Curr Oncol, Vol. 19, pp. e239-243; doi: http://dx.doi.org/10.3747/co.19.948

Use and delivery of granulocyte colony–stimulating factor in breast cancer patients receiving neoadjuvant or adjuvant chemotherapy—single-centre experience

X. Zhu MD, N. Bouganim MD,† L. Vandermeer BSc,† S.F. Dent MD,*† G. Dranitsaris PhD,‡ and M.J. Clemons MD*†*

ABSTRACT

Background

Use of granulocyte colony-stimulating factor (G-CSF) as primary prophylaxis against chemotherapy-induced neutropenia has significant cost implications. We examined use of G-CSF for early-stage breast cancer patients at our centre. The study also examined the pattern of nurse-led patient teaching with respect to drug self-administration.

Methods

Patients who received G-CSF between November 2009 and October 2010 were identified from pharmacy records. After consent had been obtained, electronic charts were examined to extract data on chemotherapy and use of G-CSF. Patients were contacted by telephone to obtain information on the utilization of home-care nursing visits for G-CSF administration.

Results

The study analyzed 36 patients. Median age was 58 years (range: 31–78 years). Of the 36 patients, 30 (83%) had received adjuvant treatment, and 6 (17%), neoadjuvant treatment. Most patients (71%) received 10 days (range: 7–10 days) of filgrastim. Of the 36 patients, 29 (81%) received G-CSF as primary prophylaxis. In 90% of those patients, primary prophylaxis commenced with the taxane component of treatment. Of the 36 patients, 7 (19%) received G-CSF after neutropenia, including 2 who had febrile neutropenia. In 96% of the patients, injections were received at home with the help of a nurse; those patients were subsequently taught self-injection techniques. The median number of nursing visits was 2 (range: 1–3 visits). Most patients were satisfied with the home care and G-CSF teaching they received.

Conclusions

Most of the G-CSF used in breast cancer treatment during the study period was given for primary prophylaxis. A major reason for the decision to use G-CSF appears to have been physician-perceived risk of febrile neutropenia. Delivery of G-CSF by home-care nurses was well received by patients.

KEY WORDS

Growth factor, breast cancer, chemotherapy, neutropenia, febrile neutropenia, prophylaxis, drug administration

1. INTRODUCTION

Among the most common and life-threatening side effects of modern adjuvant chemotherapy for breast cancer are neutropenia and febrile neutropenia. Although neutropenia can cause delays in treatment and dose reductions that might reduce treatment efficacy, febrile neutropenia is more serious, being associated with significant morbidity and mortality. The risk of febrile neutropenia can be reduced using a range of potential strategies, including dose reductions and delays in treatment, but the most frequent strategy is the use of granulocyte colony–stimulating growth factors (G-CSFs). Use of G-CSFs has been shown to reduce the incidence of febrile neutropenia when administered with chemotherapy[1]. The G-CSFs can be administered for patients who have previously experienced an episode of febrile neutropenia during therapy ("secondary prophylaxis"). They may also be given to prevent febrile neutropenia, usually in patients receiving chemotherapy regimens with a greater than 20% risk of febrile neutropenia ("primary prophylaxis").

Although G-CSFs have side effects such as transient fevers and arthralgias, those effects are felt to be outweighed by the benefits. However, using G-CSF as primary prophylaxis against febrile neutropenia

during chemotherapy has significant cost implications. The costs include direct drug acquisition costs and the costs related to drug administration, because G-CSF is given subcutaneously. The financial implications of G-CSF use are particularly important given that no trials have shown any benefit in terms of survival with the use of these agents. In part because of those concerns, major cancer societies, including the American Society of Clinical Oncology (ASCO), have created guidelines on the use of G-CSF in the primary prophylaxis setting[2], as shown in Table I.

Here, we examine the pattern of G-CSF use [filgrastim (Neupogen: Amgen, Thousand Oaks, CA, U.S.A.) and pegfilgrastim (Neulasta: Amgen)] for early-stage breast cancer patients at our cancer centre, and whether such use adhered to ASCO guidelines. In addition, we also examine the frequency of home-care nursing utilization in the delivery of these medications.

2. METHODS

Patients who received neoadjuvant or adjuvant chemotherapy plus filgrastim or pegfilgrastim during treatment for early-stage breast cancer between November 2009 and October 2010 at The Ottawa Hospital Cancer Centre were eligible for inclusion in the study. Figure 1 depicts the process of patient recruitment.

After we obtained approval from our institutional research ethics board, patients fulfilling the selection criteria were contacted by telephone to inform them of the study. Interested patients were mailed a copy of the study description and a consent form for examination of their electronic chart. Reminder calls were placed to patients to maximize response rates, and duplicate consent forms were sent to patients if needed.

TABLE I The American Society of Clinical Oncology 2006 guideline for the use of granulocyte colony-stimulating factor for prophylaxis

Indication for primary prophylaxis:
• Age > 65 years
• Poor performance status
• Extensive prior treatment, including radiation
• Combined chemoradiation
• Malignant infiltration of bone marrow
• Open wounds or active infections
• Risk of febrile neutropenia > 20% for the chemotherapy being administered
Indication for secondary prophylaxis:
• Neutropenic complication in earlier cycle of chemotherapy without primary prophylaxis

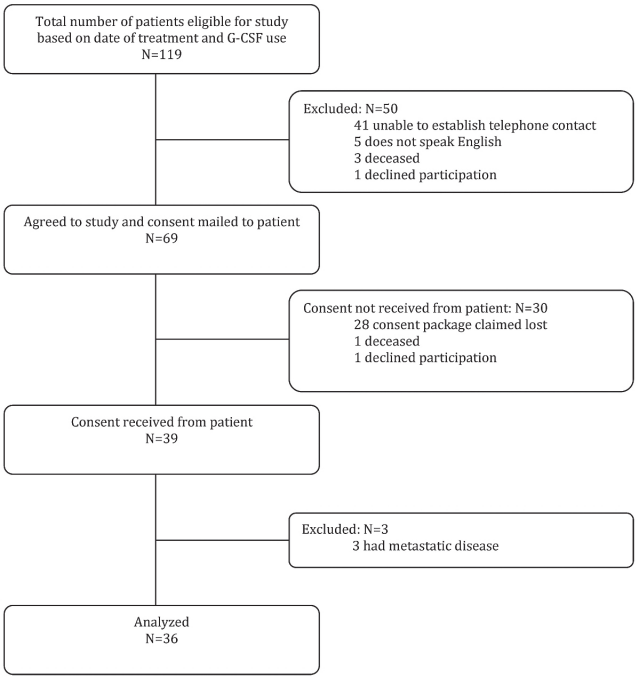

FIGURE 1 *Patient recruitment flowchart.*

After written consent was obtained from the patients, charts were examined, and chemotherapy and G-CSF usage data were extracted. Adherence to ASCO guidelines was determined by abstracting disease stage, age, comorbidities, and treatment history and plan from the chart, and by comparing those data against the established ASCO criteria for prophylactic use of G-CSF. Use of G-CSF was considered to be adherent to guidelines if any ASCO criterion was met.

Telephone interviews were used to inquire about the administration of G-CSF, including the identity of the person providing the injection, the frequency and duration of home nursing visits, and the patient's satisfaction and concerns with the teaching process for the injection technique. Patient satisfaction was assessed using a simple scale of "excellent," "good," or "less than good."

3. RESULTS

We identified 119 patients as eligible for the study. Of those 119 patients, 69 allowed consent forms to be sent, and 39 patients (57%) completed the forms. Subsequently, 3 patients were found to be ineligible because of metastatic disease at time of treatment, leaving 36 patients in the final analysis. Table II documents patient characteristics and chemotherapy regimens. Most patients had no serious medical comorbidities; the most common chronic health issues were hypertension and hypothyroidism.

Of the 36 patients in the analysis, 31 (86%) received adjuvant treatment, and 5 (14%), neoadjuvant treatment. Filgrastim was given to 34 patients

TABLE II Patient characteristics and chemotherapy regimens

Characteristic	*Value*
Age (years)	
Median	58
Range	31–78
Menopausal status [*n* (%)]	
Premenopausal	12 (33)
Postmenopausal	24 (67)
Nodal stage [*n* (%)]	
Node-negative	14 (39)
1–3 Positive	14 (39)
≥4 Positive	8 (22)
Tumour size [*n* (%)]	
≤2 cm	16 (44)
>2 cm	20 (56)
ER/PR status [*n* (%)]	
Negative	6 (17)
Positive	30 (83)
HER2 status [*n* (%)]	
Negative	31 (86)
Positive	5 (14)
Chemotherapy (*n* patients)	
FEC-D	18
TC	12
AC (docetaxel)	5
AC (paclitaxel, dose dense)	1

ER = estrogen receptor; PR = progesterone receptor; HER2 = human epidermal growth factor receptor 2; FEC-D = 5-fluorouracil–epirubicin–cyclophosphamide, then docetaxel; TC = docetaxel–cyclophosphamide; AC = doxorubicin–cyclophosphamide.

(94%), with 70% receiving a 10-day course and 30% receiving a 7-day course. Most patients received FEC-D (5-fluorouracil–epirubicin–cyclophosphamide, followed by docetaxel) or TC (docetaxel–cyclophosphamide) chemotherapy.

Of patients receiving G-CSF, 29 (81%) received it as primary prophylaxis. In that primary prophylaxis group, 6 patients (21%) met ASCO criteria for primary use of G-CSF by virtue of being more than 65 years of age. In the rest of the group, no patient met any ASCO criterion, resulting in an overall guideline adherence rate of 21%. In the latter patients, the most common rationale cited for primary prophylaxis was physician-perceived risk of febrile neutropenia associated with therapy. In 90% of cases, primary prophylaxis commenced with the taxane component of the treatment. Secondary prophylaxis with G-CSF was given to 7 patients (19%) after documented neutropenia, with 2 of those patients having experienced febrile neutropenia.

Of patients receiving G-CSF, 96% received the injections at home with the help of a nurse. Subsequently, they were taught self-injection techniques. Most patients were able to inject themselves independently after instruction; 2 patients continued to receive injections provided by family members or friends. The reasons cited for non-self-administration included existing expertise of a family member or friend with needles and patient preference. The median number of nursing visits for G-CSF injection purposes was 2 (range: 1–3 visits), but many patients continued to receive home care for maintenance of central venous catheters. On average, each visit took less than 30 minutes. Most patients were highly satisfied with the home care and G-CSF teaching they received. All but 1 patient rated those aspects "excellent."

4. DISCUSSION AND CONCLUSIONS

The use of G-CSF is associated with significant costs. A recent economic analysis of G-CSF use estimated the cost of filgrastim and pegfilgrastim to be, respectively, US$280 daily for up to 10 days and US$2100 per dose[3]. Costs related to the administration of these drugs are more nebulous and difficult to ascertain; they may vary depending on the local practice patterns of health care delivery. One study estimated the cost of each injection to be approximately US$20 and potentially as much as US$100[4]. Taken together, the acquisition and administration costs for routine use of these medications imposes a considerable financial burden on the health care system.

The foregoing facts have been acknowledged by major cancer societies, including ASCO, and have in part led to the creation of guidelines on the use of G-CSF[2]. Consideration of primary prophylaxis was recommended for patients more than 65 years of age; patients with poor performance status, malignant bone marrow infiltration, open wounds, active infections, or other serious medical comorbidities; patients who had received extensive prior treatment or who were receiving combined chemoradiation; and patients receiving a chemotherapy regimen with a documented rate of febrile neutropenia exceeding 20%. Most of the patients in our study sample received G-CSF as primary prophylaxis, but only 21% met established ASCO criteria, all by virtue of their age. The most commonly cited reason for use of G-CSF in this setting, as documented in the drug request letters on record to the Ministry of Health, was the expected risk of febrile neutropenia associated with therapy.

The documented incidence of febrile neutropenia in the literature varies, and the condition is more frequently associated with taxane-containing chemotherapy regimens[5], which represented 100% of the regimens in the present study. Correspondingly, initiation of primary prophylaxis in our study most often coincided with the taxane portion of the regimen. In the original landmark trials that validated

their use, TC and FEC-D were both shown to be associated with relatively low rates of febrile neutropenia. In U.S. Oncology Trial 9735, which compared TC with AC (doxorubicin–cyclophosphamide) in the adjuvant therapy of early-stage breast cancer, both arms achieved rates of febrile neutropenia less than 10%[6]. However, several recent retrospective studies showed a higher rate of febrile neutropenia with TC (25%–50%) in the absence of primary prophylaxis[7,8]. The rate of febrile neutropenia associated with FEC-D has also been shown to be higher than previously thought. In the pivotal PACS 01 trial[9] with FEC-D, the rate of febrile neutropenia was approximately 11%, but a recent study involving 4 cancer centres in Ontario found the rate of febrile neutropenia from adjuvant FEC-D to be approximately 31% when routine primary prophylaxis was not administered[10]. Experiences such as those likely contributed to the perception of elevated risk of febrile neutropenia by oncologists at our centre, leading to their advocacy for coverage of G-CSF as primary prophylaxis in association with the regimens in use.

Given the increasingly significant rates of febrile neutropenia seen in recent retrospective studies with these taxane-containing regimens, the use of G-CSF as primary prophylaxis warrants consideration even for regimens not traditionally viewed as having a high febrile neutropenia risk. Although not directly correlated with survival, primary prophylaxis using G-CSF has been shown to greatly reduce febrile neutropenia, febrile neutropenia–related hospitalization, and the use of antibiotics[11]. In the Ontario study, the rate of febrile neutropenia in the group of patients that received primary prophylaxis was just 6%, compared with the 31% in those that did not, representing a relative risk of 0.20[10]. The cost of primary prophylaxis is nontrivial, and has been estimated in one study to be $48,000 per febrile neutropenia event avoided using pegfilgrastim[12]. However, the same study showed that the price per quality-adjusted life-year of using this approach was not substantially different from that for several other commonly accepted practices such as providing ondansetron for cisplatin-induced emesis. Costs may be further reduced through shortened—but possibly equally efficacious—regimens of G-CSF administration. One recent study compared 8-day, 5-day, and 4-day schedules of filgrastim together with a single dose of pegfilgrastim in patients receiving dose-dense AC–paclitaxel[13]. No significant difference was found in the rates of febrile neutropenia, but the 4-day regimen was associated with savings of nearly US$4000 per patient. The study was limited by its single-centre nature and non-randomized design. Larger randomized studies will be helpful in affirming and validating this novel approach.

Given that G-CSF is administered subcutaneously, our centre has adopted a system whereby home care nurses teach the patient to self-administer medications. Our study examined that form of delivery of G-CSF in the community and the associated satisfaction rates among patients. Most patients were very satisfied with the current home care nurse–led teaching program. In most cases, patients were able to take over administration of the G-CSF after 1 or 2 scheduled visits.

One limitation of our study is the small number of patients in the study and the suboptimal response rate. Despite the fact that nearly 120 patients were identified for the study, only 39 patients completed written consent, and 50 patients were not able to provide initial verbal permission for the mailing of the consent documents. That initial failure to gain permission most often stemmed from an inability to contact the patients by telephone. Ultimately, 69 patients gave verbal permission for the mailing, and they were sent packages with consent forms. Only 39 patients (57%) were able to complete the consent forms as required. That response rate represents a potential source of bias, because the patients who were most motivated to complete the study may also have been the ones most motivated to learn how to inject medications. The study results may therefore overestimate the success of the home care injection teaching strategy.

Techniques for increasing response rates to study mailings have been well documented in the literature[14], and indeed we used several such strategies in our study. Patients were provided with pre-stamped and pre-addressed envelopes for returning completed consent forms. Up to 2 telephone calls were placed to patients to remind them to return the consent forms, and duplicate consent packages were sent to patients who either did not receive them initially or who misplaced them. Although these strategies may have improved the response rate, they led to greater utilization of staff and limited financial resources.

In summary, this single-centre study was performed to examine how growth factor support is being used in a real-world non-trial setting. The results show an increasing trend toward G-CSF use for primary prophylaxis. Clearly, given the considerable costs associated with these agents, other strategies such as using fewer days of filgrastim or identifying the patients at greatest risk of febrile neutropenia need to be explored. The study also shows that patients can be rapidly taught how to self-administer these agents at home, thereby reducing the need for hospital-based services.

5. CONFLICT OF INTEREST DISCLOSURES

This study was supported entirely by divisional funding; no pharmaceutical sponsorship was involved. MC has received research funding and honoraria for talks from Amgen Pharmaceuticals.

6. REFERENCES

1. Kuderer NM, Dale DC, Crawford J, Lyman GH. Impact of primary prophylaxis with granulocyte colony–stimulating factor on febrile neutropenia and mortality in adult cancer patients receiving chemotherapy: a systematic review. *J Clin Oncol* 2007;25:3158–67.
2. Smith TJ, Khatcheressian J, Lyman GH, *et al.* 2006 Update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline. *J Clin Oncol* 2006;24:3187–205.
3. Lyman GH, Lalla A, Barron RL, Dubois RW. Cost-effectiveness of pegfilgrastim versus filgrastim primary prophylaxis in women with early-stage breast cancer receiving chemotherapy in the United States. *Clin Ther* 2009;31:1092–104.
4. Lyman G, Lalla A, Barron R, Dubois RW. Cost-effectiveness of pegfilgrastim versus 6-day filgrastim primary prophylaxis in patients with non-Hodgkin's lymphoma receiving CHOP-21 in United States. *Curr Med Res Opin* 2009;25:401–11.
5. Ferguson T, Wilcken N, Vagg R, Ghersi D, Nowak AK. Taxanes for adjuvant treatment of early breast cancer. *Cochrane Database Sys Rev* 2007;:CD004421.
6. Jones S, Holmes FA, O'Shaughnessy J, *et al.* Docetaxel with cyclophosphamide is associated with an overall survival benefit compared with doxorubicin and cyclophosphamide: 7-year follow-up of US Oncology research trial 9735. *J Clin Oncol* 2009;27:1177–83.
7. Chan A, Fu WH, Shih V, Coyuco JC, Tan SH, Ng R. Impact of colony-stimulating factors to reduce febrile neutropenic events in breast cancer patients receiving docetaxel plus cyclophosphamide chemotherapy. *Support Care Cancer* 2011;19:497–504.
8. Soong D, Haj R, Leung MG, *et al.* High rate of febrile neutropenia in patients with operable breast cancer receiving docetaxel and cyclophosphamide. *J Clin Oncol* 2009;27:e101–2.
9. 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.
10. Madarnas Y, Dent SF, Husain SF, *et al.* Real-world experience with adjuvant FEC-D chemotherapy in four Ontario regional cancer centres. *Curr Oncol* 2011;18:119–25.
11. Vogel CL, Wojtukiewicz MZ, Carroll RR, *et al.* First and subsequent cycle use of pegfilgrastim prevents febrile neutropenia in patients with breast cancer: a multicenter, double-blind, placebo-controlled phase III study. *J Clin Oncol* 2005;23:1178–84.
12. Ramsey SD, Liu Z, Boer R, *et al.* Cost-effectiveness of primary versus secondary prophylaxis with pegfilgrastim in women with early-stage breast cancer receiving chemotherapy. *Value Health* 2009;12:217–25.
13. Hendler D, Rizel S, Yerushalmi R, *et al.* Different schedules of granulocyte growth factor support for patients with breast cancer receiving adjuvant dose-dense chemotherapy: a prospective nonrandomized study. *Am J Clin Oncol* 2011;34:619–24.
14. Edwards P, Roberts I, Clarke M, *et al.* Methods to increase response rates to postal questionnaires. *Cochrane Database Sys Rev* 2007;:MR000008.

Correspondence to: Mark J. Clemons, Division of Medical Oncology, The Ottawa Hospital Cancer Centre, 501 Smyth Road, Ottawa, Ontario, K1H 8L6. ***E-mail:*** mclemons@toh.on.ca

* Department of Medicine, University of Ottawa, Ottawa, ON.
† Division of Medical Oncology, The Ottawa Hospital Cancer Centre, Ottawa, ON.
‡ Statistical consultant, Toronto, ON.