A Real World Study: What is The Proper Dose of PEG-rhG-CSF for Grade IV Myelosuppression in Asian Cancer Patients?

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Research Article

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Abstract

Purpose To evaluate the efficacy, safety and cost-effectiveness of different doses of PEGylated recombinant human granulocyte stimulating factor (PEG-rhG-SF) for grade IV myelosuppression in Asian cancer patients.

Methods One hundred and thirty-two cases of patients with malignant tumors who had grade IV myelosuppression after chemotherapy from January 2019 to December 2020 were collected. According to the different doses, they were divided into two groups: 76 cases in group A (3mg PEG-rhG-CSF) and 56 cases in group B (6mg PEG-rhG-CSF). Clinical efficacy and adverse reactions were compared, and treatment cost was calculated so that cost-effectiveness analysis in pharmacoeconomic was compared between two groups.

Results There was no significant difference in clinical efficacy between group A and group B ($p > 0.05$). There were no death, febrile neutropenia (FN) and hospitalization during the chemotherapy cycles. The incidences of adverse reactions were 15.79% and 32.14% in group A and group B and showed a significant difference ($p < 0.05$). The cost of these two regimens was RMB 1713 for group A and RMB 3418 for group B, the regimen in group A was more economical.

Conclusion The regimen in group A (3mg PEG-rhG-CSF) is the proper option for grade IV myelosuppression in Asian cancer patients, considering the efficacy, safety, and cost-effectiveness analysis.

Introduction

Neutropenia is the most common hematological toxicity of chemotherapy, which is directly related to the risk of infection or even death. It is also the main reason for inadequate dosage and delaying of chemotherapy cycle, which has bad influence on the prognosis of patients[1]. Recombinant human granulocyte stimulating factor (rhG-CSF) is the standard option for the prevention of chemotherapy-induced neutropenia. However, Owing to short half-life of rhG-CSF, frequent injection is often needed which leads to poor compliance[2].

PEGylated recombinant human granulocyte stimulating factor (PEG-rhG-CSF), a long-acting formulation of rhG-CSF, is a protein formed by polyethyleneglycol covalently bound to the N-terminus of the amino acid sequence of rhG-CSF[3, 4]. PEG-rhG-CSF has a longer half-life and allows for less frequent dosing. A single injection of PEG-rhG-CSF can significantly reduce the frequency and pain of injections, and effectively raise white blood cells (WBC) and absolute neutrophil count (ANC)[5, 6]. PEG-rhG-CSF was FDA-approved at the dose of 6 mg per chemotherapy cycle. Although a lot of research has been performed to examine the efficacy of PEG-rhG-CSF as support for chemotherapy-induced neutropenia, little data can be found on the proper dose of PEG-rhG-CSF in Asian cancer patients[7–9].

An additional consideration was that the fixed dose of 6 mg might result in an altered safety profile in Asian patients who are always lighter than Western patients. Previous study showed that the duration of grade IV myelosuppression was 2.2 ± 0.9 days, 1.5 ± 0.9 days, and 1.4 ± 0.7 days in the 1.8, 3.6, and 6.0 mg groups in Japanese patients, respectively[10]. This finding indicated that PEG-rhG-CSF efficacy peaked at 3.6 mg and a 3.6 mg dose may be safe and effective for Japanese patients. Another study also demonstrate a single dose of 60 µg/kg or 100 µg/kg PEG-rhG-CSF per cycle produced a similar effect in patients receiving less-intense chemotherapy regimens[11], suggested that less-intense regimens may require fewer than 100 µg/kg of PEG-rhG-CSF. Phase III study show that 100 ug/kg PEG-rhG-CSF used as a prophylaxis for intensive chemotherapy regimens may be too strong for less aggressive regimens, and could lead to more toxic side effects[12].

Moreover, PEG-rhG-CSF is relatively expensive. In the real world practice, the dosage at 3 mg/cycle is more commonly used than 6 mg/cycle due to economic considerations, and dosage at 3 mg/cycle can also achieve some therapeutic effect. To provide reference for clinical use, clinical efficacy, safety and cost-effectiveness analysis between two different doses of PEG-rhG-CSF were compared in the present study.

Materials And Methods

Patients

We collected 132 patients (70 male, 53%) with malignant tumors having grade IV myelosuppression after chemotherapy in the First Affiliated Hospital of Science and Technology of China (USTC) from January 2019 to December 2020 with an average age of 57.1 ± 10.9 years. All patients received PEG-rhG-CSF 24 h after chemotherapy as a single subcutaneous injection per chemotherapy cycle. This study was approved by the First Affiliated Hospital of USTC, Division of Life Sciences and Medicine, University of Science and Technology of China.

Patients were eligible for study enrollment if they met the following inclusion criteria: (1) Patients with malignant tumor diagnosed by histopathology and/or cytology; (2) Aged ≥ 18 years old; (3) No obvious blood system disease; (4) Eastern Cooperative Oncology Group Performance Status (ECOG-PS): 0–2; (5) Estimated survival ≥ 3 months; (6) Patients with grade IV myelosuppression($WBC < 1.0 \times 10^9/L$ or $ANC < 0.5 \times 10^9/L$)caused by chemotherapy, and were intend to use PEG-rhG-CSF.

Patients were excluded if they: (1) Patients received hematopoietic stem cell transplantation or bone marrow transplantation; (2) Patients with allergic diseases, allergies, or allergic to this product or other biological products derived from genetically engineered E. coli; (3) Patients with severe mental or nervous system disorder, which may affect informed consent and/or adverse reaction presentation or observation; (4) Patients with severe infections throughout the body.

Treatment settings

All patients were treated by PEG-rhG-CSF (specification: 3 mg/1 ml) and divided into two groups. Patients chose 3 mg per cycle in group A and chose 6 mg per cycle in group B as treating dosage. All cytotoxic agents were administrated on day 1 of the 21-day regimens. PEG-rhG-CSF was subcutaneously injected at the lower edge of the deltoid muscle with 3 minutes pressing during 24 hours after chemotherapy, and it was a single-dose administration in each chemotherapy cycle. The WBC and ANC values were recorded in both groups during the chemotherapy cycle. The recovery results were evaluated before the following cycle (3 weeks per cycle).

Efficacy evaluation criteria

WBC and ANC outcomes after treatment were collected during the chemotherapy cycle, as well as patient's condition changes. (1) WBC outcome: $WBC \geq 4.0 \times 10^9/L$ was classified as Normal; $3.0 \times 10^9/L \geq WBC > 4.0 \times 10^9/L$ was classified as Grade 1; $2.0 \times 10^9/L \geq WBC > 3.0 \times 10^9/L$ was classified as Grade 2; $1.0 \times 10^9/L \geq WBC > 2.0 \times 10^9/L$ was classified as Grade 3 and $0 \geq WBC > 1.0 \times 10^9/L$ was classified as Grade 4. (2) ANC outcome: $ANC \geq 2.0 \times 10^9/L$ was classified as normal; $1.5 \times 10^9/L \geq ANC > 2.0 \times 10^9/L$ was classified as Grade 1; $1.0 \times 10^9/L \geq ANC > 1.5 \times 10^9/L$ was classified as Grade 2; $0.5 \times 10^9/L \geq ANC > 1.0 \times 10^9/L$, was classified as Grade 3 and $0 \geq ANC > 0.5 \times 10^9/L$ was classified as Grade 4.

ECOG-PS was used to describe patients' subjective symptomatic experience, including physical function, anxiety, depression, fatigue, sleep disturbance, and pain. ECOG-PS scale (range: 0–5) was independently scored by physician oncologists to predict clinical outcomes after PEG-rhG-CSF administration.

Safety evaluation criteria

Adverse drug reactions in patients after administration were observed and recorded throughout the chemotherapy cycle as to likely related to treatment. The adverse reactions were classified according to the NCI Common Terminology Criteria for Adverse Events (CTCAE version 4.0)[4].

Cost determination

The costs of pharmacoeconomics include direct costs, indirect costs, and hidden costs. Relatively, indirect and hidden costs are related to more incalculable factors, and the difference between these two is not quite significant. So in this study, only direct costs were evaluated between the two groups. Direct costs include expenses for drugs, inspections, injections, materials, and treatment of adverse reaction. In this study, all expenses are the same between group A and group B, except drug costs, and all expenses are calculated according to the price standard of the Anhui provincial drug procurement platform[13].

Statistical analysis

Most of the statistical analysis was performed using SPSS 22.0. The clinical efficacy was compared using a two-sample hierarchical rank-sum test, and the safety comparison was performed using a chi-square test ($R \times C$ contingency table). All statistical tests were performed using a two-sided test. $P < 0.05$ was determined that the difference was statistically significant.

Results

Patient's characteristics

According to the different dosage of PEG-rhG-CSF, 76 cases treated with PEG-rhG-CSF at the dose of 3 mg were included in group A (35 males and 41 females), while 56 cases treated at dose of 6 mg was included in group B (35 males and 21 females). There were no significant differences in gender, age, body weight, physical condition and cancer type between two groups ($p > 0.05$) and the case data were consistent at baseline (Table 1).

Table 1
Patient characteristics in two different dosing regimens

Variables	PEG-rhG-CSF		P value
	Group A (n, %)	Group B (n, %)	
Sex, n			
Male	35(46.1)	35(62.5)	0.061
Female	41(53.9)	21(37.5)	
Age, years			
≤ 60	44(57.9)	30(53.6)	0.621
>60	32(42.1)	26(46.4)	
Body weight, kg			
≤ 60	46(60.5)	33(58.9)	0.853
>60	30(39.5)	23(41.1)	
ECOG-PS, n			
0	52(68.4)	40(71.4)	0.731
1	20(26.3)	13(23.2)	
2	4(5.3)	3(5.4)	
Cancer type, n			
Lymphoma	16(21.0)	13(23.2)	0.636
Lung	24(31.6)	13(23.2)	
Gastric	12(15.8)	9(16.1)	
Ovarian	6(7.9)	8(14.3)	
Breast	12(15.8)	6(10.7)	
Colon	6(7.9)	7(12.5)	
Total	76	56	

Efficacy

WBC and ANC value

After treatment according to the prescribed dosage regimen in each group, the clinical outcomes of the WBC and ANC before the following cycle of chemotherapy were evaluated. There were no death, febrile neutropenia (FN) and hospitalization during the chemotherapy cycles. The outcomes of WBC and ANC in

two different doses of PEG-rhG-CSF treatment was shown in Table 2. The incidence of Grade 3/4 WBC in group A and group B was 2.6% and 3.6%. The incidence of Grade 3/4 ANC in group A and group B was 2.6% and 5.3%. It turned out that no significant difference was seen in the outcome of WBC and ANC between two different doses of PEG-rhG-CSF ($p > 0.05$).

Table 2
The outcomes of WBC and ANC in two different dosing regimens

Category	WBC		ANC	
	Group A (n, %)	Group B (n, %)	Group A (n, %)	Group B (n, %)
Normal	50(65.8)	45(80.3)	67(88.2)	51(91.1)
Grade 1	21(27.6)	3(5.4)	2(2.6)	2(3.6)
Grade 2	3(4.0)	6(10.7)	5(6.6)	0(0)
Grade 3	1(1.3)	1(1.8)	1(1.3)	2(3.6)
Grade 4	1(1.3)	1(1.8)	1(1.3)	1(1.7))
Total	76	56	76	56
<i>Z</i>	-1.382		-0.508	
<i>P</i>	0.167		0.611	
WBC, white blood cells; ANC, absolute neutrophil count.				

ECOG-PS score

ECOG-PS scores were collected from medical records. ECOG-PS in group A and group B was consistent at baseline before PEG-rhG-CSF treatment and improved in both group A and group B after PEG-rhG-CSF administration. There were no significant differences in ECOG-PS scores between two groups after treatment ($p > 0.05$) (Table 3).

Table 3
Eastern Cooperative Oncology Group Performance Status (ECOG-PS) score

ECOG-PS, n	PEG-rhG-CSF		Z value	P value
	Group A (n, %)	Group B (n, %)		
0	62(81.6)	48(85.7)	-0.634	0.526
1	12(15.8)	7(12.5)		
2	2(2.6)	1(1.8)		
Total	76	56		

Table 4
The cost in two different dosing regimens

Cost constituents	Group A (3mg)		Group B (6mg)	
	Cost (RMB)	Number	Cost (RMB)	Number
Drug cost	1705	1	1705	2
Injection fees	5	1	5	1
Material fees	3	1	3	1
Overall cost	1713		3418	

Safety

The incidence of adverse reactions was 15.79% (12/76) in group A and 32.14%(18/56) in group B, respectively. The main adverse reactions in the two groups included skeletal muscle pain, fever, and fatigue. Skeletal muscle pain was the most common reaction, including 5 cases (6.6%) in group A and 13 cases (23.2%) in group B. Fever was seen in 5 cases (6.6%) in group A and 3 cases (5.4%) in group B and fatigue was seen in 2 cases (2.6%) in group A and 2 cases (3.6%) in group B. In the two groups, the incidence of adverse reactions was statistically different ($p < 0.05$), but the symptoms were relatively mild and tolerable according to patient's complaint. No subject had to withdraw from the study due to an adverse event.

Cost-Effectiveness analysis

Cost-effectiveness analysis is aimed to find the most economical treatment option achieving the same therapeutic effect. There was no significant difference in the clinical efficacy in group A and group B ($p > 0.05$), but the adverse reactions between two groups were statistically significant ($p < 0.05$), so cost-effectiveness analysis method was used for pharmacoeconomic evaluation. The results showed that the overall cost in group A was 1713 RMB, including drug cost 1705 RMB, injection fees 5 RMB and material fees 3 RMB, while the overall cost in group B was 3418 RMB, including drug cost 3410 RMB, injection fees 5 RMB and material fees 3 RMB. From cost-effectiveness perspective, group A was more economical ($p < 0.05$) ((Table 5).

Table 5
Cost-effectiveness analysis in two different dosing regimens

Group	Cost	Effect (E, %)		C/E		$\Delta C/\Delta E$	
		Normal	Normal /Grade 1	Normal	Normal /Grade 1	Normal	Normal /Grade 1
Group A	1713	88.16	90.79	19.43	18.87	/	/
Group B	3418	91.07	94.64	37.53	36.12	585.91	442.86

The expense and effect of each treatment plan may vary in different populations or medical units and the data may have potential uncertain biases. The sensitivity analysis showed that the medicine cost drops by 10% and injection and material fees rise 5% and no changes was found.

Discussion

This study was designed to compare the efficacy, safety and cost-effectiveness analysis of two different doses of PEG-rhG-CSF for grade IV myelosuppression in Asian cancer patients. The results showed the clinical efficacy between 3 mg PEG-rhG-CSF group and 6 mg PEG-rhG-CSF group was not statistically significant. It suggests that PEG-rhG-CSF 3 mg provided a similar degree of hematopoietic support for grade IV myelosuppression compared with PEG-rhG-CSF 6 mg.

Phase II/III studies demonstrated that the efficacy and adverse reactions of once-per-cycle PEG-rhG-CSF were similar to those of repeated injection of rhG-CSF in the prevention of chemotherapy-induced neutropenia[14–16]. The single administration of PEG-rhG-CSF may allow for less injection, better compliance, convenience and potential cost-savings, reducing the burden for both health-care workers and patients[17–19].

Phase I study show PEG-rhG-CSF is a concentration-dependent drug within a certain range[20, 21]. The mean ANC remained above 10,000 /mm³ for 8-day period with doses of 30–60 ug/kg. Increasing doses of PEG-rhG-CSF beyond 60 ug/kg did not result in a further increase in the ANC_{max} and AUC_{ANC} [22]. In our study, we demonstrated that PEG-rhG-CSF 3 mg provided neutrophil support and a safety profile to Chinese cancer patients in a manner similar to PEG-rhG-CSF 6 mg. When there is evidence that the safety and efficacy of a certain drug are equivalents between two therapies, the lower-cost option was given priority with the indicator of cost. Since patients already bear a heavy burden for anti-tumor treatment, the cost analysis of treatment is one of the main factors that need to be considered in current clinical practice. While 6 mg PEG-rhG-CSF cost twice of 3 mg dose, which showed that 3 mg group was more economical[13, 23]. Given the convenience and economic burden, dosage at 3 mg/cycle may be the

proper option for grade IV myelosuppression after chemotherapy in the clinical practice in Asian cancer patients.

The main adverse reactions caused by PEG-rhG-CSF were skeletal muscle pain, fever, and fatigue[7, 11, 18]. The incidence of adverse reactions shows a significant difference between two groups. But the symptoms were relatively mild and tolerable. No serious adverse events were observed. Skeletal muscle pain in group B occurred more frequently than in group A but was controlled by acetaminophen at two groups. In addition to skeletal muscle pain, its incidence of fever and fatigue was less than 10%, which is similar to what is observed in other studies.

However, considering that the sample size in this study is relatively small, and the number of adverse reactions observed is limited, in addition with the influence of the patient's previous treatment on the efficacy not been considered, there are certain limitations about this study and further evaluation is needed with an expansion of sample size.

Our study shows that compared with 6 mg/cycle regimen, 3 mg/cycle may be the proper dose of PEG-rhG-CSF for grade IV myelosuppression in Asian cancer patients, considering the efficacy, safety and cost-effectiveness analysis. It is a small sample study of Real-World study and we're looking forward to more prospective studies to verify this viewpoint clinically.

Declarations

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Authors' contributions: Xinhua Han contributed to the conceptualization of the study, acquisition of funding, and final approval of the manuscript. All authors contributed to study design. Data collection and analysis were performed by Changfang Fu and Yan Li. Manuscript development and writing were led by Changfang Fu in consultation with Xinhua Han and Yan Li. All authors commented on previous versions of the manuscript and approved the final manuscript.

Ethics approval: The study was approved by the First Affiliated Hospital of USTC, Division of Life Sciences

and Medicine, University of Science and Technology of China.

Consent to participate: Participants were informed that consent was implied, which was voluntary and

Anonymous and allowed participants were able to withdraw at any time.

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References

1. Krzemieniecki K, Sevela P, Erdkamp F et al (2014) Neutropenia management and granulocyte colony stimulating factor use in patients with solid tumours receiving myelotoxic chemotherapy – findings from clinical practice. *Support Care Cancer* 22(3):667–677
2. Fortner BV, Schwartzberg L, Tauer K et al (2005) Impact of chemotherapy-induced neutropenia on quality of life: a prospective pilot investigation. *Support Care Cancer* 13(7):522–528
3. Wu FP, Wang J, Wang H et al (2015) Clinical observation of the therapeutic effects of pegylated recombinant human granulocyte colony-stimulating factor in patients with concurrent chemoradiotherapy-induced grade IV neutropenia. *Exp Ther Med* 9(3):761–765
4. Lyman GH, Allcott K, Garcia J et al (2017) The effectiveness and safety of same-day versus next-day administration of long-acting granulocyte colony-stimulating factors for the prophylaxis of chemotherapy-induced neutropenia: a systematic review. *Support Care Cancer* 25(8):2619–2629
5. Park KH, Sohn JH, Lee S et al (2013) A randomized, multi-center, open-label, phase II study of once-per-cycle DA-3031, a biosimilar pegylated G-CSF, compared with daily filgrastim in patients receiving TAC chemotherapy for early-stage breast cancer. *Investig New Drugs* 31(5):1300–1306
6. Mouri A, Kaira K, Shiono A et al (2019) 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. *Thoracic cancer* 10(4):1005–1008
7. Huang W, Liu J, Zeng Y et al (2018) Randomized controlled clinical trial of polyethylene glycol recombinant human granulocyte colony-stimulating factor in the treatment of neutropenia after chemotherapy for breast cancer. *Cancer Chemother Pharmacol* 82(4):607–613
8. Holmes FA, Jones SE, O'Shaughnessy J et al (2002) Comparable efficacy and safety profiles of once-per-cycle pegfilgrastim and daily injection filgrastim in chemotherapy-induced neutropenia: a multicenter dose-finding study in women with breast cancer. *Annals of oncology: official journal of the European Society for Medical Oncology* 13(6):903–909
9. Xu B, Tian F, Yu J et al (2016) [A multicenter, randomized, controlled, phase clinical study of PEG-rhG-CSF for preventing chemotherapy-induced neutropenia in patients with breast cancer and non-small cell lung cancer]. *Zhonghua Zhong Liu Za Zhi* 38(1):23–27
10. Masuda N, Tokuda Y, Nakamura S et al (2015) Dose response of pegfilgrastim in Japanese breast cancer patients receiving six cycles of docetaxel, doxorubicin, and cyclophosphamide therapy: a randomized controlled trial. *Support Care Cancer* 23(10):2891–2898

11. Yan B, Zhang W, Lu F et al (2013) Safety of polyethylene glycol recombinant human granulocyte colony-stimulating factor in treating non-small cell lung cancer patients at I b stage. *Asian Pac J Trop Med* 6(11):912–915
12. Shi YK, Chen Q, Zhu YZ et al (2013) Pegylated filgrastim is comparable with filgrastim as support for commonly used chemotherapy regimens: a multicenter, randomized, crossover phase 3 study. *Anti-cancer drugs* 24(6):641–647
13. Younis T, Rayson D, Jovanovic S et al (2016) Cost-effectiveness of febrile neutropenia prevention with primary versus secondary G-CSF prophylaxis for adjuvant chemotherapy in breast cancer: a systematic review. *Breast cancer research treatment* 159(3):425–432
14. Shin KH, Lim KS, Lee H et al (2014) An assessment of the pharmacokinetics, pharmacodynamics, and tolerability of GCPGC, a novel pegylated granulocyte colony-stimulating factor (G-CSF), in healthy subjects. *Investig New Drugs* 32(4):636–643
15. Yang F, Sun XD, Yuan L et al (2017) [Comparative study on the efficacy and safety between pegfilgrastim (PEG-rhG-CSF) and recombinant human granulocyte colony-stimulating factor in promoting hematopoietic recovery after allogeneic hematopoietic stem cell transplantation after hematological malignancy]. *Zhonghua Xue Ye Xue Za Zhi* 38(10):831–836
16. Viens P, Chabannon C, Pouillard P et al (2002) Randomized, controlled, dose-range study of Ro 25-8315 given before and after a high-dose combination chemotherapy regimen in patients with metastatic or recurrent breast cancer patients. *Journal of clinical oncology: official journal of the American Society of Clinical Oncology* 20(1):24–36
17. Xie J, Cao J, Wang JF et al (2018) Advantages with prophylactic PEG-rhG-CSF versus rhG-CSF in breast cancer patients receiving multiple cycles of myelosuppressive chemotherapy: an open-label, randomized, multicenter phase III study. *Breast cancer research treatment* 168(2):389–399
18. Ashrafi F, Salmasi M (2018) Comparison of the effects of pegylated granulocyte-colony stimulating factor and granulocyte-colony stimulating factor on cytopenia induced by dose-dense chemotherapy in breast cancer patients. *J Res Med Sci* 23:73
19. Zhang JY, Liu YX, Wang H et al (2018) [The role of prophylactic use of pegylated recombinant human granulocyte colony-stimulating factor(PEG-rhG-CSF) in breast cancer receiving adjuvant chemotherapy]. *Zhonghua Yi Xue Za Zhi* 98(34):2718–2721
20. Qin Y, Han X, Wang L et al (2017) A phase I study of different doses and frequencies of pegylated recombinant human granulocyte-colony stimulating factor (PEG rhG-CSF) in patients with standard-dose chemotherapy-induced neutropenia. *Chin J Cancer Res* 29(5):402–410
21. Ishikawa M, Okada Y, Satake-Ishikawa R et al (1994) Pharmacological effects of recombinant human granulocyte colony-stimulating factor modified by polyethylene glycol on anticancer drug-induced neutropenia in mice. *Gen Pharmacol* 25(3):533–537
22. van Der Auwera P, Platzer E, Xu ZX et al (2001) Pharmacodynamics and pharmacokinetics of single doses of subcutaneous pegylated human G-CSF mutant (Ro 25-8315) in healthy volunteers: comparison with single and multiple daily doses of filgrastim. *Am J Hematol* 66(4):245–251

23. Lyman GH, Kleiner JM (2011) Summary and comparison of myeloid growth factor guidelines in patients receiving cancer chemotherapy. *Cancer Treat Res* 157:145–165