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Efficacy of pegfilgrastim administration in patients with esophageal cancer treated with docetaxel, cisplatin, and 5-fluorouracil

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Chemotherapy is among the standard treatments for esophageal cancer. The docetaxel, 5-fluorouracil, and cisplatin (DCF) protocol yields a better response rate than 5-fluorouracil plus cisplatin. However, the incidence of side effects, such as febrile neutropenia and hematologic toxicity, is also significantly high with the DCF protocol. The granulocyte colony-stimulating factor and pegfilgrastim are prophylactically administered to prevent febrile neutropenia. This retrospective study evaluated the efficacy and safety of pegfilgrastim in patients receiving DCF therapy.

Of the 65 patients who were administered DCF therapy in our hospital from 2011 through 2016, 21 received pegfilgrastim 24 hours or more after the end of chemotherapy. The protocol comprised 70 mg/m^2 each of docetaxel and cisplatin on day 1 and 700 mg/m^2 5-fluorouracil on days 1 to 5 *via* intravenous injection in a 3-week cycle. The primary endpoint was the rate of grade 3–4 neutropenia and febrile neutropenia. The mean patient age was 66.4 years. The incidence of grade 3 and 4 neutropenia was 14.2 % and 11.4 %, respectively, in the pegfilgrastim group and 31.9 % and 37.8 %, respectively, in the non-pegfilgrastim group. The incidence of febrile neutropenia in the pegfilgrastim group and non-pegfilgrastim group was 11.4 % and 40.3 %, respectively. Statistical analysis showed that the incidence of neutropenia and febrile neutropenia was significantly different ($p<0.05$) between the two groups. Pegfilgrastim prevents severe neutropenia and febrile neutropenia in patients with esophageal cancer who are treated according to the DCF protocol.

1. Introduction

Esophageal carcinoma is the eighth most common cancer in the world. More than 450000 patients are affected worldwide, and the incidence is rapidly increasing (Zhang 2013; Pennathur et al. 2013). Esophageal cancer is considered a serious malignancy characterized by early lymph node and distant metastases. Chemotherapy is among the standard treatments for patients with stage II or higher esophageal cancer (Guidelines for Esophageal Cancer Diagnosis and Treatment 2012). Currently, the standard chemotherapeutic regimen is 5-fluorouracil (5-FU) plus cisplatin (CDDP) (FP protocol). However, the response rate is only approximately 35%, and sufficient therapeutic effect has not been obtained (Iizuka et al 1992).

Recent studies showed that the combination of the DCF protocol with docetaxel (DTX) and the FP protocol yields a response rate of 67%–81%, which is higher than that of the FP protocol alone. As such, it is expected to be introduced as a new treatment regimen. Prolonged survival benefit has also been reported (Osaka et al. 2011; Noronha et al. 2014); as such, a more potent effect compared with the FP protocol is expected. However, the DCF protocol is associated with a high risk of severe hematologic toxicity and severe and fatal infection. The incidence of febrile neutropenia (FN) in DCF therapy is high at approximately 40 %. Severe hematologic toxicity has also been reported in DCF for gastric cancer. The incidence of grade 3 and 4 leukopenia is at 82 % and 65%, respectively, while that of grade 3 and 4 febrile neutropenia (FN) is at 29 % (Van Cutsem et al. 2006).

The onset of serious and fatal infections may result in delayed treatment and reduced treatment intensity. The American Society of Clinical Oncology Clinical Practice Guideline recommends the use of granulocyte colony-stimulating factor (G-CSF) (Smith et al. 2015). G-CSF is administered as a primary prophylaxis to prevent FN when chemotherapy regimens with an FN incidence rate of 20% or more is administered (Japan Society of Clinical Oncology: G-CSF proper use guidelines 2013).

Pegfilgrastim, which was released in Japan in 2014, is a sustained type of G-CSF formulated with pegylated filgrastim. It has the same effect as filgrastim and is used worldwide to suppress the onset of FN (Pegfilgrastim interview form 2016). The prophylactic effects of pegfilgrastim on neutropenia and FN have been reported in blood tumors and breast cancer, among others. However, reports showing the preventive effect of pegfilgrastim on the onset of hematological toxicity in patients who undergo DCF chemotherapy for esophageal cancer are limited (Linot et al. 2014; Vermorken et al. 2007).

Here, we investigated the effects, safety, and efficacy of daily G-CSF and pegfilgrastim administration in patients with esophageal cancer who underwent DCF chemotherapy. We also conducted a retrospective study to analyze the efficacy of daily G-CSF in preventing FN.

2. Investigations and results

2.1. Patient characteristics

This study included 65 patients (51 men and 14 women). The patients' characteristics are shown in Table 1. The average age and body surface area was 66.4±7.9 years (mean±standard deviation (SD)) and 1.59±0.16 m^2, respectively, and all of the patients were PS < 3. No patient was Stage I, while 10, 28, and 27 patients were stage II, III, and IV, respectively. The total number of patients with stage III and IV accounted for 84.6% of the overall patient population.

Table1: Patient characteristics (n = 65)

Clinical characteristics	Whole population n = 65	Administration of pegfilgrastim n = 21	No administration of pegfilgrastim n = 44
Gender male	51 (78.4)	17 (80.9)	34 (77.3)
female	14 (21.5)	4 (19.0)	10 (22.7)
Age (years)	66.4±7.9 [45-82]	67.8±7.0	65.6±8.3
BSA (m^2)	1.59±0.16	1.58±0.17	1.59±0.16
PS 0	47 (72.3)	16 (76.2)	31 (70.5)
1	10 (15.4)	4 (19.0)	6 (13.6)
2	8 (12.3)	1 (4.8)	7 (15.9)
3	0 (0.0)	0 (0.0)	0 (0.0)
4	0 (0.0)	0 (0.0)	0 (0.0)
Stage T 0	0 (0.0)	0 (0.0)	0 (0.0)
1	2 (3.1)	1 (4.8)	1 (2.3)
2	7 (10.8)	0 (0.0)	7 (15.9)
3	34 (52.3)	13 (61.9)	21 (47.7)
4	19 (29.2)	6 (28.5)	14 (31.8)
no classified	3 (4.6)	1 (4.8)	1 (2.3)
Stage N 0	8 (12.3)	2 (9.5)	6 (13.6)
1	8 (12.3)	3 (14.3)	5 (11.3)
2	31 (47.7)	10 (47.6)	21 (47.7)
3	10 (15.4)	2 (9.5)	8 (18.2)
4	6 (9.2)	3 (14.3)	3 (6.8)
no classified	2 (3.1)	1 (4.8)	1 (2.3)
Stage M 0	53 (81.5)	17 (81.0)	36 (81.8)
1	8 (12.3)	2 (9.5)	6 (13.6)
no classified	4 (6.2)	2 (9.5)	2 (4.5)

Data are shown as number of patients (percentage), number [range], or mean±SD.
Abbreviations: BSA, body surface area; PS, performance status

Table 2 shows the frequency of chemotherapy. The mean (±SD) number of cycles administered was 2.72 (±1.89). A total of 51 (78.5%) patients received two or more cycles of chemotherapy. Twenty-one patients received pegfilgrastim, while 44 patients were not treated. Chemotherapy comprised 1 to 9 cycles and 1 to 7 cycles in the pegfilgrastim and non-pegfilgrastim groups, respectively. No patient duplication occurred across the two groups. A single injection of 3.6 mg pegfilgrastim was administered between days 2 and 3 after completion of chemotherapy.

Table 2: Number of chemotherapy drugs administered

	Whole population n = 65	Administration of pegfilgrastim n = 21	No administration of pegfilgrastim n = 44
Number of patients who completed, n (%)			
1 cycle	14 (21.5)	3 (14.3)	12 (27.3)
2 cycles	31 (47.7)	13 (61.9)	18 (40.9)
>2 cycles	20 (30.8)	5 (23.8)	14 (31.8)
Number of cycles received	2.72 ± 1.89	2.67 ± 1.91	2.31 ± 1.27
Mean ± SD	2 (1; 9)	2 (1; 9)	2 (1;7)
Median (min; max)			

Data are shown as number of patients (percentage), mean±SD, or median(min; max).

2.2. Hematotoxicity and FN

Table 3 shows the hematologic toxicity and the frequency of FN divided in the pegfilgrastim and non-pegfilgrastim groups. The total number of counts in 1 to 9 cycles was 35 in the pegfilgrastim group, and the total number of counts in 1 to 7 cycles was 113 in the non-pegfilgrastim group.

The incidence of cases with grade 3 and 4 neutropenia was 14.2 % (n=5) and 11.4 % (n=4), respectively, in the pegfilgrastim group, while it was 31.9 % (n=38) and 37.8 % (n=45) in the non-pegfilgrastim group (Table 3). The incidence of grade ≥ 3 anemia and thrombocytopenia was 8.6 % (n=3) and 2.9% (n=1) in the pegfilgrastim group and was 10.9 % (n=13) 2.5% (n=3) in the non-pegfilgrastim group, respectively.

Table 3: Number of patients with leukopenia, neutropenia, and febrile neutropenia; length of hospitalization; and number of days of delay in chemotherapy administration in patients with and without pegfilgrastim administration

	Administration of pegfilgrastim n = 35	No administration of pegfilgrastim n = 113	*P* value
Leukopenia grade3	6 (17.1)	37 (31.1)	$P = 0.077$
grade4	4 (11.4)	19 (16.0)	$P = 0.446$
Neutropenia grade3	5 (14.2)	38 (31.9)	$P < 0.05$
grade4	4 (11.4)	45 (37.8)	$P < 0.05$
Number of febrile neutropenia	4 (11.4)	48 (40.3)	$P < 0.05$
Hospitalization	12.6±4.6	20.6±18.4	$P < 0.05$
Delay days	4.1±5.0	10.7±13.5	$P < 0.05$

Data are shown as number of patients (percentage), or mean±SD.
We used the non-parametric Mann-Whitney U test, and a p-value of <0.05 was considered statistically significant.

Blood transfusion was needed in 3 patients. The incidence of FN was 11.4 % (n=4) in the pegfilgrastim group and 40.3 % (n=48) in the non-pegfilgrastim group (Table 3). The mean delay was 4.1±5.0 days and 10.7±13.5 days, in the pegfilgrastim and non-pegfilgrastim groups, respectively (Table 3). The main reasons for the delay were prolonged FN, neutropenia, anorexia and fatigue.

2.3. Effects and side effects of pegfilgrastim

Of the 35 patients who received pegfilgrastim in all 1 to 9 cycles, 22 developed symptoms suspected as side effects caused by pegfilgrastim (Table 4). The main side effects were fever and increased

Table 4: Number of adverse reactions (fever, increasing LDH, pain) in patients with each course of chemotherapy (1 to 9 courses; n= 35 patients)

Cycle no.	1 n = 8	2 n = 15	3 n = 3	4 n = 3	5 n = 2	6 n = 1	7 n = 1	8 n = 1	9 n = 1
Fever	6	4	0	0	0	1	0	0	0
Increasing of LDH	3	7	0	0	0	1	0	0	0
Back pain, muscle pain, Bone pain	0	0	0	0	0	0	0	0	0

Abbreviations: LDH, lactate dehydrogenase

levels of lactate dehydrogenase (LDH). No patient developed back pain. In the pegfilgrastim group, the next course of chemotherapy was reduced in 5 patients due to FN or neutropenia (n=1) and decreased renal function (n=4). In the non-pegfilgrastim group, the next dose of chemotherapy was reduced in 31 patients due to FN or neutropenia (n=23), decreased renal function (n=10), and both FN and decreased renal function (n=2). The average number of days for pegfilgrastim administration was 7.09±0.38 days. We also planned to administer pegfilgrastim prophylaxis after completion of chemotherapy, but 3 patients developed bone marrow suppression on the day of administration and thus pegfilgrastim could not be administered.

3. Discussion

Myelosuppression is the most frequent side effect of chemotherapy. In particular, FN can be fatal; thus, early identification of patients at risk of FN and timely treatment are extremely important (Crawford et al. 2014). Preventing chemotherapy-induced FN can help to avoid delays in treatment and decrease the chemotherapy dose intensity. When a chemotherapeutic with an FN incidence rate of 20 % or more is administered, administration of G-CSF as primary prophylaxis is recommended (Japan Society of Clinical Oncology: G-CSF proper use guidelines 2013). Pegfilgrastim is used worldwide to suppress the onset of FN (Linot et al. 2014). In Japan, pegfilgrastim was released in 2014, and its efficacy in preventing neutropenia and FN have already been reported. However, reports on its efficacy for preventing hematotoxicity in patients who underwent DCF therapy for esophageal cancer are limited. In this retrospective analysis, the use of prophylactic pegfilgrastim was associated with a decreased risk of neutropenia and FN, and that caused a reduction in hospitalization period.

The primary side effects of pegfilgrastim include elevated LDH, fever, back pain, joint pain, and bone pain (Pegfilgrastim interview form 2016). However, back pain, bone pain, and joint pain were not observed in our study. Patients undergoing chemotherapy are receiving dexamethasone as an antiemetic from days 1 to 5. This suggests that the pain may be masked by the anti-inflammatory analgesic effect of the steroid.

A benefit of pegfilgrastim was even noted in terms of hospitalization period and delays in chemotherapy treatment. Pegfilgrastim administration leads to shortened hospitalization period and prevented treatment delays. Approximately half of the general hospitals in Japan use the Diagnosis Procedure Combination medical system, and the insurance generally falters when the hospitalization period is prolonged. In our study, the duration of hospitalization among patients with esophageal cancer was approximately 6 days shorter in those who were treated with pegfilgrastim than that in those who were not. Chemotherapy for esophageal cancer costs 25,000 yen per day (DPC Electronic Score Table Diagnostic Group Traits of Classification Schedule 2016), which equals 150,000 yen per 6 days. Eventually, medical expenses could be reduced even if pegfilgrastim is expensive at 106,660 yen (Ministry of Health Labour Welfare: drug price list items and information on genetic drugs 2017).

In the United States, using pegfilgrastim rather than daily filgrastim for patients with cancer helped to limit hospitalization costs in relation to neutropenia (Naeim et al. 2013). Furthermore, the use of pegfilgrastim can reduce the consumption of broad-spectrum antibiotics and may therefore suppress the development of antibiotic-resistant bacteria. This indicates the high cost efficiency of pegfilgrastim. Collectively, these findings indicate the possibility that pegfilgrastim can not only prevent infection and delays in chemotherapy administration, but also limit treatment costs.

However, because DCF has been continued for 5 days, leukocytes and neutrophils have already decreased before 24 h after the end of chemotherapy, which is when pegfilgrastim can be administered thus it is possible that it cannot be administered. In fact, in our study, there were also 3 patients who did not receive pegfilgrastim as scheduled.

Although this study included a small number of patients only and had a retrospective design, our results clearly indicate that prophylactic administration of pegfilgrastim significantly suppressed the onset of neutropenia and FN. It is necessary to investigate further when we should administer pegfilgrastim in such cases when chemotherapy is performed for long hours such as with the DCF protocol.

4. Experimental

4.1. Patients

In this study, we examined 68 patients with esophageal cancer treated with DCF chemotherapy. Three patients were excluded from the analysis because treatment was interrupted for personal reasons (n=1) and because of the development of renal dysfunction that is a contraindication for CDDP injection (n=2). The eligibility criteria were age between 20 and 85 years; Eastern Cooperative Oncology Group (ECOG) performance status (PS) of < 3; and adequate organ function (white blood cell (WBC) count ≥ 3000/mm^3; neutrophil count ≥ 1500/mm^3; hemoglobin ≥ 10 g/dl, platelet count ≥ 100,000/mm^3; total bilirubin ≤ 2.0 mg/dl; serum creatinine ≤ 1.5 × the institutional upper limit of normal (ULN), and serum aspartate aminotransferase and alanine aminotransferase ≤ 2.5 × ULN). A total of 65 patients met the eligibility criteria. Complete blood count and biochemistry tests were performed at the beginning of the chemotherapy regimen, or as necessary. The chemotherapy regimen consisted of intravenous administration of 70 mg/m^2 each of DTX and CDDP on day 1 and 700 mg/m^2 of 5-FU from days 1 to 5.

Chemotherapy was repeated every 21 days. Neoadjuvant chemotherapy regimen comprised 2 or 3 cycles. Meanwhile, chemotherapy was repeated until disease progression or unacceptable toxicity in cases of unresectable advanced cancer. Pegfilgrastim (3.6 mg) was injected after 24 hours or more after the end of chemotherapy. This study included both patients with unresectable advanced cancer and those who underwent preoperative chemotherapy. DCF therapy was performed as a standard treatment for patients with unresectable advanced esophageal cancer (Yamasaki et al 2011). The non-pegfilgrastim group received a daily G-CSF when FN or neutropenia developed, or when such symptoms were predicted to occur. G-CSF was used until WBC and neutrophil counts recovered to normal state.

4.2. Survey and evaluation method

This was a retrospective and observational study. We reviewed the medical and medication records of patients admitted between January 2011 and April 2016 at the Osaka General Medical Center, Osaka, Japan. We retrieved the following data from the medical records of the patients: age, sex, medication, treatment history, clinical laboratory data, and the side effects of medication. We used the Common Terminology Criteria for Adverse Events (ver. 4.0) to evaluate the degree of leukopenia, neutropenia, anemia, and thrombocytopenia. The 7th edition of the Union for International Cancer Control (UICC) TNM classification of malignant tumors was used for staging (Sobin and Gospodarowicz 2009). All patients provided written informed consent prior to treatment.

4.3. Statistical analysis

Statistical analysis was performed using the EZR (Easy R) software. We used the non-parametric Mann-Whitney U test, and a *P*-value of <0.05 was considered statistically significant. The primary endpoint was the rate of grade 3–4 leukopenia, neutropenia, and FN, and the secondary endpoint was hospitalization and cycle delay.

4.4. Ethical considerations

This study was approved by an ethics committee of Osaka General Medical Center (Approval number: 28-S0706). This research was conducted in accordance with the

Helsinki Declaration, and we processed the data so that individual patients could not be identified and privacy was ensured.

Conflicts of interest: The authors declare that they have no competing interests.

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