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Original Article

A comparative analysis between pegfilgrastim and lenograstim administered to patients receiving cytotoxic chemotherapy for squamous cell carcinoma of the esophagus

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Background: This study aimed to clarify whether or not switching lenograstim for pegfilgrastim enables the sustained effects of decreasing neutropenia and shortening the length of hospitalization in patients receiving taxane-based chemotherapy.
Methods: Patients being treated docetaxel and nedaplatin therapy in our facility were enrolled in this study. In the first courses of therapy, we administered lenograstim when grade 3 neutropenia occurred (group A). In the second or subsequent courses of therapy, we administered lenograstim when grade 2 neutropenia occurred through March 2015 (group B) and then administered pegfilgrastim on day 2 of chemotherapy from April 2015 (group C). We retrospectively evaluated the incidence of severe neutropenia and febrile neutropenia (FN), length of hospitalization, and other adverse events.
Results: FN was observed in 10% (4/41) of group B and 0% (0/36) of group C (p=0.0511). Grade 3-4 neutropenia occurred in 76% (31/41) of group B and 3% (1/36) of group C (p<0.0001). The median length of hospitalization was 12 days in group B and 6 days in group C (p<0.0001).
Conclusion: Pegfilgrastim significantly reduced the incidence of neutropenia and the length of hospitalization. Pegfilgrastim may therefore improve the quality of life of these patients.

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Introduction

Taxanes are widely used to treat esophageal squamous cell cancer (ESCC). We administer a course of docetaxel and nedaplatin (DOC/CDGP) per day to cisplatin-pretreated relapsed or refractory ESCC patients as second-line chemotherapy and then repeat the course every four to six weeks.

One of the adverse events caused by the administration of such chemotherapeutic agents is a high FN incidence. In this treatment, the neutrophil nadir is typically observed around 7 to 10 days after the administration, and the incidence of febrile neutropenia (FN) is relatively high; we previously reported that 4.3%-25% of patients suffered FN despite the administration of granulocyte-colony stimulating factor (G-CSF)[1, 2]. In order to avoid the occurrence of FN or to treat FN itself, patients treated with these chemotherapeutic agents have to be monitored and injected with G-CSF and antibiotics in hospital until the neutrophil count reaches a normal level. This required monitoring period takes about 2 weeks. Therefore, although the injection of the chemotherapeutic agents itself takes only one day, the entire treatment period for patients injected with these agents takes about 2 weeks.

Polyethylene glycol (PEG) modified G-CSF (PEGylated G-CSF) was found to be less affected by renal clearance, leading to an increased plasma half-life compared with non-PEGylated G-CSF[9]. Pegfilgrastim, a PEGylated G-CSF, has been reported to be effective in preventing FN after cytotoxic chemotherapy in patients with colorectal and breast cancer, lymphoma, and myeloma[3–10]. Of note: no report has so far been published regarding patients with

esophageal cancer, especially those treated with DOC/CDGP, although the preventative effect of pegfilgrastim for FN is known to be related to the chemotherapeutic regimen, and not to the type of cancer.

We retrospectively analyzed the patients who received DOC/CDGP before and after the implementation of pegfilgrastim and investigated the efficacy of this regimen, especially with regard to shortening the duration of neutropenia, reducing the occurrence of neutropenia, and shortening the length of hospitalization.

Materials and Methods

Eligibility

Patients with histologically-confirmed squamous cell carcinoma of the esophagus who were treated DOC/CDGP therapy as second-line chemotherapy at our institution from January 2013 to April 2017 were enrolled in the present study. The eligible patients had been treated with the same dose of DOC/CDGP on multiple occasions while concomitantly being treated with G-CSF. Oral and written informed consent was obtained before each of the 29 patients received the treatment.

This study was approved by the Human Ethics Review Committee of Tokyo Medical and Dental University (No. 2138) and was carried out in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice.

Treatment

Initially, at the first session of DOC/CDGP therapy, DOC (60 mg/m^2) was administered intravenously; thereafter, CDGP (80 mg/m^2) was administered intravenously. We started the daily administration of lenograstim (100 μg) when grade 3 leukocytopenia or neutropenia was detected and continued the administration until the leukocyte count exceeded 6,000/mm^{3}in principle (January 2013 to April 2017, 29 courses). We categorized these courses of therapy as group A. DOC/CDGP treatment was repeated every four to six weeks as many times as possible until evidence of disease progression was observed.

We reduced the dose of DOC/CDGP to 80% if grade 3 neutropenia lasting for over 5 days occurred during the course of DOC/CDGP and then excluded the decreased dose administration courses from the analysis because our study design was based on a comparison of same dose. After the second therapy session, we started the daily administration of lenograstim when grade 2 leukocytopenia or neutropenia occurred and continued the administration until the leukocyte count exceeded 6,000/mm^3 (January 2013 to March 2015, 41 courses). We categorized these courses of therapy as group B.

We administered a single dose of pegfilgrastim (3.6 mg) after 24 h had passed since the second or subsequent courses of DOC/CDGP (March 2015 to April 2017, 36 courses). We categorized these courses of therapy as group C.

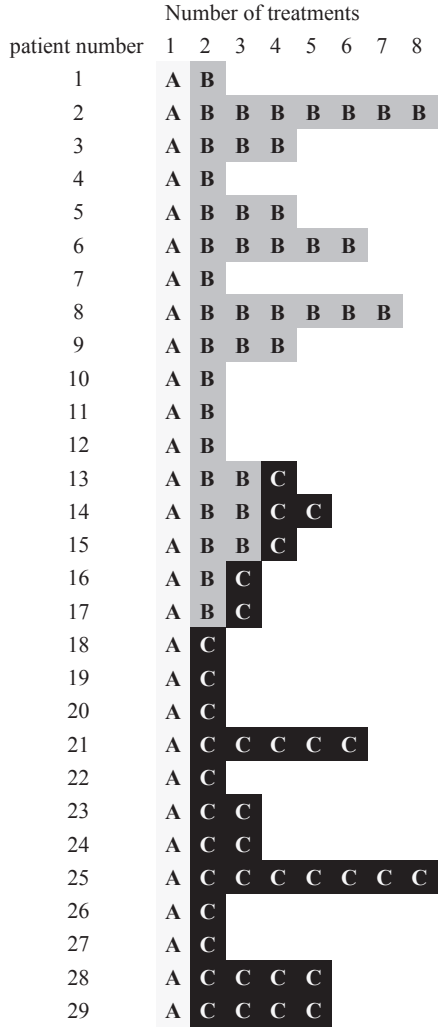

Figure 1. Categorization of all 106 courses of treatment administered to the 29 eligible patients in light of the usage of G-CSF products

A: A highlighted in white stands for the first course of chemotherapy with lenograstim administered when Grade 3 leukocytopenia or neutropenia was observed.

B: B highlighted in gray stands for the second or subsequent courses of chemotherapy with lenograstim administered when Grade 2 leukocytopenia or neutropenia was observed.

C: C highlighted in black stands for the second or subsequent courses of chemotherapy with pegfilgrastim administered after 24 h had passed since the chemotherapy.

Figure 1 shows how the 106 courses of therapy administered to eligible 29 patients were categorized into group A, B, or C. The patients were discharged from our hospital when it was confirmed that their neutrophil counts had increased from the nadir and that all other non-hemotoxicities were evaluated as grade 0 to 2.

Assessment

The treatment was evaluated based on the following items: the incidence and the duration of leukocytopenia, neutropenia, and febrile neutropenia and the length of hospitalization. Toxicities were assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.03 (CTCAE v4.03)[11].

First, we compared the aforementioned items between Groups A and C in order to assess the effectiveness of lemograstim and pegfilgrastim. However, Group A started to use lenograstim after Grade 3 leukocytopenia or neutropenia emerged, while Group C used pegfilgrastim prophylactically before the emergence of these conditions. Therefore, an accurate comparison of these two drugs requires mitigating the influence of the different initiation times for the administration of the drug. For this reason, we also compared Groups B and C. Group B started to use lenograstim once Grade 2 leukocytopenia or neutropenia was noted.

Statistical analyses

All of the statistical evaluations were performed using the Stat View 5.0 software package (HULINKS Inc., Tokyo, Japan). The chi-squared test was used to compare the data observed between groups. The Mann-Whitney U test was used to compare the continuous values within each group. P values of <0.05 were considered to indicate statistical significance.

Results

Patient characteristics

The characteristics of the eligible patients are shown in Table 1. The median age was 68 years old, the median body mass index was 18.6 kg/m^2, and 24 (83%) patients had undergone surgery or chemoradiotherapy previously.

Adverse events

Adverse events of DOC/CDGP therapy in group A, B and C are shown in Tables 2, 3, and 4, respectively. A total of 83% (24/29) of patients experienced Grade 3 or 4 neutropenia in group A, 76% (31/41) in group B, and 3% (1/36) in group C. FN occurred in 14% (4/29) of courses in group A, 10% (4/41) of courses in group B, and no courses in group C. Few other adverse events evaluated as grade 3 or 4 were observed in all groups.

Table 1. Baseline characteristics of patients (n=29)

Parameter		Number of patients (%)
Sex	Male	24 (83)
	Female	5 (17)
ECOG PS	1	29 (100)
Age (years)	Median	68
	IQR	64-74
Height (cm)	Median	163.6
	IQR	159.8-168.7
Weight (kg)	Median	51.6
	IQR	45.5-55.9
BMI (kg/m^2)	Median	18.6
	IQR	17.8-20.6
Previous therapy	Operation*1 and CT	10 (34)
	Operation and CRT	9 (31)
	CT only	5 (17)
	CRT only	5 (17)

ECOG PS, Eastern Cooperative Oncology Group Performance Status; IQR, interquartile range; CT, chemotherapy; CRT, chemoradiotherapy
*1: Including esophagectomy and esophageal by-pass surgery

Efficacy

The efficacy of groups A and C is compared in Table 5. FN occurred in 14% (4/29) of courses in group A and no courses in group C ($p<0.0001$). Grade 3-4 neutropenia was observed in 83% (24/29) of group A and in 3% (1/36) of group C ($p<0.0001$). The median duration of grade 3-4 neutropenia was 2 days in group A and 0 days in group C ($p<0.0001$). The median length of hospitalization was 13 days in group A and 6 days in group C ($p<0.0001$).

The efficacy of groups B and C is compared in Table 6. FN was observed in 10% (4/41) of courses in group B and in no courses (0/36) in group C ($p=0.0543$). Grade 3-4 neutropenia was observed in 76% (31/41) of group B and in 3% (1/36) of group C ($p<0.0001$). The median duration of grade 3-4 neutropenia was 2 days in group B and 0 days in group C ($p<0.0001$). The median length of hospitalization was 12 days in group B and 6 days in group C ($p<0.0001$).

Table 2. Adverse events of therapy in group A (n=29)

	Grade of adverse event					Incidence of grade 3 or 4
	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	
leukocytopenia	0	0	4	21	4	86%
neutropenia	0	1	4	15	9	83%
anemia	0	11	16	2	0	7%
thrombocytopenia	18	9	1	1	0	3%
AST elevation	17	12	0	0	0	0%
ALT elevation	25	4	0	0	0	0%
ALP elevation	23	6	0	0	0	0%
febrile neutropenia	25	-	-	4	0	14%
general fatigue	6	18	5	0	0	0%
anorexia	6	10	12	1	0	3%
nausea	16	7	6	0	0	0%
diarrhea	23	2	3	1	0	3%
stomatitis	25	2	2	0	0	0%
fever	25	4	0	0	0	0%
back pain	25	2	2	0	0	0%

AST, aspartate transaminase; ALT, alanine transaminase; ALP, alkaline phosphatase

Table 3. Adverse events of therapy in group B (n=41)

	Grade of adverse event					Incidence of grade 3 or 4
	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	
leukocytopenia	0	0	5	33	3	88%
neutropenia	1	2	7	19	12	76%
anemia	0	18	21	2	0	5%
thrombocytopenia	17	14	10	0	0	0%
AST elevation	17	23	1	0	0	0%
ALT elevation	24	16	1	0	0	0%
ALP elevation	38	3	0	0	0	0%
febrile neutropenia	37	-	-	4	0	10%
general fatigue	3	28	10	0	0	0%
anorexia	3	15	23	0	0	0%
nausea	28	8	5	0	0	0%
diarrhea	31	10	0	0	0	0%
stomatitis	33	5	3	0	0	0%
fever	37	3	1	0	0	0%
back pain	39	1	1	0	0	0%

AST, aspartate transaminase; ALT, alanine transaminase; ALP, alkaline phosphatase

Table 4. Adverse events of therapy in group C (n=36)

	Grade of adverse event					Incidence of grade 3 or 4
	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	
leukocytopenia	31	3	1	1	0	3%
neutropenia	32	1	2	1	0	3%
anemia	0	22	11	3	0	8%
thrombocytopenia	7	17	9	3	0	8%
AST elevation	24	12	0	0	0	0%
ALT elevation	36	0	0	0	0	0%
ALP elevation	22	14	0	0	0	0%
febrile neutropenia	36	-	-	0	0	0%
general fatigue	13	18	5	0	0	0%
anorexia	11	14	11	0	0	0%
nausea	26	7	3	0	0	0%
diarrhea	31	4	1	0	0	0%
stomatitis	34	2	0	0	0	0%
fever	35	1	0	0	0	0%
back pain	32	4	0	0	0	0%

AST, aspartate transaminase; ALT, alanine transaminase; ALP, alkaline phosphatase

Table 5. Comparison between groups A and C

Parameter		Group A (n=29)	Group C (n=36)	*p*
Grade 3 or 4 of leukocytopenia (%)		25 (86)	1 (3)	<0.0001
duration (days)	Median	2	0	<0.0001
	IQR	1-3	0-0	
Grade 3 or 4 of neutropenia (%)		24 (83)	1 (3)	<0.0001
duration (days)	Median	2	0	<0.0001
	IQR	1-3	0-0	
Grade 3 or 4 of febrile neutropenia (%)		4 (14)	0 (0)	0.020
duration (days)	Median	0	0	0.023
	IQR	0-0	0-0	
Subcutaneous injection of G-CSF (times)	Median	4	1	<0.0001
	IQR	3-6	1-1	
Hospitalization (days)	Median	13	6	<0.0001
	IQR	12-14	5-8	

IQR, interquartile range

Table 6. Comparison between groups B and C

Parameter		Group B (n=41)	Group C (n=36)	*p*
Grade 3 or 4 of leukocytopenia (%)		36 (88)	1 (3)	<0.0001
duration (days)	Median	2	0	<0.0001
	IQR	1-3	0-0	
Grade 3 or 4 of neutropenia (%)		31 (76)	1 (3)	<0.0001
duration (days)	Median	2	0	<0.0001
	IQR	1-3	0-0	
Grade 3 or 4 of febrile neutropenia (%)		4 (10)	0 (0)	0.051
duration (days)	Median	0	0	0.056
	IQR	0-0	0-0	
Subcutaneous injection of G-CSF (times)	Median	6	1	<0.0001
	IQR	5-6	1-1	
Hospitalization (days)	Median	12	6	<0.0001
	IQR	11-13	5-8	

IQR, interquartile range

Discussion

We examined the effects of a single fixed dose of pegfilgrastim and the multiple daily use of lenograstim, which were mainly administered to prevent FN due to cytotoxic chemotherapy.

First, we compared groups A and C (Table 5). The incidence of FN, grade 3 or 4 leukocytopenia and neutropenia, their duration, and the days of hospitalization were all significantly lower in group C than in group A. However, the possibility that this result reflected the difference in starting time for administering G-CSF cannot be ruled out, as lenograstim was started when Grade 3 neutropenia was observed in group A, while the administration of pegfilgrastim was started uniformly started after 24 h had passed since the chemotherapy finished in group C. Regarding the initiation of lenograstim administration, the median time since the chemotherapy was 8.0 days in group A.

We adopted different timings for the dosing of each drug as shown above because we considered adopting the same dosing schedules for different drugs to be meaningless for several reasons. First, the pharmacokinetics of these two drugs were quite different. When a single subcutaneous injection of 3.6 mg of pegfilgrastim was administered, the plasma Tmax was 109.8 h, the plasma half-life 29.3 h, and the plasma Cmax 96.8 ng/mL (unpublished data; Kyowa Hakko Kirin Co., Ltd., Inc., Tokyo, Japan). Thus, once pegfilgrastim is administered, the plasma concentration of filgrastim can be estimated to be 7.98 ng/mL at 10 days after the administration of DOC/CDGP using the above-mentioned data. Based on these data, we considered that single administration of pegfilgrastim at an early stage had a long-lasting effect for preventing severe neutropenia. In contrast, when a single subcutaneous injection of 40 μg of lenograstim was administered, the plasma half-life was 4.39 h, and the plasma Cmax was 0.478 ng/mL (unpublished data; Chugai Pharmaceutical Co., Ltd., Tokyo, Japan). Therefore, lenograstim requires daily administration. Furthermore, even if lenograstim is administered before neutropenia occurs, such administration is considered to be meaningless.

Changing the starting criteria for the administration of lenograstim to the occurrence of Grade 1 leukocytopenia or neutropenia is problematic because Grade 1 leukocytopenia or neutropenia is observed in some patients before the chemotherapy. We therefore decided to administer lenograstim to patients when Grade 2 leukocytopenia or neutropenia occurred in second and subsequent courses of DOC/CDGP before the introduction of pegfilgrastim (referred to as group B).

In group B, regarding the initiation of lenograstim administration, the median days since chemotherapy was 7.0 days. The timing of the initiation of lenograstim administration in group B was therefore relatively early compared to that in group A. Table 6 compares groups B and C. Compared to the multiple daily use of lenograstim,

the one-time administration of pegfilgrastim tended to reduce the occurrence rate of FN, significantly reduced the occurrence rate and duration of grade 3 or 4 leukocytopenia and neutropenia, and shortened the period of hospitalization. Furthermore, among the 29 courses in group A, 4 patients (14%) experienced FN, and among the 41 courses of group B, 4 patients (10%) experienced FN. No significant difference was shown between these two groups (p=0.601). This result suggested that the earlier administration of lenograstim did not carry an advantage.

In terms of the cost-effectiveness, pegfilgrastim tended to incur fewer medical costs, due to the single-course nature of DOC/CDGP therapy; indeed, the total costs of blood test, imaging test, oral medicine and injection for one course of treatment with pegfilgrastim and lenograstim were about 270,000 yen and about 310,000 yen on average, respectively.

As previously mentioned, the length of hospitalization was an average of 6 days when pegfilgrastim was administered and an average of 13 days when lenograstim was administered. Therefore, pegfilgrastim seemed to offer more efficient treatment. Furthermore, when a patient develops severe neutropenia or FN, additional medical resources are consumed, and the length of hospitalization is extended, resulting in ballooning medical care costs. For these reasons, the administration of pegfilgrastim seems advantageous from a financial perspective in light of its extremely high effectiveness in preventing neutropenia and presumed effectiveness in preventing FN.

Although this study had a small sample size and was a retrospective study, we showed that, compared with the multiple daily use of lenograstim, the one-time administration of pegfilgrastim after 24 h have passed since taxane-based chemotherapy reduced the occurrence rate of severe neutropenia to 1/20 and almost halved the length of hospitalization. Therefore, we concluded that the administration of pegfilgrastim at the above-mentioned dosage can help improve the quality of life for patients.

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