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Primary Prophylaxis of Febrile Neutropenia With Pegfilgrastim in Small-cell Lung Cancer Patients Receiving Amrubicin as Second-line Therapy

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Abstract. *Background/Aim: We evaluated the efficacy of primary prophylaxis with pegfilgrastim (PEG) for febrile neutropenia (FN) in small cell lung cancer (SCLC) patients receiving amrubicin (AMR). Patients and Methods: A retrospective cohort study was conducted in patients with SCLC receiving AMR as second-line therapy. Results: A total of 33 patients were treated with AMR (no PEG group), while 13 patients were treated with AMR plus prophylactic administration of PEG (PEG group). The severity of neutropenia was significantly reduced in the PEG group compared to the no PEG group (p=0.02). The incidence of FN in the no PEG and PEG groups was 27.3% and 7.7%, respectively. The time to development of FN tended to be longer in the PEG group compared to the no PEG group (p=0.132). Conclusion: Primary prophylaxis with PEG may be beneficial in reducing the risk of FN in patients with SCLC receiving AMR.*

Lung cancer is the most common cause of cancer-related death, and small-cell lung cancer (SCLC) makes up approximately 15% of lung cancers (1, 2). Amrubicin (AMR), a third-generation synthetic anthracycline with potent topoisomerase II inhibitory properties, shows promise as a second-line treatment in patients with SCLC (3) and has been recommended as a second-line treatment for patients with SCLC in Japanese Lung Cancer Society guidelines.

Pawel *et al*. reported that the efficacy and safety profiles of AMR and topotecan hydrochloride (TOPO) as second-line treatment for SCLC are comparable, though febrile neutropenia (FN) occurred more frequently with AMR than TOPO (10.0% for AMR *vs*. 3.0% for TOPO, p=0.003) (4). Moreover, several Japanese studies of AMR in patients with recurrent SCLC who had previously been treated with chemotherapy reported a high incidence of FN, which ranged from 13.8%-35%, a higher frequency than that reported by Pawel *et al*. (4-7).

Neutropenia is a common adverse event (AE) associated with the administration of anticancer agents that increases the risk of developing FN, which sometimes leads to sepsis and death (8, 9). Granulocyte-colony-stimulating factors (G-CSFs), which stimulate production of mature functional neutrophils, have been shown to reduce the incidence of FN when used as prophylaxis following chemotherapy (10). Guidelines recommend primary prophylaxis with G-CSFs for patients above a FN risk threshold of 20% or patients with risk factors that may increase the overall risk of FN when using a chemotherapy regimen associated with FN of 10-20% (11, 12). However, AMR regimens are not included where primary prophylaxis with G-CSFs is usually employed.

Pegylated filgrastim, or pegfilgrastim (PEG), is a recombinant protein of G-CSF. A single dose of PEG administered once per chemotherapy cycle is equivalent to multiple daily injections of filgrastim for neutrophil support during myelosuppressive chemotherapy (13). PEG has been shown to prevent FN in patients with solid tumors (14-16).

The aim of this retrospective study was to investigate the incidence of FN in patients with SCLC who received AMR

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Key Words: Pegfilgrastim, granulocyte colony-stimulating factor, febrile neutropenia, amrubicin, small-cell lung cancer.

Table I. *Patient characteristics in patients with and without prophylaxis with pegfilgrastim.*

	No PEG group (N=33)	PEG group (N=13)
Gender (male/female), n (%)	27 (81.8)/6 (18.2)	10 (76.9)/3 (23.1)
Age (y)	71 (66-78)	69 (68-72)
Height (cm)	162.3 (156.5-166.3)	162.2 (158.0-165.7)
Body weight (kg)	61.5 (51.2-66.6)	51.4 (46.3-64.9)
Laboratory data		
Serum creatinine (μmol/l)	76.9 (60.9-102.5)	70.7 (58.3-84.0)
Neutrophil count ($\times10^9$/l)	3.9 (3.4-5.1)	4.9 (3.5-5.5)
White blood cells ($\times10^9$/l)	5.6 (4.8-7.4)	5.8 (5.5-8.4)
Hemoglobin (g/l)	110 (99-128)	113 (104-118)
Platelets ($\times10^9$/l)	217 (163-227)	222 (151-242)
Prior chemotherapy, n (%)		
CBDCA+ETP	23 (69.7)	8 (61.5)
CBDCA+CPT-11	1 (3.0)	0
CDDP+ETP	4 (12.1)	3 (23.1)
CDDP+CPT-11	5 (15.2)	1 (7.7)
ETP	0	1 (7.7)
Previous radiation therapy, n (%)	14 (42.4)	5 (38.5)
Episode of FN at first-line chemotherapy, n (%)	7 (21.2)	3 (23.1)
Initial dose of AMR(mg/m^2)	37.7 (35.3-38.9)	38.1 (36.2-39.4)

Data indicate median, 25-75th percentiles unless otherwise indicated. CBDCA: Carboplatin; PEG: pegfilgrastim; FN: febrile neutropenia; AMR: amrubicin; CDDP: cisplatin; ETP: etoposide; CPT-11: irinotecan.

Table II. *Comparison of the hematological toxicity between patients with and without primary prophylaxis with pegfilgrastim (PEG).*

	No PEG group (N=33)	PEG group (N=13)	*p*-Value
Neutropenia			0.02
None	1 (3.0%)	5 (38.5%)	
Grade 1	0	0	
Grade 2	8 (24.2%)	2 (15.4%)	
Grade 3	6 (18.2%)	2 (15.4%)	
Grade 4	18 (54.5%)	4 (30.8%)	
Leukopenia			0.002
None	0	4 (30.8%)	
Grade 1	0	2 (15.4%)	
Grade 2	12 (36.4%)	2 (15.4%)	
Grade 3	12 (36.4%)	3 (23.1%)	
Grade 4	9 (27.3%)	2 (15.4%)	
Anemia			0.921
None	0	0	
Grade 1	12 (36.4%)	5 (38.5%)	
Grade 2	11 (33.3%)	5 (38.5%)	
Grade 3	10 (30.3%)	3 (23.1%)	
Grade 4	0	0	
Thrombocytopenia			0.177
None	4 (12.1%)	0	
Grade 1	17 (51.5%)	8 (61.5%)	
Grade 2	6 (18.2%)	1 (7.7%)	
Grade 3	6 (18.2%)	2 (15.4%)	
Grade 4	0	2 (15.4%)	

Fisher's exact test was used to analyze the data.

as second-line therapy, and to evaluate the effect of PEG administration for FN prophylaxis.

Patients and Methods

Study design and patients. We conducted a single-center, retrospective cohort study at Gifu University Hospital. Study participants were patients with SCLC receiving AMR as a second-line therapy with or without prophylactic administration of PEG in the Department of Respiratory Medicine between January 2013 and May 2018. The incidence of FN, hematological toxicity, number of treatment cycles of AMR therapy and progression-free survival (PFS) were compared between patients receiving and not receiving prophylactic administration of PEG. Data were collected from electronic medical records in the central database of our hospital. Patient characteristics are shown in Table I.

AMR therapy. AMR was dissolved in 50 ml normal saline and administered at a dose of 40 mg/m^2 for 3 days, every 3 weeks. For antiemesis, intravenous granisetron (3 mg) and dexamethasone (6.6 mg) were administered before chemotherapy, and oral dexamethasone (4 mg) was administered on days 4 and 5. Because 6 mg PEG had not yet been approved in Japan, patients on PEG received a subcutaneous injection of 3.6 mg on day 5. If grade 4 leukopenia, grade 4 neutropenia, or FN was observed in No PEG group cases, granulocyte colony-stimulating factor (G-CSF) was administered.

Definition of study outcome and assessment of AEs. The primary study outcome was time to first FN from the start of second line treatment. The severity of FN and hematological toxicities, including leukopenia, neutropenia, anemia, and thrombocytopenia, was graded according to the Common Terminology Criteria for Adverse Events (CTCAE, National Cancer Institute, MD, USA) version 4.0 (U.S. Department of Health and Human Services, National Institutes of Health National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0, 2009) (17). PFS was defined as the time from the start of second-line therapy to the first tumor progression or death.

Statistical analysis. We analyzed the data with IBM SPSS version 22 (IBM Japan Ltd., Tokyo, Japan) and R software version 3.6.1. A two-sided p-value <0.05 was considered statistically significant. Patients' characteristics are expressed as the median with 25th and 75th percentiles for continuous variables, and as frequencies and percentages for categorical variables. Fisher's exact test was used to compare the severity of hematological toxicity between PEG and control groups. The Kaplan–Meier method was used to estimate cumulative FN and PFS rates, and differences between groups were compared using the log-rank test. We calculated the hazard ratios (HR) for FN and PFS using a multivariable Cox proportional hazards model. To avoid overfitting, we restricted covariates to two variables, and adjusted for age and episodes of FN by previous cancer chemotherapy as confounders. Comparison of the median number of treatment cycles was evaluated by the Mann-Whitney *U*-test.

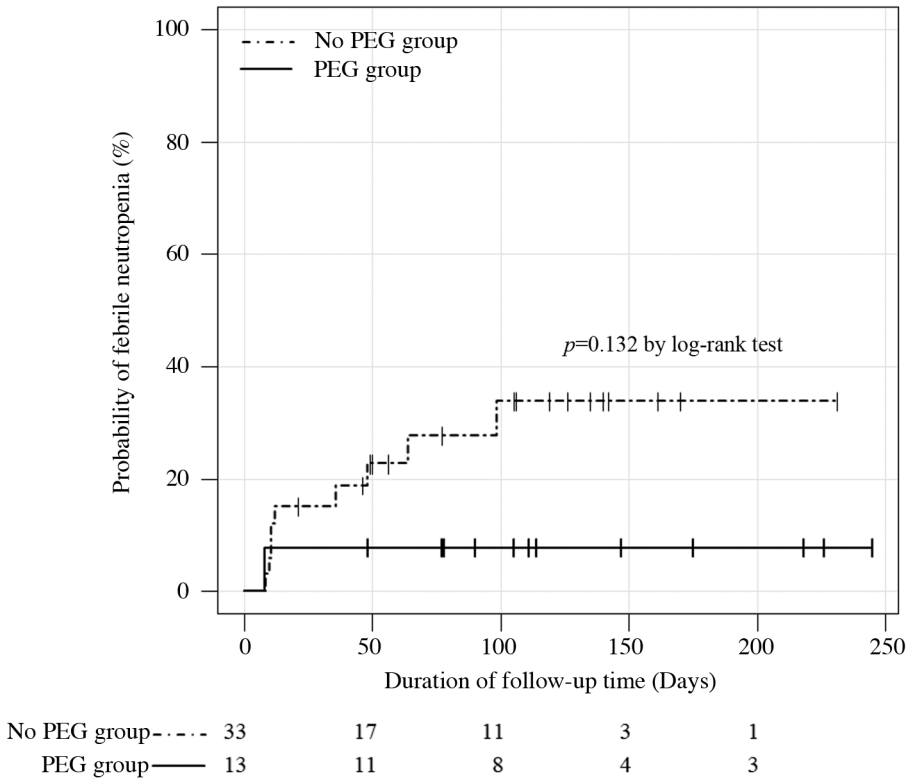

Figure 1. *Kaplan–Meier curves of febrile neutropenia in patients with small cell lung cancer who received amrubicin chemotherapy in the no pegfilgrastim (PEG) group and the PEG group.*

Ethics statement. The present study was conducted according to the guidelines for human studies of the ethics committee of Gifu University Graduate School of Medicine and the Government of Japan, and was approved by the University's institutional review board (approval no. 2019-071). In view of the retrospective nature of the study, informed consent from the subjects was not mandated. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Results

Patients. A total of 46 cases of SCLC receiving AMR as a second-line therapy were studied. Among them, 33 were treated with AMR without prophylactic administration of PEG from January 2013 to September 2016 (no PEG group). The other 13 patients were treated with AMR plus prophylactic administration of PEG from October 2016 to May 2018 (PEG group).

The proportions of patients who had received prior carboplatin + etoposide, carboplatin + irinotecan, cisplatin + etoposide, cisplatin + irinotecan and etoposide were 69.7%, 3.0%, 12.1%, 15.2% and 0% in the no PEG group and 61.5%, 0%, 23.1%, 7.7% and 7.7% in the PEG group, respectively. The rates of previous radiation therapy and episodes of FN at first-line chemotherapy were 42.4% and 21.2% in the no PEG group and 38.5% and 23.1% in the PEG group, respectively. The initial dose of AMR was 37.7 mg/m^2 [25-75th percentiles (IQR)=35.3-38.9] in the no PEG group and 38.1 mg/m^2 (IQR 36.2-39.4) in the PEG group (Table I).

Incidence of hematological toxicity and febrile neutropenia. The severity of neutropenia and leukopenia was significantly reduced in the PEG group compared to the no PEG group (p=0.02 for neutropenia, p=0.002 for leukopenia, Table II). There were no significant differences in the severity of anemia and thrombocytopenia between the two groups (Table II).

The incidence of FN in the no PEG and PEG groups was 27.3% (9/33) and 7.7% (1/13), respectively. As shown in Figure 1, the time to development of FN was longer in the PEG group than in the no PEG group, although not to a statistically significant degree (p=0.132 by log-rank test). In Cox proportional hazard analysis with adjustment for age and episodes of FN in first-line chemotherapy, prophylaxis with PEG tended to reduce the risk of FN (HR=0.25, 95%CI=0.03-2.02, p=0.195, Table III).

Comparison of the treatment cycle and PFS between patients without and with primary prophylaxis with PEG. The median number of treatment cycles tended to increase in the PEG group than in the control group [4.6 (IQR=1-9) for the PEG group *vs*. 3.1 (IQR=1-8) for the no PEG group, p=0.066]. Median PFS was significantly longer in the PEG group than in the no PEG group [164 days (95%CI=113.0-215.0) *vs*. 83 days (95%CI=45.6-120.4), HR=0.32 (95%CI=0.14-0.73), p=0.007 by the Cox proportional hazards model adjusted for age and the presence or absence of episodes of FN at first-line chemotherapy, p=0.015 by the log-rank test] (Figure 2).

Table III. *Multivariable Cox proportional hazard analysis associated with febrile neutropenia (FN) in patients with small cell lung cancer receiving amrubicin as second-line therapy.*

Factors	HR	95% CI	*p*-Value
Prophylactic use of PEG	0.25	0.03-2.02	0.195
Age	1.05	0.97-1.14	0.212
Episode of FN at first-line chemotherapy	5.53	1.53-19.92	0.009

Hazard ratio (HR) and 95% confidence intervals (CI) are indicated. PEG: Pegfilgrastim.

Discussion

In this retrospective cohort study, the incidence of FN was 27.3% in the no PEG group, which is consistent with previous Japanese clinical trials: 13.8% reported by Inoue *et al*., 26.8% reported by Murakami *et al*., and 35% reported by Asao *et al*. (5-7). The rate was 7.7% in patients receiving prophylactic administration of PEG, with a longer time to onset. Cox proportional hazard analysis adjusted for age and the presence or absence of an episode of FN in first-line chemotherapy also showed that prophylaxis with PEG also tended to reduce the risk of FN. On the other hand, the severity of neutropenia (p=0.02) and leukopenia (p=0.002) was significantly reduced in the PEG group compared to the no PEG group. Therefore, the reduction in the severity of neutropenia and leukopenia by primary prophylaxis with PEG may have led to a low incidence of FN. Current guidelines from the United States and Europe recommend the use of primary prophylaxis with G-CSFs when the risk of FN is >20% (12, 13), and it may be recommended in patients with SCLC receiving AMR therapy.

Because 6.0 mg PEG has not yet been approved in Japan, PEG was administered at a dose of 3.6 mg in this study. Masuda *et al*. demonstrated in a randomized controlled trial of dose response of PEG in Japanese breast cancer patients receiving docetaxel, doxorubicin, and cyclophosphamide therapy that the durations of grade 4 neutropenia in the first cycle were 2.2±0.9 days, 1.5±0.9 days, and 1.4±0.7 days with PEG doses of 1.8, 3.6, and 6.0 mg, respectively (18). They concluded that a PEG dose of 3.6 mg may be safe and effective for Japanese patients.

Several Japanese studies have reported the efficacy of primary prophylaxis with 3.6 mg PEG in several cancer regimens. Kosaka *et al*. demonstrated in a phase III placebo-controlled, double-blind, randomized trial of the prophylactic use of 3.6 mg PEG that the incidence of FN in breast cancer patients receiving docetaxel/cyclophosphamide chemotherapy was significantly lower in the PEG group than in the placebo group (1.2 *vs*. 68.8%, p<0.001) (15). Second, Kasahara *et al*. reported in a single-arm, single-center, phase II study that the incidence of FN using administration of primary prophylaxis with 3.6 mg PEG was 5% in patients with non-small cell lung cancer (NSCLC) who received docetaxel and ramucirumab treatment (19). Finally, Ohkura *et al*. showed in a single-center retrospective analysis of patients with esophageal cancer treated with an initial docetaxel, 5-fluorouracil, and cisplatin regimen that patients who received primary prophylaxis with 3.6 mg PEG had a significantly lower incidence of FN than patients who did not (3.0% *vs*. 32.2%, p<0.001) (20). These results are consistent with our present results. To our knowledge, this is the first report to show the efficacy of primary prophylaxis with 3.6 mg PEG in patients with SCLC receiving AMR as second-line therapy.

The median number of treatment cycles tended to increase in the PEG group than in the no PEG group [4.6 (IQR=1-9) for PEG group *vs*. 3.1 (IQR=1-8) for the no PEG group, p=0.066], and median PFS was significantly prolonged in the PEG group compared to the no PEG group (5.5 months *vs*. 2.8 months, p<0.02). Inoue *et al*. demonstrated in a randomized phase II trial comparing AMR with TOPO in patients with SCLC previously treated with platinum-containing chemotherapy that the median number of treatment cycles and median PFS in the AMR arm were 3 (range=1-7 months) and 3.5 months, respectively (5). Moreover, primary prophylaxis of PEG has been reported to increase relative dose intensity (RDI) of neoadjuvant/adjuvant FEC-100 (fluorouracil, epirubicin and cyclophosphamide) for breast cancer and to maintain RDI of carboplatin plus docetaxel or paclitaxel for ovarian cancer (21, 22). Therefore, treatment continuation with primary prophylactic G-CSF support may have provided this improved efficacy in this study, but further large-scale studies are needed to elucidate them.

There were several limitations in the present study. First, this was a retrospective study, and potentially relevant confounding factors may have not been excluded. The PEG and no PEG groups in the study were not concurrent. Although standard therapy for SCLC did not change during the study periods, chronological bias is inevitable. Second, the sample size was very small, and we could not find a statistically significant difference in the incidence of FN. Additionally, data were obtained from a

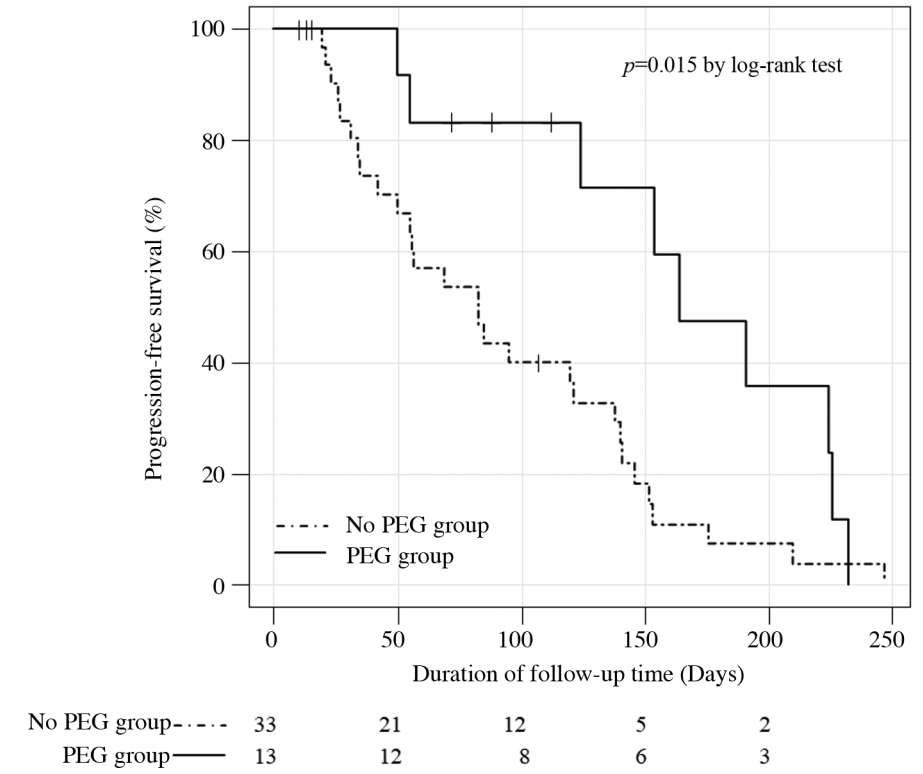

Figure 2. *Kaplan–Meier curves of progression-free survival in patients with small cell lung cancer who received amrubicin chemotherapy in the no pegfilgrastim (PEG) group and the PEG group.*

single institution. Therefore, a larger randomized control study is needed to confirm the prophylactic effect of PEG against FN in patients with SCLC receiving AMR as second-line therapy.

Conclusion

Our study revealed that AMR is associated with a high incidence of FN in the clinical practice setting. Additionally, primary prophylactic use of PEG may be appropriate, because it significantly reduces the severity of neutropenia and leukopenia induced by AMR administration and tends to reduce the risk of FN. Moreover, it may increase the number of treatment cycles and increase the therapeutic effect of AMR therapy.

Conflicts of Interest

The Authors declare that there are no conflicts of interest in relation to this study.

Authors' Contributions

Y.S. and H.I. conceived the study concepts. Y.S., H.I. M.K. and C.H. conducted the claim data analysis. H.I., Y.T. and T.I. performed the statistical analysis. J.E., K.Y., D.K., Y.S., T.G., C.S. and M.I. provided technical support. H.F. and R.K. contributed to the interpretation of data and assisted in the preparation of the manuscript. Y.S. and H.I. draft the initial manuscript. Y.O. and A.S. conducted the critical version of the manuscript. All Authors reviewed the manuscript.

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