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ORIGINAL ARTICLE

Efficacy of pegfilgrastim to support neoadjuvant dose-dense epirubicin and cyclophosphamide chemotherapy in breast cancer

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Abstract

Purpose The role of long-acting hematopoietic growth factor in supporting dose-dense chemotherapy and minimizing hematologic toxicity has not been established. We investigated the efficacy and safety of once-per-cycle pegfilgrastim in breast cancer patients receiving neoadjuvant dose-dense epirubicin and cyclophosphamide (ddEC).

Methods Newly diagnosed stage I to III breast cancer patients received four cycles of ddEC (E, 100 mg/m^2 and C, 600 mg/m^2 every 2 weeks) and 6 mg of subcutaneous pegfilgrastim on day 2 of each cycle. The primary endpoint was to evaluate the incidence of chemotherapy delay. Secondary endpoints include the incidences of febrile neutropenia (FN) and grade 3/4 neutropenia during the four ddEC cycles.

Results A total of 240 patients were enrolled and 913 ddEC cycles were administered in the study. Chemotherapy delay occurred in 15 patients (6.3% of patients, 95% CI 3.2–9.4%) for 17 cycles (1.9% of cycles, 95% CI 1.0–2.8%). The most frequent cause of chemotherapy delay was transaminase elevation (10 patients, 12 cycles). A total of 12 patients (5.0%, 95% CI 2.2–7.8%) developed 13 episodes of FN. Of the 221 patients that completed four ddEC cycles with pegfilgrastim support, 209 patients (94.6%, 95% CI 91.6–97.6%) had a 100% relative dose intensity (RDI). A RDI ≥ 85% was achieved in 217 of 221 patients (98.2%, 95% CI 96.5–99.9%). Bone pain of any grade was recorded in 85 of 220 evaluable patients (38.6%, 95% CI 32.2–45.0%).

Conclusions Pegfilgrastim is effective and safe in facilitating four cycles of neoadjuvant ddEC, with low incidences of chemotherapy delay and febrile neutropenia.

Keywords Pegfilgrastim · Febrile neutropenia · Dose-dense chemotherapy · Breast cancer

Introduction

The survival advantage of dose-dense chemotherapy over standard interval chemotherapy was first observed in randomized trials [1, 2] and later confirmed by systemic reviews and meta-analyses [3, 4]. However, dose-dense chemotherapy regimens are accompanied by an increased risk of myelosuppression and hence the administration of prophylactic granulocyte colony-stimulating factors (G-CSFs) is considered mandatory [5, 6]. In the CALGB 9741 study [1], filgrastim administration from day 3 to 10 allowed the regimens to be delivered safely. In the GIM2 trial [2], once-per-cycle pegfilgrastim was used to support dose-dense regimens.

For primary prophylaxis, filgrastim is suggested to be given daily until absolute neutrophil count (ANC) returns to normal range and an average of 10–11 injections of filgrastim were required to support ANC recovery to $>2\times10^9$/L [7]. The dosing of filgrastim in actual practice is often lower than that in controlled clinical trials. A retrospective US claims analysis reported that the mean duration of prophylactic filgrastim was 4.8 days which may compromise its efficacy [8]. Once-per-cycle fixed-dose pegfilgrastim is expected to improve patient compliance and simplify the management of chemotherapy-induced neutropenia for both patients and healthcare workers [7].

The majority of data on the efficacy and safety of pegfilgrastim have been generated in trials using standard interval (three weekly) regimens. In 2003, Dana–Farber Cancer Institute conducted a phase II trial of 135 patients to evaluate

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the use of 6 mg pegfilgrastim to support the same dose-dense chemotherapy regimen as that used in the CALGB 9741 trial and found that the incidence of FN was 1.5%. Patients in the study also had a low rate of treatment delays and a high rate of planned chemotherapy dose on time [9]. In the randomized GIM2 trial, grade 3/4 neutropenia was less frequent in patients receiving dose-dense chemotherapy with pegfilgrastim support (14.9%) than in those treated with an every-3-week regimen (44.0%, $P < 0.0001$) [2]. Another retrospective cohort study reported that patients who received filgrastim were almost three times more likely to experience a severe neutropenia episode and were significantly more likely to experience a dose reduction than those who received pegfilgrastim [10].

In this prospective single-arm study, we assessed the efficacy of pegfilgrastim in reducing the incidence of treatment delay and FN as well as maintaining relative dose intensity (RDI) when used as a support for four ddEC cycles in breast cancer patients.

Methods

Patients were treated at Peking University Cancer Hospital Breast Center. The study was conducted in accordance with the Declaration of Helsinki and was approved by the institutional review board. All patients provided written informed consents for the protocol-based treatment before enrolling into the study. Patient and tumor characteristics were prospectively collected. Estrogen and progesterone receptor (ER/PR) positivities were defined by at least 10% positive cells in immunohistochemical (IHC) analysis. HER2 positivity was defined by at least 10% HER2-expressing tumor cells in IHC analysis or by a positive fluorescence in situ hybridization (FISH) assay. This trial is registered with ClinicalTrials.gov as number NCT02944604.

Patient eligibility

Patients were enrolled from September 2016 through November 2017. Histologically confirmed invasive breast cancer patients by core needle biopsy (CNB) between the age of 18 and 65 were eligible. Eligible patients need to have stage I to III diseases (as defined by the American Joint Committee on Cancer seventh edition) and World Health Organization performance status of 0 to 1, ANC $\geq 1.5 \times 10^9$/L, hemoglobin (Hgb) ≥ 80 g/L, platelets $\geq 80 \times 10^9$/L, AST and ALT ≤ 2.5 times the normal upper limits, and bilirubin and creatinine < 1.5 times the normal upper limits. Exclusion criteria include previous chemotherapy or radiation therapy, being pregnant or nursing, known allergic reaction to G-CSFs or biosimilars, other concurrent illness such as active infection, heart failure, or other significant illness that might influence treatment tolerability.

Study design and treatment plan

Patients were scheduled to receive four cycles of preoperative epirubicin (100 mg/m^2) and cyclophosphamide (600 mg/m^2) intravenously once every 2 weeks. Pegfilgrastim (6 mg) (China Shijiazhuang Pharmaceutical Group co., Ltd., CSPC Pharma.) was given subcutaneously on day 2 (approximately 24–27 h after chemotherapy) of each cycle. Most of the patients with HER2-positive or hormone receptor (HR) negative disease received subsequent taxanes (80 mg/m^2 paclitaxel weekly for 12 weeks or 175 mg/m^2 once every 2 weeks for four cycles) after four cycles of ddEC. Trastuzumab was used concurrently with the taxanes and continued after surgery for a total duration of 1 year if indicated.

Complete blood count and blood chemistry tests were carried out 1 day prior to each treatment cycle. Safety of treatment was monitored by assessment of all adverse events. Adverse events were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Treatment with ddEC was held for ANC $< 1.5 \times 10^9$/L or platelet count $< 80 \times 10^9$/L or Hgb < 80 g/L on the scheduled day of treatment, and was resumed once the ANC or platelet count or Hgb recovered to allow treatment. Patients with grade 2 or higher transaminase (ALT or AST) or blood creatinine or bilirubin elevation also had their chemotherapy cycles held until blood chemistry abnormalities resolved to normal or grade 1. Patients received appropriate antiemetic therapy according to standard institutional practices during chemotherapy. Patients were taken off study for tumor progression or withdrawal of consent.

The primary endpoint of the study was to evaluate the incidence of chemotherapy delay. Secondary endpoints include the incidences of febrile neutropenia (FN) and grade 3/4 neutropenia. FN was defined using the National Comprehensive Cancer Network and Infectious Diseases Society of America criteria as a single oral temperature of 38.3 °C or a temperature of 38.0 °C for 1 h, with ANC $< 0.5 \times 10^9$/L [11]. All patients with FN were hospitalized, other therapeutic measures imposed include blood cultures and the administration of broad-spectrum antibiotics. Additional filgrastim administration in patients with FN was at the discretion of the treating physician.

RDI is the ratio of dose intensity (DI) received by patients to DI of the scheduled regimen. RDI and DI were calculated as follows: DI = total actual dose (mg/m^2)/total time to complete therapy (weeks); RDI (%) = (DI of actual therapy/DI of the planned regimen) × 100. The incidences of chemotherapy delay, FN, and RDI were calculated on a per protocol basis.

Statistical analysis

The sample size was calculated using the PASS v11 Home edition. The sample size calculation was based on the results

from the Dana–Farber study which reported that the incidence of chemotherapy delay was 4.9% when pegfilgrastim was used to support dose-dense regimens in breast cancer patients [9]. Using a prospective single-arm design, a sample size of 218 achieves 80% power to detect a difference of − 0.05 using a one-sided binomial test. The target significance level is one-sided 0.025. Two hundred and forty patients were planned to be enrolled (considering a 10% dropout rate). Categorical data are presented as absolute and relative frequencies. All analyses were performed using SPSS version 22 (IBM Corp., Armonk, NY, USA).

Results

Patient and tumor characteristics

A total of 240 patients were enrolled in the study and 239 received at least one dose of the study treatment. The median age was 47 (range 24–65) years. There were 235 unilateral and four bilateral cancers (243 affected breasts) with invasive ductal carcinoma being the most common histological type. Most of the patients enrolled in the study had one or more of the following risk factors: young age (≤ 35 years), hormone receptor negative, HER2-positive, lymph node positive or large primary tumor (≥ 5 cm). One hundred and fifty-nine axillas (65.4%) were found to harbor lymph node metastases by fine needle aspiration cytology (FNA) or CNB or sentinel lymph node biopsies (SLNB). Table 1 summarizes the patient and tumor characteristics of the enrolled patients.

Two hundred and twenty-one patients completed four cycles of ddEC and a total of 913 ddEC cycles were administered with pegfilgrastim support. Table 2 summarizes the reasons and time points of the 19 patients who were taken off study.

Table 1 Patient and tumor characteristics

Characteristic	*N* (%)
Age	
< 50	136 (56.9)
≥ 50	103 (43.1)
T stage (per breast)	
Tis	1 (0.4)
T1–2	210 (86.4)
T3–4	32 (13.2)
Histologic type (per breast)	
IDC	231 (95.1)
ILC	5 (2.0)
Other	7 (2.9)
Hormone receptor (per breast)	
Positive	162 (66.7)
Negative	81 (33.3)
HER-2 (per breast)	
Positive	89 (36.6)
Negative	154 (63.4)
Lymph node status (per breast)	
FNA or CNB+	122 (50.2)
SLNB+	37 (15.2)
SLNB−	68 (28.0)
SLNB visulization failure	5 (2.1)
ALND due to T3 or T4 primary tumor	11 (4.5)

IDC, invasive ductal carcinoma; *ILC*, invasive lobular carcinoma; *HER-2*, human epidermal growth factor receptor; 2; *FNA*, fine needle aspiration; *CNB*, core needle biopsy; *SLNB,* sentinel lymph node biopsy

Chemotherapy delay

Chemotherapy delay (2 days or more) occurred in 15 patients (6.3% of patients) for 17 cycles (1.9% of cycles). Table 3 shows the number of patients with a treatment delay at each cycle and the reasons for treatment delays. All causes of chemotherapy delays were resolved after proper treatment and the duration of chemotherapy delay was 1 week or less in most of the cases. Chemotherapy was delayed for 2 weeks in two cases with transaminase elevation.

FN and grade 3/4 neutropenia

A total of 12 patients (5.0%) developed 13 episodes of FN. Most of the FN episodes occurred following the first cycle (nine patients, nine cycles). All 12 patients recovered without complication and went on with their planned chemotherapy without dose reduction. Non-febrile grades 3 or 4 neutropenia was observed in only four patients (1.7%, 95% CI 0.1–3.3%) in our study.

Other hematologic toxicity

One case of grade 2 thrombocytopenia and one case of grade 3 thrombocytopenia were observed. Both occurred concurrently with FN and recovered without complication. Another 40 cases of grade 2 anemia and one case of grade 3 anemia were observed during the study. Table 4 summarizes the hematologic toxicities observed in the study.

Relative dose intensity

RDIs were calculated for the 221 patients that completed four cycles of ddEC with pegfilgrastim support. RDI was 100% in 209 of the 221 patients (94.6%), and a RDI ≥ 85% was achieved in 217 of the 221 patients (98.2%).

Table 2 Reasons and time points of the 19 patients taken off study

Cycles of treatment in study (per patient)	Reasons for being taken off	Number of patients	Treatment after being taken off
0	Pegfilgrastim was never initiated	1	Chemotherapy with filgrastim support
1	Severe gastrointestinal toxicity	1	Surgery
1	Cardiac symptom suspected to be related to epirubicin	1	Surgery
1	Suspected allergic reaction to pegfilgrastim	1	Chemotherapy with filgrastim support
1	FN	5	Chemotherapy with filgrastim support in three patients Neoadjuvant endocrine therapy in one patient Chemotherapy with taxane-containing regimen in one patient
1	Withdrew consent	2	Not available
2	Disease progression	4	Chemotherapy with taxane-containing regimen in all four patients
2	FN (after both cycles 1 and 2)	1	Chemotherapy with filgrastim support starting at cycle 3
3	Severe gastrointestinal toxicity	2	Chemotherapy with taxane-containing regimen in both patients
3	Transaminase elevation	1	Chemotherapy with taxane-containing regimen

Other toxicities

The most common toxicity considered to be related to pegfilgrastim was bone pain. Data were available to assess the incidence and severity of bone pain in 220 patients and bone pain of any grade was reported by 85 of the 220 patients (38.6%).

Pegfilgrastim dose reduction

Pegfilgrastim dose was reduced from 6 to 3 mg in 24 patients (10.0%). All dose reductions took place after a WBC count $\geq 10 \times 10^9$/L was reported 1 day prior to the following treatment cycle. A total of 55 ddEC cycles were supported with 3 mg of pegfilgrastim, and no chemotherapy delay or FN or grade 3/4 neutropenia was recorded after pegfilgrastim dose reduction.

Discussion

To date, the use of long-acting hematopoietic growth factor in facilitating dose-dense chemotherapy and minimizing hematologic toxicity is still considered investigational. The primary objective of the present study was to evaluate the incidence of chemotherapy delay during four cycles of ddEC with pegfilgrastim support. We observed a low rate of chemotherapy delay that affected only 6.3% of patients. The most common cause of chemotherapy delay was grade 2 or higher transaminase elevation, which occurred in ten patients (4.2% of patients, 95% CI 1.7–6.7%) for 12 cycles (1.3% of cycles, 95% CI 0.6–2.0%). Our previous data showed a similar incidence of grade 2 or higher transaminase elevation (5.0%) in patients receiving the same dosage of a every-3-week epirubicin and cyclophosphamide with or without fluorouracil [12]. We believe that transaminase elevation was caused by the chemotherapy drugs, irrespective of the G-CSF used.

Table 3 Number of patients with treatment delay at each cycle and the reasons for treatment delays

Cycle number	Number of patients with treatment delays	Reasons for treatment delays
1	0	
2	4	Transaminase elevation in three patients
		Grade 3 anemia in one patient
3	5	Transaminase elevation in two patients
		Grade 3 non-febrile neutropenia in one patient
		Urinary tract infection in one patient
		Prolonged gastrointestinal toxicity in one patient
4	8	Transaminase elevation in seven patients
		Prolonged gastrointestinal toxicity in one patient

Table 4 Hematologic toxicities

Grade	Neutropenia (%)	Thrombocytopenia (%)	Anemia (%)
0	218 (91.2)	236 (98.7)	132 (55.2)
1	4 (1.7)	1 (0.4)	66 (27.6)
2	1 (0.4)	1 (0.4)	40 (16.7)
3	0 (0)	1 (0.4)	1 (0.4)
4	12 febrile (5.0) 4 non-febrile (1.7)	0 (0)	0 (0)

Chemotherapy delay and dose reduction can impair the quality of chemotherapy by resulting in a lower accomplished RDI. Previous studies have shown that RDI < 85% is associated with compromised treatment outcomes [13]. Studies have reported high-accomplished RDIs when pegfilgrastim was used to support dose-dense chemotherapy (95.2 and 96.8%, respectively) [14, 15]. It is worth noting that both studies were conducted in Japan and a pegfilgrastim dosage of 3.6 mg was used. In line with these results, our study showed that 94.6% of patients achieved a RDI of 100%, and 98.2% of patients achieved a RDI of ≥ 85%. No patient had dose reduction during the study and as a result, all patients with RDIs less than 100% were due to chemotherapy delays. The low rate of chemotherapy delay and high-accomplished RDI indicate that ddEC with pegfilgrastim support is clinically feasible.

Given that FN is associated with substantial morbidity, mortality, and cost, it places a significant burden on individual patient as well as the healthcare system as a whole [16]. Meta-analyses of head-to-head comparative studies of pegfilgrastim versus filgrastim concluded that one dose of pegfilgrastim was more efficacious than filgrastim administered for up to 12–14 days (median of 11 doses) in lowering patients' risk of FN with a pooled RR of 0.64 (95% CI, 0.43–0.97) [17]. In the present study, the incidence of FN was 5.0%, which is very similar to the incidence of pooled FN (5%) reported by von Minckwitz et al. in a meta-analysis of trials that used 6 mg of pegfilgrastim as primary prophylaxis to support standard interval chemotherapy in breast cancer patients [18]. Similar rates of FNs show comparable efficacy when 6 mg of pegfilgrastim was used to support standard interval and dose-dense chemotherapy.

The incidences of treatment delay and FN reported in literature when pegfilgrastim was used to support dose-dense (or intensified dose-dense) regimens in breast cancer patients are summarized in Table 5. Most studies are retrospective in nature [10, 15, 22] or prospective with a very limited number of cases

Table 5 Published studies on the incidences of treatment delay and FN

Author	No. patients	Type of chemotherapy	Administration of pegfilgrastim	Treatment delays	FN (%)
Burstein 2005 [9]	135	ddAC×4 followed by ddPac×4	6 mg given on day 2	4.9% of cycles	2 (1.5)
Kourlaba 2015 [10]	529	idd E×3 followed by idd Pac×3 followed by idd CMF×3 or idd E×3 followed by idd CMF×3 followed by Doc or weekly Pac×3	6 mg given on day 2	7.2% of cycles	23 (4.3)
Morita 2017 [14]	51	ddEC×4	3.6 mg given on day 2	11(21.6%) of patients	1 (2)
Mizuno 2017 [15]	41	ddAC×4	3.6 mg given on day 2 or day 3	2 (4.9%) of patients	1 (2.4)
Natoli 2007 [19]	41	ddEC×4 followed by TX×2	6 mg given on day 2 during ddEC	Not available	0 (0)
Jones 2009 [20]	65	ddAC×4 or ddEC×4	6 mg given on day 2	7 (10.8%) of patients	6 (9)
Loibl 2011 [21]	351	idd E×3 followed by idd Pac×3 followed by idd C×3	6 mg given on day 2 ($n = 174$) 6 mg given on day 4 ($n = 177$)	Not available	day 2 group 8 (4.7) day 4 group 14 (8.0)
Skarlos 2009 [22]	107	idd E×3 followed by idd Pac×3 followed by idd CMF×3 or idd E×3 followed by idd CMF×3 followed by Doc or weekly Pac×3	6 mg given on day 1	61 (57%) of patents	14 (13)
Hendler 2011 [23]	57	ddAC×4 followed by weekly paclitaxel×4	6 mg given on day 2 during ddEC	7 (12.3%) of patients	6 (10.5)

dd, dose dense; *idd*, intensified dose dense

[9, 14, 19, 20, 23]. In addition, several studies used intensified dose-dense regimens which are not recommended by current guidelines [10, 21, 22]. The present study is the largest prospective study that used pegfilgrastim to support neoadjuvant dose-dense chemotherapy in breast cancer patients to date.

The incidence of non-febrile grade 3/4 neutropenia was extremely low (1.7%) in our study. This is most likely related to our routine check-up plan. WBC/ANC counts and blood chemistry tests were conducted 1 day prior to each treatment cycle for most of the patients. More cases of grade 3/4 neutropenia would have been found if WBC/ANC counts were carried out more frequently. In the current literature, the routine treatment monitor plan is inadequately reported for patients undergoing dose-dense chemotherapy with pegfilgrastim support. There is no existing consensus on the standard blood test regimen and these patients usually have their treatments monitored according to local or institutional guidelines. However, due to the low rate of hematologic toxicities observed in the present study, we propose that more frequent blood works may not be necessary. Blood tests carried out 1 day prior to each treatment cycle seem to be sufficient in this clinical scenario. The optimal blood test arrangement needs further evaluation.

Owing to its promyelogenic effects, bone pain is a common side effect after the administration of G-CSFs. When pegfilgrastim was used to support dose-dense chemotherapy, no grade 3/4 bone pain was observed by Jones et al. [20] while the bone pain of any grade was recorded in about 50% of the patients in the GIM2 trial [2]. In the present study, bone pain of any grade was reported by 85 of the 220 patients (38.6%) with evaluable data. In most of the cases, bone pain was mild to moderate and no treatment was required.

According to the American Society of Clinical Oncology (ASCO) guidelines, pegfilgrastim should be given once per cycle 24 hours after completion of chemotherapy at a fixed dose of 6 mg [6]. In our study, 24 patients (10.0%) had their pegfilgrastim doses reduced to 3 mg after a WBC count $\geq 10 \times 10^9$/L was reported 1 day prior to the following treatment cycle. Dose reduction was adopted by some of the treating oncologists having in mind that excessive WBC levels at the beginning of the following chemotherapy cycle might be associated with a worse myelosuppressive effect [24]. No chemotherapy delay or FN or grade 3/4 neutropenia was recorded after pegfilgrastim was reduced to 3 mg. The incidence of chemotherapy delay and FN were also calculated in 215 patients without dose reduction. Chemotherapy delay occurred in 7.0% of patients (95% CI 3.6–10.4%) and 2.0% of cycles (95% CI 1.1–2.9%). The incidence of the FN was 5.6% (95% CI 2.5–8.7%). We noted that studies conducted in Japan often used a dosage of 3.6 mg because the approved dose of pegfilgrastim is 3.6 mg in Japan. Two Japanese studies [14, 15] reported that the rate of FN were 2.4 and 4%, respectively, when pegfilgrastim 3.6 mg was used to support four cycles of dose-dense doxorubicin or epirubicin in combination with cyclophosphamide. These results indicate that a lower dosage of pegfilgrastim may be sufficient for primary prophylaxis in some patients. We propose that for patients in whom the initial 6 mg pegfilgrastim resulted in an "overshoot" of WBC/ANC, pegfilgrastim dose reduction may be appropriate but will need further evaluation.

A major limitation of the current trial is the lack of cost-effectiveness analysis. It is intuitive that once-per-cycle pegfilgrastim offers substantial clinical convenience to patients over more frequent dosing of filgrastim. However, formal cost analyses are not available. Previous cost-effectiveness studies indicated that pegfilgrastim is a cost-effective alternative over filgrastim [25, 26].

Conclusion

In summary, the present study demonstrates that once-per-cycle pegfilgrastim provides effective hematologic support for breast cancer patients receiving a every-2-week epirubicin and cyclophosphamide.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The study was conducted in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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