Original Article

Efficacy and safety of mecapegfilgrastim for prophylaxis of chemotherapy-induced neutropenia in patients with breast cancer: a randomized, multicenter, active-controlled phase III trial

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Background: Neutropenia is a common complication from chemotherapy. Mecapegfilgramtim (code name HHPG-19K), a long-acting recombinant human granulocyte colony-stimulating factor (rhG-CSF), has been developed. This study was to evaluate the efficacy and safety of mecapegfilgrastim for reducing neutropenia compared with filgrastim.

Methods: This was a randomized, controlled non-inferiority study. A total of 339 breast cancer patients who were eligible for (neo) adjuvant chemotherapy were randomized assigned into three groups to receive mecapegfilgrastim 100 μg/kg, mecapegfilgrastim fixed dose of 6 mg or filgrastim 5 μg/kg/day in the first cycle of chemotherapy. The primary endpoint was the duration of grade ≥3 neutropenia in cycle 1. The secondary endpoints included the duration of grade ≥3 neutropenia in cycles 2–4, incidence of grade ≥3 neutropenia, and febrile neutropenia (FN). The safety profile was also evaluated.

Results: The mean duration of grade ≥3 neutropenia was 1.06 [95% confidence interval (CI): 0.65, 1.26] days in mecapegfilgrastim 100 μg/kg group, 1.23 (95% CI: 0.84, 1.88) days in mecapegfilgrastim 6 mg group, and 2.06 (95% CI: 1.66, 2.46) days in the filgrastim group. The mean difference between mecapegfilgrastim 100 μg/kg and filgrastim was –1.00 (95% CI: –1.52, –0.48), the mean difference between mecapegfilgrastim 6 mg and filgrastim was –0.83 (95% CI: –1.36, –0.30). The upper bounds of 95% CI for the difference between mecapegfilgrastim and filgrastim were all <1 day (the predefined non-inferiority margin). For the incidence of grade ≥3 and grade 4 neutropenia, the mean duration of grade 4 neutropenia, mecapegfilgrastim showed better performance compared with filgrastim. For the incidence of FN, there was no difference between patients treated with mecapegfilgrastim and filgrastim. For safety profile, mecapegfilgrastim of two doses groups were all well-tolerated. Fixed 6 mg dose of mecapegfilgrastim exhibited comparable efficacy and safety in comparison with 100 μg/kg during 4 cycles.

Conclusions: Long-acting mecapegfilgrastim (100 μg/kg and fixed 6 mg) is very effective and well tolerated when administered in the primary prophylaxis of chemotherapy induced neutropenia and in

consecutive-cycle treatment. In some clinical parameters, mecafilgrastim is non-inferior and even superior to filgrastim. The fixed 6 mg-dose regimen showed similar efficacy and safety profile compared with 100 μg/kg regimen, and would be the preference in clinical practice, due to the convenient once-per-cycle administration and high-degree treatment compliance for the patients. This study provided new evidence for the novel long-acting rhG-CSF, mecapegfilgrastim, which would be a new alternative for clinical practice for prophylaxis of chemotherapy induced neutropenia.

Keywords: Breast cancer; long-acting granulocyte colony-stimulating factor (long-acting G-CSF); mecapegfilgrastim; filgrastim

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Introduction

Although the advances in targeted therapy and immune therapy, chemotherapy still plays a critical role in the cancer treatment strategy. Meanwhile, chemotherapy induced toxicities can adversely affect the patients' tolerance to chemotherapy and limit the effectiveness of chemotherapy. Neutropenia is a common complication, study shows that 65.5% of patients experienced a proven hematological toxicity with grade 3–4 neutropenia when treated with docetaxel, doxorubicin and cyclophosphamide (TAC) treatment regimen (1). Moreover, febrile neutropenia (FN) can be life-threatening, which associated with high risk of mortality.

The recombinant human granulocyte colony-stimulating factor (rhG-CSF), filgrastim and pegfilgrastim have been widely used for the prevention of chemotherapy-induced neutropenia (2-5). Filgrastim possesses rapid renal clearance and requires daily administration during chemotherapy. Pegfilgrastim, as the long-acting rhG-CSF, has comparable efficacy and safety profile to filgrastim, but its longer half-life allows once-per-cycle administration during chemotherapy (6,7). Therefore, pegfilgrastim could offer great convenience, which could enable better patient compliance and improved clinical outcomes (8,9). But in China, the US- and EU-approved pegfilgrastim (Neulasta) is not available, leaving the short-acting G-CSF as the major treatment option.

Mecapegfilgramtim (code name HHPG-19K), a long-acting rhG-CSF, has been developed by covalently bonding a 19-kDa polyethylene glycol (PEG) to the N terminus of filgrastim. The previous phase II study has shown that mecapegfilgrastim was well tolerated in non-small cell lung carcinoma (NSCLC) patients receiving platinum-based chemotherapy, the dose of 100 μg/kg was recommended for efficacy evaluating, and the mean plasma half-life value was 55.99 hours (10). The following phase III study showed that once-per-cycle injection of mecapegfilgrastim was as effective and safe as daily filgrastim for prophylaxis of chemotherapy-induced neutropenia in NSCLC patients (11).

For clinically evaluating all G-CSF medicines, patients with (neo)adjuvant breast cancer represent a sensitive population (12). It provides a homogenous patient population which means that they exhibit less inter-patient variation in terms of potential for treatment related toxicity and other confounding factors. Multiple randomized clinical studies have been conducted to demonstrate equivalence between biosimilar and reference G-CSF in breast cancer. In a phase II trial, mecapegfilgrastim preliminarily presented better clinical efficacy as the secondary prophylactic therapy for neutropenia and equal tolerance compared with G-CSF in one cycle treatment in breast cancer patients, and a dose of 100 μg/kg was recommended for further study (13).

In this study, we performed a randomized phase III study in patients with breast cancer. The primary objective was to further evaluate the non-inferiority of mecapegfilgrastim compared with filgrastim as the primary prophylactic therapy during the first cycle of chemotherapy with respect to duration of severe neutropenia (DSN), and also to demonstrate whether the fixed 6 mg dose showed a similar safety and efficacy to the weight-based dose of 100 μg/kg. This trial was approved by the National Medical Products Administration of China (registration number: 2010L00501) and registered on ClinicalTrials.gov (NCT01611051).

Methods

Patients

The patients who met the following criteria were enrolled:

pathologically confirmed and previously untreated breast cancer who were eligible to receive neoadjuvant or adjuvant chemotherapy defined by the study protocol; age ranging from 18 to 70 years old; body weight ≥45 kg; Eastern Cooperative Oncology Group (ECOG) performance status 0–1; expected tolerance of chemotherapy ≥4 cycles; adequate organ function: (I) normal bone marrow hematopoietic function without bleeding tendency [international normalized ratio (INR) <1.5]; (II) adequate hematologic function: hemoglobin ≥90 g/L, white blood cell (WBC) $\geq 4.0\times10^9$/L, absolute neutrophil count (ANC) $\geq 2.0\times10^9$/L, platelet count (PLT) $\geq 100\times10^9$/L; (III) adequate renal and hepatic function; (IV) no cardiopulmonary dysfunction; negative pregnancy test (blood sample or urine sample) within 7 days prior to enrollment for child bearing age females who are willing to use reliable contraception methods during the study.

The exclusion criteria include: had a history of bone marrow or stem-cell transplantation; had acute or active infection and received systemic antibiotics within 72 hours before chemotherapy; had hematologic disease could affect bone marrow function; underwent pregnancy or breast feeding; had been enrolled into other clinical trials within 4 weeks before randomization into this study; had previously received pegfilgrastim treatment; hypersensitive to PEG-rhG-CSF or rhG-CSF or other biological agents; had previously received systemic chemotherapy, definitive radiotherapy, palliative radiotherapy within 4 weeks; some special cases that the researchers determined not eligible for the study.

Study design

This was a randomized, open-label, active-control, multicenter study. The eligible patients received either anthracyclines-taxane (AT) chemotherapy (epirubicin 75 mg/m^2 combined with docetaxel 75 mg/m^2) or adriamycin and cyclophosphamide (AC) chemotherapy (epirubicin 100 mg/m^2 combined with cyclophosphamide 600 mg/m^2) on day 1 of each cycle and every 3 weeks for up to 4 cycles, except for disease progression or unacceptable toxicity.

For cycle 1, the patients were randomized at a ratio of 1:1:1 to receive a single dose of mecapegfilgrastim 100 μg/kg or a 6 mg fixed dose on day 3 (≥48 hours after chemotherapy), or filgrastim 5 μg/kg/day since day 3 (≥48 hours after chemotherapy), continuing until a documented ANC $\geq 5.0\times10^9$/L twice or ANC $\geq 15\times10^9$/L once after the expected nadir, or for up to 14 days, whichever occurred first.

For cycles 2–4, the patients in mecapegfilgrastim groups continued to receive mecapegfilgrastim 100 μg/kg or a 6 mg fixed dose on day 3 in each cycle. Patients in the control group only received filgrastim treatment in cycle 1.

Mecapegfilgrastim was provided by Hengrui Medicine Co., Ltd. (Lianyungang, China) and short-acting filgrastim was provided by Kyowa Hakko Kirin China Pharmaceutical Co., Ltd. (Shanghai, China).

Blood monitoring

In cycle 1, blood samples were collected within 24 h of the initiation of chemotherapy and on day 1, 3, 5, 7, 8, 9, 10, 11, 13, 15, 17 and 21 during cycle 1, or until an ANC $\geq 2.0\times10^9$/L was reached.

In cycles 2 to 4, blood samples were taken on day 5, 7, 9, 11, 13 and 21 of each cycle. ANC assessments during cycles 2 to 4 were performed within 24 h of chemotherapy, on day 5, 7, 9, 11, 13 and 21 of each cycle, until an ANC $\geq 2.0\times10^9$/L was achieved.

Endpoints

The primary endpoint was the mean duration of grade ≥3 neutropenia (defined as ANC $<1.0\times10^9$/L) during cycle 1 of chemotherapy. The secondary endpoints included the incidence of grade ≥3 and grade 4 neutropenia in cycles 1–4, the mean duration of grade ≥3 neutropenia in cycles 2–4, the mean duration of grade 4 neutropenia in cycles 1–4, the incidence of FN (defined as body temperature ≥38.5 ℃ concurrent with ANC $<1.0\times10^9$/L) in cycles 1–4.

The safety assessment was measured by reports of adverse events (AEs), changes in clinical laboratory values, vital signs and physical examinations.

Statistical analysis

This study was designed to show each of the mecapegfilgrastim arms is non-inferior to the filgrastim arm. The primary efficacy analyses were performed in the full analysis set (FAS). For duration of grade 3 or higher ANC decreases during cycle 1, we hypothesized the non-inferior margin as 1 day. Using an analysis of covariance (ANCOVA) model, the difference between patients treated with mecapegfilgrastim and patients treated with filgrastim would be calculated together with 95% confidence interval (CI). Non-inferiority would be established if the upper limit of the 95% CI was less than 1 day. If non-inferiority was

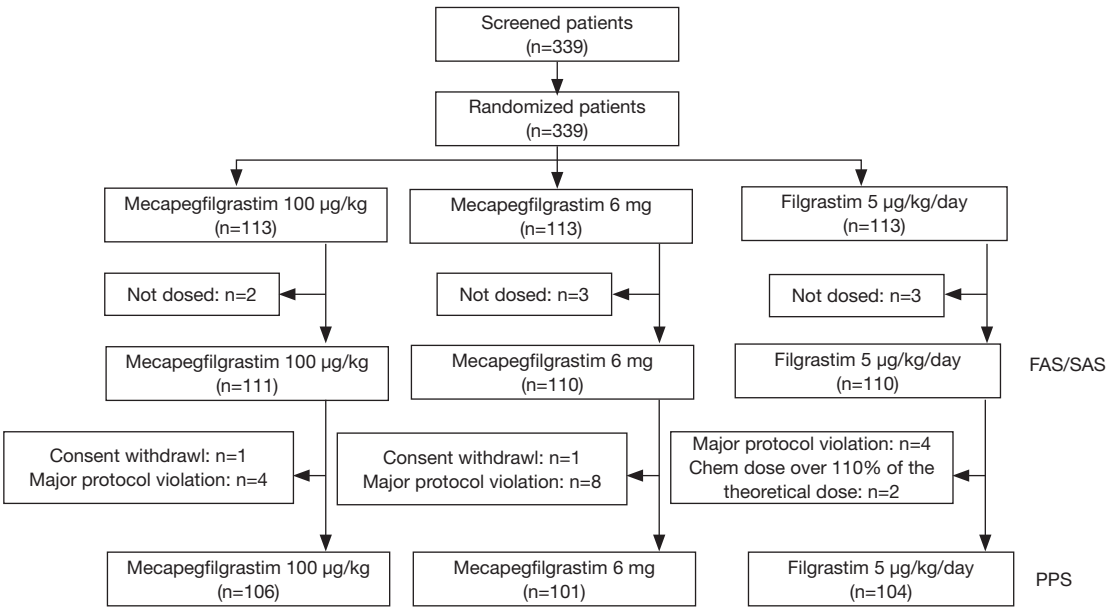

Figure 1 Patient disposition in the study. FAS, full analysis set; SAS, safety analysis set; PPS, per protocol set.

established, the upper limit of the 95% CI could be further compared to 0 for assessment of superiority.

The sample size was calculated based on the primary end point of the duration of grade ≥3 ANC decrease at the first cycle of chemotherapy. Assuming a pre-specified non-inferiority margin of 1 day and a common standard deviation of 2 days, it was calculated that a total of 258 patients (86 per arm) were required to assess non-inferiority of mecapegfilgrastim (100 μg/kg or 6 mg) to the filgrastim at a one-sided significance level of 2.5% with 90% power. In order to allow for 20% of drop-outs and major protocol violations, a total of 330 patients were planned to be randomized with 110 patients in each arm. All statistical analysis was conducted using SAS 9.3 software.

Results

Baseline characteristics

From March 2012 to November 2012, total of 339 patients from 22 centers in China were recruited into the study (*Table S1*). During the study, eight patients were excluded from the FAS, because they did not receive the treatment after randomization. At the end of cycle 1, total 331 (97.64%) patients received at least one dose of study drug and were included into the FAS. The per protocol set (PPS) included 311 patients, excluding 2 consent withdrawl, 16 major protocol violation, and 2 overdose chemotherapy treatment. The number of patients eligible for safety analysis set (SAS) was 331. *Figure 1* illustrated the detailed patient disposition in each group in this study.

Demographic characteristics and disease status of patients were similar across treatment groups. Baseline vital signs, physical examination and general clinical characteristics were comparable among the three groups. Baseline ANC levels were within the normal range for all three groups and there were no statistically significant differences among the three groups at baseline (*Table 1*).

Primary efficacy endpoint

The efficacy analysis of FAS and PPS led to identical conclusions, only the results of FAS were reported here.

The mean duration of grade ≥3 neutropenia

In cycle 1, the adjusted mean duration of grade ≥3 neutropenia was 1.06 (95% CI: 0.65, 1.26) days in mecapegfilgrastim 100 μg/kg group, 1.23 (95% CI: 0.84, 1.88) days in mecapegfilgrastim 6 mg group, and 2.06 (95% CI: 1.66, 2.46) days in the filgrastim group (*Figure 2*).

The mean difference between mecapegfilgrastim 100 μg/kg and filgrastim was –1.00 (95% CI: –1.52, –0.48), the mean difference between mecapegfilgrastim 6 mg and filgrastim was –0.83 (95% CI: –1.36, –0.30). (*Figure 2*). The upper bounds of 95% CI for the mean

Table 1 Demographic and clinical characteristics for full analysis population

Characteristic	Mecapegfilgrastim 100 μg/kg	Mecapegfilgrastim 6 mg	Filgrastim 5 μg/kg/day
Gender, n [%]			
Female	111 [100]	110 [100]	110 [100]
Mean age, years (± SD)	48.21±8.55	48.03±9.01	47.37±8.60
Mean weight, kg (± SD)	59.54±8.55	59.05±9.60	60.39±9.16
Mean BSA, m^2 (± SD)	1.59±0.12	1.58±0.13	1.60±0.13
ECOG performance status, n (%)			
0	72 (64.86)	72 (65.45)	69 (62.73)
1	39 (35.14)	38 (34.55)	41 (37.27)
Regimen, n (%)			
AC	50 (45.05)	49 (44.55)	50 (45.45)
AT	61 (54.95)	61 (55.45)	60 (54.55)
Baseline ANC (± SD), 10^9 median (min, max)	4.21±1.70, 3.92 (1.93, 9.22)	4.18±1.57, 3.82 (2.20, 10.14)	4.17±1.72, 3.90 (2.14, 12.76)

SD, standard deviation; BSA, body surface area; ECOG, Eastern Cooperative Oncology Group; AC, adriamycin and cyclophosphamide; AT, anthracyclines-taxane; ANC, absolute neutrophil count.

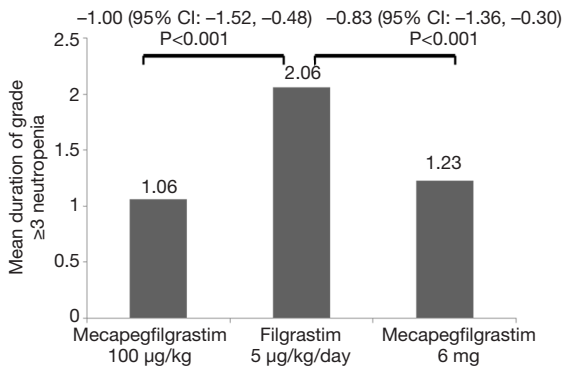

Figure 2 The mean duration of grade ≥3 neutropenia in first treatment cycle.

difference between mecapegfilgrastim and filgrastim were all <1 day (the predefined non-inferiority margin), the study met its primary endpoint.

Secondary endpoints

The incidence of grade ≥3 and grade 4 neutropenia in cycles 1–4

In cycle 1, there are 56 patients (50.45%) in mecapegfilgrastim 100 μg/kg arm, 56 patients (50.91%) in mecapegfilgrastim 6 mg arm, and 73 patients (66.36%) in filgrastim arm experienced grade ≥3 neutropenia. Compared with filgrastim arm, the incidence of grade ≥3 neutropenia was significantly lower in patient treated with mecapegfilgrastim 100 μg/kg (P=0.0147) and mecapegfilgrastim 6 mg (P=0.0064). There was no difference between the two mecapegfilgrastim arms in the incidence of grade ≥3 neutropenia (P=0.9470). There are 37 patients (33.33%) in mecapegfilgrastim 100 μg/kg arm, 33 patients (30.00%) in mecapegfilgrastim 6 mg arm, and 51 patients (46.36%) in filgrastim arm experienced grade 4 neutropenia. Compared with filgrastim, the incidence of grade 4 neutropenia was significantly lower in patient treated with mecapegfilgrastim 100 μg/kg (P=0.0454) and mecapegfilgrastim 6 mg (P=0.0036). There was no difference between the two mecapegfilgrastim arms in the incidence of grade 4 neutropenia (P=0.5688) (*Table 2*).

In cycle 2, 13 patients (15.66%) in mecapegfilgrastim 100 μg/kg arm and 18 patients (21.18%) in mecapegfilgrastim 6 mg arm experienced grade ≥3 neutropenia, there was no difference between these two groups (P=0.6917). There are seven patients (8.43%) in mecapegfilgrastim 100 μg/kg arm and nine patients (10.59%) in mecapegfilgrastim 6 mg arm experienced grade 4 neutropenia, there was no difference between these two groups (P=0.9469).

In cycle 3, the incidences of grade ≥3 neutropenia

Table 2 Secondary endpoints results in cycle 1

Secondary endpoints	Mecapegfilgrastim		Filgrastim	P value
	100 μg/kg	6 mg		
Incidence of grade ≥3 neutropenia, n (%)	56 (50.45)*	56 (50.91)*	73 (66.36)	0.0129
Incidence of grade 4 neutropenia, n (%)	37 (33.33)*	33 (30.00)*	51 (46.36)	0.0090
Duration of grade 4 neutropenia, (days, mean ± SD)	0.61±0.96*	0.54±0.88*	1.02±1.24	0.0003
Incidence of FN, n (%)	5 (4.50)	0 (0.00)	2 (1.82)	0.167

*, P<0.05 versus filgrastim arm. SD, standard deviation; FN, febrile neutropenia.

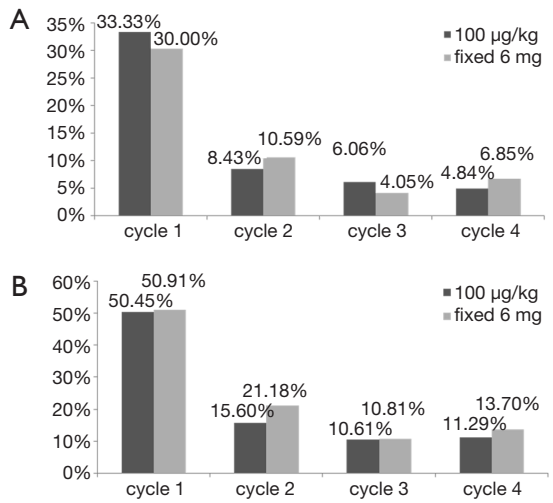

Figure 3 The incidence of neutropenia in mecapegfilgrastim 100 μg/kg group and fixed 6 mg group. (A) The incidence of grade 4 neutropenia; (B) the incidence of grade ≥3 neutropenia.

were 10.61% and 10.81% in mecapegfilgrastim 100 μg/kg and 6 mg groups. The incidences of grade 4 neutropenia were respectively 6.06% and 4.05% in these two groups. No difference was found between the two groups.

In cycle 4, the incidence of grade ≥3 neutropenia was 11.29% and 13.70% in mecapegfilgrastim 100 μg/kg and 6 mg groups. The incidence of grade 4 neutropenia was respectively 4.84% and 6.85% in these two groups. No difference was found between the two groups.

It was noted that there was a decreased trend in the incidence of grade ≥3 and grade 4 neutropenia as the treatment cycle increased (*Figure 3*).

The mean duration of grade ≥3 neutropenia in cycles 2–4

In cycle 2, the mean duration of grade ≥3 neutropenia was 0.36±0.99 days and 0.44±0.92 days in mecapegfilgrastim 100 μg/kg and 6 mg groups. In cycle 3, the mean duration of grade ≥3 neutropenia was 0.23±0.72 days and 0.26±0.79 days in mecapegfilgrastim 100 μg/kg and 6 mg groups. In cycle 4, the mean duration of grade ≥3 neutropenia was 0.63± 2.39 days and 1.04±3.14 days in the two groups. No difference was found between the two groups.

The mean duration of grade 4 neutropenia in cycles 1–4

In cycle 1, the mean duration of grade 4 neutropenia was 0.61±0.96, 0.54±0.88, and 1.02±1.24 days in mecapegfilgrastim 100 μg/kg group, mecapegfilgrastim 6 mg group, and filgrastim group. The mean difference between mecapegfilgrastim 100 μg/kg and filgrastim groups was –0.40 (95% CI: –0.73, –0.08), the mean difference between mecapegfilgrastim 6 mg and filgrastim groups was –0.51 (95% CI: –0.84, –0.18), all the differences were statistically significant. The mean difference between two mecapegfilgrastim groups was 0.10 (95% CI: –0.22, 0.43) which was not statistically significant (*Table 2*).

In cycle 2, the mean duration of grade 4 neutropenia was 0.16±0.57 and 0.22±0.70 days in mecapegfilgrastim 100 μg/kg and 6 mg groups. In cycle 3, the mean duration of grade 4 neutropenia was 0.12±0.48 and 0.08±0.40 days. In cycle 4, the mean duration of grade 4 neutropenia was 0.08±0.38 and 0.53±2.35 days. All the differences between the two groups were not significant.

The incidence of FN

In cycle 1, there are 5 (4.50%), 0 (0%), and 2 (1.82%) patients experienced FN in mecapegfilgrastim 100 μg/kg group, mecapegfilgrastim 6 mg group and filgrastim group. There was no significant difference between the three groups (*Table 2*). During cycles 2 to 4, no FN was developed in patients in mecapegfilgrastim 100 μg/kg and mecapegfilgrastim 6 mg groups.

Table 3 Subgroup analysis of duration of grade ≥3 neutropenia in cycle 1

Subgroup	Mecapegfilgrastim		Filgrastim	P value
	100 μg/kg	6 mg		
Body weight days, mean ± SD (N)				
≤70 kg	1.17±1.28 [102]*	1.32±1.82 [95]*	2.20±2.17 [94]	<0.0001
>70 kg	0.44±0.73 [9]	1.40±2.29 [15]	1.69±1.62 [16]	0.2248
Chemotherapy regimens days, mean ± SD (N)				
AC	1.32±1.46 [50]	1.59±2.47 [49]	2.06±2.18 [50]	0.0886
AT	0.93±1.05 [61]*	1.11±1.20 [61]*	2.18±2.05 [60]	<0.0001

*, P<0.05 versus filgrastim arm. SD, standard deviation; AC, adriamycin and cyclophosphamide; AT, anthracyclines-taxane.

Subgroup analysis of primary endpoints

In order to determine whether the stratification factors (age, chemotherapy regimens) confounded the assessment of efficacy, an exploratory subgroup analyses according to the baseline body weight (≤70 *vs.* >70 kg) and chemotherapy (AC *vs.* AT) was performed for cycle 1.

For patients with body weight ≤70 kg, the mean duration of grade ≥3 neutropenia were respectively 1.17±1.28, 1.32±1.82 and 2.20±2.17 days, compared with filgrastim group, the mean duration of grade ≥3 neutropenia were significantly shorter in patients with mecapegfilgrastim 100 μg/kg and 6 mg treatment, the difference were respectively –0.98 (95% CI: –1.56, –0.39) and –0.91 (95% CI: –1.51, –0.31). There is no difference between two mecapegfilgrastim arms. For patients with body weight >70 kg, no difference was found in the mean duration of grade ≥3 neutropenia between the three groups (*Table 3*).

For patients treated with AT chemotherapy, the mean duration of grade ≥3 neutropenia respectively 0.93±1.05, 1.11±1.20 and 2.18±2.05 days, compared with filgrastim group, the mean duration of grade ≥3 neutropenia were significantly shorter in patients with mecapegfilgrastim two dose regimens treatment, the difference were respectively –1.20 (95% CI: –1.81, –0.59) and –1.10 (95% CI: –1.71, –0.49). For patients treated with AC chemotherapy, there was no significant difference between the three groups (*Table 3*).

Safety analysis

In cycle 1, total 320 patients experienced AEs in mecapegfilgrastim 100 μg/kg arm (105 patients, 94.59%), mecapegfilgrastim 6 mg arm (107 patients, 97.27%) and filgrastim arm (108 patients, 98.18%). Total seven patients reported serious adverse events (SAEs) in mecapegfilgrastim 100 μg/kg (three patients), mecapegfilgrastim 6 mg (one patient) and filgrastim (three patients) arms. All of the SAEs were considered not related to investigational treatment by the investigators. No unexpected AE was observed. The most frequently reported AEs possibly related to treatment were shown in *Table 4*. Grade 3 AEs were reported in mecapegfilgrastim 100 μg/kg group (two patients), 6 mg fixed dose group (three patients) and filgrastim group (two patients). Overall, no significant difference was detected among the three groups in terms of the incidence of all AEs, the treatment related AEs, and the SAEs.

Discussion

Neutropenia is the main dose-limiting toxicity of chemotherapy, always leading to dosage adjustment or treatment interruption, which could compromise the efficacy, so it is very important to ensure sufficient treatment cycles and dosage for chemotherapy. In a phase II trial, mecapegfilgrastim demonstrated better clinical efficacy and similar safety profile as the secondary prophylactic therapy for neutropenia compared with filgrastim in breast cancer patients (13).

However, in above phase II trial, the evaluation of the efficacy and safety of mecapegfilgrastim was mainly focused on the secondary prophylactic therapy in one treatment cycle. This phase III trial was designed to further investigate the efficacy and safety of mecapegfilgrastim as the primary prophylactic therapy in four consecutive treatment cycles, and also to explore whether the fixed 6 mg dosage showed a similar safety and efficacy to the weight-based dose of

Table 4 The most frequently reported AEs related to treatment drugs

AEs, n (%)	Mecapegfilgrastim		Filgrastim	P value
	100 μg/kg	6 mg		
Hematologic AEs				
Hemoglobin decline	14 (12.61)	15 (13.64)	7 (6.36)	>0.05
Thrombocytopenia	5 (4.50)	12 (10.91)	5 (4.55)	>0.05
Neutrocytosis	3 (2.70)	2 (1.82)	2 (1.82)	>0.05
Leukocytosis	1 (0.90)	1 (0.91)	1 (0.91)	>0.05
Thrombocytosis	6 (5.41)	8 (7.27)	7 (6.36)	>0.05
Non-hematologic AEs				
Constipation	3 (2.70)	5 (4.55)	1 (0.91)	>0.05
Back pain	3 (2.70)	1 (0.91)	1 (0.91)	>0.05
Fatigue	17 (15.32)	15 (13.64)	9 (8.18)	>0.05
Diarrhea	3 (2.70)	3 (2.73)	1 (0.91)	>0.05
AST increase	5 (4.50)	2 (1.82)	3 (2.73)	>0.05
ALT increase	4 (3.60)	3 (2.73)	3 (2.73)	>0.05
Joint pain	4 (3.60)	5 (4.55)	1 (0.00)	>0.05
Muscle pain	7 (6.31)	6 (5.45)	1 (0.91)	>0.05
Creatinine reduction	7 (6.31)	3 (2.73)	0 (0.00)	>0.05
Poor appetite	11 (9.91)	10 (9.09)	4 (3.64)	>0.05

AEs, adverse events; ALT, glutamic-pyruvic transaminase; AST, glutamic-oxaloacetic transaminase.

100 μg/kg. The results of this study showed that the single dose of mecapegfilgrastim (at either 100 μg/kg or 6 mg) was as safe and effective as daily injections of filgrastim as the primary prophylactic therapy in the first chemotherapy cycle in breast cancer patients, which was consistent with the results of some other phase II and phase III studies in breast cancer or other malignant tumors.

DSN was considered as a sensitive endpoint in assessing biosimilarity of filgrastim in (neo) adjuvant breast cancer, any variations in DSN can be considered as a direct consequence of differences between activity of reference and biosimilar filgrastim (12). Moreover, risk of infection is directly proportional to severity and duration of neutropenia, making DSN a clinically relevant endpoint (14,15). As for the primary endpoint of this study, the mean duration of grade ≥3 neutropenia in both mecapegfilgrastim groups were non-inferior to that in the filgrastim group in cycle one. The mean difference of the duration of grade ≥3 neutropenia between mecapegfilgrastim 100 μg/kg and filgrastim was –1.00 day (95% CI: –1.52, –0.48 day), the difference between mecapegfilgrastim 6 mg and filgrastim was –0.83 day (95% CI: –1.36, –0.30 day). The upper bounds of 95% CI for the mean difference between mecapegfilgrastim and filgrastim were all within the predefined margin of 1 day, which indicated that the efficacy of mecapegfilgrastim in reducing duration of grade ≥3 neutropenia was non-inferior to filgrastim.

Furthermore, the upper bounds of 95% CI for the mean difference between mecapegfilgrastim and filgrastim were all <0, which indicated that compared with filgrastim, mecapegfilgrastim at dosage of either 100 μg/kg or 6 mg might be superior in reducing duration of grade ≥3 neutropenia. The superiority might be the result of the longer half-life time of 55.99 hours and the unique linking structure of mecapegfilgrastim. For the duration of grade 4 neutropenia, compared with filgrastim, the duration of grade 4 neutropenia were significantly shorter in patients treated with mecapegfilgrastim 100 μg/kg and the fixed dosage of 6 mg. The reduced DSN could be associated with decreased risk of infection and shorter period of

hospitalization, which could save and make good use of the limited medical resources to serve more patients, and make the patients spend more time with their family at home.

In this study, for some secondary endpoints (the incidence of grade ≥3 and grade 4 neutropenia, the mean duration of grade 4 neutropenia), there were significant differences between two dosage groups of mecapegfilgrastim and filgrastim, indicating that in some parameters, mecapegfilgrastim may be better than filgrastim in supporting cytotoxic chemotherapy. These results were consistent with the results from phase III study of the mecapegfilgrastim in NSCLC, which showed that for the duration of grade 4 neutropenia in cycles 2 to 4 and for the incidence of FN, the differences between mecapegfilgrastim and filgrastim were significant (11). And the phase II trial of mecapegfilgrastim in breast cancer also showed similar results (13). A systematic review also revealed similar results, showing better efficacy and effectiveness for pegfilgrastim than filgrastim (16). All these results suggest that longer-acting rhG-CSF might provide additional clinical benefit, the mechanism for such findings was unclear.

In our study, we further evaluated the efficacy of mecapegfilgrastim in consecutive-cycle applications, which showed a declining trend of the incidence of grade ≥3 and grade 4 neutropenia along with the treatment cycles increased (*Figure 2*), which indicated that patients may benefit more from consecutive-cycle treatment of mecapegfilgrastim (at either 100 μg/kg or 6 mg) in prevention of severe neutropenia. This hypothesis would be further evaluated in the well-designed clinical trials.

In clinical practice, a fixed-dose regimen would begenerally preferred for administration. However, there were concerns about the fixed dosage for the lack of efficacy in over-weighted patients and occurrence of sever AEs in less-weighted patients. So, in this study, we added a fixed-dose group of mecapegfilgrastim at 6 mg, and compared the efficacy of the two dosage regimens of mecapegfilgrastim (100 μg/kg and a fixed dosage of 6 mg) in different-weight subgroups in all 4 cycles. The results showed, there was no significant difference between the fixed 6 mg and 100 μg/kg of mecapegfilgrastim in duration of grade ≥3 neutropenia, incidence of grade ≥3 neutropenia and incidence of bone pain during all cycles. The previous studies also demonstrated that mecapegfilgrastim fixed 6 mg or 100 μg/kg dosage provided comparable benefit as filgrastim (2,11). Thus, the efficacy and safety of the fixed 6 mg-dose regimen is appropriate for patients, and should be recommended in the clinical practice in terms of the convenience of administration.

In China, AT and AC chemotherapy regimens were commonly used in clinical practice, and were also recommended in Chinese treatment guidelines for breast cancer patients. These two regimens have proven dose limiting hematological toxicity with grade 3–4 neutropenia. In this study, for AT regimen, patients treated with mecapegfilgrastim experienced shorter duration of grade ≥3 neutropenia compared with filgrastim. For patients treated with AC regimen, mecapegfilgrastim exhibited comparable efficacy with filgrastim for the duration of grade ≥3 neutropenia. These results indicated that patients treated with mecapegfilgrastim might benefit more for neutropenia prophylaxis when they treated with AT chemotherapy, which possessed stronger myelosuppression than AC chemotherapy.

For safety profile, there was no significant difference between mecapegfilgrastim (either 100 μg/kg or fixed 6 mg) and filgrastim in terms of the incidence of all AEs, including the common events of pain and decreased hemoglobin. In this phase III study, no unexpected AEs, fixed-dosage related AEs, nor consecutive-cycle related AEs were found. All of the SAEs were considered not related to the investigational treatment by the investigators. Patients in megapegfilgrastim groups were well tolerated.

There is also a limitation in this study. We only included the breast cancer patients in AT/AC chemotherapy regimens limited by the rules of randomized-control-study design. In the future, we plan to evaluate the effectiveness and safety of mecapegfilgrastim further in the real-world study, in which more practical chemotherapy regimens would be included.

In conclusion, this study demonstrated that long-acting mecapegfilgrastim (100 μg/kg and fixed 6 mg) is very effective and well tolerated when administered in the primary prophylaxis of chemotherapy induced neutropenia and in consecutive-cycle treatment. In some clinical parameters, mecafilgrastim is non-inferior and even superior to filgrastim. The fixed 6 mg-dose regimen showed similar efficacy and safety profile compared with 100 μg/kg regimen, and would be the preference in clinical practice, due to the convenient once-per-cycle administration and high-degree treatment compliance for the patients. This study provided new evidence for the novel long-acting rhG-CSF, mecapegfilgrastim, which would be a new alternative for clinical practice for prophylaxis of chemotherapy induced neutropenia.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethics 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. This study was approved by the Ethics Committee of the medical center (2011-11-102), and the protocol was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. All patients or their guardians signed the informed consent before enrollment. This trial was approved by the National Medical Products Administration of China (registration number: 2010L00501) and registered on ClinicalTrials.gov (NCT01611051).

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Supplementary

Table S1 Medical centers participating in this study

No.	Centers	Mecapegfilgrastim 100 μg/kg (N=111)			Mecapegfilgrastim 6 mg (N=110)			Filgrastim 5 μg/kg/day (N=110)		
		Total	FAS	PPS	Total	FAS	PPS	Total	FAS	PPS
13	Liaocheng People's Hospital	19	19	19	22	22	22	17	17	17
31	The First Affiliated Hospital of Xinxiang University	19	19	18	15	15	15	11	11	11
1	The Fifth Medical Center of Chinese PLA General Hospital	10	10	8	15	13	13	17	17	14
14	Chongqing Cancer Hospital	11	11	10	4	4	4	12	11	11
11	The First Affiliated Hospital of Nanchang University	5	5	5	8	8	8	10	10	9
8	Harbin Medical University Cancer Hospital	9	8	8	4	4	4	6	6	5
5	Sichuan Province People's Hospital	6	6	6	6	6	5	5	5	5
4	Zhongshan University Shanghai Cancer Center	7	7	7	5	4	4	3	3	3
9	Fudan University Shanghai Cancer Center	5	5	5	4	4	3	5	5	5
12	The First Affiliated Hospital of Guangzhou Medical University	5	5	5	2	2	2	4	4	4
20	Hunan Province Cancer Hospital	2	2	2	5	5	4	2	2	2
25	The First Affiliated Hospital of China Medical University	2	2	2	2	2	2	5	5	4
32	First Hospital Affiliated of Nanhua University	2	2	2	3	3	3	4	4	4
18	Shanxi Province Cancer Hospital	2	2	1	3	3	2	3	2	2
6	Chengdu Military General Hospital	1	1	1	5	5	2	0	0	0
29	Harbin Medical University General Hospital	3	3	3	1	1	1	2	2	2
23	Wuhan General Hospital of Guangzhou Military	1	1	1	2	2	1	2	2	2
15	Yangzhou First People's Hospital	1	1	1	2	2	2	1	1	1
19	Xiangya HospitalCentral South University	1	1	1	2	2	1	1	1	1
28	The First Affiliated Hospital of Xi'an Jiaotong University	1	1	1	1	1	1	1	1	1
21	Wuhan Union Medical College Hospital	1	0	0	0	0	0	1	0	0
26	The Second Affiliated Hospital of Zhejiang University	0	0	0	2	2	2	0	0	0
17	The Fourth Hospital of Hebei Medical University	0	0	0	0	0	0	1	1	1
Total		113	111	106	113	110	101	113	110	104