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Efficacy and safety of 3 mg pegylated recombinant human granulocyte colony-stimulating factor as support to chemotherapy for lung cancer

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Abstract

Background: NCCN guidelines recommend a dose of 100 μg/kg or a fixed dose of 6 mg pegylated recombinant human granulocyte colony-stimulating factor (PEG rhG-CSF) for chemotherapy-induced neutropenia. However, a single dose of 60 μg/kg or 100 μg/kg produced a similar neutrophil response among patients with chemotherapy-induced neutropenia (CIN). Thus, this prospective randomized study was designed to investigate the efficacy of 3 mg PEG rhG-CSF in preventing acute lower respiratory tract infection (ALRTI) after chemotherapy.

Methods: Patients with stage IIIB/IVA lung cancer who underwent chemotherapy were randomly divided into a (i) control group, and (ii) treatment group subject to 3 mg PEG rhG-CSF after chemotherapy. Patients in the control group were administered rhG-CSF (5 μg/kg) when decreased absolute neutrophil count (ANC) reached grade 3 of adverse events. The primary outcome was incidence of ALRTI, and the secondary outcomes included ANC, febrile neutropenia (FN), incidence of delayed chemotherapy, infection-related medical expenses and adverse reactions.

Results: Compared with the control group, there was a significant decrease in the incidence of ALRTI (9.6% vs. 24.6%, $p < 0.01$), FN (1.7% vs. 7.3%, $p < 0.001$) and neutropenia (8.3% vs. 23.3%, $p < 0.01$) in the PEG-rhG-CSF group. The incidence of ALRTI was significantly correlated with the grade of CTCAE on ANC. The main adverse reactions of PEG-rhG-CSF were pain and fatigue, among which three cases showed pain of ≥ grade 3. The cost of infection-associated medical expenditure in the treatment group was greatly reduced compared with the control group ($p < 0.001$).

Conclusions: ALRTI could well be prevented after prophylactic application of PEG-rhG-CSF (3 mg), and was related to the reduced neutropenia.

KEYWORDS
human granulocyte, lung cancer, neutropenia, pegylated recombinant human granulocyte colony-stimulating factor

INTRODUCTION

Chemotherapy is an effective therapeutic strategy for treating patients with advanced lung cancer that cannot be entirely managed after the administration of tyrosine kinase inhibitors or immune checkpoint inhibitors. To the best of our knowledge, the main chemotherapy-related toxicity is myelosuppression, while chemotherapy-induced neutropenia (CIN) is associated with an increased risk of pulmonary infection, especially in those individuals with lung cancer.[1,2]

Febrile neutropenia (FN) is a common, life-threatening complication in patients with hematological malignancy who undergo chemotherapy. It is defined as an oral temperature of ≥38.5°C, or body temperature ≥ 38.0°C sustained for at least 1 h or that occurs twice within 24 h, and absolute neutrophil count (ANC) < 0.5×10^9/l in peripheral blood,

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or expected decrease over the subsequent 48 h.[3] A high number of cancer patients (10%–22%) present with FN after chemotherapy, and the incidence of FN in patients with lung cancer is relatively low compared with those with hematological malignancies.[4] However, the incidence of pneumonia in patients with lung cancer after chemotherapy has previously been reported to be approximately 2-fold higher than that of other solid tumors.[2,5]

Some patients present with acute bronchitis after chemotherapy, which may lead to a delay in chemotherapy, increased antibiotic use, longer hospital stay, as well as increased healthcare spending.[6] To the best of our knowledge, few studies have focused on acute bronchitis after chemotherapy. In a previous study by Crawford et al., the probability of infection caused by CIN was still high in the case of neutropenia, and even the neutrophil counts did not meet the FN criteria. In addition, the incidence of infection was even higher followed by a longer duration of a low ANC.[7]

For lung cancer patients, the myelosuppression induced by chemotherapy is usually not severe, with an extremely low incidence of FN compared with other malignancies, especially hematological malignancies.[8,9] Pegylated recombinant human granulocyte colony-stimulating factor (PEG rhG-CSF) has been widely utilized for treating lung and breast cancer, as well as hematological malignancies. According to the NCCN guidelines, a recommended dose of PEG rhG-CSF for chemotherapy-induced neutropenia is a single dose of 100 μg/kg or a fixed dose of 6 mg per chemotherapy cycle.[10] Although a few studies have reported that a dose of 6 mg PEG rhG-CSF is safe and effective for patients receiving a less intense chemotherapy regimen,[11,12] further investigation is still required to illustrate whether a dose of 6 mg or 100 μg/kg is suitable for these patients. Zhang et al. proposed a dose of 3 mg PEG rhG-CSF as a support for a dose-dense epirubicin/cyclophosphamide-paclitaxel (ddEC-P) regimen among Chinese breast cancer patients with positive auxiliary lymph nodes.[13] In a previous study of different doses and frequencies of PEG rhG-CSF in patients with CIN, a single dose of 60 μg/kg or 100 μg/kg produced a similar neutrophil response.[14] In addition, there has been a study on the efficacy and safety of 1.8, 3.6, and 6.0 mg pegfilgrastim after chemotherapy in breast cancer. Among them, this finding indicated that pegfilgrastim efficacy peaked at 3.6 mg.[15] This prospective randomized study was designed to investigate the efficiency of 3 mg PEG rhG-CSF in preventing acute lower respiratory tract infection (ALRTI) after chemotherapy.

METHODS

Patients

In this prospective study, we included stage IIIB–IV lung cancer patients with normal bone marrow function who were admitted to the Department of Respiratory and Critical Care Medicine Qilu Hospital of Shandong University between April 2017 and January 2019. The inclusion criteria were as follows: (i) Aged 18–75 years, and (ii) an ECOG performance status of 0 or 1. Patients were excluded from the study if they met the following criteria: (i) previous exposure to G-CSF or other erythropoietic drug; (ii) pregnant or those in a lactation period; (iii) had immunodeficient diseases or coagulation disorders; (iv) a history of hematonosis; (v) had received administration of antibiotics within 72 h; (vi) had active infection; (vii) a history of FN; (viii) had other current diseases, such as heart failure, or psychiatric illness that might affect treatment compliance, as well as (ix) those with absolute neutrophil count (ANC) > 1.5×10^9/l, hemoglobin >90 g/l, platelets >100×10^9/l, ALT, AST, bilirubin and creatinine <1.5-fold of the upper limits of the normal range. Ethical approval for the trial was obtained before its initiation. All patients provided their written informed consent for inclusion in this study.

Treatment and control groups

The patients scheduled for chemotherapy were divided into two groups: the treatment group in which patients only received PEG-rhG-CSF for prevention of pneumonia, and the control group who received no PEG-rhG-CSF. All the enrolled patients were in the first-line chemotherapy phase and would receive platinum-containing regimens. Chemotherapy regimen, chemotherapy cycle, age and gender were considered as the stratified factors. On day 1, patients received the chemotherapy, respectively. The regimens for squamous cell carcinoma were as follows: Paclitaxel 150 mg/m^2 and carboplatin AUC = 5 (Calvert formula: carboplatin dosage [mg] = AUC [mg/ml/min] × creatinine clearance rate [Ccr] [ml/min] + 25). Patients with nonsquamous cell carcinoma were recommended to undergo the following therapy: Pemetrexed 500 mg/m^2 and carboplatin AUC = 5. SCLC: etoposide 100 mg/m^2 and cisplatin 50 mg/m^2 (day 1–2).

PEG-rhG-CSF administration

PEG-rhG-CSF (Qilu Pharmaceutical Group) was subcutaneously administered at a dose of 3 mg on day 2 in each treatment cycle. Blood count was measured on day 5 and 9 after treatment.

Adverse events and dose modifications

Treatment-emergent adverse events (TEAEs) were recorded within 30 days after chemotherapy. The severity of the adverse events (AEs) was defined based on the Common Terminology Criteria for Adverse Events (CTCAE). Before receiving chemotherapy, the patients were required to be in a state of adequate hematological recovery that was defined by neutrophil count of ≥2.0×10^9/l. For those with a neutrophil count of less than 2.0×10^9/l, G-CSF (3–5 days) was

used to treat adverse events. For those with a neutrophil count of less than 2.0×10^9/l on day 7, the dose should be reduced by 15% during the same remaining cycles of the same chemotherapy. However, neutropenia (CTCAE grade 1, 2, 3 or 4) was recorded in the electronic Case Report Form, in order to evaluate the efficiency of PEG-rhG-CSF. Those patients in which there was a delay in receiving chemotherapy for more than four days due to neutropenia, ALRTI or other AE were recorded.

Extra medical expenses

This refers to the extra medical expenses caused by neutropenia and respiratory tract infection in patients from the end of the chemotherapy cycle to the next treatment, especially including antibiotics, related treatment, prolonged hospitalization and related costs. The expenditure of 3 mg PEG-rhG-CSF should be included in the total expenses for the patients in the treatment group.

Outcomes

In this study, the primary outcome was the incidence of ALRTI including pneumonia and bronchitis. Pneumonia was diagnosed based on the following criteria: chest imaging indicated new patchy infiltration, leaf or segmental consolidation, or ground-glass shadow, according to the previous description.[16] Bronchitis was diagnosed based on clinical signs and symptoms, as well as a computed tomography (CT) scan.[17] The secondary outcome was ANC, FN, incidence of delayed chemotherapy, infection-related medical expenses and adverse reactions. Data on the parameters mentioned above were collected in one cycle of the first-line chemotherapy.

Statistical analysis

All statistical analysis was performed using IBM SPSS Statistics for Windows, Version 22.0 (IBM Corp.). A *t*-test, descriptive statistics, and Chi-square test were used to analyze the data. A

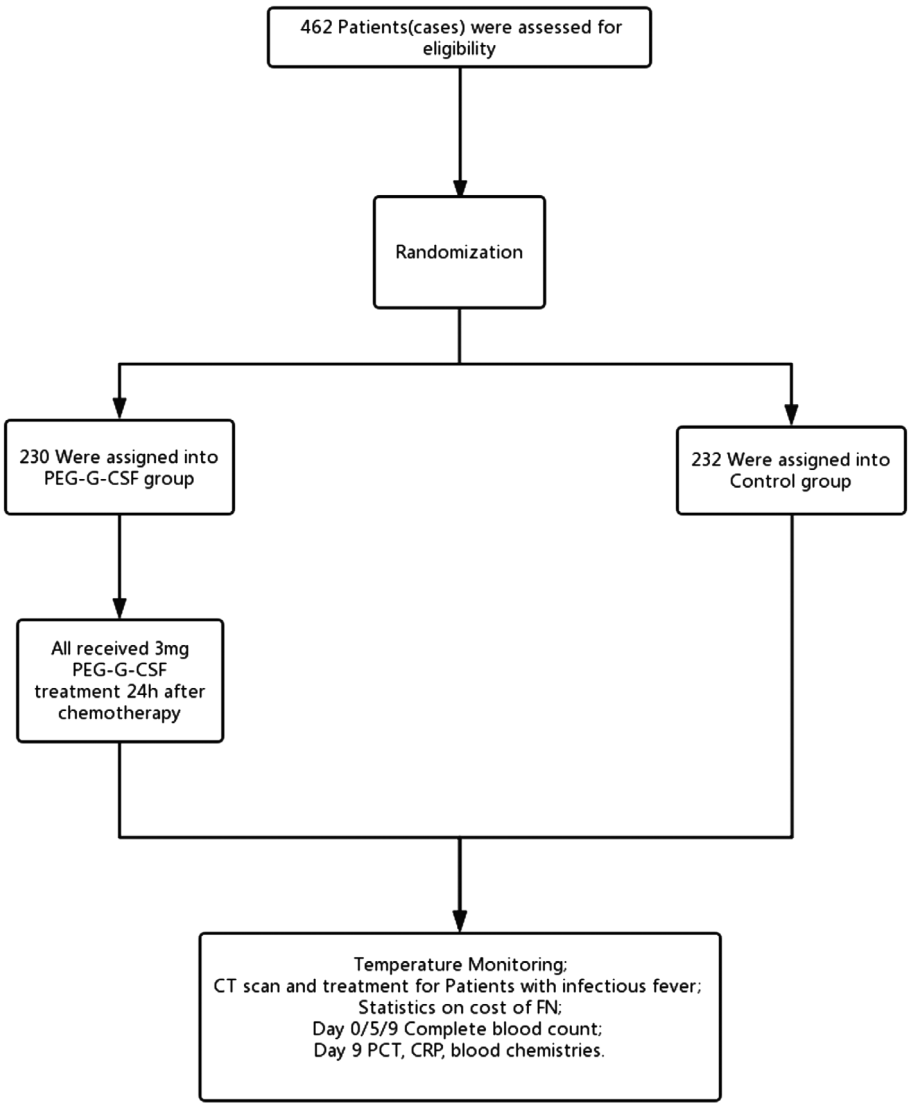

FIGURE 1 Study flow chart: Eligibility, randomization and analysis

p-value of less than 0.05 was considered statistically significant. Analysis of the data was stratified by chemotherapy regimens and cycles, age and other risk factors.

RESULTS

Patient demographics

In total, 489 patients were enrolled into this study, among which 27 cases were censored for lost to follow-up ($n = 12$) or incomplete records ($n = 15$). Finally, 462 cases were included in this study at stage IIIB–IV, with the histopathological types of non-small cell lung cancer (NSCLC) or small cell lung cancer (SCLC) (Figure 1). The median age in the treatment and control groups was 62 years (53–68 years) and 62 years (55–65 years), respectively. The patient characteristics are shown in Table 1. There were no statistical differences in the baseline demographics between the PEG-rhG-CSF group and the control group.

Comparison of ALRTI incidence between both groups

The incidence of acute lower respiratory tract infection in the patients who received prophylactic utilization of PEG rhG-CSF (3 mg) was significantly lower than that of the control group. The incidence of ALRTI in the PEG-rhG-CSF group was significantly lower than that of the control group (24.6% vs. 9.6%, $p < 0.01$). Patients in the control group were more likely to present with pneumonia compared with those who underwent treatment with PEG-rhG-CSF (13.4% vs. 5.7%, $p < 0.01$, Figure 2).

Change in neutrophil counts after administration

In the follow-up, the number of subjects lost was 25 and 31 in the PEG-rhG-CSF group and control group, respectively. After excluding the patients with loss of partial data, 205 and 201 cases were finally included in the treatment and control groups, respectively. The ANC was measured on days 0, 5 and 9 after chemotherapy, respectively. There were no statistical differences at the baseline levels between the two groups (Table 2 and Figure 3). Nevertheless, ANC showed a significant increase on days 5 and 9 ($p < 0.0001$). Compared with the data of day 5, ANC had fallen back on day 9 in the treatment group ($p < 0.001$, Figure 3a and b). Also, ANC of the study group was higher than that of the control group as previously ($p < 0.0001$, Figure 3c).

Treatment efficacy of PEG rhG-CSF on preventing neutropenia and FN

The overall incidence of neutropenia in the control group was significantly higher than of the PEG rhG-CSF group

TABLE 1 Characteristics of enrolled patients

Characteristic	PEG-rhG-CSF group ($n = 230$)	Control group ($n = 232$)
Median age (range) - year	62 (53–68)	62 (55–65)
Gender		
Male	145	141
Female	85	91
Average cycles of chemotherapy	2.3 ± 0.2	2.5 ± 0.2
ECOG performance - status score (%)		
0	133 (57.8)	146/232 (62.9)
1	97 (42.2)	86/232 (37.1)
Histopathological type (%)		
Nonsquamous cell NSCLC	162 (70.4)	163 (70.3)
Squamous cell carcinoma	30 (13.0)	28 (12.0)
SCLC	38 (16.5)	41 (17.7)
Complications (%)		
COPD	45 (19.6)	42 (18.1)
Diabetes	46 (20.0)	41 (17.7)
Cardiovascular diseases	55 (23.9)	62 (26.7)
Hematological disease	0 (0)	0 (0)
Other	27 (11.7)	20 (8.6)
EGFR-TKI administration - no. (%)	18 (7.8)	14 (6.0)
Concurrent radiotherapy (SCLC) (%)	11 (4.8)	12 (5.2)

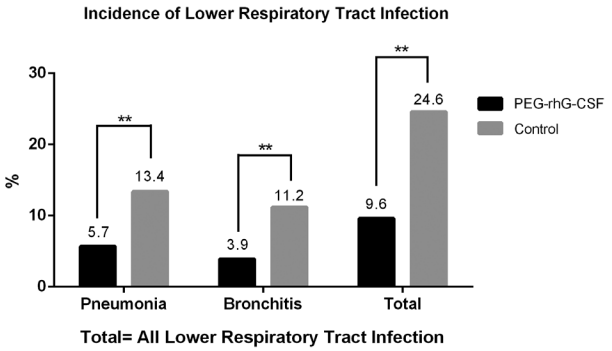

FIGURE 2 The incidence of lower respiratory tract infection in treatment group and control. Total means all ALRTI, including pneumonia and bronchitis (**$p < 0.01$)

TABLE 2 Average values of ANC of patients after administration

Day	PEG-rhG-CSF ($n = 205$)[a]	Control ($n = 201$)[b]	*p*-value
0	5.35 ± 0.15	5.69 ± 0.17	0.15
5	11.26 ± 0.30	4.91 ± 0.17	<0.0001
9	6.22 ± 0.25	3.66 ± 0.14	<0.0001

Abbreviation: ANC, absolute neutrophil count.
Note: All data are shown as mean ± SEM.
[a]Some data from 25 patients were lost to follow-up.
[b]Some data from 31 patients were lost to follow-up in the control group.

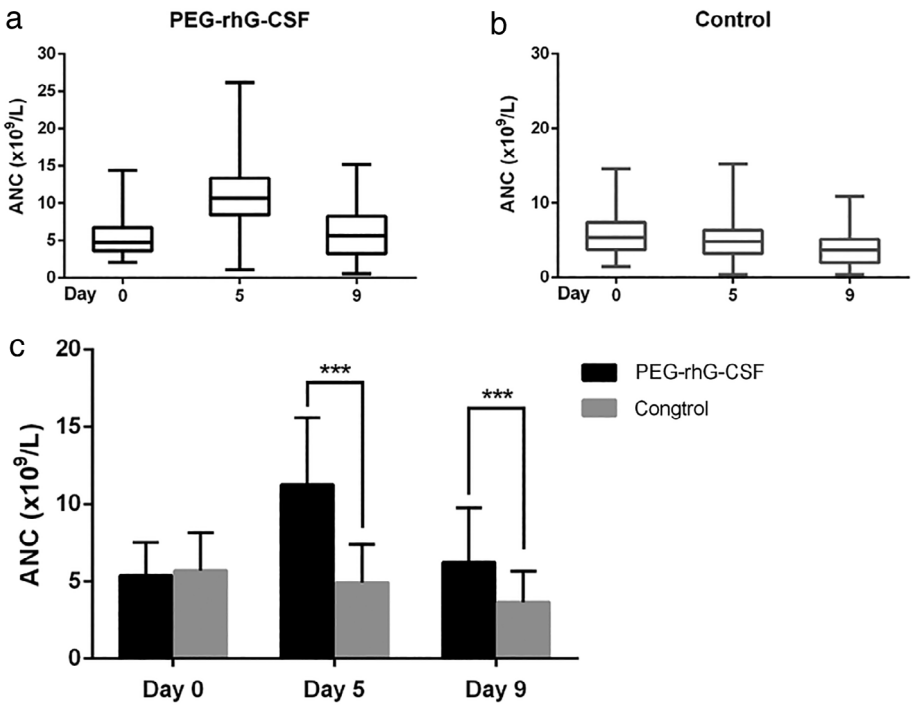

FIGURE 3 (a) Change of ANC in the treatment group on days 0, 5, 9. (b) The change of ANC in the control group on days 0, 5, 9. (c) Comparison on ANC of two groups (***$p < 0.001$)

TABLE 3 Number and incidence of neutropenia, and febrile neutropenia

	PEG-rhG-CSF group ($n = 230$) Number of patients (percent)	Control group ($n = 232$)	*p*-value
Grade 1/2 neutropenia	13 (5.7)	29 (12.5)	0.01
Grade 3/4 neutropenia	6 (2.6)	26 (11.2)	<0.001
Total neutropenia	19 (8.3)	55 (23.7)	<0.01
FN[a]	4 (1.7)	17 (7.3)	<0.001

[a]New or aggravating respiratory tract symptoms. Chest x-ray or CT scan may show newly emerging patchy shadows or other infective features.
Abbreviation: FN, febrile neutropenia.

TABLE 4 Incidence of pneumonia and bronchitis in patients with or without neutropenia

	Lower respiratory tract infection		
	Pneumonia Number of patients (percent)	Bronchitis	Total
PEG-rhG-CSF ($N = 230$)			
Not neutropenia ($n = 211$)	9 (4.3)	7 (3.3)	16 (7.6)
Grade 1/2 neutropenia ($n = 13$)	2 (15.3)	1 (7.6)	3 (23.1)
Grade ≥ 3 neutropenia ($n = 6$)	2 (33.3)	1 (33.3)	3 (50.0)
Total neutropenia ($n = 19$)	4 (21.1)	2 (10.5)	6 (31.6)
Control ($N = 232$)			
Not neutropenia ($n = 178$)	14 (7.3)	12 (6.7)	26 (14.6)
Grade 1/2 neutropenia ($n = 29$)	7 (24.1)	5 (17.2)	12 (41.3)
Grade ≥ 3 neutropenia ($n = 26$)	11 (42.3)	9 (34.6)	20 (76.9)
Total neutropenia ($n = 55$)	17 (30.9)	14 (29.1)	31 (56.4)

(23.7% vs. 8.3%, $p < 0.01$). In the PEG rhG-CSF group, the overall incidence of grade 1/2 neutropenia showed a significant decline compared with the control group (5.7% vs. 12.5%, $p = 0.01$), as well as grade 3/4 neutropenia (2.6% vs. 11.2%, $p < 0.001$). For the FN rate, there was a significant decrease in the PEG rhG-CSF group compared with that of the control group (1.7% vs. 7.3%, $p < 0.001$, Table 3).

TABLE 5 Number and incidence of neutropenia and febrile neutropenia in the subgroups

		Neutropenia Number of patients (percent)	*p*-value	Acute lower respiratory tract infection	*p*-value
PEG-rhG-CSF ($N = 230$)	PEG-rhG-CSF-A ($n = 162$)	12 (7.4)		13 (8.0)	
	PEG-rhG-CSF-Sq ($n = 30$)	3 (7.8)		3 (10.0)	
	PEG-rhG-CSF-Sc ($n = 38$)	4 (10.5)	$p > 0.05$	6 (15.8)	$p > 0.05$
Control ($N = 232$)	Control-A ($n = 163$)	34 (20.9)	163	34 (20.9)	
	Control-Sq ($n = 28$)	6 (21.4)		7 (25.0)	
	Control-Sc ($n = 41$)	14 (34.1)	$p > 0.05$	16 (39.0)	$p = 0.054$

Abbreviations: A, adenocarcinoma; Sq, squamous cell carcinoma; Sc, small cell carcinoma.

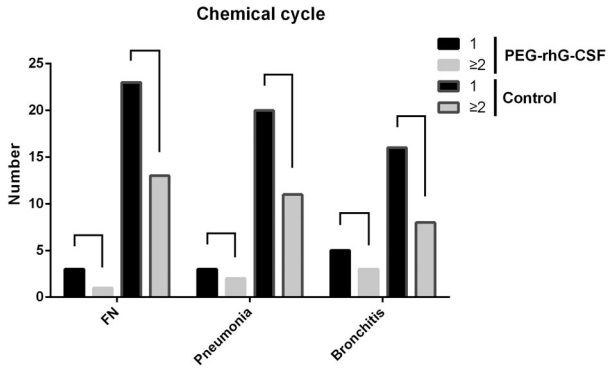

FIGURE 4 Respective incidence of FN, pneumonia, and bronchitis in patients who were treated with chemotherapy in the PEG-G-CSF and control groups. These mainly occurred in the first cycle of chemotherapy (60%–75%) for consecutive patients with a similar tendency shown in both groups

Relationship between neutropenia and ALRTI

Regarding the incidence of ALRTI, significant differences were found between the two groups according to variable ANC levels. In the control group, data analysis was conducted by Chi square test ($\chi^2 = 36.6587$, $p < 0.0001$). Fisher's exact test was used in the treatment group as the number of samples in each subgroup was small ($p = 0.0025$).

In addition, the incidence of ALRTI gradually increased as the even lower ANC level. The probability of ALRTI in patients with normal ANC was much lower than that in patients with neutropenia, and patients with grade 3/4 neutropenia suffered ALRTI more frequently than patients with grade 1/2 (Cochran Armitage trend test, treatment group: $Z = 3.8376$, $p < 0.0001$; control group, $Z = 5.7898$, $p < 0.0001$, Table 4).

Impact of chemotherapy regimens and cycle

There were no significant differences in the incidence of ALRTI and neutropenia among the subgroups in the chemotherapy regimens. The data of SCLC were nearly twofold higher than that of NSCLC, but with no statistical differences ($p > 0.05$, Table 5). In addition, approximately 60%–75% of FN and infection caused by chemotherapy occurred in the first cycle (Figure 4), which was similar for bronchitis and pneumonia.

Adverse events (AEs)

Adverse events occurred in 78.70% and 84.5% of patients in the treatment and control groups, respectively. Despite interference by chemotherapy, there was a significant increase in fatigue (33.0%) in the treatment group compared with the control group ($p < 0.05$), which was also the most common side-effect in patients treated with PEG-rhG-CSF. The incidence of pain including myalgia and arthralgia was 15.7%. Excluding infection, fever was only 5.6% in the treatment group (Table 6) within three days after chemotherapy. Except for fatigue, all the AEs after administration of PEG rhG-CSF were not higher than the control group ($p > 0.05$). Some side-effects were found to be greater than 30%, including nausea, vomiting, abdominal distention, anorexia and other gastrointestinal reactions, but these were not higher than the control group. All the AEs could be easily managed using a standard protocol.

Among the AEs ≥ grade 3, three patients in the treatment group had back or lower limb pain, but the reason could not be clearly identified as due to chemotherapy or PEG rhG-CSF. In terms of thrombocytopenia, there was only an increase by one case in the treatment group compared to the control group. The incidence of anemia and gastrointestinal reaction were similar in both groups. Nausea, vomiting and diarrhea were AEs of ≥ grade 3, but these were mainly related to chemotherapy. No grade 5 AEs were observed in both groups. All AEs improved according to the guidelines (Table 7).

Influence on chemotherapy delay, hospital readmission rate, antibiotic use and related medical expenditure

There was no dose reduction and only three patients had a treatment delay after administration of PEG-rhG-CSF. This could be completely improved after secondary prevention of

TABLE 6 Incidence of treatment-related adverse events

Event (%)	PEG-rhG-CSF group ($n = 230$) Number of patients (percent)	Control group ($n = 232$)
Fatigue	76 (33.0)[a]	36 (15.5)
Fever[b]	13 (5.6)	7 (3.0)
Pain[c]	36 (15.7)[d]	17 (7.3)
Nausea	74 (32.2)	85 (36.6)
Vomiting	27 (11.7)	22 (9.5)
Diarrhea	29 (12.6)	23 (9.9)
Constipation	47 (20.4)	44 (19.0)
Anorexia	58 (25.2)	62 (26.7)
Peripheral neuropathy	18 (7.8)	16 (7.0)
Oral mucositis	20 (8.7)	19 (8.2)
Rash	8 (3.4)	6 (2.6)
Hypertension	12 (5.2)	10 (4.3)
Paresthesia	11 (4.8)	8 (3.4)
Anemia	61 (26.5)	64 (27.5)
Thrombocytopenia	43 (18.7)	28 (12.1)
Venous thrombosis	3 (1.3)	4 (1.7)
Abnormal ALT	26 (11.3)	31 (13.3)
Abnormal Cr	7 (3.0)	5 (2.2)

Note: All the adverse events are shown with the rate ≥ 1%.
[a]Exclusion of infective fever.
[b]The data of PEG-G-CSF was higher than that of the control group ($p < 0.05$).
[c]Pain including bone pain, myalgia, and arthralgia.
[d]The data of PEG-G-CSF was higher than that of the control group ($p < 0.05$).

TABLE 7 Incidence of treatment-related adverse events (grade ≥ 3)

Event (%)	PEG-rhG-CSF group ($n = 230$) Number of patients (percent)	Control group ($n = 232$)
Pain	3 (1.3)	0 (0)
Nausea	13 (5.7)	11 (4.7)
Vomiting	8 (3.5)	6 (2.6)
Diarrhea	6 (2.6)	8 (3.4)
Peripheral neuropathy	3 (1.3)	4 (1.7)
Thrombocytopenia	6 (2.6)	4 (1.7)
Anemia	4 (1.7)	5 (2.2)

Note: There was no statistical difference in all of the above ($p > 0.05$).

PEG rhG-CSF (or at an increased dose to 6 mg). Hospital readmission rate of the treatment group was significantly higher than that of the control group (15.9% vs. 3.0%, $p < 0.01$). Medical expenditure in the treatment group was significantly lower than that of the control group (2104 ± 114 CNY vs. 2982 ± 391 CNY, $p < 0.0001$). Preventive application of PEG rhG-CSF contributed to a reduction of associated medical expenditure. There were relative differences on a larger scale in expenditure in the control group, where there were particularly high costs due to hospitalization as a result of pneumonia, treatment delay, or even ICU admission.

DISCUSSION

Lung cancer is the leading cause of cancer-related death in China.[18] Although molecular-targeted drugs can significantly improve the prognosis, only some adenocarcinoma patients benefit from it. However, chemotherapy-related bone marrow suppression limits the implementation of chemotherapy. In addition, chemotherapy-induced agranulocytosis, infection and other factors are the main reasons for delayed chemotherapy and rising expenditure.[2,19]

G-CSF can be used to attenuate myelosuppression after chemotherapy. It has been reported that bone marrow suppression accounts for 38% of the delay in a 3-week regimen of chemotherapy, but the application of G-CSF reduces the proportion to 15%.[19] Therefore, the guidelines recommend that 6 mg PEG rhG-CSF is the first choice for prevention of CIN. PEG rhG-CSF is considered as an ideal substitute for the treatment of myelotoxicity, and G-CSF is nowadays mainly used for salvage treatment. Compared with G-CSF, PEG rhG-CSF can significantly reduce the number of repeat injections, and thereby has the advantage of fewer injections and less side effects. It can prevent the occurrence of FN, improve the quality of life of chemotherapy patients, and reduce the risk of chemotherapy delay.[20,21]

Respiratory tract infection is the most common infection, and lung cancer is one of its susceptible factors. The incidence of respiratory infection after chemotherapy is significantly higher than that of other malignancies, especially ALTRI that interferes with progression of the chemotherapy planning regimen. In this study, the risk of new ALRTI after chemotherapy was as high as 24.6% in patients with no administration of PEG-rhG-CSF, while the incidence of pneumonia was 13.4% after PEG-rhG-CSF, which is consistent with the results of a previous study.[2]

Neutropenia leads to a remarkable increase in infection. In previous studies, when ANC decreased by one week, the probability of infection caused by grade 3–4 neutropenia was 10%–30%.[7,22] Previously, few studies have focused on the relationship between neutropenia (<grade 3) and respiratory infection.[2,3] In this study, all grade 1–4 neutropenia could cause lower respiratory tract infection, especially pneumonia. The incidence increased with the grade of neutropenia. The rate of ALRTI in patients with grade 1–2 neutropenia was up to 41.3%, which was much higher than that in patients with normal ANC. The rate in patients with neutropenia of grade 3 or above was 76.9%. Primary prevention of neutropenia should not merely focus on FN. The application of PEG rhG-CSF can effectively reduce the incidence of pneumonia and bronchitis by preventing neutropenia, which also reduces the incidence of FN.

In a hospital-based study of patients admitted with febrile neutropenia from 2006 to 2015, Al-Tawfiq et al. reported that the source of infection could be identified in

27.5% of the patients with FN, and was found to be mainly bacteremia and pneumonia. Fatal infection rate was 11.2%. About 81% of the patients showed signs of infection on chest imaging, and the incidence of pneumonia was 9.2%.[23] As for the different intensity of chemotherapy in different types of malignant tumor, the incidence of FN in different types of cancer chemotherapy was significantly different. The incidence of FN in lymphoma after chemotherapy was more than 50%; however, it was only 15%–20% in breast, lung, and ovarian cancers.[3] Although the incidence of CIN was not higher than that in other cancers, such as liver cancer, respiratory infection may on the contrary be higher. The anatomical and physiological changes caused by lung cancer increase the susceptibility of patients to ALTRI. The incidence of pneumonia caused by chemotherapy of lung cancer is also higher than that of other solid tumors.[24]

According to the recommendation of the NCCN guidelines, a dose of 6 mm is suggested for PEG rhG-CSF in clinical practice.[25,26] However, the clinical application of the dose relies entirely on the differences in race and cancer types. In addition, PEG-rhG-CSF still has its own adverse effects. In a previous study, a dose of 3 mg was effective in Chinese breast cancer patients who were scheduled to receive a dose-dense every-two-week epirubicin/cyclophosphamide-paclitaxel regimen.[13] On this basis, we investigated the efficiency of 3 mg for the preventive therapy of lung cancer patients scheduled to undergo chemotherapy.

The AEs of PEG rhG-CSF included musculoskeletal pain, fever, chills, body aches, flu symptoms, shortness of breath and allergic reactions.[26,27] In a previous study, Zhang et al. reported that the incidence of pain was 35% with 6 mg PEG-rhG-CSF.[13] In this study, 3 mg of PEG rhG-CSF contributed to a decrease in AEs. The incidence of pain in particular was reduced to only 15.7%. Our data showed that the main adverse reactions of 3 mg PEG rhG-CSF are still fatigue and pain. However, gastrointestinal reaction, rash, anemia, thrombocytopenia and other aspects showed no statistical differences compared with those of the control group. Additionally, the incidence of most adverse reactions was similar with the average level after chemotherapy according to a previous study.[28] This implied that these AEs may be associated with the chemotherapy rather than PEG-rhG-CSF.

Patients who underwent chemotherapy had an up to 15.0-fold increase in the odds of showing neutropenia compared with their counterparts who received no chemotherapy. These patients with neutropenia were reported to have large incremental expenditures in hospital stay and emergency room visits.[29] In this study, compared with the overall treatment cost of PEG rhG-CSF primary prevention and salvage treatment after neutropenia, the infection-related medical expenses in the control group who received no primary prevention using PEG-rhG-CSF was even higher. The increase in expenditure in the control group mainly included anti-infection treatment, hospitalization expenses including ICU stay, and additional expenditure caused by treatment delay. Therefore, a dose of 3 mg PEG rhG-CSF can significantly reduce the cost of treatment, the economic burden of patients and medical insurance payments compared with the 6 mg PEG rhG-CSF regimen.

There are some limitations in this study. We were unable to compare the efficiency of a dose of 3 mg and a dose of 6 mg in this study. In future, more studies are required to illustrate the comparison between the two doses.

Prophylactic application of 3 mg PEG rhG-CSF may contribute to a reduction in the risks of ALRTI, related to the reduced neutropenia. We recommend the use of 3 mg PEG rhG-CSF for primary prevention in lung cancer after chemotherapy, as in this study we found that it was associated with reduced infection rate and pain in Chinese lung cancer patients compared with the recommended dose of 6 mg following the NCCN guidelines.

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CONFLICT OF INTEREST

All authors have completed the ICMJE uniform disclosure form. The authors have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

The authors have completed the Data Sharing Statement. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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