

# Pegfilgrastim Maintains Relative Dose Intensity and Decreases Hospitalisations in Patients With Endometrial Cancer

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**Abstract.** *Background/Aim:* Data are limited regarding the use of pegfilgrastim in gynaecologic oncology. We evaluated its efficacy for maintaining dose intensity during chemotherapy. *Patients and Methods:* We retrospectively examined the data of 65 women (26 pegfilgrastim users) who underwent primary surgical treatment for stages IB-IV endometrial cancer and had adjuvant chemotherapy containing platinum and taxane; the primary outcome was a relative dose intensity  $\geq 85\%$ . *Results:* In the pegfilgrastim vs. the control group, body mass index ( $26.6 \pm 5.9$  vs.  $23.4 \pm 4.4$ ), rate of relative dose intensity  $\geq 85\%$  (88.5% vs. 15.4%), plus other adverse event incidences were significantly higher; rate of neutropenia, total hospital visits during chemotherapy ( $11.0 \pm 2.1$  vs.  $18 \pm 5.6$  days), unscheduled hospital visits ( $1.1 \pm 1.8$  vs.  $5.8 \pm 5.1$  days), and unscheduled granulocyte colony-stimulating factor injections ( $0.58 \pm 1.7$  vs.  $6.4 \pm 5.1$  days) were significantly lower. *Conclusion:* Pegfilgrastim can maintain a dose intensity of  $\geq 85\%$  during chemotherapy for the treatment of gynaecologic cancers and decrease hospital-visit frequency.

The relative dose intensity is the total dose of a chemotherapeutic drug that is compared against a standard dose and schedule across the total duration of chemotherapy. Relative dose intensity has been suggested as a prognostic factor in several cancers (1, 2). Relative dose intensity is considered an important predictive factor even in the survival of patients with metastatic solid tumours (3). In gynaecologic oncology, there is a published report on ovarian cancer and

relative dose intensity, wherein reduced relative dose intensity for ovarian cancer was a risk factor of overall survival (OS) (1). The abovementioned study was a retrospective study among patients with ovarian cancer; however, there is strong evidence of an association between relative dose intensity and OS in breast cancer or aggressive lymphoma, and granulocyte colony-stimulating factor (G-CSF) improved the chances of attaining a higher relative dose intensity (2). In another recent study, G-CSF was reported to support a relative dose intensity of 85% or higher (4).

Pegfilgrastim is a long-acting G-CSF that has the most widespread application for approved indications, and supports a relative dose intensity greater than 85% in patients with lung and breast cancer (5, 6). However, there are limited data on the use of pegfilgrastim in gynaecologic oncology. There are limited regimens specified in the National Comprehensive Cancer Network guidelines on chemotherapy for uterine neoplasms (7). Therefore, the relative dose intensity of the first chemotherapy could be crucial to patient outcome and survival.

This study was conducted to evaluate the efficacy of pegfilgrastim in the maintenance of relative dose intensity as adjuvant therapy for endometrial cancer. Moreover, we investigated the utility of pegfilgrastim in reducing hospital visits in patients with endometrial cancer.

## Patients and Methods

This single-centre retrospective study was conducted among women who underwent primary surgical treatment for uterine neoplasms of stages IB-IV [International Federation of Gynecology and Obstetrics (FIGO)] at the Saitama Medical Center, Jichi Medical University, Saitama, Japan between 2014 and 2018. The study inclusion criteria were age over 20 years and treatment with adjuvant chemotherapy containing platinum and taxane. The exclusion criteria were a history of other cancers or the use of a single-agent adjuvant chemotherapy. In this study, patients were assigned into two groups: the pegfilgrastim group and the historical control group. Of the 65 patients eligible for study inclusion, 26 patients routinely received pegfilgrastim, and the remaining patients did not receive pegfilgrastim during their treatment. Pegfilgrastim use was initiated from January 2015 at the study centre. Patients were treated with

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Table I. Patient characteristics of the study population.

	Pegfilgrastim group N=26	Non-pegfilgrastim group N=39	p-Value
Age	61.5±9.7	62.3±11.3	0.59
Body mass index	26.6±5.9	23.4±4.4	0.016*
Stage, N (%)			0.095
I	11 (42.3)	27 (69.2)	
II	4 (15.4)	5 (12.8)	
III	7 (26.9)	6 (15.4)	
IV	4 (15.4)	1 (2.6)	
Histopathology, N (%)			0.27
Endometrioid	19 (73.1%)	31 (79.5)	
Serous	4 (15.4%)	1 (2.6%)	
Clear cell	1 (3.8%)	3 (7.7%)	
Carcinosarcoma	2 (7.7%)	4 (10.3%)	

\*p-value<0.05 indicates significance.

chemotherapy in accordance with the guidelines of the Japan Society of Gynecologic Oncology (8). The study protocol was approved by the institutional review board of the Jichi Medical University (S19-127). The requirement for informed consent was waived by the institutional ethics body because of the retrospective nature of the study and a comprehensive written consent had been pre-obtained, for the use of patient data for research purposes.

Two chemotherapeutic regimens were used in the study population: [1] paclitaxel 175 mg/m<sup>2</sup> plus carboplatin that was dosed to an area under the curve of concentration-time curve of 6 every 3 weeks; or [2] docetaxel 75 mg/m<sup>2</sup> plus carboplatin dosed to an area under the curve of concentration-time curve of 6 every 3 weeks, in patients anxious about developing peripheral neuropathy or adverse events with the paclitaxel-carboplatin regimen. Patients routinely received intravenous injections of pegfilgrastim from January 2015, when it became available for use at the hospital. Patients routinely underwent follow-up laboratory investigations 14 days after the administration of chemotherapy, regardless of whether pegfilgrastim was used. As part of the routine institutional policy, patients received a G-CSF injection if Grade 3 or higher neutropenia was detected.

We recorded the demographics and clinical characteristics of the study participants including body mass index, treatment regimens, FIGO staging, and histological type of the tumour. The primary outcome was a relative dose intensity of 85% or greater. The secondary outcomes were adverse events such as neutropenia, anaemia, thrombocytopenia, increased serum levels of creatinine and aspartate aminotransferase, peripheral sensory neuropathy, nausea/vomiting, and infections, which were graded in accordance with the criteria specified in the Common Terminology Criteria for Adverse Events version 5.0.

All statistical analyses were undertaken in JMP, version 10.0.0 (for Windows; SAS Institute Japan, Minato, Japan). Demographic variables were reported as mean and standard deviation, whereas data with non-normal distribution were reported as median and range. We used the Kolmogorov-Smirnov variables test to assess normality of distribution of the continuous variables. For variables with normal distribution, continuous data were compared with the ANOVA test. For variables with non-normal distribution, data were

Table II. Pegfilgrastim and relative dose intensity in the study groups.

RDI	Pegfilgrastim group N=26	Non-pegfilgrastim group N=39	p-Value
≥85%	23 (88.5%)	6 (15.4%)	<0.001*
<85%	3 (11.5%)	33 (84.6%)	

RDI: Relative dose intensity. \*p-value<0.05 indicates significance.

compared using the Wilcoxon signed-rank test. Fisher's exact test was used to study the associations between all demographic parameters. For all statistical tests, a two-sided p-value less than 0.05 was considered indicative of statistical significance. For the hazard ratio, we estimated 95% confidence intervals (95% CIs). Based on our previous research (unpublished findings), we estimated a sample size of 15 patients in both groups and an overall study population of 30 patients, wherein 80% of patients in the pegfilgrastim group would be expected to have a relative dose intensity of 85% or higher, and 30% of patients in the non-pegfilgrastim group would have a relative dose intensity of 30% or higher.

## Results

A total of 65 patients (age, 62.4±10.6 years) were included in the study. Patients were divided into a pegfilgrastim (routinely received pegfilgrastim; n=26; age 61.5±9.7 years) and a non-pegfilgrastim arm (did not receive pegfilgrastim; n=39; 62.3±11.3 years). There was no significant between-group difference in age (p=0.59), but patients in the pegfilgrastim group had significantly higher body mass index versus the non-pegfilgrastim group (26.6±5.9 vs. 23.4±4.4, respectively; p=0.016). The other patient demographics and clinical characteristics are presented in Table I. In the pegfilgrastim group, one of the patients used docetaxel-carboplatin, because of anxiety regarding peripheral neuropathy, and another patient switched to the docetaxel-carboplatin treatment because of symptomatic peripheral neuropathy. In the non-pegfilgrastim group, two patients used docetaxel-carboplatin because of anxiety about peripheral neuropathy, and one patient switched to docetaxel-carboplatin chemotherapy after developing symptoms of peripheral neuropathy. All other patients were treated with a paclitaxel-carboplatin regimen.

In the pegfilgrastim group, the rate of relative dose intensity of 85% or greater was significantly higher (88.5% vs. 15.4%; Table II) than estimated. Three patients in this group achieved relative dose intensity of less than 85% because of Grade 3 thrombocytopenia.

Other causes for a relative dose intensity of less than 85% in these patients were neutropenia or infection.

The pegfilgrastim group had a significantly lower reported adverse event rate for neutropenia, although the rate of other

Table III. Adverse events in the study population.

Adverse events	Pegfilgrastim group N=26	Non-pegfilgrastim group N=39	p-Value
Neutropenia, Grade $\geq 3$	3 (11.5%)	36 (92.3%)	<0.001*
Anaemia, Grade $\geq 2$	5 (19.2%)	3 (7.7%)	0.17
Thrombocytopenia, Grade $\geq 2$	4 (15.4%)	1 (2.6%)	0.057
Elevated serum aspartate aminotransferase, Grade $\geq 1$	6 (23.1%)	17 (43.6%)	0.09
Elevated serum creatinine, Grade $\geq 1$	0	2 (5.1%)	0.24
Nausea/vomiting, Grade $\geq 1$	3 (11.5%)	1 (2.6%)	0.14
Infections	0	10 (25.6)	0.005*

\*p-value<0.05 indicates significance.

adverse events was higher in the pegfilgrastim group (Table III). In the non-pegfilgrastim group, 10 patients had infections, and recovered with antibiotic therapy.

Furthermore, total hospital visits for chemotherapy, unscheduled hospital visits due to infection or for receiving additional doses of G-CSF if required, and unscheduled G-CSF injections were significantly lower in the pegfilgrastim group (11.0 $\pm$ 2.1 vs. 18 $\pm$ 5.6 days,  $p \leq 0.001$ ; 1.1 $\pm$ 1.8 vs. 5.8 $\pm$ 5.1 days,  $p < 0.001$ ; and 0.58 $\pm$ 1.7 vs. 6.4 $\pm$ 5.1 days,  $p < 0.001$ , respectively; Table IV).

## Discussion

This study presents the first report of the efficacy of pegfilgrastim in maintaining the relative dose intensity in the chemotherapeutic management of endometrial cancer. Pegfilgrastim not only maintained the relative dose intensity but also decreased the number of hospital visits.

In patients with endometrial cancer, pegfilgrastim effectively maintained the relative dose intensity during adjuvant chemotherapy. In gynaecologic oncology, the reduced relative dose intensity in patients with ovarian cancer is a risk factor for low OS (1). In other cancers too, reduced relative dose intensity is a risk factor for low OS (2). Pegfilgrastim is a long-acting G-CSF that is approved for most of the indications of G-CSF therapy, and supports the maintenance of relative dose intensity above 85% in patients with lung and breast cancer (5, 6). Our study found similar efficacy of pegfilgrastim in the maintenance of a relative dose intensity of 85% or greater and recommends the use of adjuvant therapy with pegfilgrastim in the field of gynaecologic oncology.

Table IV. Frequency of hospital visits in the study population.

Hospital visits	Pegfilgrastim group N=26	Non-pegfilgrastim group N=39	p-Value
Total visits during chemotherapy	11.0 $\pm$ 2.1	18 $\pm$ 5.6	<0.001*
Unscheduled visits for additional injection of G-CSF, or because of infection	1.1 $\pm$ 1.8	7.8 $\pm$ 5.1	<0.001*
Unscheduled G-CSF injection	0.58 $\pm$ 1.7	6.4 $\pm$ 5.1	<0.001*

\*p-value<0.05 indicates significance.

Pegfilgrastim was also found to be useful in decreasing hospital visits. In Japan, approximately 30% of the cancer patients belong to the working age group (9). It has been reported that 64.5% of the patients find it difficult to continue biweekly hospital visits (10). In addition, approximately 77.4% of patients experienced difficulty in taking leave from work. A review article has reported that the use of pegfilgrastim is recommended along with chemotherapy, in cancer patients (11). Furthermore, in a meta-analysis, the risk of severe neutropenia was found to be reduced with pegfilgrastim (12).

The rate of neutropenia was significantly lower in the pegfilgrastim group; however, the incidence of other adverse events tended to be higher in this group. The first and subsequent cycles of pegfilgrastim in patients with breast cancer markedly reduced the incidence of febrile neutropenia and febrile neutropenia-related hospitalisations (13). Therefore, although the incidence of neutropenia reduced and the relative dose intensity was maintained, the incidence of other adverse events appeared to increase. This is similar to the effects seen with dose-dense chemotherapy, where patients often need blood transfusions and delay chemotherapy cycles because of anaemia and thrombocytopenia (14). However, in our study, only three patients in the pegfilgrastim group developed thrombocytopenia. Other patients in the pegfilgrastim group achieved a relative dose intensity of 85% or greater. Our regimens were conventional and not dose-dense regimens, such as those reported in the study by Katsumata *et al.* (14). Therefore, the usual regimens could maintain a relative dose intensity with therapeutic feasibility and a decreased incidence of neutropenia and infection, using adjuvant pegfilgrastim therapy.

At present, the cost factor poses a major economic burden in cancer treatment (15-21). Cancer patients are unable to work due to poor health and end up with reduced work productivity (15-18). The financial implications of cancer

may further increase as constraints on working capacity reduce employment-based health insurance options and limit the patients' resources for healthcare. These factors together may contribute to the phenomenon of financial ramifications of cancer treatment. Therefore, our study proposes a possible solution to manage these problems.

Our study suggests that pegfilgrastim assists in decreasing the number of hospital visits. This could be helpful in minimising face-to-face contact between the medical staff and patients, which is an ongoing need in the current COVID-19 pandemic situation (22).

Our study's limitations are as follows: 1) all limitations and risk of bias inherent to retrospective studies; 2) a small sample size; 3) potential selection bias, considering that all subjects were recruited from a single institution; and 4) the results may neither be extrapolated nor generalised to other populations.

In conclusion, pegfilgrastim was useful in the maintenance of a relative dose intensity in the required therapeutic range in the treatment of endometrial cancer. Moreover, pegfilgrastim decreased the number of hospital visits.

### Conflicts of Interest

K. Chikazawa received lecture honoraria from Ethicon (Tokyo, Japan), Terumo (Tokyo, Japan), and Chugai Pharmaceutical Co. (Tokyo, Japan). R. Konno received research funds from Yakult Pharmaceutical Industry Co. (Tokyo, Japan) and Chugai Pharmaceutical Co. (Tokyo, Japan), and lecture honoraria from Japan Vaccine Co. (Tokyo, Japan), MSD Japan (Tokyo, Japan), and Chugai Pharmaceutical Co. (Tokyo, Japan). The funding organisations did not contribute to any aspect of conducting or reporting of this study. The other co-authors have no conflict of interests to declare regarding this study.

### Authors' Contributions

K. Chikazawa conceptualized the study and planned the study design. K. Chikazawa and T. Ito undertook data collection and analysis. K. Chikazawa conducted statistical analysis. K. Chikazawa drafted the manuscript. T. Kuwata and R. Konno reviewed and finalized the manuscript. K. Chikazawa and K. Imai drafted the initial and final manuscript. A. Kimura and K. Hiroyoshi collected data. Y. Miho analyzed data. T. Kuwata and R. Konno reviewed and edited the final manuscript.

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