Original Article

Effect of 3 mg versus 6 mg pegfilgrastim on the prevention of febrile neutropenia in breast cancer patients receiving docetaxel and cyclophosphamide: a retrospective study

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Background: An ECCOPG (Eastern China Cooperative Oncology Pharmacy Group) funded study was designed to compare the effect of 3 versus 6 mg pegfilgrastim for primary prevention of febrile neutropenia (FN) in Chinese breast cancer patients retrospectively.

Methods: Patients undergoing a docetaxel and cyclophosphamide chemotherapy regimen, followed by pegfilgrastim, for primary prevention during 2018 and 2020 were retrospectively enrolled in the present study. The patients were divided into 2 groups according to the dose of pegfilgrastim. The incidence of severe neutropenia (absolute neutrophil count $<0.5\times10^9$/L), incidence of FN, and recovery time were calculated to compare the efficacy of different groups. P<0.05 was considered statistically significant.

Results: A total of 295 patients were enrolled, 150 in the 3 mg pegfilgrastim group and 145 in the 6 mg pegfilgrastim group. No significant differences were found in the incidence of severe neutropenia (3 *vs.* 6 mg, 39.3% *vs.* 34.5%, P=0.401) and the incidence of FN (3 *vs.* 6 mg, 7.3% *vs.* 8.3%, P=0.830). Median recovery time was 2 days for both groups (P=0.485).

Conclusions: 3 mg pegfilgrastim may be effective and safe for Chinese breast cancer patients as the primary prevention for FN. Prospective studies are needed to further confirm the prophylactic effect of 3 mg pegfilgrastim.

Keywords: Breast cancer; febrile neutropenia (FN); pegfilgrastim; primary prevention

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Introduction

Febrile neutropenia (FN) is a common adverse event caused by chemotherapy. Patient who develops FN will risk life-threatening infection (1-3). Once a patient develops severe neutropenia or FN, chemotherapy doses in the next cycle usually need to be reduced or delayed. However, these countermeasures may reduce the efficacy of the regimens, which could lead to decreased survival rates (4,5). Depending on recombinant DNA technology, granulocyte-colony stimulating factor (G-CSF) was introduced to reduce the risk of FN. With the support of G-CSF, chemotherapy regimens with high risk of FN could be administered at

planned dosage and intervals.

According to duration, G-CSF can be divided into filgrastim(short-acting) and pegfilgrastim (long-acting). Pegfilgrastim has a polyethylene glycol (PEG) molecule that covalently binds to filgrastim. Using PEG modification, the serum half-life of filgrastim is prolonged from 3 h to 2 days. A placebo-controlled phase III study with breast cancer patients showed that the incidence of FN was 17% and 1% in the placebo and prophylactic pegfilgrastim groups (6). Furthermore, pegfilgrastim in prophylactic use can remarkably reduce the incidence of FN-related hospitalization and the use of antibiotics to treat infection.

Guidelines for the use of G-CSF have been established by the National Comprehensive Cancer Network (NCCN), American Society of Clinical Oncology, and European Organization for Research and Treatment of Cancer (7-9). Based on FN risk of chemotherapy regimens and patient-specific risks, the prophylactic use of G-CSF is recommended for patients with a 20% or greater risk of FN.

In the NCCN guidelines, the recommended dose of prophylactic pegfilgrastim is 6 mg. However, in clinical practice, pegfilgrastim prescriptions can be either 3 or 6 mg, based on the physician's experience and choice. A series of studies in Japan showed that a low dose (3.6 mg) of pegfilgrastim demonstrated no difference compared with 6 mg pegfilgrastim in terms of efficacy and adverse events (10-13). Studies on Chinese patients, however, are lacking.

The present study was carried out in patients undergoing a docetaxel and cyclophosphamide (TC) regimen, which is a standard chemotherapy for primary breast cancer with high risk of FN (>20%). The aim of the present study was to evaluate the prophylactic effects of low-dose pegfilgrastim.

We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/apm-21-267).

Methods

Patients

Patients undergoing TC chemotherapy regimen, followed by pegfilgrastim, for primary prevention during 2018 to 2020 were retrospectively enrolled in the present study. Patients who met the following criteria were enrolled: female, aged 20–65 years old, pathohistological diagnosis of stages I–III primary invasive breast carcinoma, baseline absolute neutrophil count (ANC) $\geq 2\times10^9$/L, baseline platelet count $\geq 100\times10^9$/L, baseline hemoglobin concentration >10 g/dL, baseline aspartate aminotransferase and alanine aminotransferase levels ≤2.5 times the upper limit of the normal range, baseline total bilirubin content ≤1.5 times the upper limit of the normal range, and baseline creatinine level ≤1.5 mg/dL. Patients who had a history of radiation therapy before chemotherapy, a history of stem cell or bone marrow transplantation, or comorbid malignancies other than breast cancer were excluded from the study.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was a retrospective institutional review analysis of maintained database, it was performed in accordance with the Institutional Ethical Committee rules and individual consent for this retrospective analysis was waived.

Groups

The patients were divided into 2groups according to the dose of pegfilgrastim. At 24–72 h after chemotherapy, patients were prescribed a single dose of 3 or 6 mg pegfilgrastim for FN prophylaxis. Patients were enrolled into either the 3 mg pegfilgrastim group or 6 mg pegfilgrastim group according to their dose.

Efficacy measurements

The primary endpoints were the incidence of severe neutropenia (ANC $<0.5\times10^9$/L) and FN (severe neutropenia with fever). The secondary endpoint was recovery times, which started from ANC nadir to ANC $\geq 2\times10^9$/L. Data of ANC were recorded from blood tests; adverse events were collected from patients' electronic medical records.

Statistical analysis

The sample size was designed to detect a statistically significant difference with a power of 80% and reached a 2-sided significance level of 5% using Pearson's χ^2-test. Based on a previous study, we assumed that 11% of the patients in the 3 mg-pegfilgrastim group and 3% of patients in the 6 mg-pegfilgrastim group would develop FN (10). Therefore, the sample size was nearly 150 patients per group.

Demographic and clinical variables were summarized as frequencies, proportions, and central tendency (mean, median). Continuous variables, such as body surface area, were analyzed by Student's *t*-test. Quantitative variables, such as carcinoma stage, were analyzed by χ^2-test. Median

Table 1 Summary of demographic and baseline characteristics

Baseline characteristics	3 mg pegfilgrastim (n=150)	6 mg pegfilgrastim (n=145)	P value
Age, mean, years	51.8	51.9	>0.05
Body surface area, mean, m^2	1.57	1.54	>0.05
Stage			>0.05
IIA	82	77	IIA
IIB	51	55	IIB
III	17	13	III
Lymph node involvement			>0.05
pN0	103	92	
pN (+)	44	46	
Unknown	3	7	
ER and/or PgR			>0.05
ER and/or PgR (+)	108	97	
ER and PgR (–)	42	48	

ER, estrogen receptor; PgR, progesterone receptor; (+), positive; (–), negative.

Table 2 Comparison of prophylactic efficacy in the first chemotherapy cycle

Primary and secondary points	3 mg pegfilgrastim (n=150)	6 mg pegfilgrastim (n=145)	P value
Incidence of severe neutropenia (%)	59 (39.3)	50 (34.5)	0.401
Incidence of febrile neutropenia (%)	11 (7.3)	12 (8.3)	0.830
Nadir of ANC (mean)	0.54	0.59	0.255
Median recovery time (days)	2	2	0.485

ANC, absolute neutrophil count.

variables, such as recovery days, were analyzed by Mann-Whitney *U*-test. The statistical outcomes set 95% as the confidence interval. All data were analyzed by SPSS version 22 (IBM, Armonk, NY, USA).

Results

Patients' baseline characteristics

Between 2018 and 2020, a total of 295 patients were included in the study. Patients' baseline characteristics are shown in *Table 1*. In terms of patients' baseline characteristics, there were no differences between the 2 groups. The mean age was 51.8 and 51.9 years, and the mean body surface area was 1.57 and 1.54 for the 3 mg and 6 mg pegfilgrastim groups, respectively (*Table 1*).

Efficacy

The outcomes of prophylactic efficacy in the first chemotherapy cycle are shown in *Table 2*. The incidence of severe neutropenia was 39.3% and 34.5%, the rate of FN was 7.3% and 8.3%, and nadir of ANC was 0.54×10^9/L and 0.5×10^9/L in the 3 mg and 6 mg pegfilgrastim groups, respectively. Median recovery time was 2 days for both groups (*Table 2*).

Adverse events

Nausea and vomiting, diarrhea, constipation, neutropenia, thrombocytopenia, and anemia were common adverse events related to chemotherapy. Muscle or bone pain were main adverse events associated with pegfilgrastim, which

Table 3 Adverse events

Adverse events	3 mg pegfilgrastim (n=150), n (%)	6 mg pegfilgrastim (n=145), n (%)
Nausea and vomiting	104 (69.3)	89 (61.4)
Diarrhea	66 (44.0)	60 (41.4)
Constipation	43 (28.7)	47 (32.4)
Muscle or bone pain	14 (9.3)	17 (11.7)
Neutropenia (≥ grade 3)	59 (39.3)	50 (34.5)
Thrombocytopenia (≥ grade 3)	5 (3.3)	3 (2.1)
Anemia (≥ grade 3)	0 (0)	1 (0.7)

occurred in 14 (9.3%) patients in the 3 mg pegfilgrastim group, and 17 (11.7%) patients in the 6 mg pegfilgrastim group (*Table 3*).

Discussion

For the prevention of FN, short-acting G-CSFs need daily injection after chemotherapy till ANC returns to normal level, while long-acting G-CSF (pegfilgrastim) only needs to be given as a single dose per cycle of chemotherapy. In the past 2 decades, pegfilgrastim has rapidly replaced filgrastim due to its advantages in convenience, compliance, and efficacy (14-16). There is a large market for pegfilgrastim in China; however, few studies have discussed the relationship between its dose and effect. The innovation of our study is we used data on Chinese patients, the dose response may be different from other races. The result of the study may help deciding more appropriate dose of pegfilgrastim on primary prophylaxis.

According to a survey of patients from 9 cities in China (Shanghai, Beijing, Chengdu, Guangzhou, Harbin, Hangzhou, Shenyang, Tianjin, Zhengzhou), 9,967 breast cancer patients were prescribed pegfilgrastim in the past year. Seventy percent of these patients paid with national health insurance. Of these, 60% used 6 mg pegfilgrastim for prophylactic use. The findings of the present study indicate that 3 mg pegfilgrastim is as effective as 6 mg pegfilgrastim, which would result in a significant cost reduction when choosing 3 mg pegfilgrastim for FN prevention compared with 6 mg pegfilgrastim, especially in Chinese medical insurance expenditure.

Prospective studies often use the duration of severe neutropenia (DSN) as a primary endpoint to evaluate the effect of G-CSF, which is defined as the number of days that a patient has ANC $<0.5\times10^9$/L in a cycle (17,18). However, DSN is not available in retrospective studies. In the present study, we used the incidence of severe neutropenia, incidence of FN, and recovery time to compare the efficacy of different treatment groups; these parameters provide a similar view for comparing the efficacy of G-CSF prevention.

The findings of the present study indicated that there was no significant difference in efficacy between the 2 dose groups in the prevention of FN. In a Japanese retrospective study with 97 breast cancer patients, 3.6 mg pegfilgrastim was found to be effective in primary prevention (12). A subsequent phase II clinical trial with 87 breast cancer patients further confirmed that 3.6 mg pegfilgrastim were effective for chemotherapy-induced neutropenia (10). As the Japanese are also Asian populations, this could be applied to Chinese patients.

In the present study, most of the adverse events recorded in the electronic medical records were associated with chemotherapy. Muscle and bone pain were common adverse events associated with pegfilgrastim. The incidence of muscle and bone pain was similar in the 2 dose groups of pegfilgrastim, which confirms that both 3 and 6 mg pegfilgrastim are tolerable in breast cancer patients receiving TC.

This study is comparatively small-sampled with data in one cancer center in China, our intention is to further expand our study to other high-risk FN chemotherapy protocols using data from more cancer centers in China. The most appropriate and cost-effective dose of pegfilgrastim should be evaluated for FN prophylaxis, which could reduce national health insurance costs.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was a retrospective institutional review analysis of maintained database, it was performed in accordance with the Institutional Ethical Committee rules and individual consent for this retrospective analysis was waived.

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