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BRIEF REPORT

Clinical significance of primary prophylactic pegylated-granulocyte-colony stimulating factor after the administration of ramucirumab plus docetaxel in patients with previously treated non-small cell lung cancer

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Abstract

Whether primary prophylactic pegylated-granulocyte-colony stimulating factor (PEG-G-CSF) should be administered immediately after the initiation of ramucirumab plus docetaxel (DR) to prevent the occurrence of febrile neutropenia (FN) is unclear. Our retrospective study aimed to elucidate whether PEG-G-CSF could control the occurrence of FN as a result of DR in patients with previously treated non-small-cell lung cancer. Thirty-three patients with previously treated non-small-cell lung cancer who had received DR were eligible for our analysis. Of the 33 patients, 29 received prophylactic PEG-G-CSF immediately after DR, but none developed FN. However, FN was observed in 2 (50%) of the 4 patients that were not administered PEG-CSF. The overall response and disease control rates in the 29 patients with prophylactic PEG-GSF were 31% and 62%, respectively. The median progression-free and overall survival rates of the patients with and without prophylactic PEG-GSF were 177 and 163 days ($P = 0.20$), and 628 and 274 days ($P = 0.13$), respectively. Primary prophylactic PEG-G-CSF suppressed the occurrence of FN secondary to the administration of DR.

Introduction

Non-small cell lung cancer (NSCLC) is a severe disease associated with cancer death. Although docetaxel is the only accepted regimen after the failure of first-line chemotherapy for advanced NSCLC, docetaxel plus ramucirumab (DR) has been verified as a promising option for the treatment of patients with previously treated advanced NSCLC.[1,2] However, during randomized phase III and Japanese phase II studies, febrile neutropenia (FN) was reported in 13.3% and 34.2% of patients administered this drug regimen, respectively.[1,2] Little information is available about the causes of the increased risk of FN and the link to this regimen. Primary prophylactic granulocyte-colony stimulating factor (G-CSF) is recommended when FN occurs more frequently than in 20% of patients.[3] Recently, Hata *et al.* reported that when primary prophylactic pegylated-G-CSF (PEG-G-CSF) was initiated in 52 patients with previously treated NSCLC who had received DR, none experienced FN, whereas FN occurred in 3 (33%) of the 9 patients who were not administered prophylactic PEG-G-CSF.[4] It is unclear whether PEG-G-CSF should be administered immediately after the initiation of DR, but it may be able to control the occurrence of FN. We investigated the clinical significance of primary prophylactic PEG-G-CSF in patients with previously treated NSCLC administered DR.

Methods

The inclusion criteria were: pathologically proven NSCLC, an Eastern Cooperative Oncology Group performance status (PS) score of 0–2, age > 20 years, a history of receiving first-line chemotherapy, a history of receiving DR, and the availability of efficacy data of DR. This study was approved by the institutional ethics committee of our institution. The acute toxicities were graded in accordance with the Common Terminology Criteria for Adverse Events version 4.0. Tumor

responses were evaluated in accordance with Response Evaluation Criteria in Solid Tumors version 1.1.[5] Docetaxel 60 mg/m^2 and ramucirumab 10 mg/kg were intravenously administered every three weeks, and primary prophylactic PEG-G-CSF was administered on day two after the initiation of DR. Any adverse events in the first course of DR were evaluated. The overall response rate (ORR) was defined as the best response recorded from the initiation of treatment until disease progression or recurrence. Overall survival (OS) was determined as the interval from the first day of chemotherapy to death from any cause. Progression-free survival (PFS) was defined as the interval from the first day of chemotherapy to the first sign of disease progression or death. Statistical significance was indicated by $P < 0.05$. Statistical analyses were performed using Student's t and χ^2 tests for continuous and categorical variables, respectively. The Kaplan–Meier method was used to estimate survival as a function of time, and survival differences were analyzed by log-rank tests.

Results

Between October 2016 and June 2018, the records of 33 patients with previously treated NSCLC who had received DR were retrospectively reviewed at our institution and determined as eligible for our analysis. The current study includes patient information from our previous study.[6] Of the 33 patients, 29 had received primary prophylactic PEG-G-CSF immediately after DR administration, but none developed FN; however, FN was observed in 2 (50%) of the 4 patients that were not administered primary prophylactic PEG-G-CSF, on days 8 and 10, respectively, during the first course of DR. Although these patients required hospitalization and antibiotic therapy, their clinical course was good. However, their dosage of docetaxel in the next course of DR was reduced from 60 to 48 mg/m^2 and prophylaxis of PEG-G-CSF was administered on day 2 after the administration of DR. The demographics were well balanced in the patients with and without primary prophylactic PEG-G-CSF (Table 1). The adverse events that occurred in patients treated with DR are shown in Table 2. In our study, 30 of the 33 patients were treated with nivolumab before the administration of DR.

The efficacy and clinical course of DR with or without prophylactic PEG-G-CSF is shown in Table 3. The median number of cycles of this combination was 4 (range: 1–12). Regardless of the primary prophylactic PEG-G-CSF support, 10 patients required dose reduction of docetaxel because of the incidence of adverse events, such as grade 4 leukopenia and neutropenia, and grade 3 diarrhea. However, there did not appear to be a significant difference in the administration conditions and the efficacy of DR between the patients that received prophylactic PEG-G-CSF and those that did not.

Table 1 Patient characteristics

Variables	With prophylactic PEG-G-CSF N = 29	Without prophylactic PEG-G-CSF N = 4	*P*
Age			0.69
median (range)	69 (31–78)	67.5 (60–71)	
Gender			0.27
Male	17 (58.6%)	4 (100%)	
Female	12 (41.4%)	0 (0%)	
Smoking history			> 0.99
No	11 (37.9%)	1 (25%)	
Yes	18 (62.1%)	3 (75%)	
PS (ECOG)			0.06
0–1	27 (93.1%)	2 (50%)	
> 2	2 (6.9%)	2 (50%)	
Histology			0.55
AC	21 (72.4%)	3 (75%)	
SCC	3 (10.3%)	1 (25%)	
NSCLC	4 (13.8%)	0 (0%)	
EGFR mutation			> 0.99
Mutant	4 (13.8%)	0 (0%)	
Wild type	25 (86.2%)	4 (100%)	
Prior number of regimens			0.59
Median(range)	2 (1–6)	2 (1–2)	
Prior bevacizumab			0.60
Administered	15 (51.7%)	1 (25%)	
None	14 (48.3%)	3 (75%)	
Prior immunotherapy			0.33
Administered	27 (93.1%)	3 (75%)	
None	2 (6.9%)	1 (25%)	

AC, adenocarcinoma; ECOG, Eastern Cooperative Oncology Group; NSCLC, non-small cell lung cancer; PEG-G-CSF, pegylated-granulocyte-colony stimulating factor; PS, performance status; SCC, squamous cell carcinoma.

Ten patients (10/29, 34.5%,) with and two (2/4, 50%) without PEG-G-CSF received antibiotics after the initiation of DR. The overall response rate (ORR) and disease control rate (DCR) in the 29 patients administered prophylactic PEG-G-CSF were 31.0% and 62.0%, respectively. We then analyzed the efficacy of DR by age in 29 patients that received prophylactic PEG-G-CSF (Table 4). The treatment delivery and efficacy of DR with prophylactic PEG-G-CSF were not significantly different between patients aged > 75 years ($n = 6$) and < 75 years ($n = 23$). The ORR and DCR of patients aged > 75 years were 33.3% and 66.7%, respectively.

The median PFS and OS for all patients ($n = 33$) after the administration of DR were 176 and 358 days, respectively. In the patients with and without prophylactic PEG-G-GSF, the median PFS was 177 and 163 days ($P = 0.20$) and the median OS was 628 and 274 days ($P = 0.13$), respectively (Figure S1). Moreover, in the 29 patients treated with prophylactic PEG-GSF, the median PFS in patients aged > 75 ($n = 6$) and < 75 ($n = 23$) was 212 and 156 days ($P = 0.13$) and the median OS was 283 and 358 days ($P = 0.88$), respectively.

Table 2 Adverse events in patients administered docetaxel and ramucirumab

	All grade		≧Grade3	
Adverse event	With prophylactic PEG-G-CSF N = 29	Without prophylactic PEG-G-CSF N = 4	With prophylactic PEG-G-CSF N = 29	Without prophylactic PEG-G-CSF N = 4
Hematological				
Leukopenia	8 (27.6%)	1 (25%)	3 (10.3%)	1 (25%)
Neutropenia	2 (6.9%)	1 (25%)	2 (6.9%)	1 (25%)
Anemia	9 (31.0%)	1 (25%)	1 (3.4%)	0
Thrombocytopenia	7 (24.1%)	0	1 (3.4%)	0
Febrile neutropenia	0	2 (50%)	0	2 (50%)
Non-hematological				
Appetite loss	6 (20.7%)	1 (25%)	0	0
Nausea	4 (13.8%)	0	0	0
Oral mucositis	3 (10.3%)	3 (75%)	0	0
Diarrhea	7 (24.1%)	1 (25%)	3 (10.3%)	1 (25%)
Numbness	1(3.4%)	0	0	0
Myalgia	1(3.4%)	0	0	0
Skin disorder	4(13.8%)	0	0	0
Interstitial pneumonia	2(6.9%)	1(25%)	1(3.4%)	0
Nasal bleeding	4 (13.8%)	1 (25%)	0	0
Proteinuria	15 (51.7%)	2 (50%)	0	0
Hypertension	0	1 (25%)	0	0

PEG-G-CSF, pegylated-granulocyte-colony stimulating factor.

Table 3 Clinical course and response of docetaxel and ramucirumab with or without prophylactic PEG-G-CSF

Variables	With prophylactic PEG-G-CSF N = 29	Without prophylactic PEG-G-CSF N = 4	*P*
No. of cycles (range)			
Docetaxel	4 (1–12)	5 (2–8)	0.61
Ramucirumab	4 (1–12)	4.5 (1–8)	0.63
Frequency of dose reduction (%)			
Docetaxel	10 (34.5%)	3 (75%)	0.27
Ramucirumab	0	0	
Response			
CR	0	0	
PR	9 (31.0%)	2 (50%)	
SD	9 (31.0%)	0	
PD	2 (6.9%)	0	
NE	9 (31.0%)	2 (50%)	
Overall response rate	31.0%	50%	0.58
Disease control rate	62.0%	50%	> 0.99
No. of patients administered sequence therapy			0.57
Yes	19 (65.5%)	2 (50%)	
No	8 (27.6%)*a*	2 (50%)	

[a] Two patients were continuously administered docetaxel plus ramucirumab. CR, complete response; NE, not evaluable; PD, progressive disease; PEG-G-CSF, pegylated-granulocyte-colony stimulating factor; PR, partial response; SD, stable disease.

Table 4 Clinical course and response of docetaxel and ramucirumab with prophylactic PEG-G-CSF

Variables	Age > 75 years N = 6	Age < 75 years N = 23	*P*
No. of cycles (range)			
Docetaxel	2.5 (1–7)	5 (1–12)	0.26
Ramucirumab	1 (1–6)	4 (1–12)	0.06
Frequency of dose reduction (%)			
Docetaxel	2 (33.3%)	8 (34.8%)	0.94
Ramucirumab	0	0	
Response			
CR	0	0	
PR	2 (33.3%)	7 (30.4%)	
SD	2 (33.3%)	7 (30.4%)	
PD	0	2 (8.7%)	
NE	2 (33.3%)	7 (30.4%)	
Overall response rate	33.3%	30.4%	>0.99
Disease control rate	66.7%	60.8%	>0.99
No. of patients administered sequence therapy			>0.99
Yes	4 (66.7%)	15 (47.6%)	
No	2 (33.3%)	6 (28.6%)*a*	

[a] Two patients were continuously administered docetaxel plus ramucirumab. CR, complete response; NE, not evaluable; PD, progressive disease; PEG-G-CSF, pegylated-granulocyte-colony stimulating factor; PR, partial response; SD, stable disease.

Discussion

Our data show that the administration of primary prophylactic PEG-G-CSF immediately after DR could prevent the risk of FN resulting from chemotherapy. No patients who received primary prophylactic PEG-G-CSF experienced FN after DR, and were then able to continue with systemic chemotherapy. Among these 33 patients, some may not have needed the prophylaxis with PEG-G-CSF, however, there are no established biomarkers that permit the exclusion of such patients. Patients treated with other regimens also exhibited a reduced incidence of FN after receiving primary prophylactic PEG-G-CSF in clinical settings. The decrease in FN incidence led to a drop in the treatment-related death rate. It has been proven that the risk of mortality increases in patients with cancer who develop FN.[7]

In our study, the ORR of DR in the 29 patients administered prophylactic PEG-G-CSF appeared to be similar to that of previous studies.[1,2] Although the efficacy and safety of DR in patients with NSCLC aged > 75 years is unclear, our study indicated that DR is active and tolerable in elderly patients if prophylactic PEG-G-CSF is administered. No statistically significant difference in the ORR and survival was observed between patients aged > 75 years (n = 6) and < 75 years (n = 23). As only small numbers of patients not treated with prophylactic PEG-G-CSF (n = 4) or aged > 75 (n = 6) were evaluated, there are a number of limitations in the comparative analyses in this study. A well-balanced patient sample is necessary to compare the efficacy and safety in patients administered prophylactic PEG-G-CSF to those that are not. We also found that the frequency of dose reduction of docetaxel appeared to be lower in the patients administered prophylactic PEG-G-CSF (34.5%) than in those who were not (75%) (Table 3). The reduction in FN occurrence by prophylactic PEG-G-CSF may contribute to improvements in the delivery of docetaxel treatment. However, prophylactic PEG-G-CSF may not affect the treatment delivery of DR in patients aged > 75, although it reduced the frequency of docetaxel dose reduction. Although prophylactic PEG-G-CSF has additional costs, it may improve the quality of life of patients who receive the treatment.

In Japan, major concerns have emerged about the occurrence of FN when DR is administered to patients with previously treated NSCLC. Although it remains unclear whether the administration of a primary prophylactic PEG-G-CSF is the most appropriate strategy to overcome the problem, we believe that primary prophylactic administration is recommended for FN, according to the results of our investigation and those of a previous study.[4] However, limitations are evident because these studies are not prospective but retrospective investigations. Several prospective studies are currently in progress in Japan, and we believe that the results of these studies will confirm our results.

In conclusion, primary prophylactic PEG-G-CSF suppresses the occurrence of FN secondary to the administration of DR. Clinicians should therefore consider the use of primary prophylactic PEG-G-CSF when DR is initially administered.

Disclosure

AM, KK, and HK received research grants and received honorarium as speakers from the Eli Lilly Company. The remaining authors report no conflict of interest.

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Supporting Information

Additional Supporting Informationmay be found in the online version of this article at the publisher's website:

Figure S1. Kaplan–Meier survival curves of overall survival (OS) (A1) and progression-free survival (PFS) (A2) according to according to prophylaxis with pegylated-granulocyte-colony stimulating factor (PEG-G-CSF).

