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Filgrastim biosimilar for neutropenia in gynecological cancer patients receiving chemotherapy: a prospective, single-center, non-randomized, open trial

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Few clinical studies have compared the efficacy of a filgrastim biosimilar with that of the original filgrastim in gynecological cancer. This study compared the efficacy of a filgrastim biosimilar to that of the original filgrastim for treating neutropenia that developed following chemotherapy for gynecological cancer. Forty gynecological cancer patients undergoing chemotherapy were enrolled in this study. Efficacy was evaluated by the recovery of the absolute neutrophil count following administration of filgrastim biosimilar or original filgrastim in patients who developed neutropenia after undergoing chemotherapy. The incidence of febrile neutropenia (FN) was also evaluated. The neutrophil count after filgrastim biosimilar administration showed a change similar to that observed with the original filgrastim. The incidence of FN was the same for both drugs. Filgrastim biosimilar had similar efficacy to that of original filgrastim in patients who developed neutropenia following chemotherapy for gynecological cancer.

1. Introduction

The incidence of neutropenia after a chemotherapy session is known to affect the subsequent treatment schedule. One useful treatment of febrile neutropenia (FN), arising from chemotherapy, is the use of granulocyte colony-stimulating factors (G-CSFs), which increase the effectiveness of the chemotherapy treatment by allowing increased dose intensity (Aapro et al. 2011). However, the increase in medical costs due to the use of G-CSFs is an economic concern because these medicines are expensive (Link 1994).

Filgrastim is a non-glycosylated recombinant human form of G-CSF (rhG-CSF) produced by *Escherichia coli* bacteria and contains an additional N-terminal methionine. A biosimilar rhG-CSF preparation has been developed using gene-splicing in *E. coli* as a biosimilar of the original filgrastim. The pharmacokinetic and pharmacodynamic bioequivalence between the biosimilar drug and the original filgrastim has been confirmed in clinical pharmacology studies using healthy volunteers (Lubenau et al. 2009). A phase III study has also provided evidence for efficacy equivalent to original filgrastim, unlike the case for conventional generic drugs, in patients undergoing breast cancer chemotherapy (del Giglio et al. 2008). No incidences of problematic adverse events were reported in the safety evaluations.

Biosimilar filgrastim is, therefore, of equivalent quality to the original filgrastim. Treatment with filgrastim biosimilar is reportedly beneficial in ameliorating severe neutropenia and FN in patients with non-Hodgkin's lymphoma receiving chemotherapy (Engert et al. 2009), but few clinical studies have compared the efficacy and safety for treatment of gynecological cancer.

The primary aim of the present study was to compare the effectiveness of the filgrastim biosimilar and original filgrastim. We show that the filgrastim biosimilar had similar efficacy, was well tolerated in gynecological cancer patients undergoing chemotherapy and had very similar effectiveness to original filgrastim in stimulating neutrophil recovery.

2. Investigations and results

2.1. Patient characteristics

A total of 40 patients were enrolled in our study between August 2013 and December 2015; 20 received the original filgrastim, and 20 received the biosimilar. No significant differences were found between the two groups regarding age, body weight, menopause status, platelet counts, serum creatinine, total bilirubin, aspartate aminotransferase (AST), and alanine transaminase (ALT). Patients in both groups had ovarian, cervical, or uterine cancer and underwent tri-weekly paclitaxel + carboplatin (TC) therapy (Table 1).

2.2. Duration of neutropenia

Table 2 shows a comparison of the duration of neutropenia (absolute neutrophil count; ANC < 1,000/mL) after the administration of biosimilar filgrastim or original filgrastim. No significant difference was evident between the two groups. The average period for recovery from neutropenia was 2.5±1.0 days with the filgrastim biosimilar and 3.4±1.8 days with the original filgrastim (Table 2).

2.3. Incidence of febrile neutropenia

The FN incidence was 20.0% in both groups. The original filgrastim group experienced FN at 8.7±1.2 days after chemotherapy, while the biosimilar filgrastim group experienced FN at 10.7±3.5 days, but this difference was not statistically significant.

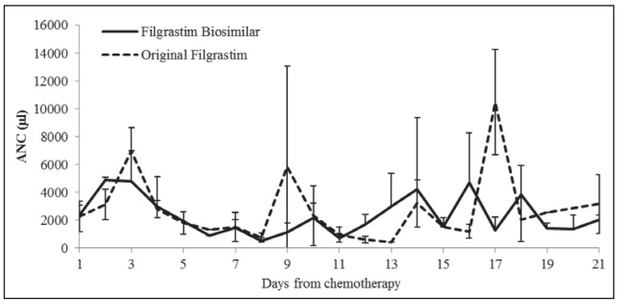

Fig.: Mean±SD of absolute neutrophil count from day 1 to 21. ANC = absolute neutrophil count; SD = standard deviation.

Table 1: Patient demographics and characteristics

Characteristic		Filgrastim biosimilar group (N = 20)	Original filgrastim group (N = 20)	P values
Age (years) (median, range)		65.0 (42–73)	61.5 (57–77)	0.650
Body weight (kg) (mean ± SD)		50.9 ± 11.2	45.8 ± 15.6	0.370
ECOG Performance status	0	19	19	0.990
	1	1	1	
Menopause status	Premenopause	9	8	0.108
	Postmenopause	11	12	
Diagnosis	Ovarian cancer	10	10	0.188
	Uterine cancer	7	6	
	Cervical cancer	2	4	
	Others	1	0	
Neutrophil count (cells/mm^3) (mean ± SD)		2294.2 ± 725.5	2495.0 ± 1293.1	0.333
Platelet count (/ml) (mean ± SD)		221,820 ± 725,52	256,560± 37,860	0.452
Serum creatinine (mg/dl) (mean ± SD)		0.65 ± 0.17	0.60 ± 0.13	0.552
Total bilirubin (mg/dl) (mean ± SD)		0.41 ± 0.20	0.45 ± 0.16	0.556
AST (IU/l) (mean ± SD)		18.2 ± 6.2	15.9 ± 13.0	0.654
ALT (IU/l) (mean ± SD)		19.4 ± 6.4	19.4 ± 6.4	0.642
Duration of filgrastim administration (day) (mean ± SD)		2.5 ± 1.1	3.0 ± 1.2	0.233
Chemotherapy	TC tri-weekly	14	16	0.343
	Dose-dense TC	2	3	
	DC	2	0	
	Others	2	1	

TC: paclitaxel + carboplatin, DC: docetaxel + carboplatin; ECOG: Eastern Cooperative Oncology Group; AST: aspartate aminotransferase; ALT: alanine aminotransferase

2.4. Change of the neutrophil count

The Figure shows the change of the neutrophil count for cycle 1. In both groups, the ANC showed a similar change in both groups for the duration of treatment, and a decrease in the neutrophil count was found after chemotherapy initiation from day 5. In comparison with day 1 (before chemotherapy initiation), an average neutrophil count showed a minimum value after the start of therapy on day 13 and day 8 after chemotherapy in filgrastim biosimilar and original filgrastim, respectively. The sudden increase of ANC was also found after G-CSF administration in the original filgrastim group (Fig.).

3. Discussion

Biosimilars have been defined as biotech drugs that show quality, safety, and efficacy comparable to the original product. The clinical efficacy of the filgrastim biosimilar and the original filgrastim was confirmed previously in a phase III randomized controlled study of hematological malignancy. The safety and tolerability of both medicines were similar in patients with non-Hodgkin's lymphoma (Engert et al. 2009).

All G-CSFs are approved based on a phase I study and efficacy as well as a safety test phase III study conducted in Europe. However, efficacy, safety of chronic administration, and immunogenicity remain poorly understood. Therefore, patients should be followed up by a chief physician (for traceability), and pharmacovigilance should be maintained in post-marketing. Sagara et al. (2013) compared the efficacy of a filgrastim biosimilar product in patients with breast cancer and reported similar effectiveness to that of the original for treatment of FN following chemotherapy (Sagara et al. 2013). A previous study reported that ~60% of febrile neutropenic events occurred during the first cycle of therapy (Crawford et al. 2008).

In accordance with the literature, change in the neutrophil count was investigated during the first cycles of chemotherapy in the present study. In a multicenter observational study of 337 patients, original filgrastim and biosimilar filgrastim were seen to have comparable efficacy in treating neutropenia (Sevinç et al. 2018). In that study, patients with gynecological cancer were not enrolled. A more recent study showed that the incidence of FN was statistically equivalent between individuals treated with original filgrastim and biosimilar filgrastim during their first chemotherapy cycle, and FN-related health care resource utilization and medical costs among patients who developed FN were substantial in 3,542 patients with nonmyeloid cancers (Schwartzberg et al. 2018). The present study is, therefore, the first to compare the effectiveness of biosimilar filgrastim and original filgrastim in patients with gynecological cancer. Our results confirm that the biosimilar has equivalent efficacy to the original product.

Gynecological cancer is typically treated with a regimen that combines carboplatin with paclitaxel as the first line treatment, but the incidence of FN is reported as 9% for both dose-dense and

Table 2: Comparison of duration of neutropenia and onset rate febrile neutropenia between filgrastim biosimilar and original filgrastim

	Filgrastim biosimilar group (N = 20)	Original filgrastim group (N = 20)	P values
Duration of neutropenia (mean ± SD, days)	2.5 ± 1.0	3.4 ± 1.8	0.904
Duration of neutropenia (median, days)	3	3.5	
Maximum	4	7	
Minimum	1	1	
Occurrence of FN, no. (%)	4 (20.0%)	4 (20.0%)	1.000
Mean days from the start of chemotherapy to the occurrence of FN (days)	10.7 ± 3.5	8.7 ± 1.2	0.310

FN, febrile neutropenia

tri-weekly TC (Katsumata et al. 2009). In this study, the incidence of FN among patients with gynecological cancers undergoing chemotherapy was statistically equivalent between those treated with original filgrastim *versus* biosimilar filgrastim during the first chemotherapy cycle. However, the incidence of FN was higher than previously reported for both the filgrastim biosimilar and original filgrastim groups (both groups had an incidence of 20%, respectively). In the present study, both drugs were administered from day 7 to day 14 after a start of chemotherapy. In the previous study, filgrastim was administered from day 5 to day 14. The difference of the duration each filgrastim administration is one reason why the incidence of FN in the present study was higher than in the previous study.

This study has some limitations. The study design was not randomized and blinded, the trial was a single-center study, and the number of patients was small. Nevertheless, even considering these limitations, the results support the contention that biosimilar filgrastim could be a reasonable treatment drug for neutropenia.

4. Experimental

4.1. Study design and patients

This study was designed as a prospective, single-center, non-randomized, open trial to compare the effectiveness of filgrastim biosimilar and original filgrastim. Patients who met the eligibility criteria and exclusion criteria and who underwent chemotherapy for treatment of ovarian, cervical, or uterine cancer between August 2013 and December 2015 were enrolled in the study. Eligibility criteria were as follows: (1) an Eastern Cooperative Oncology Group (ECOG) performance status (PS) score of 0–1; (2) 2.5 instances of ANC ≥ 1,500/ml, platelet count ≥ 100,000/ml, and aspartate aminotransferase (AST) and ALT < the upper limit of the institution reference value (AST: 33 IU/l, ALT: 22 IU/l); 1.5 instances of total bilirubin < the upper limit of the institution reference value (1.50 mg/dl); and 1.5 instances of serum creatinine < the upper limit of the institution reference value (1.07 mg/dl). Exclusion criteria were (1) patients with liver and kidney dysfunction; (2) patients with hypersensitivity; (3) patients whose attending doctor considered them to be inappropriate for the study; (4) patients who had received radiotherapy less than four weeks before chemotherapy initiation; and (5) patients with bone marrow infiltration.

4.2. Chemotherapy

Patients received carboplatin at a dose calculated to produce an area under a curve of 6 mg/ml per min on day 1 of a 21-day cycle. Carboplatin was given as an intravenous infusion over 1 h. In tri-weekly TC therapy, patients received paclitaxel given as a 3 h intravenous infusion at a dose of 180 mg/m^2 on day 1. In dose-dense TC therapy, patients received paclitaxel as a 1 h intravenous infusion at a dose of 80mg/m^2 on days 1, 8, and 15. In DC therapy, patients also received docetaxel as a 2 h intravenous infusion at a dose of 70 mg/m^2 on day 1.

4.3. Administration of filgrastim

Patients received a daily injection of biosimilar filgrastim or original filgrastim when neutrophil cell counts were < 500/mL, or < 1,000/mL with a fever > 38.0 °C (measured armpit). The dose of filgrastim biosimilar (subcutaneous, 50 mg/m^2) was equivalent to the dose of original filgrastim (Gran® Roche), as approved in Japan. Injections of either filgrastim or the biosimilar were given daily for a maximum of 14 days. Filgrastim biosimilar and original filgrastim were provided by Mochida Pharmaceutical Co., Ltd, and Chugai Pharma Co., Ltd., respectively.

4.4. Assessment of clinical efficacy for febrile neutropenia

Biosimilar filgrastim administration was stopped when an ANC of ≥5,000/mL was detected. Administration of any other drugs, including hematopoietic growth factors (G-CSFs, erythropoietin, granulocyte macrophage CSFs), leukopenia drug therapy, immunotherapy agents, steroids (except for pre-medication), systemic antimicrobial and antibiotic agents (except for fever > 38.0 °C), and antipyretics (except for fever > 38.0 °C or the topical administration of non-steroidal anti-inflammatory agents), was prohibited during the study. Patient information was recorded, including age, body weight, ECOG PS, menopause status, diagnosis, ANC, platelet count, serum creatinine total bilirubin, AST, and ALT before chemotherapy, the chemotherapy regimen, the duration of filgrastim administration, and the duration of neutropenia after chemotherapy. Neutropenia incidence (FN incidence), as a primary endpoint during the neutropenia (ANC < 1,000/mL) period in cycle 1 was evaluated.

4.5. Statistical analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS) for Windows (SPSS Inc., Chicago, IL, USA). Data are expressed as mean±standard deviation (SD). Differences between the two groups were analyzed by the Mann-Whitney U test or Welch's *t* test. A value of $P < 0.05$ was considered statistically significant.

4.6. Ethics

This study was carried out with the approval of the Oita University medical department's Ethical Review Board (approval number: 750; July 17, 2014) and UMIN Clinical Trial Registry (UMIN000019110). All personal patient information remained anonymous.

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Conflicts of interest: None declared

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