ORIGINAL ARTICLE

Dose response of pegfilgrastim in Japanese breast cancer patients receiving six cycles of docetaxel, doxorubicin, and cyclophosphamide therapy: a randomized controlled trial

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Abstract

Purpose A phase II, open-label, dose-finding, randomized study was performed to evaluate the recommended dose of pegfilgrastim in Japanese breast cancer patients.

Methods Patients received 1.8, 3.6, or 6.0 mg of pegfilgrastim once per chemotherapy cycle for up to 6 cycles. Patients received docetaxel, doxorubicin, and cyclophosphamide (TAC) therapy followed by pegfilgrastim on the next day.

Results Pegfilgrastim was administered to 87 women with stage II/III invasive breast carcinoma. The duration of grade 4 neutropenia in the first cycle, the primary endpoint, was 2.2 ± 0.9 days, 1.5 ± 0.9 days, and 1.4 ± 0.7 days in the 1.8, 3.6, and 6.0 mg groups, respectively. This finding indicated that pegfilgrastim efficacy peaked at 3.6 mg. Pegfilgrastim doses up to 6.0 mg were considered safe.

Conclusion A 3.6-mg pegfilgrastim dose may be safe and effective for Japanese patients. A confirmatory study is required to establish safety and efficacy at this dose for intensive anti-cancer chemotherapy.

Keywords Pegfilgrastim · TAC chemotherapy · Breast cancer · Febrile neutropenia · G-CSF · Granulocyte-colony stimulating factor

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Introduction

Febrile neutropenia (FN) is a clinical condition characterized by the development of fever in association with neutropenia. The risk of FN increases with the duration of neutropenia [1, 2]. Infection, often manifested by FN, may become serious and potentially life threatening. Therefore, to prevent FN, chemotherapy doses are often reduced or dose intervals are extended. However, reduced relative dose intensity may reduce the efficacy of chemotherapy regimens, leading to decreased survival rates, particularly in curative settings [3–7]. For these reasons, granulocyte-colony stimulating factor (G-CSF) is used to reduce the risk of chemotherapy-associated FN. G-CSF may improve therapeutic outcomes by helping anticancer drugs to be administered at planned dosages and intervals. Guidelines for the recommended use of G-CSF based on FN risk have been established by the American Society of Clinical Oncology, National Comprehensive Cancer Network, and European Organization for Research and Treatment of Cancer [8–10]. Prophylactic use of G-CSF is based on the intensity

of chemotherapy regimens and patient-specific risks and is recommended for patients with a 20 % or greater risk of FN.

Pegfilgrastim is a drug with a polyethylene glycol (PEG) molecule, approximate molecular weight of 20,000, covalently bound to the N-terminal residue of G-CSF (filgrastim). Pegfilgrastim is produced by recombinant DNA technology and expressed in *Escherichia coli*. PEG-modified protein is known to decrease kidney clearance, inhibit protease-mediated hydrolysis, and prolong serum half-life. The serum half-life of pegfilgrastim has been reported to be 2 to 3 days, which is longer than the approximately 3-h half-life of filgrastim.

A placebo-controlled study in patients with early-stage breast cancer showed that the incidence rates of FN were 17 and 1 % in the placebo and pegfilgrastim groups, respectively [11]. Therefore, prophylactic pegfilgrastim can remarkably reduce the incidence of FN. Furthermore, pegfilgrastim has been shown to reduce the incidence of FN-related hospitalizations and the use of intravenous antibiotics to treat infection. In the curative setting, highly myelosuppressive chemotherapy regimens may be required to treat patients with early-stage breast cancer. TAC, dose-dense doxorubicin plus cyclophosphamide followed by paclitaxel, and TC (docetaxel plus cyclophosphamide) regimens are widely used in the clinical setting and have been shown to result in favorable clinical outcomes.

While pegfilgrastim has been widely studied in the United States and European populations, it has not been evaluated in the Japanese population. Therefore, a phase II dose-finding study of pegfilgrastim was performed in Japanese patients with early-stage breast cancer. To evaluate the efficacy of pegfilgrastim in this population, TAC therapy, a highly myelosuppressive chemotherapy that is used in the adjuvant treatment of early stage breast cancer, was selected. The primary endpoint of this study was the duration of severe (grade 4) neutropenia in the first cycle (DSN).

Materials and methods

Patients

This study was conducted in accordance with the Declaration of Helsinki. The institutional review boards of the participating centers approved the protocol. Informed consent was obtained from all patients before beginning any study-related procedures.

Women who met the following inclusion criteria were eligible for study entry: aged 20–64 years of age; pathohistological and clinical diagnosis of stage II or III primary invasive breast carcinoma; Eastern Cooperative Oncology Group performance status ≤ 2; chemotherapy naïve; plan to receive full-dose adjuvant or neoadjuvant TAC therapy; absolute neutrophil count (ANC)$\geq 2 \times 10^9$/L; platelet count

$\geq 100 \times 10^9$/L; hemoglobin concentration ≥ 10 g/dL; aspartate aminotransferase and alanine aminotransferase levels ≤ 2.5 times the upper limit of the normal range in each institute; total bilirubin content ≤ 1.5 times the upper limit of the normal range in each institute; creatinine level ≤ 1.5 mg/dL; left ventricular ejection fraction ≥ 50 %; and negative hepatitis B (hepatitis B surface antigen and hepatitis B core antibody) test result within 3 months of enrollment. Patients with a history of radiation therapy within 4 weeks of enrollment, history of bone marrow or stem cell transplantation, or comorbid malignancies other than breast cancer were excluded from the study.

Study design

This was a multicenter, randomized, open-label, dose-finding study to evaluate the safety and efficacy of a single injection of pegfilgrastim per chemotherapy cycle in Japanese patients. Patients were randomized via a dynamic allocation method and were assigned in a 1:1:1 ratio to each pegfilgrastim cohort (1.8, 3.6, and 6.0 mg) after stratification according to chemotherapy status (neoadjuvant or adjuvant) and investigational site (Fig. 1).

Chemotherapy treatment

On day 1 of each chemotherapy cycle, patients received an intravenous infusion of doxorubicin (50 mg/m^2), followed by intravenous infusions of cyclophosphamide (500 mg/m^2) and docetaxel (75 mg/m^2). Chemotherapy was repeated every 3 weeks for up to 6 cycles.

Full-dose chemotherapy was administered on day 1 of the next cycle to patients who met the following criteria: ANC $\geq 1.5 \times 10^9$/L, platelet count $\geq 100 \times 10^9$/L, hemoglobin concentration ≥ 8 g/dL, aspartate aminotransferase and alanine aminotransferase levels ≤ 2.5 times the upper limit of the normal
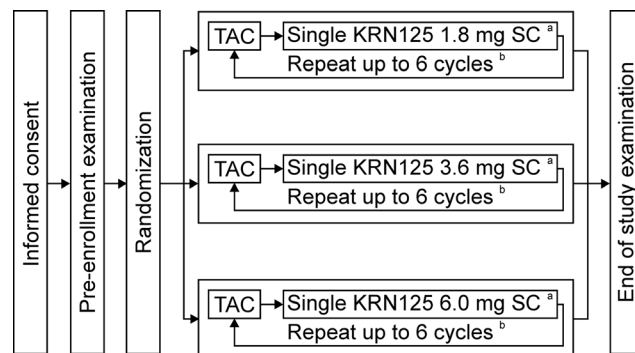
Fig. 1 Study schema *Superscript letter a* indicates that pegfilgrastim (KRN125) was administered subcutaneously (SC) 24 h after docetaxel administration on day 2 of each cycle. *Superscript letter b* indicates that chemotherapy cycle was defined as the interval from the day of TAC (docetaxel, doxorubicin, and cyclophosphamide) initiation to the day before the next TAC course. The maximum duration of each chemotherapy cycle was 42 days

range in each institute, total bilirubin content ≤1.5 times the upper limit of the normal range in each institute, and creatinine level ≤1.5 mg/dL. In addition, any adverse events, including peripheral neuropathy, edema, constipation, and weight loss, must have been cured completely or reduced to below grade 2. Any non-hematologic adverse events other than hair loss, peripheral neuropathy, edema, weight loss, and constipation must have been cured completely or reduced to grade 1. After adverse event recovery to the appropriate level, chemotherapy was resumed at the full dose administered in the previous cycle. Patients whose chemotherapy was delayed for more than 3 weeks were eliminated from the study.

If any grade 3 or 4 critical adverse event, including FN, prolonged neutropenia, thrombocytopenia, abdominal pain, diarrhea, nausea, vomiting, or nerve disorder, occurred in the previous cycle of TAC therapy, and dose reduction was deemed necessary by the investigator, the dosage of each anticancer drug was reduced 20 % in the next cycle. Dose reduction was allowed only once.

Supportive treatment consisted of 20 mg of dexamethasone administered intravenously on day 1 and 4 mg of dexamethasone administered orally twice daily on days 2 and 3. Prophylactic antibiotics were prohibited in the first cycle of chemotherapy.

Study treatment

On day 2 of each chemotherapy cycle (24 h after chemotherapy completion), patients received a single subcutaneous injection of pegfilgrastim at a fixed dose of 1.8 g, 3.6, or 6.0 mg.

G-CSF treatment was generally prohibited during the study period. However, rescue G-CSF treatment was allowed only when three consecutive days of concurrent fever (≥38 °C) and grade 4 neutropenia occurred in cycle 1 or when three consecutive days of fever accompanied by ≥1 episode of grade 4 neutropenia occurred in subsequent cycles.

Efficacy measurements

Blood samples were obtained for complete blood counts (CBCs). During cycle 1, CBC was measured daily from days 1 to 4, followed by daily measurements until ANC $\geq 1 \times 10^9$/L post-nadir was achieved, and thereafter measured every 2 days up to day 21. During all subsequent cycles, CBC was measured on days 1 to 3, 8, and 15. Axillary body temperature was measured daily and recorded throughout the study.

The primary efficacy endpoint of this study was DSN, which was defined as the number of days in which the patient had an ANC $<0.5 \times 10^9$/L during cycle 1 of TAC therapy. The secondary efficacy endpoints included ANC profile, ANC nadir, and proportion of patients who developed FN in the first cycle. FN was defined as an axillary body temperature ≥38 °C with concurrent ANC $<0.5 \times 10^9$/L.

Safety endpoints

The safety endpoints were incidence of adverse events, changes in vital signs, and laboratory tests. Adverse events that occurred after pegfilgrastim administration were documented. Serum was collected at the beginning and end of the study to detect antibodies capable of neutralizing the biological effects of either pegfilgrastim or filgrastim.

Data sets and statistical analysis

The objective of this trial was to estimate the mean DSN in order to determine the recommended dose of pegfilgrastim. Efficacy and safety were assessed based on the per protocol set and safety analysis set, respectively. Standard deviation of DSN in each group was assumed to be 1.4, based on a previous trial [15]. With 22 patients in each group, the mean DSN would be calculated with the standard error of approximately 0.3. Assuming that 10 % of patients would be withdrawn, the planned total sample size was 75 patients (25 patients per dosage group).

A three-contrast test was conducted in the dose response analysis: linear reduction (1, 0, −1), reduction at 6.0 mg (1, 1, −2), and plateau at 3.6 mg (2, −1, −1).

Adverse events were classified according to the Japanese version of the Medical Dictionary for Regulatory Activities preferred terms and were graded by severity according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0).
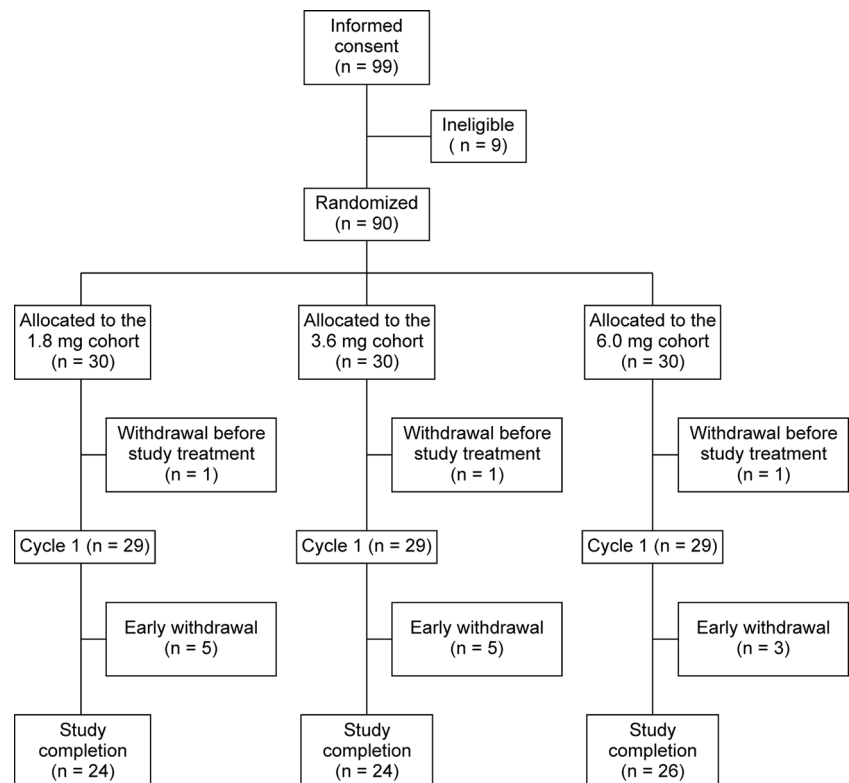
All analyses were performed using SAS software (version 9.1.3).

Results

Patients

Between November 2009 and April 2010, a total of 90 Japanese patients were randomized to the three pegfilgrastim dosage groups (30 patients per group). A total of 87 patients received pegfilgrastim and were included in the per protocol set and the safety analysis set. Three patients randomized to each group (one each from the 1.8, 3.6, and 6.0 mg groups) were excluded from the analysis of efficacy endpoints because they withdrew from the study before receiving chemotherapy or the study drug. Two of these patients withdrew because of allergic reactions caused by docetaxel. One of these patients could not receive TAC therapy because of health problems and withdrew (Fig. 2).

A total of 13 patients withdrew from the study after receiving the study drug, including 5 (16.7 %) patients in the 1.8-mg group, 5 (16.7 %) patients in the 3.6-mg group, and 3 (10.0 %) patients in the 6.0-mg group. Of these patients, 1 patient in the

Fig. 2 Patient consort diagram

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                                    │  Informed    │
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  │ the 1.8 mg     │              │ the 3.6 mg     │              │ the 6.0 mg      │
  │ cohort (n = 30)│              │ cohort (n = 30)│              │ cohort (n = 30) │
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1.8-mg group developed drug hypersensitivity (allergic reaction to docetaxel) and discontinued the study. Two patients in the 1.8-mg group, 1 patient in the 3.6-mg group, and 2 patients in the 6.0-mg group were eliminated from the study because of treatment changes. One patient in the 3.6-mg group withdrew from the study because of progression of the primary disease during neoadjuvant treatment. The other patients were eliminated from the study because of informed consent withdrawal. A total of 74 patients completed the trial.

Patient baseline characteristics are shown in Table 1. Patient characteristics were not different among the three dosage groups. The median (range) age was 46.0 years (33–63 years), 47.0 years (26–64 years), and 48.0 years (26–64 years); the mean body weight was 52.3, 56.3, and 53.2 kg; and the mean body surface area was 1.50, 1.55, and 1.51 in the 1.8-, 3.6-, and 6.0-mg groups, respectively. A median of 6 cycles of chemotherapy was administered to all dosage groups.

Efficacy

In cycle 1 of TAC therapy, ANC decreased to $<0.5 \times 10^9$/L in 28 (96.6 %) patients, 25 (86.2 %) patients, and 27 (93.1 %) patients in the 1.8-, 3.6-, and 6.0-mg groups, respectively. DSN (mean±standard deviation), the primary endpoint, was 2.2±0.9 days, 1.5±0.9 days, and 1.4±0.7 days in the 1.8-, 3.6-, and 6.0-groups, respectively (Fig. 3a). The dose-response analysis, which was conducted based on the three-contrast test, showed a reduction of DSN from 1.8- to 3.6-mg pegfilgrastim followed by a plateau from 3.6 to 6.0 mg ("plateau from 3.6 mg"), with the smallest P value among the three-contrast ($P=0.001$). Pegfilgrastim efficacy stratified by chemotherapy setting (adjuvant or neoadjuvant) showed similar dose responses.

FN occurred in 2 (6.9 %) patients in the 1.8-mg group, 3 (10.3 %) patients in the 3.6-mg group, and 1 (3.4 %) patient in the 6.0-mg group with no statistically significant difference between the groups (Table 2). In cycle 1 of TAC therapy, 1 patient in the 3.6-mg group received G-CSF on days 7 and 8 as rescue treatments.

Changes in the mean ANC in cycle 1 of TAC therapy are shown in Fig. 3b. The mean ANC peaked on day 3 of study drug administration in all groups, and nadir occurred on day 7 in the 1.8-mg group and day 6 in the 3.6- and 6.0-mg groups. ANC almost reached the baseline values after day 11 in all groups.

The ANC at nadir (mean±standard deviation) was $0.184 \pm 0.212 \times 10^9$/L in the 1.8-mg group, $0.240 \pm 0.208 \times 10^9$/L in the 3.6-mg group, and $0.255 \pm 0.287 \times 10^9$/L in the 6.0-mg group (Table 2).

Safety

All 87 patients experienced adverse events. Non-hematologic adverse events that occurred in ≥50 % of patients in all groups were alopecia, nausea, malaise, constipation, dysgeusia, decreased appetite, vomiting, and diarrhea (Online Resource 1).

Table 1 Summary of demographic and baseline characteristics for patients evaluable for efficacy (per protocol set)

		Pegfilgrastim		
		1.8 mg $n=29$	3.6 mg $n=29$	6.0 mg $n=29$
Age (y)	Median (range)	46.0 (33–63)	47.0 (26–64)	48.0 (26–64)
Body weight (kg)	Mean±SD	52.3±6.7	56.3±9.3	53.2±8.4
	<60 kg	25 (86.2 %)	18 (62.1 %)	24 (82.8 %)
	≥60 kg	4 (13.8 %)	11 (37.9 %)	5 (17.2 %)
Body surface area (m^2)	Mean±SD	1.50±0.10	1.55±0.14	1.51±0.12
Chemotherapy	Neoadjuvant	14 (48.3 %)	15 (51.7 %)	15 (51.7 %)
	Adjuvant	15 (51.7 %)	14 (48.3 %)	14 (48.3 %)
Primary disease	Infiltrating ductal carcinoma	28 (96.6 %)	27 (93.1 %)	26 (89.7 %)
	Special type	1 (3.4 %)	2 (6.9 %)	3 (10.3 %)
Clinical stage	IIA	10 (34.5 %)	10 (34.5 %)	12 (41.4 %)
	IIB	14 (48.3 %)	9 (31.0 %)	11 (37.9 %)
	IIIA, IIIB, IIIC	5 (17.2 %)	10 (34.5 %)	6 (20.7 %)
Lymph node involvement	pN0	5 (17.2 %)	9 (31.0 %)	10 (34.5 %)
	pN(+)	23 (79.3 %)	20 (69.0 %)	18 (62.1 %)
	Unknown	1 (3.4 %)	0 (0 %)	1 (3.4 %)
ER and/or PgR(+)		20 (69.0 %)	20 (69.0 %)	21 (72.4 %)
ER and PgR(−)		9 (31.0 %)	9 (31.0 %)	8 (27.6 %)

ER estrogen receptor, *PgR* progesterone receptor, *SD* standard deviation

Most of these events were considered to be associated with TAC therapy.

No adverse events resulted in death. Serious non-fatal adverse events occurred in four patients in the 1.8-mg group (upper respiratory tract inflammation, cystitis, pneumonia, and radius fracture) and 1 patient in the 6.0-mg group (decreased appetite and malaise).

Bone pain and back pain are common adverse events associated with G-CSF. Bone pain occurred in 1 (3.4 %) patient in each group. Throughout the course of chemotherapy, back pain was observed in 3 (10.3 %) patients in the 1.8-mg group, 6 (20.7 %) patients in the 3.6-mg group, and 8 (27.6 %) patients in the 6.0-mg group. Because these adverse events were grade 2 or lower in severity and could be controlled without treatment or with non-steroidal anti-inflammatory drugs, there were no safety concerns in any of the groups.

Hematologic adverse events

Grade 3 or 4 neutropenia occurred in 29 (100 %) patients in the 1.8-mg group, 29 (100 %) patients in the 3.6-mg group, and 28 (96.6 %) patients in the 6.0-mg group in all TAC cycles. Grade 3 or 4 thrombocytopenia occurred in 4 (13.8 %) patients in the 3.6-mg group and 4 (13.8 %) patients in the 6.0-mg group in all TAC cycles. Grade 3 or 4 anemia occurred in 1 (3.4 %) patient in the 1.8-mg group and 1 (3.4 %) patient in the 6.0-mg group in all cycles (Table 3).

Antibody formation

Serum antibodies to pegfilgrastim or filgrastim were tested using the BIAcore assay for all patients who received the study drug; antibodies were not detected in any patients.

Discussion

DSN, the primary endpoint of this study, has been shown to be well correlated with the incidence of FN [1, 2]. The European Medicines Agency (formerly the European Medicines Evaluation Agency) guidelines describe DSN as an acceptable surrogate endpoint for the exploratory and confirmatory trials of G-CSF [12]. According to these guidelines, DSN was set as the primary endpoint of this study. In phase III studies conducted in the USA, Canada, European countries, and Australia, pegfilgrastim administered at a 100 μg/kg dose or 6-mg fixed dose regardless of body weight had a similar effect on DSN [13, 14]. Based on these findings, pegfilgrastim at a fixed dose of 6 mg is widely used in the world.

The safety of pegfilgrastim at doses of 30, 60, and 100 μg/kg was evaluated in a clinical pharmacological study in Japanese lung cancer patients [15]. The study results demonstrated the safety and tolerability of a single subcutaneous pegfilgrastim injection up to 100 μg/kg. In the present study, three fixed pegfilgrastim doses of 1.8, 3.6, or 6.0 mg were
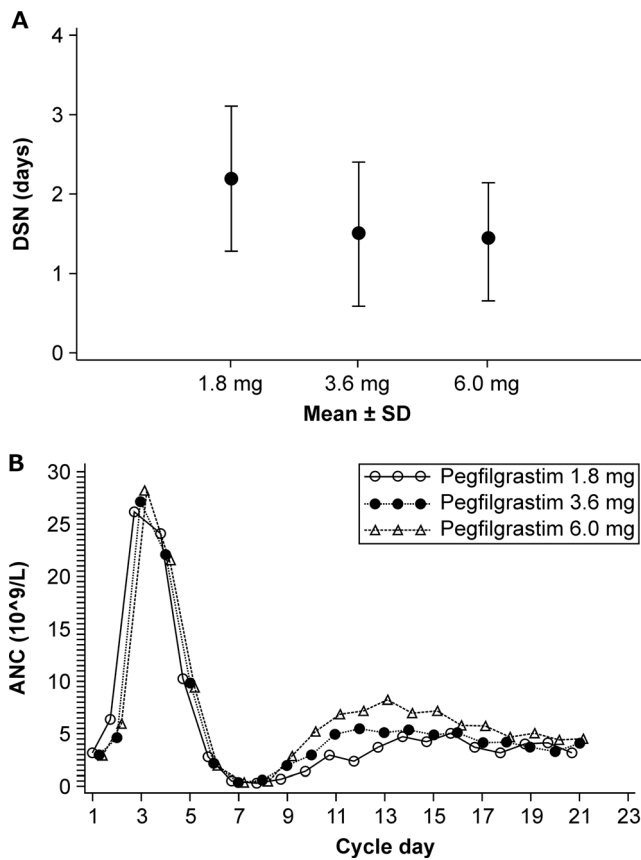
Fig. 3 **a** Duration of severe neutropenia (DSN) in the first cycle. **b** Median absolute neutrophil count (ANC) for cycle 1. *SD* standard deviation

used to determine the recommended pegfilgrastim dose in Japanese patients with breast cancer. DSN was 2.2±0.9 days, 1.5±0.9 days, and 1.4±0.7 days in the 1.8-, 3.6-, and 6.0-mg groups, respectively. Analysis of the dose-response relationship between pegfilgrastim dose and DSN revealed a significant "linear reduction" (P=0.005), significant "plateau at 3.6 mg" (P=0.001), and non-significant reduction at 6.0 mg (P=0.092).

A dose-finding study of pegfilgrastim conducted in the USA also showed a linear shortening of DSN in response to pegfilgrastim (30, 60, or 100 μg/kg) injection in breast

Table 2 The incidence of FN and nadir of ANC (per protocol set)

		Pegfilgrastim		
		1.8 mg n=29	3.6 mg n=29	6.0 mg n=29
FN[a]	n (%)	2 (6.9 %)	3 (10.3 %)	1 (3.4 %)
Nadir of ANC ($\times 10^9$/L)	Mean±SD	0.184±0.212	0.240±0.208	0.255±0.287

FN febrile neutropenia, *ANC* absolute neutrophil count, *SD* standard deviation

[a] FN was defined as body temperature ≥38 °C

Table 3 Grade 3 or 4 hematologic adverse events across all cycles

	Pegfilgrastim		
	1.8 mg n=29	3.6 mg n=29	6.0 mg n=29
Neutropenia	29 (100 %)	29 (100 %)	28 (96.6 %)
Leukocytopenia	29 (100 %)	28 (96.6 %)	28 (96.6 %)
Anemia	1 (3.4 %)	0 (0.0 %)	1 (3.4 %)
Thrombocytopenia	0 (0.0 %)	4 (13.8 %)	4 (13.8 %)
Lymphopenia	13 (44.8 %)	13 (44.8 %)	11 (37.9 %)

Data are presented as *n* (%)

cancer patients undergoing doxorubicin/docetaxel chemotherapy [16]. In a phase I trial in Japan, lung cancer patients undergoing chemotherapy received a single injection of pegfilgrastim if they experienced grade 4 neutropenia in the previous cycle [15]. In another phase I trial in lung cancer patients conducted in the USA, single-dose pegfilgrastim or daily filgrastim was administered 14 days prior to initial chemotherapy dosing and again after chemotherapy [17]. Both of these clinical trials revealed a non-linear trend in pharmacokinetic parameters, such as C_{max} and area under the concentration curve. However, differences in race, study design, and chemotherapy regimens may have contributed to the discrepancy in pegfilgrastim dose responses in these phase II trials. The approved dose of filgrastim for chemotherapy-induced neutropenia in Japan is one fourth to one half of the dose approved in other foreign countries. Compared with the approved pegfilgrastim dose of 6 mg in Europe and the USA, lower pegfilgrastim doses provided adequate efficacy in Japanese patients undergoing chemotherapy.

Although different regimens were used, the DSN response to 3.6-mg pegfilgrastim in Japanese patients in our study was similar to the DSN response to 6.0-mg pegfilgrastim in phase III trials conducted in the USA, Canada, European countries, and Australia (1.5±0.9 days vs. 1.8±1.4 days) [13, 14]. Considering the difference in regimens and patient populations, as well as the fact that the previous trials were conducted approximately a decade ago, it is difficult to make cross-trial comparisons among these groups.

In the present study, all patients experienced adverse events; however, most adverse events were associated with cancer chemotherapy. Pegfilgrastim was well tolerated up to 6.0 mg.

Based on our results, 3.6 mg of pegfilgrastim may be a safe and effective dose. However, because this study was conducted as an exploratory dose-finding study in Japanese patients, a confirmatory study is required.

This study was conducted in breast cancer patients receiving TAC therapy. The BCIRG001 study compared the

efficacy and safety of TAC therapy and FAC (fluorouracil/doxorubicin/cyclophosphamide) therapy as adjuvant chemotherapy in 1047 node-negative breast cancer patients. The BCIRG001 study showed that 5-year progression-free survival and overall survival were significantly longer in the TAC therapy group than in the FAC therapy group, and this significant difference was maintained at 10 years [18, 19]. At the time 237 subjects were enrolled, the incidence of FN was significantly higher in the TAC therapy group than in the FAC therapy group (24.7 vs. 2.5 %; $P<0.001$) [20]. Although the use of prophylactic antibiotics was initially mandated in the TAC therapy group, the prophylactic use of G-CSF was not allowed. Therefore, the study protocol was revised to specify the prophylactic use of G-CSF in the TAC therapy group. Prophylactic G-CSF decreased the incidence of FN in the TAC therapy group from 24.7 to 6.5 %. Based on the results of the BCIRG001 study, the National Comprehensive Cancer Network guidelines indicate the use of filgrastim support in all cycles of TAC therapy.

Because G-CSF is not currently indicated for the primary prophylaxis of FN induced by breast cancer chemotherapies in Japan, intensive chemotherapy regimens are rarely used in Japan. If breast cancer is treated with intensive chemotherapy regimens, such as TAC, which is commonly used in Europe and the USA, a pre-planned dose reduction from the standard dose is needed. Conversely, according to various reports, dose reduction in cancer chemotherapy attenuates therapeutic effects [3–7]. It is important to administer cancer chemotherapy at effective doses, as maintenance of relative dose intensity may affect clinical outcomes, particularly in the adjuvant setting.

In our study, TAC therapy with prophylactic pegfilgrastim support was conducted safely, even in the outpatient setting. The proportion of patients who developed FN was 6.9 % in all pegfilgrastim dosage groups. Prophylactic pegfilgrastim at a fixed dose of 3.6 mg is expected to allow cancer chemotherapy to be administered at the same dose intensity for Japanese breast cancer patients as that used for patients in Western countries.

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