC, thereby resulting in an earlier initiation of chemotherapy from the time of diagnosis. Both FAC and FEC cumulative doses were administered in a median of six cycles over 4 months, totalling respective anthracycline doses of approximately 202 and 260 mg/m^2.

The administration of doxorubicin and epirubicin was then broken down into dosage ranges within which patients were assessed for the development of CT and myelosuppression (Table 3). Toxicity to the heart was characterised by abnormal electrocardiogram (ECG) changes, clinically diagnosed CHF, and abnormal ($\leq$ 50%) LVEF relative to baseline.

Overall, there were 28 cases of doxorubicin-induced ECG changes compared to 22 cases of ECG abnormalities secondary to epirubicin (Table 3). There were 2 cases of clinically diagnosed CHF in the FAC group compared to 1 case in the FEC group. With regard to abnormal changes in LVEF, there were 3 documented cases in the FAC group compared to none in the FEC group. As illustrated in Table 3, only 1 patient received doxorubicin in doses exceeding 500 mg/m^2 compared to a total of 11 patients in the FEC group. In these 11 patients, there were two episodes of abnormal ECG changes and no cases of CHF. It was interesting to note that the 1 patient who received doxorubicin above 500 mg/m^2 developed CHF requiring hospital admission with supportive care.

The second aspect of CT examined was anthracycline-induced hospitalisation. There was a total of 5 patients in the FAC group who developed doxorubicin-induced cardiac abnormalities requiring hospital admission. These were characterised by atrial fibrillation and atrial ventricular (AV) block (2 cases), CHF (2 cases), and supraventricular tachycardia (1 case). There was one reported cardiac-related death among the 5 patients. In subjects who received epirubicin-based chemotherapy, there were only 2 cases of CT requiring hospital admission where 1 patient had a clinical diagnosis of epirubicin-induced CHF and another developed ventricular tachycardia. There were no epirubicin-related deaths reported.

One of the FEC patients had a sudden death as a result of an acute myocardial infarction (MI). A review of the circumstances behind this case revealed that the MI was secondary to a tricyclic antidepressant overdose. As a result, the patient was categorised as not having developed epirubicin-induced cardiac abnormalities. A comparison of the length of hospitalisation as a result of CT demonstrated that patients in the doxorubicin group required a median of 7 hospital days compared to a median of 3 days in the 2 patients receiving epirubicin.

Economic analysis

The total hospital cost for each admission was estimated. This included the cost of routine monitoring in patients with cardiac complications, hospital resources such as drug therapy, patient care and cardiologist consultations (Appendix). The cost of CT in the 5 FAC cases was C$4268.08/episode compared to C$2447.28/episode in the 2 FEC cases (Table 4).

A comparison of the cost of CT per course of chemotherapy was then conducted. A total of 506 and 499 FAC and FEC cycles, respectively, were administered to the 100 patients in

Table 3. Cardio- and myelotoxicities with cumulative doses of doxorubicin/epirubicin in patients with breast cancer

Cumulative dose of doxorubicin/epirubicin (mg/m²)	No. of patients		Cases of cardiotoxicity						Cases of myelosuppression			
			ECG changes		CHF		Abnormal LVEF*		Therapy delay		Dose reduction	
	FAC	FEC	FAC	FEC	FAC	FEC	FAC	FEC	FAC	FEC	FAC	FEC
< 47	6	3	1	0	0	0	0	0	0	0	0	0
47–100	22	26	11	8	0	0	0	0	7	2	5	6
101–200	21	13	7	6	0	1	0	0	7	3	13	3
201–300	25	27	0	6	0	0	0	0	9	13	15	7
301–400	19	10	2	0	0	0	1	0	11	3	9	1
401–500	6	10	4	0	1	0	1	0	6	16	1	13
501–600	1	7	3	2	1	0	1	0	0	3	0	5
601–700	0	1	0	0	0	0	0	0	0	1	0	3
701–800	0	2	0	0	0	0	0	0	0	1	0	0
801–900	0	1	0	0	0	0	0	0	0	0	0	0
Total	100	100	28	22	2	1	3	0	40	42	43	38

* Abnormal left ventricular ejection fraction (LVEF) ≤ 50%. See Table 1 for abbreviations of FAC and FEC. ECG, electrocardiogram; CHF, congestive heart failure.

Table 4. Overall cost per case of FAC- and FEC-induced cardiotoxicity

Characteristic	FAC	FEC
Number of hospital admissions	5	2
Total number of hospital days	38	6
Cost (C$) of hospitalisation per case (range)	3647.00 (1042–7294)	1563.00 (1042–2084)
Cost of cardiac monitoring (range)	90.10 (16–472)	105.46 (75–136)
Cost of cardiovascular drug therapy (range)*	80.21 (7–178)	426.82 (41–812)
Cost of cardiologist consultations (range)	105.40 (105–211)	210.80 (0–422)
Patient care costs (range)	247.10 (71–494)	141.21 (94–188)
Total cost (C$) of cardiotoxicity per case (range)	4268.08 (1240–8251)	2447.28 (2445–2450)

* Includes ECGs, chest X-rays and LVEFs. See Table 1 for abbreviations of FAC and FEC.

Table 5. Cost comparison of drug toxicity per course of FAC and FEC chemotherapy

Characteristic	FAC	FEC	*P* value*
Number of courses administered	506	499	
Cardiotoxicity			
Number of hospital admissions	5	2	
Total cost (C$) of cardiotoxicity per course of chemotherapy (range)†	80.77 (0–8251)	51.90 (0–2450)	0.64
Febrile neutropenia			
Number of hospital admissions	25	14	
Total cost (C$) of febrile neutropenia per course of chemotherapy (range)‡	268.20 (0–16463)	145.72 (0–11028)	0.058

* Determined by the Mann–Whitney U-test. † Includes cost of hospitalisation, cardiac monitoring, cardiologist consults and supportive care. ‡ Includes cost of hospitalisation, blood products, antibiotics, laboratory tests and infectious disease consults.
See Table 1 for abbreviations of FAC and FEC.

each group. The overall cardiac related cost per FAC course was C$80.77 compared to C$51.90 per FEC cycle, resulting in an absolute cost saving of approximately C$30.00 per FEC course (Table 5). As a result of the low incidence of CT detected in the patient samples, the economic difference was not statistically significant ($P = 0.64$).

The drug costs of FAC and FEC were not included in the analysis because, at this institution, the two equidose protocols are currently cost equivalent. A closer examination of the chemotherapy data revealed that patients in the FEC groups received approximately 58 mg/m² more anthracycline relative to FAC patients (Table 2). Based on the current epirubicin negotiated price, this would translate to an increase in the drug budget of approximately C$45 000 for every 100 breast cancer patients receiving FEC as opposed to FAC. This increment to the budget should be partially offset by reduced supportive care drug costs and may contribute to cost savings in other areas of the hospital (*vide infra*).

Myelosuppression

The development of myelosuppression was characterised by a reduced granulocyte count ($< 1.0 \times 10^9$/l) requiring a delay in therapy or a chemotherapy dose reduction. There were a total of 40 cases in the FAC and 42 cases in the FEC group where patients required a delay in the administration of subsequent chemotherapy (Table 3). When delays were required, therapy was deferred for a median of 7 days in both groups. It was interesting to note that only 50% (21/42) of dose delays in the FEC patients occurred at anthracycline doses below 400 mg/m², while in the FAC cohort, 85% (34 of 40) of therapeutic delays occurred below the 400 mg/m² cumulative dosage (Table 3).

There were 43 and 38 cycles of FAC and FEC that required a dosage reduction secondary to myelosuppression, respectively

(Table 3). When patients in the FAC group required a reduction, the dose was decreased by approximately 21% compared to 23% in the FEC group. As with therapeutic delays, it should be noted that only 45% (17/38) of dose reductions in the FEC group occurred at anthracycline doses below 400 mg/m^2. However, the majority (42/43) of dose reductions in the FAC sample occurred below the 400 mg/m^2 cumulative dosage. These results suggest that, unlike the doxorubicin protocol, dosage reduction and delays secondary to epirubicin myelosuppression are less prevalent at the lower dosage ranges.

The most interesting data retrieved in this part of the analysis were the occurrence of FN requiring hospitalisation. The results revealed 25 hospital admissions with a median of 7 hospital days in the FAC group compared to only 14 admissions in the FEC group also with a median of 7 days. Patients in both groups were treated empirically with antibiotics which included ceftazidime, tobramycin and vancomycin until they defervesced. There were five septic deaths reported in the FAC group but only one in the group receiving FEC. Overall, there was a general trend towards a lower incidence of FN in FEC patients ($P = 0.074$).

Economic analysis

The total hospital cost per case of FN was estimated for each admission. This included the cost of hospital resources for supportive care including blood products, antibiotics, ID consultations, patient care, and routine laboratory tests (Appendix). The cost of FN in the 25 FAC cases was C$5418.62/episode compared to C$5193.83/episode in the 14 FEC cases (Table 6).

One component of the economic differences between protocols that deserves mention is the cost of blood products. The combined cost of platelet and red cell transfusions secondary to epirubicin toxicity was approximately 9-fold greater in patients who received epirubicin than those incurred by the doxorubicin sample (Table 6). On closer examination, this difference was primarily due to 1 FEC patient who developed prolonged thrombocytopenia and anaemia requiring multiple transfusions.

A cost comparison between FAC and FEC was also conducted with regard to the development of fever and neutropenia after a course of therapy. As with the former analysis, the drug costs of FAC and FEC were not included. The overall cost per FAC cycle was C$268.20 compared to C$145.72 per FEC cycle, resulting in a saving of approximately C$122.00 per course of FEC (Table 5). The results of the statistical analysis revealed that the difference was on the threshold of being statistically significant ($P = 0.058$).

Table 6. Overall cost per case of FAC- and FEC-induced febrile neutropenia

Characteristic	FAC	FEC
Number of hospital admissions	25	14
Total number of hospital days	214	109
Cost (C$) of hospitalisation per case (range)	4459.76 (1042–14067)	4056.36 (1563–7294)
Cost of blood products (range)	6.89 (0–70)	61.46 (0–640)
Cost of antibiotic therapy (range)*	473.72 (20–1034)	631.68 (0–2263)
Antibiotic monitoring costs (range)	20.24 (0–69)	21.36 (0–126)
Patient care costs (range)	171.35 (94–388)	162.24 (106–235)
Laboratory test costs (range)	286.66 (67–904)	260.73 (100–469)
Total cost (C$) of febrile neutropenia per case (range)	5418.62 (1235–16463)	5193.83 (2041–11028)

* Includes infectious disease consultations. See Table 1 for abbreviations of FAC and FEC.

Estimating the hospital cost of anthracycline-induced toxicity per 100 patients

Cardiotoxicity. From the sample of 200 breast cancer patients receiving approximately six cycles of chemotherapy, there was a 5% incidence rate of doxorubicin-induced CT requiring hospitalisation compared with a rate of 2% in the epirubicin sample. This resulted in a difference (±95% CI) in the incidence of 3 ± 5% in favour of the FEC protocol.

The cost of CT in the 5 FAC cases was C$4268.08/episode compared to C$2447.28/episode in the 2 FEC cases (Table 4). Using the difference in the incidence of CT determined from the retrospective audit (3 ± 5%), there would be an estimated 3 ± 5 more cases of anthracycline-induced cardiac events requiring hospitalisation with the doxorubicin protocol for every 100 patients. Combining this estimate with the cost per episode (C$4268.08), translated to an institutional cost saving (±95% CI) of C$12 804 ± C$21 340 for the management of CT if epirubicin were used in place of doxorubicin.

Myelosuppression. From the sample of 200 breast cancer patients receiving approximately six cycles of chemotherapy per patient, there was a 25% incidence rate of doxorubicin-induced FN requiring hospitalisation compared to a rate of 14% in the epirubicin sample. This resulted in a difference (±95% CI) of 11 ± 11% in favour of the FEC protocol.

The cost of FN in the 25 FAC cases was C$5418.63/episode compared to C$5193.82/episode in the 14 FEC cases (Table 6). Using the difference in the incidence of FN determined from the retrospective audit (11 ± 11%), there would be an estimated 11 ± 11 more cases of anthracycline-induced fever and neutropenia requiring hospitalisation with the doxorubicin protocol for every 100 patients. Combining the estimate with the cost per episode (C$5418.62), translated to an institutional saving (±95% CI) of C$59 604 ± C$59 604 for the management of FN if epirubicin were used instead of doxorubicin.

DISCUSSION

The development of CT, particularly CHF, is among the most severe side-effects associated with anthracycline-based breast cancer chemotherapy. A reduction in the risk of this adverse event is highly desirable from both the patient and hospital perspective. Preventing this abnormality in women undergoing treatment for breast cancer may improve their quality of life.

Considering the institutional perspective, hospital policy decision makers are faced with the difficult task of allocating scarce resources into the many available programs. The treatment of CT can have a large impact on a health care budget. O'Connell and Bristow reported the results of a study measuring the economic impact of heart failure in the U.S.A. [13]. Using data from the National Inpatient Profile and the Health Care Financing Administration (HCFA), the investigators determined that US$5.45 billion was spent by the HCFA towards the hospital management of heart failure. Any resultant policy change that reduces the incidence of cardiac abnormalities could have a substantial impact on the global health care budget.

Our study measured incidence rates of cardiac dysfunction which required hospitalisation at 5 and 2% in FAC and FEC patients, respectively. This corresponds to an odds ratio of a cardiac event requiring hospitalisation of approximately 2.6 to 1 for FAC compared to FEC. These results are consistent with the outcomes of other studies reporting an increased risk of cardiac abnormalities associated with FAC chemotherapy [11, 12].

The reduced risk of CT with epirubicin may translate to an economic benefit. By utilising FEC instead of FAC, the results of the current study revealed an absolute cost saving of approximately C$30.00 per cycle of chemotherapy. However, because of the insufficient statistical power, this difference was not statistically significant (Table 5).

When the decreased incidence of a cardiac event was considered on a patient population basis, the results were interesting. The current hospital policy of substituting FEC for all FAC orders may result in a saving (±95% CI) of approximately C$12 804 ± C$21 340 for every 100 patients treated. These savings would primarily be in the form of reduced hospital costs for CT (Table 4).

The second adverse event measured in the current study was the occurrence of FN. This is of paramount concern to the oncologist because the development of infection remains a leading cause of treatment-related death in patients undergoing therapy for cancer [20, 21]. The management of FN can also be an expensive undertaking. In a recent study conducted by Fine and colleagues in two Canadian teaching hospitals, the cost of treating FN in patients with solid organ tumours was approximately C$5757 [15]. Our results are similar to those of Fine and colleagues in that the costs of treating an episode of FAC- and FEC-induced FN were C$5418.62 and C$5193.83, respectively (Table 6).

The results of our retrospective audit revealed a 25 and 14% incidence rate of FN in patients treated with FAC and FEC, respectively, corresponding to an odds ratio (0–0.14) of 2.0 for FAC. These outcomes are similar to those of the Italian Multicentre Breast Study which reported incidence rates of grades 3 and 4 leucopenia of 28 and 15% in FAC and FEC patients, respectively [11]. When the cost of FN was considered on a per cycle basis, the economic impact of FN secondary to FAC and FEC was C$268.20 and C$145.72, for an absolute cost saving of approximately C$122 per cycle of FEC (Table 5). This difference was on the threshold of being statistically significant ($P = 0.058$).

When the reduced incidence of FN associated with epirubicin was considered for every 100 patients treated, the cost savings were larger than those of CT. Substituting FEC for all FAC orders may save the institution (±95% CI) approximately C$59 604 ± C$59 604. If the cost savings from reduced CT (C$12 804) are combined with those from FN, the cost savings to PMH could amount to almost C$72 500 per 100 breast cancer patients.

Randomised comparative trials (RCT) are considered to be the best source of unbiased clinical and economic data [22]. However, there are situations where the implementation of RCT are not always possible because of ethical, logistic or economic circumstances. In these situations, retrospective study designs may be appropriate. Furthermore, the use of retrospective methodology may also have the advantage of reflecting the use of a drug in actual clinical practice rather than the ideal conditions generated by RCT. With these considerations, the retrospective methodology utilised in this study was deemed to be appropriate.

In this analysis, institutional cost savings are reported by the use of epirubicin instead of doxorubicin. However, these economic benefits require some clarification. While it is correct to say that some of the savings would be reflected in the pharmacy drug budget, the majority of savings would be in avoiding hospital admissions. However, if an admission is prevented by the use of epirubicin, the empty bed will most likely be filled by another patient. If this situation arose, nursing and consultant time may be spent in treating other patients. The overall outcome of this scenario would be to increase patient volumes with current staffing levels resulting in the improvement of hospital efficiency. However, if patient levels were to remain constant, then long-term hospital savings could be realised by bed closures and staff reductions.

The economic issue of increased pharmacy costs should also be addressed. Even though there may be cost savings in other areas of the hospital as a result of epirubicin's improved toxicity profile, the use of FEC instead of FAC would most likely cause an incremental increase in the pharmacy drug budget secondary to more patients receiving increased doses of potentially curative chemotherapy. Increased pharmacy chemotherapy expenditures as opposed to higher costs for supportive care would be an efficient use of hospital resources. It is also reasonable to assume that reducing the incidence of FN and cardiac complications would have a positive impact on patient quality of life.

The results from the current analysis were generated from only one institution. In order to address the issue of study generalisability, we conducted a survey of 14 cancer centres in the provinces of Ontario and Quebec. The results revealed that nine of 14 (64%) hospitals surveyed used equidose FAC or FEC as their primary metastatic breast cancer protocol. The use of either regimen was based on physician discretion. Therefore, it appears the results of the current study may be applicable to the nine treatment centres described above. Further application of our results to the international setting would require data adjustment based on the most commonly used protocol(s).

Regardless of the available clinical data, there still exists considerable controversy regarding equivalent potency at equal doses of epirubicin and doxorubicin [9]. However, the favourable toxicity profile of epirubicin may result in its use in a dose intensification strategy. There is evidence of a dose response to epirubicin in advanced breast cancer [23]. A randomised trial from the U.K. compared doses of 50–100 mg/m^2 both given every 3 weeks. The investigators reported a significantly improved response rate at the higher dose [24]. The ability of patients to tolerate higher epirubicin doses along with its reduced risk of costly side-effects makes it an attractive alternative to doxorubicin. This hypothesis is currently being investigated in a NCIC phase I clinical trial.

In conclusion, the results of this study support a recent decision by the Medical Breast Group of PMH to utilise exclusively the FEC protocol in the treatment of patients with breast cancer. Such a treatment policy may avoid episodes of anthracycline-induced CT and FN which could save the hospital almost C$72 500 for every 100 patients receiving approximately six courses of treatment.

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Acknowledgements—The authors wish to express their gratitude to Drs D. Warr and M. Minden, Department of Medical Oncology, Princess Margaret Hospital and Dr A.S. Detsky, Division of General Internal Medicine and Clinical Epidemiology, Toronto Hospital, for their review of the manuscript. This study was supported by a grant from Pharmacia Inc.

APPENDIX

Summary of supportive therapy costs

Cost breakdown		Cost (C$)
Cardiovascular drugs i.v.	Digoxin	3.11/0.5 mg
	Diltiazem	13.00/25 mg
	Procainamide	10.15/g
	Verapamil	17.98/5 mg
Antibiotics i.v.	Acyclovir	69.48 500 mg
	Amphotericin	37.35/5 mg
	Cefazolin	1.92/g
	Ceftazidime	15.20/g
	Tobramycin	5.39/80 mg
	Vancomycin	13.11/g
	Preparation time	2.25/dose
	Administration time	3.30/dose
	Cost of supplies (mini-bags, needles, etc.)	2.28/dose
Blood products	Pooled platelet	37.06/unit bag
	Red blood cells (packed)	32.70/unit bag
Laboratory tests	Blood cultures	28.00/test
	CBC (complete blood count differential)	21.71/test
	Serum creatinine	3.10/test
	Serum Mg and K	9.82/test
	Serum AST (serum glutamic oxaloacetic transaminase), ALP (alkaline phosphatase) and ALT (serum glutamic pyruvic transaminase)	15.51/test
	Tobramycin peak and trough	11.50/test
	Vancomycin peak and trough	11.50/test
Cardiac monitoring	Chest X-ray (two-view)	30.71/each
	Electrocardiogram	15.50/each
	Echocardiogram	74.60/each
	LVEF (resting)	229.68/each
Daily hospitalisation		521.00/day
Patient care costs	Clinical examination	48.20/each
	Physician visits	11.77/each
Consultation costs	Infectious disease	112.00/each
	Cardiologist*	105.40/each

* Obtained from the Ontario Ministry of Health [25]. LVEF, left ventricular ejection fraction.