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Pegfilgrastim Drastically Lowered Risk of Febrile Neutropenia in Japanese Patients with Thoracic Malignancy Receiving Cytotoxic Chemotherapy - a Retrospective Single Institutional Study

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Abstract

Objective: Pegfilgrastim was introduced to the Japanese market in December 2014. The domestic dose is 3.6mg whereas 6mg for the rest of the world. Our aim of this retrospective study was to examine the impact of this low-dose pegfilgrastim on prevention of febrile neutropenia (FN) onset in Japanese patients with thoracic malignancy receiving chemotherapy, by comparing its frequency before and after introduction of pegfilgrastim.

Study Design (Methods): We retrospectively reviewed all chemotherapy lines that started from July 2012 to December 2015 in our department. 92 lines of cytotoxic chemotherapy in 74 patients were found and enrolled. These lines of chemotherapy were divided into two groups according to the period of pegfilgrastim introduction to our institute. Various clinical profiles, onsets of G3/G4 neutropenia and FN were also investigated for each line of chemotherapy.

Results: Poorer performance status (p=0.0355), previous chemotherapy (p=0.0095) and radiotherapy (p=0.0186) were significantly more frequent in after pegfilgrastim group. The risk of FN onset in after pegfilgrastim group had been reduced to the one-seventh compared with before pegfilgrastim group (p=0.0179, odds ratio 6.752) by multivariate analysis.

Conclusion: Our study proved that this lowered dose of pegfilgrastim was effective to reduce FN risk in actual Japanese patients with thoracic malignancy.

Keywords: Thoracic malignancy; Lung cancer; Febrile neutropenia; Pegfilgrastim; Chemotherapy.

Objective

In cytotoxic anticancer chemotherapy for thoracic malignancies, a major factor to reduce the dose of the agent(s), or to delay or cease the regimen, is febrile neutropenia (FN). Pegfilgrastim (G-Lasta® subcutaneous injection 3.6mg, Kyowa Hakko Kirin, Tokyo, Japan), a long acting formulation of recombinant granulocyte-colony stimulating factor (G-CSF), has been introduced to the Japanese market of insured medicine since December 2014.

Pegfilgrastim is now widely used by 6mg per body worldwide as Neulasta® (Amgen, Thousand Oaks, CA, USA), whereas the dose was reduced to 3.6mg in Japan. This dose was adjusted to the Japanese patients according to the results of domestic dose-determining studies by company data on file. However, we could not find any study that inspected the actual effectiveness of 3.6mg of pegfilgrastim in Japanese patients with lung cancer receiving chemotherapy besides one small study that was performed before its release in Japanese patients [1]. The frequency of the use of pegfilgrastim in lung cancer chemotherapy in various countries is unknown but studies reported from the rest of the world seem still not many [2].

Our department has started anticancer chemotherapy since July 2012, because of withdrawal of Department of Respiratory Medicine from our hospital in December 2011. During the first three months after we have just started, we performed anticancer chemotherapy with cytotoxic agents in 6 patients with thoracic malignancy. Unfortunately, four of them developed FN, and two of them died of acute exacerbation of interstitial pneumonitis occurred subsequently to FN. Thus, to date, we have been much sensitive about FN onset in patients during receiving cytotoxic chemotherapy.

Pegfilgrastim has also been introduced to our hospital since December 2014 and we have started to use it since January 2015 to increase the safety of our chemotherapy. However, pegfilgrastim does not seem to be widely used for patients with thoracic malignancy receiving chemotherapy in Japan because the report describing about its effectiveness is seldom seen even in the Japanese literature. Our aim of this study was to examine the impact of low-dose pegfilgrastim on prevention of FN onset in actual Japanese patients with thoracic malignancy receiving chemotherapy. In this article, the results of introduction of low-dose pegfilgrastim to our institute and its contribution to the safety of our chemotherapy were retrospectively investigated and presented with two actual clinical case reports.

Study Design (Methods)

Patients and Methods

We retrospectively reviewed clinical records of our department for chemotherapy lines that started from July 2012 to December 2015. We found 110 lines of chemotherapy that had been performed in 97 patients with various thoracic malignancies, including primary lung cancer, mesothelioma, and thymic cancer. Informed consent for the use of their clinical data in later clinical studies was obtained at a time of starting chemotherapy from each individual patient and the institutional review board approved this retrospective study. Continuation or switching maintenance therapy was not included in this number. Of 110 lines, 6 lines of gefitinib, 6 lines of afatinib, 2 lines of crizotinib, 1 line of erlotinib, and 1 line of pazopanib were excluded. Two more lines were also excluded because these were ceased for anaphylaxis by the first injection. Thus, 92 lines for 74 patients were enrolled in this study. These lines of chemotherapy were divided into two groups according to the period of pegfilgrastim introduction to our institute, as “Before PF” group (including the chemotherapy lines that had been started before December 2014) and “After PF” group (including the chemotherapy lines that had been started after January 2015). The grading of neutropenia was according to Common Terminology Criteria for Adverse Events v4.03 [3].

Various clinical profiles, laboratory data before the first administration of the agents, onsets of G3/G4 neutropenia and FN were also investigated for each line of chemotherapy. The chemotherapy as neoadjuvant therapy was included into the chemotherapy for advanced disease. Differences between both groups were analysed to figure out the effects of pegfilgrastim introduction. Possible risk factors of G3/G4 neutropenia and FN were also investigated. Data were compared between groups by the following methods. The Mann–Whitney U–test was used to compare continuous variables, such as patient ages, body weight, and laboratory data. Pearson's chi-square test was used to compare categorical data between groups. Fisher's exact test was used to compare categorical data with low expected values. Logistic regression model was used for multivariate analysis.

Results

Overview of Our Chemotherapy

Since we've started anticancer chemotherapy in July 2012, the numbers of patients, and the numbers of lines of chemotherapy performed in these patients were both increasing annually, as 15 lines in 13 patients in 2012, 18 lines in 15 patients in 2013, 32 lines in 30 patients in 2014, and 46 lines in 39 patients in 2015. The lines of chemotherapy for patients with recurrent disease (n=35, 32%), and those for patients with advanced disease (n=39, 35%), and those for operable patients both as neoadjuvant therapy (n=5, 5%) and as adjuvant therapy (n=31, 28%), were almost one-third of the total for each. The most frequent objective disease was primary lung cancer (n=91, 83%). Others were mesothelioma (n=9, 8%), sarcoma (n=5, 5%), cancers of unknown primary site (n=4, 4%), and thymic cancer (n=1, 1%). Cytotoxic platinum-doublet chemotherapy was the main regimen as used in two-thirds of the lines (n=74, 67%). Non-platinum cytotoxic monotherapy (n=18, 16%), epidermal growth factor receptor tyrosine kinase inhibitors and anaplastic lymphoma kinase inhibitors (n=16, 15%) were both similarly in number. Bevacizumab alone was in 2 lines (2%). Details of the agents used in 110 chemotherapy lines were, carboplatin plus paclitaxel (n=16, 15%), carboplatin plus nabpaclitaxel (n=15, 14%), carboplatin plus S-1 (n=12, 11%), cisplatin plus pemetrexede (n=10, 9%), carboplatin plus pemetrexede (n=10, 9%), pemetrexede monotherapy (n=6, 5%), vinorelbine monotherapy (n=6, 5%), afatinib (n=6, 5%), gefitinib (n=6, 5%), carboplatin plus etoposide (n=3, 3%), and others (n=20, 18%).

Onset rates of G3/G4 and febrile neutropenia in all 92 chemotherapy lines

Of all 92 lines performed in 74 patients, G4, G3, G2, G1, and no neutropenia occurred in 19 (21%), 19 (21%), 9 (10%), 1 (1%), and 44 (48%) lines, respectively. Febrile neutropenia occurred subsequently in 12 (13%) lines. Seven (58%) of them were progressed after G4 neutropenia, 4 (33%) were after G3, and 1 (8%) was after G2 neutropenia.

Onset rates of G3/G4 and febrile neutropenia according to each regimen

Onset rates of G3/G4 neutropenia according to each performed regimen were shown in Table 1. Total rate of G3/G4 neutropenia onset in all 92 lines of chemotherapy were 42.4%. Total rate of FN onset in all 92 lines of chemotherapy were 13.0%.

Risk factors of G3/G4 neutropenia by univariate and multivariate analysis

Factors predicting the onset of G3/G4 neutropenia by univariate analysis were shown in the left half of Table 2. Result of multivariate analysis on factors predicting the onset of G3/G4 neutropenia indicated that higher value of serum creatinine (odds ratio per 1mg/dL 4.568, 95% confidential interval 0.7611-32.61, p=0.0976), and chemotherapy started before pegfilgrastim introduction (odds ratio 4.006, 95% confidential interval 1.540-11.16, p=0.0042) were independent risk factors predicting the onset of G3/G4 neutropenia. Age 65 years or more (p=0.1140), smoking within

a year (p=0.3329), adjuvant or advanced/recurrent disease (p=0.1254) were also examined but not significant.

Risk factors of febrile neutropenia by univariate and multivariate analysis

Results of univariate analysis on risk factors for FN onset were also shown in right half of Table 2. By multivariate analysis, chemotherapy for advanced or recurrent disease rather than adjuvant therapy (odds ratio 1.648^e-8, 95% confidential interval 0-0.2455, p=0.0010), higher value of serum creatinine (odds ratio per 1mg/dL 35.36, 95% confidential interval 2.497-5376, p=0.0116), and chemotherapy started before pegfilgrastim introduction (odds ratio 6.752, 95% confidential interval 1.361-53.57, p=0.0179) were independent risk factors, as well. Age 65 years or more was also examined however it was not significant (p=0.1783).

Comparison of background characteristics of the chemotherapy lines before and after introduction of pegfilgrastim, and periodical changes of onset rates of both G3/G4 and febrile neutropenia

The results of comparison of background characteristics of the chemotherapy lines in both Before PF and After PF groups were shown in Table 3. Though multiple unfavourable factors for neutropenia onset were found more frequently in After PF group than Before PF group, G3/G4 neutropenia occurred significantly less frequently in After PF group and its risk of the onset was approximately one-fourth compared with Before FP group (p=0.0009, odds ratio 4.410). Febrile neutropenia developed also significantly less frequently in After PF group and its risk of the onset had been reduced to only one-fifth compared with Before PF group (p=0.0306, odds ratio 5).

Periodical changes of onset rates of both G3/G4 and febrile neutropenia was shown in Figure 1. The onset rates of both G3/G4 and febrile neutropenia were drastically reduced significantly after pegfilgrastim introduction.

Actual cases those who received pegfilgrastim for prevention of neutropenia

The patients who actually received pegfilgrastim were shown in Table 4. Pegfilgrastim was used in 7 lines (16%) of all 42 chemotherapy lines that were performed after pegfilgrastim introduction to our institute in January 2015. Neutropenia never occurred in all those 7 cases and the interested chemotherapy had all been accomplished without any delay or dose-reduction. As an adverse effect, only G1 bony pain occurred in one case.

Case 1: Primary prophylaxis of FN by pegfilgrastim

This case was given as #7 in Table 4. The patient was 75 year-old male, presenting neck mass and small solitary right lung mass in chest X-ray. Fine needle aspiration cytology from the neck mass disclosed malignancy. Positron emission tomography (PET) showed increased uptake of fluorodeoxyglucose (FDG) in the cervical and the right lung masses (Figure 2A). The right lung mass was excised via thoracoscopic procedure for therapeutic diagnosis. The pathology of the lung mass disclosed large cell neuroendocrine carcinoma, and the patient was diagnosed to have cervical thymic cancer with solitary right lung metastasis. Then the patient received total radiation therapy of 70 Gy by 35 fractions to the neck, and subsequently received chemotherapy with carboplatin and etoposide per 3 weeks for 6 courses. This regimen was known as high risk for the onset of neutropenia, and he was elderly and just after radiotherapy. For these reasons, pegfilgrastim was introduced from the first course as primary prophylaxis of neutropenia. The chemotherapy was accomplished without any adverse effect, any delay or dose-reduction. All lesions were disappeared in PET taken after 8 months from the lung biopsy and he was considered in complete clinical response (Figure 2B).

Case 2: Secondary prophylaxis of FN by pegfilgrastim for a patient receiving weekly regimen

Pegfilgrastim needs 2-weeks interval between each administration of anticancer agents. Thus, the use for a patients receiving weekly regimen is difficult. In this case, pegfilgrastim was introduced for patients on weekly regimen, as given as #2 in Table 4. The patient was 74 year-old male, with unresectable lung cancer of stage 3B in the right hilum involving the mediastinum (Figure 2C), of which pleomorphic carcinoma was confirmed by surgical biopsy. In his past history, left upper lobectomy was performed for previous lung cancer 9 years ago. Stereotactic radiation therapy was carried out for another bilateral lung cancer 2 years ago. He had emphysema and was asthmatic, receiving inhaled corticosteroid and beta2 stimulant therapy. He also was diabetic and had been on insulin therapy already for years. Chronic renal failure with nephrotic syndrome was complicated and his estimated glomerular filtration rate was 39%. Furthermore, he had been receiving 4-drug regimen; isoniazid, rifampin, pyrazinamide, and ethambutol for active pulmonary tuberculosis, until just 2 weeks before the surgical lung biopsy. He also had a history of chemotherapy for malignant lymphoma 2 years ago, and his neutrocyte and lymphocyte count were 2400 and 900 /μL, respectively. He was enough high risk for neutropenia, but he wish to receive chemotherapy. Thus, we scheduled 6 courses of carboplatin (Day 1) and weekly nabpaclitaxel (Day 1, 8, and 15) therapy by 3 weeks for him, and had been started. On the day 28, that was the day 1 for the scheduled second course, he developed G3 neutropenia. Filgrastim and levofloxacin were prophylactically administrated immediately, and the neutropenia was improved without any infectious signs. We decided to elongate the period of chemotherapy interval from 3 weeks to 4 weeks, and pegfilgrastim was administrated on the Day 16 of the second and later courses. After that, the chemotherapy was accomplished without any adverse effect, any delay or dose-reduction. PET scan that was taken 6 months after the start of the chemotherapy, showed disappearance of FDG uptake and he was considered in complete clinical response, also (Figure 2D).

Discussion

Pegfilgrastim could be a strong supportive option to make intense chemotherapy possible, without any delay or dose reduction even in patients with thoracic malignancy in many cases. But pegfilgrastim does not seem widely used in patients with thoracic malignancy in Japan, even after more than a year has been past since its introduction to the market of insured medicine.

One reason would be the high cost of pegfilgrastim, and this could be same in the rest of the world [4]. The second reason could be the fact that the use of pegfilgrastim is prophylactic. Its effect is hardly recognizable for patients or physicians in charge because pegfilgrastim does not improve any symptom or any results of diagnostic imaging or tumor markers, just makes chemotherapy safer and possibly keep it intense.

The third reason would be due to a concern about possibility of long-lasting adverse effect such as bony pain or fever. For the use of secondary prophylaxis, careful observation of the patients after filgrastim injection for FN during previous cycle of chemotherapy would be helpful to predict the possible adverse effect of pegfilgrastim. An appropriate use of nonsteroidal anti-inflammatory drugs could manage the problem [5].

The fourth reason could be an inconvenience caused by time lag of administration. Pegfilgrastim is recommended to administrate not less than 24 hours after the last injection of anticancer agent. Otherwise FN could be onset more frequently [6, 7]. Nevertheless, single injection of pegfilgrastim on the day after chemotherapy is still more convenient than multiple daily injection of conventional filgrastim for both patients and medical stuff.

The fifth reason is that pegfilgrastim is not suitable for weekly regimen because next injection of the anticancer agent is not recommended within 14 days after last administration of pegfilgrastim. Many patients with lung cancer are treated with various weekly regimens. To use pegfilgrastim in such patients, the extension between the last and the next injection of the anticancer agent may be needed like our presented case 2. But such irregular alternation of chemotherapy schedule supported by pegfilgrastim should be verified for its feasibility and safety, by further well-designed studies [8].

The last reason is either due to the small population of patients with thoracic malignancy receiving chemotherapy for "curative" intent. The rate of chemotherapy supported with pegfilgrastim for curative intent was smaller in patients with lung cancer than other malignancies [9]. For "non-curative" intent, many physicians are likely to avoid the risk of adverse effects of chemotherapy by reducing the dose of the agent or delay the administration schedule, without using pegfilgrastim, especially if the patient is regarded as being high risk for neutropenia. However, as presented in our study, introduction of pegfilgrastim could drastically decrease the frequency of FN onset without any adverse effect in our institute in a short period. Careful selection of the cases for the use of pegfilgrastim would be more beneficial. More than that, the use of pegfilgrastim also may bring favourable impact on survival, even if the patient is high risk and the chemotherapy is "non-curative" intent.

However, there is no clear-cut criterion for primary prophylactic use of G-CSF. National Comprehensive Cancer Network (NCCN) stated a guideline for the use of G-CSF in patients receiving chemotherapy [10]. It shows some algorithms of considering the use of G-CSF according to possible risk factors reviewed from various retrospective studies [11]. But weight of each risk factor still remained unknown and is not considered. Even according to the guideline, selection of patients for primary prophylactic use of G-CSF is still widely depending upon the intuitional thought and the experience of each physician. Complicated overall assessment is still needed for each individual patient by regarding various immeasurable factors. Clear-cut criteria by using scoring system or similar method, considering the weight of various risk factors are awaited.

Our study also demonstrated some useful information about risk factors when considering such selection. Elderly was one of the important factor predicting both G3/G4 neutropenia and FN by univariate analysis in our study, but it was not significant for both by multivariate analysis. However, the guideline is clearly stated that the elderly is one of the important factors when considering the use of G-CSF.

Smoking history was not significant factor for both G3/G4 neutropenia and FN. However, smoking within a year was likely to predict G3/G4 neutropenia in our study. Smoking would have some impact on human bone marrow [12]. Chronic smoking stimulates bone marrow and causes leucocytosis with increased number of immature circulating granulocytes. The influence of smoking upon toxicity of chemotherapy was merely reported but it does not seem affecting toxicity profile of chemotherapy with docetaxel and paclitaxel [13].

Advanced or recurrent disease is another important factor for both G3/G4 neutropenia and FN in our study, as it was clearly stated in the guideline as well. Chemotherapy without cisplatin was another significant factor for the onset of FN in our study. This could be because monotherapy without platinum is usually selected for weakened or high risk patients with advanced or recurrent disease.

Renal dysfunction was also strong independent risk factor of the onset of both G3/G4 neutropenia and FN in our study. In the literature, several reports could be found describing about high value of creatinine clearance could predict chemotherapy-induced neutropenia [14, 15]. By renal dysfunction, extended circulating time of anticancer agent would be likely to induce neutropenia. Or high serum titer of creatinine might be reflected by systemic vascular disease, elderly, or renal damage by previous chemotherapy. Prophylactic use of pegfilgrastim should be considered if high serum value of creatinine or estimated glomerular filtration rate (or creatinine clearance) were found.

Introduction of pegfilgrastim was also strong independent factor to reduce the onset of G3/G4 neutropenia and FN, and certainly made our chemotherapy safer, as reducing the risk of G3/G4 neutropenia to the one fourth and the risk of FN to the one seventh, approximately. This risk reduction was achieved even the patients after introduction of pegfilgrastim had higher risks such as significant poorer performance status, more frequent history of previous chemotherapy, and lower rates of oral care, than those before introduction.

Furthermore, these results were brought by lower dose of pegfilgrastim that was set to 3.6mg for Japan domestic use whereas international setting is 6mg. Our study proved that this lowered dose of pegfilgrastim was safe and still much effective to reduce FN risk in Japanese patients with thoracic malignancy. Another study showed that this reduced dose was safe and effective for Japanese patient with breast cancer, also [16]. The reason why 3.6mg is suitable and enough doses for only Japanese patients is unknown.

In other Asian countries besides Japan, pegfilgrastim is used by 6mg like the rest of the world. However, the governments of these Asian countries introduced pegfilgrastim into their own market without performing dose-escalation study for their own people. In these countries, the dose was determined as 6mg as just imported as it is, according to the world market. But our results suggest that suitable dose of pegfilgrastim could be varied according to the ethnic differences, especially in Asian countries. Detailed dose-setting by considering ethnical difference may be needed and would be beneficial to increase the safety of pegfilgrastim use in each country.

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Table 1. Onset rate of G3/G4 and febrile neutropenia according to the regimens

Reasons	Regimens	Performed chemotherapy lines	G3/G4 neutropenia # of onset	G3/G4 neutropenia Rate %	Febrile neutropenia # of onset	Febrile neutropenia Rate %
SCLC etc.	CDDP+CPT11	2	2	(100.0)	2	(100.0)
	CDDP+VP16	1	0	(0.0)	0	(0.0)
	CBDCA+VP16	3	2	(66.7)	0	(0.0)
	SCLC, subtotal	6	4	(66.7)	2	(33.3)
Adjuvant CT	CBDCA+PTX	11	8	(72.7)	0	(0.0)
	CBDCA+NabPTX	11	7	(63.6)	0	(0.0)
	Adjuvant, subtotal	22	15	(68.2)	0	(0.0)
CT for advanced or recurrent disease	CDDP+PEM	10	2	(20.0)	2	(20.0)
	CBDCA+PEM	10	4	(40.0)	1	(10.0)
	CBDCA+PEM+Bev	1	0	(0.0)	0	(0.0)
	PEM	6	1	(16.7)	1	(16.7)
	PEM-based, subtotal	27	7	(25.9)	4	(14.8)
	CBDCA+PTX	3	1	(33.3)	0	(0.0)
	CBDCA+NabPTX	5	4	(80.0)	1	(20.0)
	CBDCA+PTX+Bev	3	1	(33.3)	0	(0.0)
	PTX-based, subtotal	11	6	(54.5)	1	(9.1)
	CBDCA+S-1	12	0	(0.0)	0	(0.0)
	CDDP+GEM	1	0	(0.0)	0	(0.0)
	DTX+GEM	1	1	(100.0)	1	(100.0)
	DTX	1	1	(100.0)	1	(100.0)
	GEM	2	1	(50.0)	0	(0.0)
	VNR	6	3	(50.0)	3	(50.0)
	ADM+IFO	1	1	(100.0)	0	(0.0)
	Bev	2	0	(0.0)	0	(0.0)
	Others, subtotal	26	7	(26.9)	5	(19.2)
Total		92	39	(42.4)	12	(13.0)

SCLC, small cell lung cancer; CDDP, cisplatin; CPT11, camptothecin 11; VP16, etoposide; CBDCA, carboplatin; PTX, paclitaxel; PEM, pemetrexede; Bev, bevacizumab; S-1, oral fluorinated pyrimidine agent with tegafur, gimestat, and otastat potassium; Gem, gemcitabine; VNR, vinorelbine; ADM, adriamycin; IFO, ifosfamide

TABLE 2. Factors predicting onset of G3/G4 and febrile neutropenia in 92 chemotherapy lines by univariate analysis

		Onset of G3/G4 neutropenia								Onset of febrile neutropenia							
		Non-neutropenia		G3/G4 Neutropenia		Odds	95% confidential			Non-FN		FN		Odds	95% confidential		
Factors	Units	n	mean±S.D.	n	mean±S.D.	ratio	interval		p value	n	mean±S.D.	n	mean±S.D.	ratio	interval		p value
Age	yrs	53	66.1±10.8	39	70.7±8.0				0.0265	80	67.2±10.0	12	73.8±6.7				0.0206
Age 65	65 or more : Less than 65	31:22		33:6		3.903	1.397	- 10.90	0.0071	53:27		11:1		5.604	0.6869	- 45.71	0.0744
Sex	M:F	34:19		30:9		0.5368	0.2112	- 1.364	0.1883	52:28		12:0		0	-	- -	0.0140
Smoking	Y:N	42:11		32:7		1.197	0.4175	- 3.433	0.7374	62:18		12:0		-	-	- -	0.0669
Quit smoking <1y	Y:N	18:35		7:32		0.4253	0.1571	- 1.152	0.0880	22:58		3:9		0.8787	0,2176	- 3.548	0.8559
Adjuvant CT or CT for Advanced/Reccurrent Disease	Aduvant: Adv/Rec	14:39		17:22		2.152	0.8933	- 5.187	0.0850	31:49		0:12		0	-	- -	0.0081
CT with platimum	Y:N	41:12		31:8		1.134	0.4135	- 3.111	0.8067	66:14		6:6		0.2121	0.05957	- 0.7553	0.0109
Performance status	0-2:3,4	43:10		35:4		2.035	0.5874	- 7.049	0.2558	70:10		8:4		0.2857	0.07253	- 1.125	0.0610
Body weight	kg	53	58.4±10.5	39	56.7±9.7				0.6241	80	57.8±9.9	12	56.7±12.3				0.9077
Body weight loss <3m	kg	53	1.7±4.8	39	2.4±4.3				0.4694	80	1.7±4.9	12	4.5±6.1				0.3102
White blood cell count	/μL	53	6790±1840	39	6980±2660				0.5586	80	6580±1750	12	8800±3710				0.0374
Neutrocyts count	/μL	53	4540±1530	39	4770±2580				0.6129	80	4330±1410	12	6680±3850				0.0099
Lymphcyte couint	/μL	53	1380±680	39	1920±1810				0.4261	80	1410±648	12	1270±531				0.8117
Hematocrit	%	53	37.65±5.29	39	36.86±4.20				0.2519	80	37.01±4.80	12	39.36±4.93				0.1624
Creatinine	mg/dL	53	0.808±0.250	39	0.905±0.291				0.0210	80	0.813±0.250	12	1.091±0.287				0.0011
Estimated GFR	mL/min	53	72.0±18.5	39	55.0±14.7				0.1282	80	71.8±18.8	12	55.0±14.7				0.0049
Total bilirubin	mg/dL	52	0.43±0.16	39	0.51±0.25				0.1222	79	0.44±0.15	12	0.63±0.37				0.0543
AST	U/L	53	21.0±9.5	39	21.9±9.1				0.5162	80	21.1±9.6	12	23.3±6.9				0.1547
ALT	U/L	53	16.8±10.6	39	15.6±10.0				0.6066	80	16.7±10.8	12	13.8±5.1				0.7892
PT-INR		48	1.104±0.319	39	1.135±0.266				0.1497	75	1.122±0.309	11	1.086±0.184				0.8919
Albumin	g/dL	53	3.72±0.56	39	3.81±0.71				0.9652	80	3.74±0.64	12	3.76±0.54				0.9768
Total cholesterol	mg/dL	49	191.7±36.5	39	182.2±35.3				0.1375	75	187.0±37.1	12	190.9±29.9				0.7257
Cholinesterase	U/L	50	256.0±70.7	39	255.6±162.0				0.1404	76	261.1±124.4	12	222.2±60.8				0.2126
C-reactive protein	mg/dL	53	1.62±2.89	39	1.23±2.08				0.9617	80	1.36±2.45	12	2.09±3.34				0.2990
Hemoglobin A1c	%	45	6.00±070	39	6.10±0.89				0.7521	71	6.09±0.82	12	5.81±0.15				0.3504
Diabetes mellitus	Y:N	14:39		12:27		1.238	0.4964	- 3.088	0.6467	25:55		1:11		0.2	0.02446	- 1.634	0.1002
Insulin use	Y:N	4:49		2:37		0.6621	0.1150	- 3.811	0.6424	6:74		0:12		0		-	0.3265
Other cancer history	Y:N	18:35		12:27		0.8614	0.3561	- 2.097	0.7468	27:53		3:9		0.6543	0.1635	- 2.617	0.5465
Previous chemotherapy	Y:N	19:34		10:29		0.6171	0.2479	- 1.536	0.2946	26:54		3:9		0.6923	0.1728	- 2.773	0.6020
Previous radiationtherapy	Y:N	11:42		4:35		0.4364	0.1276	- 1.492	0.1686	14:66		1:11		0.4285	0.05109	- 3.594	0.4228
Oral care within 3 months	Y:N	13:40		8:31		0.7940	0.2928	- 2.154	0.6490	19:61		2:10		0.6421	0.1292	- 3.190	0.5856
Before or after induction period of PF	Before PF :After PF	21:32		29:10		4.419	1.787	- 10.93	0.0009	40:40		10:2		5	1.029	- 24.27	0.0306
White blood cell count at diagnosis of neutropenia										38	2240±860	12	1380±640				0.0027
Neutrocytes count at diagnosis of neutropenia										38	802±388	12	558±113				0.1129
Lymphcytes count at diagnosis of neutropenia										38	1140±475	12	616±417				0.0011
CRP at diagnossi of neutropenia										37	0.79±1.11	12	13.00±9.01				<0.0001

CT, chemotherapy; GFR, glomerular filtration rate; AST, aspartate transaminase; ALT, alanine transaminase; PT-INR, prothrombin time-international normalized ratio; PF, pegfilgrastim

TABLE 3. Comparison of backgrounds of chemotherapy lines before and after introduction of pegfilgrastim

Factors	Units	Before PF (Before Dec 2014) n	Before PF (Before Dec 2014) mean±S.D.	After PF (After Jan 2015) n	After PF (After Jan 2015) mean±S.D.	Odds ratio	95% confidential interval		*p* value
Age	y	50	69.6±8.2	42	66.2±11.4		-		0.2553
Age 65	65 or more	39:11		25:17		2.411	0.9709	5.987	0.0551
Sex	M:F	40:10		24:18		0.3333	0.1323	- 0.8397	0.0176
Smoking	Y:N	42:8		32:10		-	-	- -	0.3469
Quit smoking <1y	Y:N	11:39		14:28		0.5641	0.2232	- 1.425	0.2235
Adjuvant CT or CT for Advanced/Reccurrent Disease	Aduvant: Adv/Rec	20:30		11:31		1.879	0.7710	- 4.578	0.1628
CT with platimum	Y:N	41:9		31:11		1.616	0.5966	- 4.380	0.3428
Performance status	0-2:3,4	46:4		32:10		3.594	1.036	- 12.47	0.0355
Body weight	kg	50	57.5±9.6	42	56.9±10.9			-	0.9719
Body weight loss <3m	kg	50	1.9±4.0	42	2,3±5.3			-	0.7554
White blood cell counts	/μL	50	7130±2410	42	6570±1930			-	0.5253
Neutrocytes counts	/μL	50	4840±2340	42	4400±1590			-	0.6748
Lymphcytes couints	/μL	50	1440±636	42	1340±634			-	0.1869
Hematocrit	%	50	37.51±4.51	42	37.09±5.28			-	0.8110
Creatinine	mg/dL	50	0.844±0.275	42	0.855±0.268			-	0.7717
Estimated GFR	mL/min	50	71.6±19.7	42	67.3±18.4			-	0.3213
Total bilirubin	mg/dL	50	0.46±0.16	41	0.47±0.25			-	0.7007
AST	U/L	50	20.6±7.3	42	22.4±11.2			-	0.7238
ALT	U/L	50	15.3±6.8	42	17.4±13.3			-	0.4745
PT-INR		48	1.077±0.186	38	1.169±0.389			-	0.9099
Albumin	g/dL	50	3.83±0.64	42	3.67±0.60			-	0.2810
Total cholesterol	mg/dL	48	186.9±34.4	39	188.3±38.5			-	0.6479
Cholinesterase	U/L	48	266.5±153.1	40	243.0±51.2			-	0.8275
C-reactive protein	mg/dL	50	1,16±1.91	42	1.80±3.17			-	0.8677
Hemoglobin A1c	%	48	6.01±0.86	35	6.09±0.70			-	0.2697
Diabetes mellitus	Y:N	15:35		11:31		1.208	0.4833	- 3.019	0.6861
Insulin use	Y:N	2:48		4:38		0.3958	0.06879	- 2.278	0.2851
Other cancer history	Y:N	14:36		16:26		0.6319	0.2629	- 1.519	0.3035
Previous chemotherapy	Y:N	10:40		19:23		0.3026	0.1204	- 0.7606	0.0095
Previous radiationtherapy	Y:N	4:46		11:31		0.2451	0.07151	- 0.8398	0.0186
Oral care within 3 months	Y:N	15:32		6:36		2.571	0.8954	- 7.384	0.0736
G3/G4 neutropenia	Y:N	29:21		10:32		4.419	1.787	- 10.93	0.0009
Febrile neutropenia	Y:N	10:40		2:40		5	1.030	- 24.28	0.0306

TABLE 4. Patients who received pegfilgrastim for prevention of neutropenia

Case #	Age	Sex	Disease	Pathology	Reason	Regimen	Neutropenia	Period of PF Induction
1	77	M	Lung cancer	SCLC	Adjuvant	CBDCA+VP-16	G4	2nd course
2	74	M	Lung cancer	Pleomorphic ca.	Adjuvant	CBDCA+NabPTX	G3	2nd course
3	48	F	Lung cancer, with Cushing syndrome	Carcinoid	Adjuvant	CDDP+VP-16		1st course
4	70	F	Lung cancer	Adenoca.	Inoperable	CBDCA+PEM	G3	2nd course
5	46	F	Mesothelioma	Epithelial	Neoadjuvant	CDDP+PEM	G2	3rd course
6	72	F	Lung cancer	Adenoca.	Recurrent	CBDCA+PEM	G2	2nd course
7	75	M	Thymic cancer	LCNEC	Inoperable	CBDCA+VP-16		1st course

PF, pegfilgrastim; SCLC, small cell lung cancer; CBDCA, carboplatin; VP16, etoposide; PTX, paclitaxel; CDDP, cisplatin; PEM, pemetrexed

Figure 1: Changes in onset rates of G3/G4 neutropenia and febrile neutropenia in 110 chemotherapy-lines before and after introduction of pegfilgrastim.

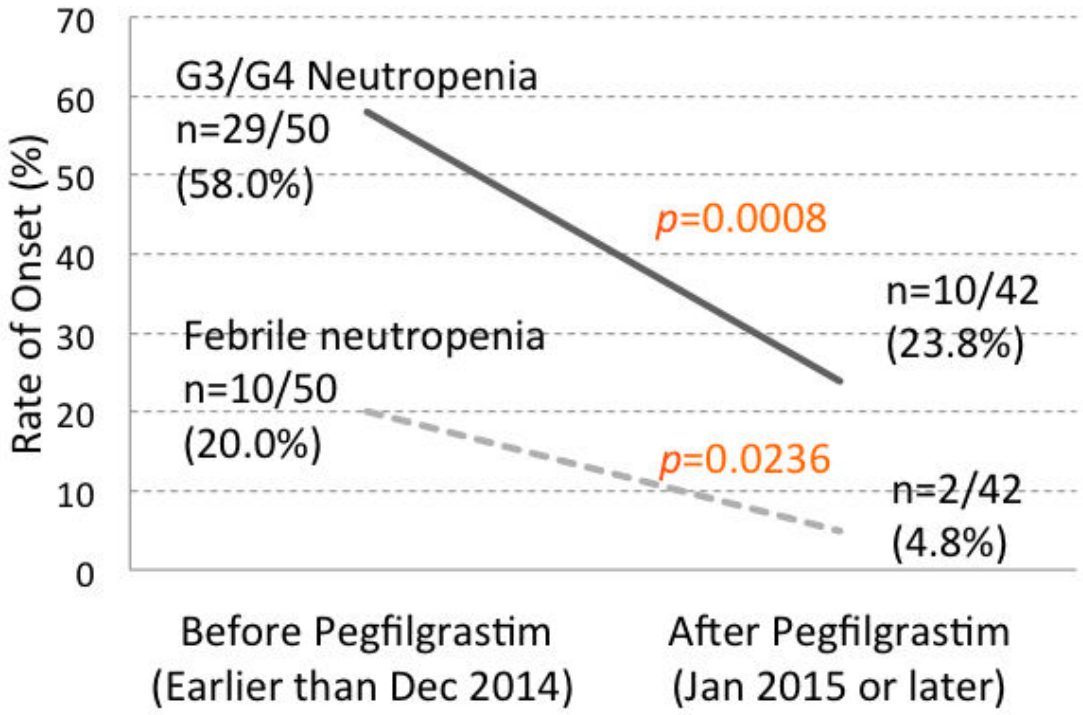

Figure 2: A. Fluorodeoxyglucose (FDG)-positron emission tomographic (PET) scan shows increased uptake of FDG in cervical thymic cancer (black arrow) and solitary metastatic site of the right lung (white arrow). **B.** PET scan after right lung resection, total radiation therapy to the neck, and successful completion of 6 courses of chemotherapy with carboplatin and etoposide, without any delay or dose-reduction by supportive therapy using pegfilgrastim. All lesions are disappeared and he is considered in complete clinical response. **C.** Fluorodeoxyglucose (FDG)-positron emission tomographic (PET) scan shows increased uptake of FDG in lung cancer in the right hilum involving the mediastinum (white arrow) and contralateral mediastinal lymph node is also visualized (black arrow). **D.** PET scan after successful completion of 6 courses of chemotherapy with carboplatin and nabpaclitaxel. Pegfilgrastim was introduced from the second course because of G3 neutropenia developed a week after the first course. All lesions are disappeared and he is considered in complete clinical response.