Real-world experience with adjuvant FEC-D chemotherapy in four Ontario regional cancer centres

Y. Madarnas MD,† S.F. Dent MD,‡ S.F. Husain MD,* A. Robinson MD,§ S. Alkhayyat MD,|| W.M. Hopman MA,# J.L. Verreault BHSc BEd,‡ and T. Vandenberg MD||*

ABSTRACT

Background

The efficacy of adjuvant chemotherapy with FEC-D (5-fluorouracil–epirubicin–cyclophosphamide followed by docetaxel) is superior to that with FEC-100 alone in women with early-stage breast cancer. As the use of FEC-D increased in clinical practice, health care providers anecdotally noted higher-than-expected toxicity rates and frequent early treatment discontinuations because of toxicity. In the present study, we compared the rates of serious adverse events in patients who received adjuvant FEC-D chemotherapy in routine clinical practice with the rates reported in the PACS-01 trial.

Methods

We retrospectively reviewed all patients prescribed adjuvant FEC-D for early-stage breast cancer at 4 regional cancer centres in Ontario. Information was collected from electronic and paper charts by a physician investigator from each centre. Data were analyzed using chi-square tests, independent samples *t*-tests, one-way analysis of variance, and univariate regression.

Results

The 671 electronic and paper patient records reviewed showed a median patient age of 52.2 years, 229 patients (34.1%) with N0 disease, 508 patients (75.7%) with estrogen or progesterone receptor–positive disease (or both), and 113 patients (26%) with HER2/*neu*–overexpressing breast cancer. Febrile neutropenia occurred in 152 patients (22.7%), most frequently at cycle 4, coincident with the initiation of docetaxel [78/152 (51.3%)]. Primary prophylaxis with hematopoietic growth factor support was used in 235 patients (35%), and the rate of febrile neutropenia was significantly lower in those who received prophylaxis than in those who did not [15/235 (6.4%) vs. 137/436 (31.4%); $p < 0.001$; risk ratio: 0.20].

Conclusions

In routine clinical practice, treatment with FEC-D is associated with a higher-than-expected rate of febrile neutropenia, in light of which, primary prophylaxis with growth factor should be considered, per international guidelines. Adoption based on clinical trial reports of new therapies into mainstream practice must be done carefully and with scrutiny.

KEY WORDS

Febrile neutropenia, FEC-D chemotherapy, breast cancer, toxicity, growth factor

1. INTRODUCTION

Breast cancer is the most common malignancy in Canadian women, and yet despite an increasing incidence, breast cancer mortality rates in Canada have declined since 1975, largely as a result of the increased use of screening mammography and improvements in adjuvant systemic treatment [1]. Early adjuvant chemotherapy studies demonstrated improved disease-free and overall survival with first-generation alkylator-based regimens [2,3]. Subsequent clinical trials demonstrated improved disease-free and overall survival with anthracycline-based regimens (which have now been the standard of care for women with high-risk early-stage breast cancer for more than a decade [4]), and epirubicin-based regimens such as cyclophosphamide–epirubicin–5-fluorouracil (5FU) [5] and FEC-100 (5FU–epirubicin–cyclophosphamide) [6] have been the second-generation regimens in common use across Ontario since the mid-1990s. More recently, the addition of taxanes to the anthracycline backbone has demonstrated added benefit, and those agents have been increasingly incorporated into third-generation adjuvant chemotherapy regimens [7–10].

In 1997, a European group initiated the PACS-01 trial, which compared a hybrid taxane-containing regimen (FEC for 3 cycles followed by docetaxel for 3 cycles: FEC-D) to FEC-100 for 6 cycles. Final results of the PACS-01 study were published in December 2006 [11]. Compared with FEC-100, sequential FEC-D resulted in an 18% reduction in the relative risk of relapse and an absolute survival gain of 4% in women with node-positive early-stage breast cancer. The investigators reported a favourable toxicity profile for FEC-D, with a rate of febrile neutropenia of 11.2% compared with 8.4% for FEC-100, both in the absence of primary growth factor support or antibiotic administration.

The PACS-01 trial was practice-changing, and FEC-D was rapidly adopted in many cancer centres across Ontario as the standard third-generation chemotherapy regimen for high-risk early-stage breast cancer. But within the 1st year of adoption, clinicians began reporting higher-than-expected rates of febrile neutropenia and other serious life-threatening complications leading to early termination of treatment and, in some cases, death.

The generalizability of large randomized controlled trials and their translation into effective and safe care of patients in the general population has been of interest recently [12–17]. We undertook a multi-institutional review of patients with early-stage invasive breast cancer treated with adjuvant FEC-D chemotherapy at 4 tertiary cancer centres in Ontario, examining supportive care practices and toxicity during the course of adjuvant chemotherapy. We compared toxicity rates in patients who received the FEC-D regimen in routine clinical practice with rates from the PACS-01 trial. Our main interests were the rate of febrile neutropenia, the use of growth factor support (primary or secondary), the rates and patterns of hospital admission, and fatalities occurring in this patient population.

2. METHODS

Our study received research ethics board approval at each of the 4 participating institutions: The Ottawa Hospital Cancer Centre, the Cancer Centre of Southeastern Ontario, the London Regional Cancer Program, and the Northeastern Ontario Regional Cancer Centre, all of which belong to the Cancer Care Ontario network.

The province of Ontario has universal health care with a single payer/provider, the Ministry of Health and Long-Term Care. Cancer Care Ontario is the agency charged with the planning and coordination of cancer services in Ontario, and that agency serves as advisor to the government on cancer. Among its other roles, Cancer Care Ontario directs and oversees the allocation of public funding to hospitals and other cancer care providers to ensure the delivery of quality and timely cancer services to the residents of Ontario. Approximately half the cancer care in the province is delivered through 1 of 12 regional cancer centres affiliated with Cancer Care Ontario; the other half is delivered through non-affiliated community hospitals or through the Princess Margaret Hospital.

All Cancer Care Ontario regional cancer centres use the same electronic order system for chemotherapy, through which all female patients who were prescribed adjuvant FEC-D chemotherapy for early-stage breast cancer were identified using a regimen query of the electronic pharmacy records at each centre. Our study included only the patients who had completed their entire course of adjuvant chemotherapy between June 1, 2006, and December 31, 2008, at each participating centre. Patients who had received some or all of their chemotherapy through affiliated satellite clinics were excluded.

Authors at the respective centres used a similar case report template to collect demographic, disease-related, and treatment-related information from the electronic and paper files of the study patients. For accuracy, data were verified with a second pass through the records. Data were then stored in an anonymized secure database at each site, accessible only to the investigators. These data were pooled, with any incongruent data being verified by the originating centre, and they were then jointly analyzed. Because there were centre-to-centre variations in the variables collected, the data from the 4 centers were comparatively evaluated, and the following common variables were identified for use in the present analysis: patient age, tumour (T) and nodal (N) stage, tumour estrogen receptor (ER) and human epidermal growth factor receptor 2 (HER2) status (for all but 1 site), incidence of febrile neutropenia, cycle of first occurrence of febrile neutropenia, hospital and intensive care unit (ICU) admission and duration, primary or secondary prophylaxis with hematopoietic growth factors, treatment-related mortality, and cause of death.

At each centre, FEC-D chemotherapy (5FU 500 mg/m^2, epirubicin 100 mg/m^2, and cyclophosphamide 500 mg/m^2 on day 1 every 21 days for 3 cycles, followed by docetaxel 100 mg/m^2 on day 1 every 21 days for 3 cycles) was prescribed through the electronic chemotherapy order system per the methods described in the PACS-01 publication [11]. Body surface area was calculated based on actual body weight, and chemotherapy doses were not capped for a body surface area greater than 2 m^2.

Based on the supportive care regime reported in PACS-01 [11], no prophylactic antibiotics or hematologic growth factors were used. Chemotherapy was administered at the full dose on day 21 if the patient's absolute neutrophil count (ANC) was 1500/mm^3 or higher. Dose adjustments were made at the clinician's discretion per institutional standards. Those adjustments included cycle delay and chemotherapy dose reduction for an ANC of 1000–1500/mm^3, and cycle

delay and introduction of hematopoietic growth factor support in all subsequent cycles for an ANC of less than 1000/mm^3 or occurrence of febrile neutropenia (defined as a documented temperature of 38.5°C or higher, with an ANC of less than 1000/mm^3). In most centres, patients who experienced febrile neutropenia were admitted to hospital for management; a few were managed using an outpatient oral antibiotic protocol. Secondary prophylaxis with filgrastim was introduced only after the occurrence of a febrile neutropenic event or dose delay.

Filgrastim is not currently funded for use as primary prophylaxis for the FEC-D regimen, and thus, secondary growth factor prophylaxis was the predominant form of hematologic growth factor use at the time this regimen first came into use. However, as clinical experience with the toxicity profile of the regimen evolved, primary growth factor prophylaxis was increasingly used in patients who could access the drug through private insurance, with substantial variability between the centres. Patients with HER2-overexpressing breast cancer received adjuvant trastuzumab administered concurrently with the docetaxel or sequentially upon completion of chemotherapy. Patients with ER- or progesterone receptor–positive breast cancer received adjuvant endocrine therapy upon completion of chemotherapy, per institutional guidelines. When indicated, adjuvant radiotherapy was administered upon completion of chemotherapy, per institutional standards.

The data were first evaluated descriptively, with means, standard deviations, and ranges being calculated for continuous data, and frequencies and percentages for categorical data. Chi-square tests (Pearson or Fisher exact tests, as appropriate) were then used to examine the association between factors such as centre, T status, N status, primary prophylaxis, febrile neutropenia, and recurrence. The association between age and febrile neutropenia was assessed using an independent-samples *t*-test. A one-way analysis of variance was used to compare age across the 4 centres, and univariate logistic regression was used to generate an odds ratio for the association between primary growth factor prophylaxis and febrile neutropenia.

3. RESULTS

Data were collected for 671 patients attending the 4 regional cancer centres in Ontario. Table I outlines the demographics and tumour characteristics of the study population and the rates of febrile neutropenia within various subcategories. Mean age was 52.2 years (range: 24–78 years), and 10.4% of the patients were 65 years of age or older. In keeping with a high-risk population, most of the patients [432 (64.4%)] had axillary node–positive disease, about three quarters [508 (75.7%)] had endocrine-sensitive disease, and 113 of the 435 patients for whom HER2/*neu* was reported (26%) had tumours that overexpressed HER2/*neu*.

Table II and Figures 1 and 2 illustrate the frequency and pattern of rates of observed events. Across the entire study population, febrile neutropenia occurred in 152 patients (22.7%). A trend toward a higher rate of febrile neutropenia was observed among women 65 years of age and older compared with those under 65 [19 of 70 (27.1%) vs. 133 of 601 (22.1%), $p = 0.34$]. Most episodes of febrile neutropenia occurred during the docetaxel phase of chemotherapy [101 of 152 (66.5%) vs. 51 of 152 (33.6%) while on FEC], with more than half of all episodes of febrile neutropenia occurring at cycle 4 upon initiation of docetaxel [78 of 152 (51.3%)]. In the 2 centres at which these data were specifically collected, 15 of 158 patients (9.8%) failed to complete 6 cycles of chemotherapy, for a completion rate of 90.2%.

Hospitalization was required for 137 of the study patients (20.4%), representing 90.1% of those who experienced febrile neutropenia. Of those 137 patients, 7 required admission to the ICU (5.1%). During treatment, 3 deaths (0.4%) were observed, 2 of which occurred in the group with febrile neutropenia (developed at cycle 1 and cycle 4). The average age of the 3 patients who died was 56 years, and none had received primary prophylaxis. Two were admitted to the hospital, both to the ICU. Cause of death was

TABLE I Population characteristics and percent developing febrile neutropenia (FN) by subcategory

Category	*Patients [*n *(%)]*		p
	Overall[a]	*With FN*	*value*[b]
Centre	671	152 (22.7)	
1	278 (41.4)	49 (17.6)	<0.001
2	230 (34.3)	45 (19.6)	
3	127 (18.9)	45 (35.4)	
4	36 (5.4)	13 (36.1)	
Age (years)	52.2±9.6 (range: 24–78)		
≤50	298 (44.4)	67 (22.5)	0.98
51–60	244 (36.4)	55 (22.5)	
61–69	106 (15.8)	24 (22.6)	
≥70	23 (3.4)	6 (26.1)	
Nodal status			
N0	229 (34.1)	63 (27.5)	0.09
N+	432 (64.4)	84 (19.4)	
Nx/missing	10 (1.5)	0 (0.0)	
ER+ or PR+, or both	508 (75.7)	109 (21.5)	0.49
HER2/*neu* overexpression[a]	113 (26.0)	25 (22.1)	0.75

[a] Denominator is 671 except for HER2/*neu* overexpression, which was not reported for centre 2 and for a few patients at other centres, making the denominator for the "Overall" column in that category 435.
[b] By chi-square test.
ER+ = estrogen receptor–positive; PR+ = progesterone receptor–positive.

TABLE II Neutropenic events and supportive care

Variable	*Patients*	
	(n)	*(%)*
Febrile neutropenia [FN (first episode)]	152	22.7
Growth factor use		
Primary prophylaxis[a]	235	35.0
Secondary prophylaxis[b]	136	31.2
Hospitalization for FN	137	20.4
Admission to intensive care unit	7	5.1
Death	3	0.4
Cycle of chemotherapy with FN		
1 (FEC)	33	21.7
2 (FEC)	6	4.0
3 (FEC)	12	7.9
4 (docetaxel)	78	51.3
5 (docetaxel)	21	13.8
6 (docetaxel)	2	1.3

Relationship between FN and growth factor use	*Patients with FN*		p *Value*
	(n)	*(%)*	
Centre			
1[c] (*n*=278)	49	17.6	<0.001
2[c] (*n*=230)	45	19.6	
3 (*n*=127)	45	35.4	
4 (*n*=36)	13	36.1	
Primary prophylaxis (*n*=671)			
No (*n*=436)	137	31.4	<0.001
Yes (*n*=235)	15	6.4	

[a] Denominator is the entire cohort of 671 patients.
[b] Denominator is the intention-to-treat remainder of the cohort: 436 patients.
[c] Two centers adopted primary prophylaxis during the study period.
FEC = 5-fluorouracil–epirubicin–cyclophosphamide followed by docetaxel.

identified as sepsis in 2 patients and hemorrhagic colitis in 1 patient.

Primary use of growth factor became more common over the course of the study and was given to 235 patients (35%) in our cohort. Of the remaining 436 patients, 136 (31.2%) received secondary growth factor prophylaxis for the cycles of treatment remaining after a first episode of febrile neutropenia or after either or both of a chemotherapy dose delay or dose reduction. A few patients who received secondary growth factor prophylaxis never experienced febrile neutropenia [4.1% (probably those who experienced delays in treatment or dose reductions because of uncomplicated neutropenia)].

Table II also illustrates the relationship between growth factor use and rates of febrile neutropenia. The observed rates of febrile neutropenia differed significantly between centres, with the centres that adopted primary prophylaxis reporting significantly

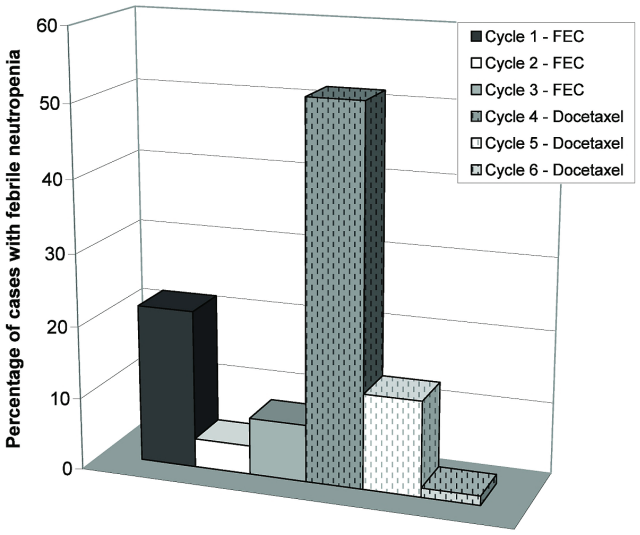

FIGURE 1 Rates of febrile neutropenia by cycle of chemotherapy in women with early-stage breast cancer at 4 Ontario cancer centres. FEC = 5-fluorouracil–epirubicin–cyclophosphamide.

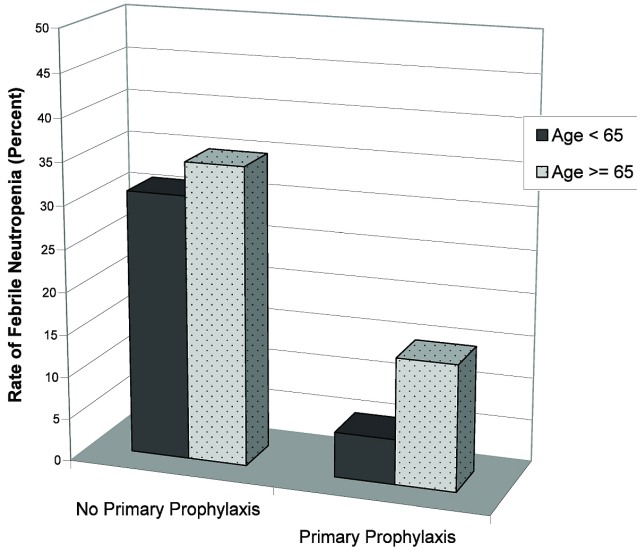

FIGURE 2 Rates of febrile neutropenia by age group and growth factor use in women with early-stage breast cancer at 4 Ontario cancer centres. $p < 0.001$ by Pearson chi-square test.

lower event rates. Only 15 of the 235 patients who received primary growth factor prophylaxis (6.4%) developed febrile neutropenia, whereas 137 of the 436 who did not (31.4%) went on to develop febrile neutropenia ($p < 0.001$), for a 0.20 relative risk for febrile neutropenia with the use of primary growth factor prophylaxis. Among the 137 patients who developed febrile neutropenia in the absence of primary growth factor support, only 117 (85.4%) received secondary growth factor support; the others presumably received another intervention to minimize a recurrent event.

Using the available variables, exploratory analyses were conducted for possible predictors of febrile

neutropenia: T stage, $p = 0.8$; N stage, $p = 0.1$; ER status, $p = 0.5$; HER2 status, $p = 0.8$; centre, $p < 0.001$; growth factor use, $p < 0.001$ for primary or secondary. The only significant factors to emerge were centre and the absence of growth factor support, such that patients not receiving primary growth factor prophylaxis were 6.7 times more likely to develop febrile neutropenia (95% confidence limits: 3.8, 11.8). The logistic regression from which the latter odds ratio was obtained was therefore univariate, because centre was confounded with use of primary growth factor prophylaxis. Age distribution was similar in all centres, and although the rate of febrile neutropenia was highest in patients 65 years of age or older, age was not a significant factor in the development of febrile neutropenia ($p = 0.98$). Information on comorbidity, body size, chemotherapy dose, and dose intensity was not uniformly available.

4. DISCUSSION AND CONCLUSIONS

In sharp contrast with the PACS-01 publication [11], we found a high rate of febrile neutropenia (22.7%) and treatment discontinuation (9.8%) among women receiving adjuvant FEC-D chemotherapy for early-stage breast cancer in routine clinical practice. Others have recently reported that toxicity rates with another emerging regimen (docetaxel–cyclophosphamide) are significantly higher in routine clinical practice than were reported in the pivotal publication [17]. What accounts for such observations is not evident, but a number of plausible explanations can be considered, including fundamental differences in the patient population, treatment delivery, supportive care, and other unmeasured factors. Despite a patient cohort of similar median age [52.2 years (range: 24–78 years) vs. 50 years (range: 25–67 years) for PACS-01] and an identical treatment prescription, the rate of febrile neutropenia among the patients in our population who did not receive primary growth factor prophylaxis was almost 3 times the rate reported in PACS-01 (31.4% vs. 11.2%).

There are some differences between the two populations that could explain our observations. In our cohort, 10.4% of the patients were 65 years of age or older, but only women 64 years of age or younger were enrolled in PACS-01. In keeping with a high-risk population, most of our patients had axillary node–positive disease, which also contrasts with PACS-01, whose entire population had axillary node–positive disease. A number of patient-related risk factors for febrile neutropenia have been described, including comorbidity, advanced age, and performance status [18,19]. Although we did not specifically collect information on comorbidity, women with early breast cancer are generally healthy and young, and they harbour few risk factors that would increase their susceptibility to develop febrile neutropenia. Our population was also relatively young, but in contrast to the PACS-01 population, all of whom were younger than 65, women 65 years of age and older accounted for 10% of our cohort. Although it is well accepted that patients enrolled on clinical trials are highly selected, our patients were nonetheless considered by their treating oncologists to be fit enough to receive aggressive third-generation chemotherapy.

As occurred in PACS-01, a rise in the rate of febrile neutropenia occurred at cycle 4 in our study, coincident with the initiation of docetaxel treatment. The PACS-01 authors explicitly state in their methods that primary growth factor prophylaxis was prohibited in the study, but that on day 21, institution of secondary growth factor support was allowed, together with a delay of at least 7 days for an ANC below 1500/mm^3 or for an episode of febrile neutropenia. However, they also state that, if instituted at cycles 1–3, growth factor support should be withdrawn at cycle 4. In our current practice, growth factor support is continued through all remaining chemotherapy cycles once instituted for an event.

Except for the discontinuation of growth factor support at cycle 4, the PACS-01 use of secondary growth factor support appeared similar to routine clinical practice in most of our local settings at the time our cohort was assembled. In PACS-01, secondary growth factor support was reported to have been used in 27% of patients receiving FEC-100 and in 22.2% of patients receiving FEC-D. We did not have a local cohort of patients treated with FEC-100 for comparison.

A significant limitation of our study is that we did not collect data on the reason for secondary growth factor introduction, and thus, we cannot discern between secondary growth factor use for dose delay or reduction or for febrile neutropenia.

Antibiotic prophylaxis was prohibited in PACS-01, and antibiotic prophylaxis is not routinely used in our centres. We did not collect information on received dose and dose intensity, nor were those data reported in the PACS-01 paper; however, the authors did report that 96.1% and 97% of patients completed 6 cycles of FEC-D and FEC respectively, results that also contrast with the lower completion rate of 90.2% for FEC-D in our cohort.

Regimen-dependent risk factors for febrile neutropenia have also been described [18]. In particular, regimens containing particularly myelotoxic agents such as docetaxel have higher rates of hematologic toxicity, which accords with the observation by the authors of PACS-01, and by our group, of a dramatic increase in febrile neutropenia with the institution of docetaxel at cycle 4. We did not collect information on hematologic parameters for our study, but the day of the actual blood draw varies in our routine clinical practice according to the distance the patient has to travel to the cancer centre, the preferences of patient and the health care provider, and issues of laboratory access such as weather and holidays. It is therefore possible that variations in the day of the blood draw (day 21 ± 2 or 3 days) or

the start of steroid premedication before docetaxel start could account for some of our observations.

Various factors affecting the external validity of clinical trials have been described [16], ranging from differences in the patient populations, to care provision, and to the conduct of trial-specific activities. Supportive measures are also an important part of toxicity prevention and management that would be expected to be well established and honed in tertiary regional cancer centres, such that it is unlikely that our cohort received any less supportive care than required. However, it is possible that unaccounted-for supportive measures were received by patients enrolled on PACS-01. Others have postulated a similar explanation for such observations [17], and a recent paper [12] demonstrated that, of clinical trial reports, a significant proportion lack essential therapeutic details necessary for appropriate adoption of the reported therapy in the real world. Specifically, the authors found that premedication, growth factor support, and dose adjustments for toxicities—all of which are likely to have significant impact on adverse events experienced by patients—were the least-reported details. Furthermore, other factors such as weight-bearing exercise [20], diet, use of central venous access devices, and co-administration of alternative or homeopathic preparations could also play a role.

As an effective third-generation chemotherapy regimen, FEC-D has been rapidly adopted into clinical practice across Ontario because of improved breast cancer outcomes and acceptable toxicity based on information from the PACS-01 publication [11]. Our dataset is, to our knowledge, the largest outside of a clinical trial to describe rates of febrile neutropenia with adjuvant FEC-D chemotherapy for early breast cancer. We describe a "real world" experience with this regimen in the context of 4 tertiary cancer centres serving the entire community within their jurisdictions.

Our study has significant limitations inherent in its retrospective nature. We did not collect information on comorbidity predisposing to febrile neutropenia. The retrospective data collection also limits accurate capture and grading of all adverse events, which may in fact contribute to underreporting of adverse events experienced by patients receiving FEC-D. The collaborating centers also collected data independently and then merged their data such that only a few common variables were available for tabulation and analyses. Despite its limitations, this multicentre review demonstrates, in women receiving adjuvant FEC-D chemotherapy in routine clinical practice in Ontario, a febrile neutropenia rate well in excess of the accepted 20% threshold. Given that there is currently no reliable method of predicting the development of febrile neutropenia at the individual level in a prospective manner [21,22], we believe that, based on our observations, primary hematopoietic growth factor prophylaxis is required for the safe administration of adjuvant FEC-D chemotherapy, a recommendation that is in keeping with the current guidelines of international oncology organizations [23]. Furthermore, our data underscore the need for observational phase IV and population-based studies as soon as possible after a new treatment is introduced into clinical practice to ensure the safe translation of clinical trial results to the general population [13,14].

5. CONFLICT OF INTEREST DISCLOSURES

The authors have no financial conflicts of interest to declare.

6. REFERENCES

1. Canadian Cancer Society's Steering Committee. *Canadian Cancer Statistics 2009.* Toronto, ON: Canada Cancer Society; 2009.
2. Bonadonna G, Brusamolino E, Valagussa P, *et al.* Combination chemotherapy as an adjuvant treatment in operable breast cancer. *N Engl J Med* 1976;294:405–10.
3. Fisher B, Carbone P, Economou SG, *et al.* L-Phenylalanine mustard (L-PAM) in the management of primary breast cancer: a report of early findings. *N Engl J Med* 1975;292:117–22.
4. Early Breast Cancer Trialists' Collaborative Group. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomized trials. *Lancet* 2005;365:1687–717.
5. Levine MN, Bramwell VH, Pritchard KI, *et al.* Randomized trial of intensive cyclophosphamide, epirubicin, and fluorouracil chemotherapy compared with cyclophosphamide, methotrexate, and fluorouracil in premenopausal women with node-positive breast cancer. National Cancer Institute of Canada Clinical Trials Group. *J Clin Oncol* 1998;8:2651–8.
6. Bonneterre J, Roché H, Kerbrat P, *et al.* Epirubicin increases long-term survival in adjuvant chemotherapy of patients with poor-prognosis, node-positive, early breast cancer: 10-year follow-up results of the French Adjuvant Study Group 05 randomized trial. *J Clin Oncol* 2005;23:2686–93.
7. Bedard PL, Di Leo A, Piccart–Gebhart MJ. Taxanes: optimizing adjuvant chemotherapy for early-stage breast cancer. *Nat Rev Clin Oncol* 2010;1:22–36.
8. Ward S, Simpson E, Davis S, Hind D, Rees A, Wilkinson A. Taxanes for the adjuvant treatment of early breast cancer: systematic review and economic evaluation. *Health Technol Assess* 2007;11:1–144.
9. Nowak AK, Wilcken NR, Stockler MR, Hamilton A, Ghersi D. Systematic review of taxane-containing versus non-taxane-containing regimens for adjuvant and neoadjuvant treatment of early breast cancer. *Lancet Oncol* 2004;6:372–80.
10. Ferguson T, Wilcken N, Vagg R, Ghersi D, Nowak AK. Taxanes for adjuvant treatment of early breast cancer. *Cochrane Database Syst Rev* 2007;:CD004421.
11. Roché H, Fumoleau P, Spielmann M, *et al.* Sequential adjuvant epirubicin-based and docetaxel chemotherapy for node-positive breast cancer patients: the FNCLCC PACS 01 trial. *J Clin Oncol* 2006;24:5664–71.
12. Duff J, Leather H, Walden EO, LaPlant KD, George TJ Jr. Adequacy of published oncology randomized controlled trials to provide therapeutic details needed for clinical application. *J Natl Cancer Inst* 2010;102:702–5.

13. Vlahakes GJ. The value of phase 4 clinical testing. *N Engl J Med* 2006;354:413–15.
14. Booth CM, Mackillop WJ. Translating new medical therapies into societal benefit: the role of population-based outcome studies. *JAMA* 2008;300:2177–9.
15. Avorn J. In defense of pharmacoepidemiology—embracing the yin and yang of drug research. *N Engl J Med* 2007;357:2219–21.
16. Meyer RM. Generalizing the results of cancer clinical trials. *J Clin Oncol* 2010;28:187–9.
17. Soong D, Haj R, Leung MG, Myers R, Higgins B, Myers J, *et al.* High rate of febrile neutropenia in patients with operable breast cancer receiving docetaxel and cyclophosphamide. *J Clin Oncol* 2009;27:e101–2.
18. Crawford J, Dale D, Lyman G. Chemotherapy-induced neutropenia. Risks, consequences, and new directions for its management. *Cancer* 2004;100:228–37.
19. Srokowski TP, Fang S, Hortobagyi GN, Giordano SH. Impact of diabetes mellitus on complications and outcomes of adjuvant chemotherapy in older patients with breast cancer. *J Clin Oncol* 2009;27:2170–6.
20. Fairey AS, Courneya KS, Field CJ, Mackey JR. Physical exercise and immune system function in cancer survivors: a comprehensive review and future directions. *Cancer* 2002;94:539–51.
21. Talcott JA, Siegel RD, Finberg R, Goldman L. Risk assessment in cancer patients with fever and neutropenia: a prospective, two-center validation of a prediction rule. *J Clin Oncol* 1992;2:316–22.
22. Morrison VA. An overview of the management of infection and febrile neutropenia in patients with cancer. *Support Cancer Ther* 2005;2:88–94.
23. National Comprehensive Cancer Network (NCCN). *NCCN Clinical Practice Guidelines in Oncology: Myeloid Growth Factors*. V.1.2010. Fort Washington, PA: NCCN; 2010.

Correspondence to: Yolanda Madarnas, Department of Oncology, Division of Medical Oncology, Cancer Centre of Southeastern Ontario, 25 King Street West, Kingston, Ontario K7L 5P9.
E-mail: yolanda.madarnas@krcc.on.ca

* Cancer Centre of Southeastern Ontario, Kingston General Hospital, and Department of Medicine, Queen's University, Kingston, ON.
† Department of Oncology, Queen's University, Kingston, ON.
‡ Ottawa Hospital Cancer Centre, Department of Medicine, University of Ottawa, Ottawa, ON.
§ Northeastern Ontario Regional Cancer Centre, Sudbury Regional Hospital, Sudbury, ON.
‖ London Regional Cancer Program, Department of Oncology, University of Western Ontario, London, ON.
Department of Community Health and Epidemiology, Queen's University, Kingston, ON.