Oncology and Translational Medicine
DOI 10.1007/s10330-019-0350-0

October 2019, Vol. 5, No. 5, P218–P222

ORIGINAL ARTICLE

Application of pegylated recombinant human granulocyte colony-stimulating factor (PEG-rhG-CSF) for the prevention of neutropenia in triple negative breast cancer patients older than 65 years during adjuvant chemotherapy

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Abstract

Objective The aim of this study was to compare the efficacy and safety of pegylated recombinant human granulocyte colony-stimulating factor (PEG-rhG-CSF) and recombinant human granulocyte colony-stimulating factor (rhG-CSF) for the prevention of neutropenia in elderly breast cancer patients during adjuvant chemotherapy.

Methods A total of 45 oncology inpatients with breast cancer, who received adjuvant chemotherapy and were older than 65 years from May 2017 to October 2018 in the General Hospital of the Northern Theater of the Chinese people's Liberation Army, were included. Epirubivin Cyclophoshamide-Docetaxel (EC-T) sequential adjuvant chemotherapy was chosen. Forty-five patients were randomly divided into two groups; 25 patients in the treatment group were treated with PEG-rhG-CSF and 20 patients in the control group were not treated with PEG-rhG-CSF, but only rhG-CSF. The experimental group was treated with the PEG-rhG-CSF at the end of chemotherapy for 24–48 h, with a 6 mg subcutaneous injection once per chemotherapy cycle. In the control group, rhG-CSF was administered after 48 h of chemotherapy, with a 100 μg subcutaneous injection, 1/d, d 1–7. The dosage could be increased step by step with the exacerbation of neutropenia. The primary aims of this study was to discover the incidence of leukopenia, neutropenia, neutrophilic fever, and adverse reactions in the two groups.

Results The incidence of neutropenia, neutrophilic fever and adverse reactions decreased in the treatment group compared to the control group, but no significant difference existed between two groups ($P > 0.05$). Patients in treatment group had a lower, but not statistically significant, incidence of adverse reactions ($P > 0.05$).

Conclusion Applying PEG-rhG-CSF could be effective in preventing neutropenia in elderly patients with postoperative adjuvant chemotherapy to treat breast cancer. It may effectively control the occurrence of neutropenia after chemotherapy and reduce the chance of infection. The incidence of side effects, such as fever and bone pain, was low. The adverse drug reactions were well tolerated by patients, which could ensure the smooth progress of chemotherapy.

Received: 29 May 2019
Revised: 15 June 2019
Accepted: 27 June 2019

Key words: elderly; breast cancer; neutropenia; pegylated recombinant human granulocyte colony-stimulating factor

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Breast cancer is the most common malignant tumor in women and the leading cause of malignant tumors in women worldwide, which seriously threatens a woman's health. Chemotherapy is an important systemic adjuvant therapy and plays an role in the overall treatment of breast cancer. While improving overall survival and disease-free survival, chemotherapy drugs can also cause a series of adverse reactions. Neutropenia is considered the most severe hematological toxicity caused by chemotherapy and is the most common dose-limiting toxicity [1]. Elderly women with triple-negative breast cancers, having a poor prognosis and high risk of recurrence, are faced with high-intensity and multi-cycle postoperative chemotherapy. This will cause their bone marrow reserve and hematopoietic function to decline, with increasing occurrence of chronic underlying diseases such as hypertension and coronary heart disease. There will be a significant increase in the risk of severe neutropenia and infection after chemotherapy, and an increase in the risk of death due to discontinuation of chemotherapy. Therefore, prevention of neutropenia is important to the smooth progress of chemotherapy. The use of recombinant human granulocyte colony-stimulating factor (rhG-CSF) is a significant milestone for chemotherapy of malignant tumors [2]. It can stimulate the release of bone marrow to the peripheral blood, reduce the incidence of infection caused by the inhibition of hematopoiesis of bone marrow after chemotherapy, and ensure the completion of chemotherapy. Therefore, rhG-CSF is an effective drug for the prevention of neutropenia in tumor patients receiving chemotherapy and radiotherapy [3–4]. RhG-CSF has been widely used in clinical practice [5]. However, because plasma half-life is short, which leads to consecutive days in one chemotherapy period, rhG-CSF use causes inconvenience and suffering to patients [5–6]. Pegylated recombinant human granulocyte colony-stimulating factor (PEG-rhG-CSF) is a long-acting rhG-CSF which acts on hemopoietic stem cells, stimulates the proliferation and differentiation of mononuclear granulocyte progenitor cells after binding to cell-specific surface receptors, and plays a role in simultaneously activating terminal cells. Additionally, its half-life is long and convenient for use, which increases the clinical application for the chemoprevention of neutropenia [7]. This study was aimed at the prevention of neutropenia in elderly patients with breast cancer who needed intensive chemotherapy. Among them, 25 patients treated with PEG-rhG-CSF exhibited positive effects and safety in preventing neutropenia.

Materials and methods

Patients

A total of 45 breast cancer patients, all female, aged 65–77 years (67.8 ± 5.3 years), who were hospitalized in the Department of Oncology of our hospital and underwent 4 cycles of CE followed by 4 cycles of T chemotherapy after breast cancer surgery, were used in this study.

Breast cancer was diagnosed by pathology. There were 36 cases of invasive ductal carcinoma, 6 cases of invasive lobular carcinoma, 2 cases of sarcomatoid carcinoma, and 2 cases of medullary carcinoma. All 45 cases underwent a modified radical mastectomy. Prior to chemotherapy, blood routine examination, liver and kidney function, myocardial enzyme spectrum, and electrocardiogram examination showed no obvious abnormality.

All patients had no history of severe cardiopulmonary disease, and no history of radiation or chemotherapy. After surgery, all patients were treated with CE then D regimen for adjuvant chemotherapy.

The 45 patients were divided into a treatment group (25 cases) and control group (20 cases). There was no statistical significance in age, course of disease, surgical method, chemotherapy, and disease condition between the two groups (all $P > 0.05$). Prior to chemotherapy, informed consent was obtained from every patient.

Treatment methods

The 45 patients underwent breast cancer surgery, 4 cycles CE, and 4 cycles of D chemotherapy (specifics: Epirubicin 70 mg/m^2 dL in combination with IV (intravenous) Cyclophosphamide 600 mg/m^2 IV dL 21 days/ cycle, for a total of four cycles; followed by Docetaxel 75 mg/m^2 IV dL 21 days/ cycle, for a total of four cycles). Patients were then divided into two groups according to the envelope method: treatment group (25 cases) and control group (20 cases).

Before chemotherapy, both groups were given 5 mg of IV Dexamethasone, 1 time/dL.

Before chemotherapy, Palonosetron was given at 0.25 mg, IV, dL.

On this basis, the treatment group was given PEG-rhG-CSF by subcutaneous injection at a dose of 6 mg/ time and once per chemotherapy cycle within 48 h after 24 h of chemotherapy [1].

The control group received a subcutaneous injection of PEG-rhG-CSF at a dose of 100 μg for 48 h after chemotherapy, followed by a continuous 7 days of supportive treatment [2]. The dosage could be gradually increased with the aggravation of leukopenia [3]. Blood routine was regularly monitored during the application of PEG-rhG-CSF and rhG-CSF. Transient adverse reactions of PEG-rhG-CSF use were bone pain, allergic symptoms, and suspected allergic symptoms. Acetaminophen, nonsteroidal anti-inflammatory drugs, or other treatments may be used, including symptomatic treatment with opioids and antihistamines, or reduction of PEG-rhG-CSF dose [8].

Table 1 Comparison of leukopenia, neutropenia, and neutropenia fever between the two groups (*n*)

Group	leukopenia		χ^2	*P*	neutropenia		χ^2	*P*	neutropenia fever			*P*
	n	%			*n*	%			*n*	%		
Treatment group (25)	3	12	0.104	0.748	2	8	0.54	0.462	0	0	–	0.192
Control group (20)	4	20			4	20			2	10		

Observation indicators

Observation indexes: venous blood samples were collected on days 3, 7, 11, and 14 of the chemotherapy cycle for blood routine examination (leukopenia, neutropenia, and antibiotic use), and while blood cell (WBC) count, neutrophil count, granulocytic fever, and incidence of antibiotic use were compared between the two groups of PEG-rhG-CSF and rhG-CSF [4].

The incidence of various adverse reactions between the two groups was compared according to the World Health Organization (WHO) "classification criteria for common adverse reactions of anticancer drugs."

Statistical analysis

SPSS18.0 statistical software was used for data processing. The measurement data were expressed as $\chi \pm s$, and a *t* test was used for comparison between groups. Chi-square test, continuous correction chi-square test, and Fisher's precise test were used for comparison between the counting data groups, and $P < 0.05$ was considered statistically significant.

Results

Main efficacy

The incidence of leukopenia, neutropenia, neutropenia fever and antibiotic use in the treatment group was 12%, 8%, 4% and 4% respectively, which was significantly lower than in the control group (20%, 20%, 10% and 10%) without statistical significance (all $P > 0.05$; Table 1).

In the treatment group, two cases appeared in the entire course of chemotherapy, one case 7 days after the 3rd cycle of chemotherapy, and one case after subcutaneous injection of PEG-rhG-CSF 11 days after the 6th cycle of chemotherapy. In the treatment group, there were no patients with granulocytic fever and antibiotic prophylaxis.

One patient in the control group developed granulocytic fever 7 days later and was treated with antibiotics. Chemotherapy was delayed for 1 week, and the completion of intensive chemotherapy was ensured for the rest of the control group.

Table 2 Dynamic changes of mean neutrophils after preventive use of PEG-rhG-CSF

Time (h)	PEG-rhG-CSF (*n* = 25)	rhG-CSF (*n* = 20)	*P*
D1 (24)	28.2 ± 0.77	14.6 ± 0.65	0.000
D4 (96)	16.4 ± 1.90	15.3 ± 1.80	0.055
D7 (168)	13.3 ± 1.20	13.9 ± 1.00	0.080
D11 (264)	12.8 ± 0.79	8.6 ± 0.98	0.000
D14 (336)	8.8 ± 2.1	6.8 ± 2.3	0.004

The dynamic change of neutrophils

Two groups of granulocytes 24 h after blood tests in the drug treatment group were significantly higher than that of the treatment group (*P* values < 0.05). As more time passed, two groups of granulocytes showed no statistical difference ($P > 0.05$). However, 7, 11, and 14 days after chemotherapy, blood tests showed that the granulocytes in the treatment group were significantly higher than that of the treatment group ($P < 0.05$). All data are shown in Table 2.

Incidence of adverse reactions

The main adverse reactions in the experimental group and the control group were bone pain, pain at the injection site, fever, and fatigue, and a few patients had rashes, palpitations, and chest tightness. The number of adverse reactions in the application cycle of the experimental group was significantly lower than that in the control group, and the difference between the two groups was not statistically significant ($P > 0.5$; Table 3). All adverse reactions were I–II degrees, and patients exhibited symptomatic improvement after treatment.

Discussion

Neutropenia is considered the most severe hematologic toxicity caused by chemotherapy and the most common dose-limiting toxicity. In some patients, infection caused by neutropenia and reduction of chemotherapy dose may affect the therapeutic effect, and even increase the risk of death due to discontinuation of chemotherapy. Therefore, prevention and treatment of neutropenia has become important for the smooth progress of chemotherapy. The application of rhG-CSF is an important milestone in chemotherapy for malignant tumors [9]. The PubMed database has nearly 40 clinical studies on pegfilgrastim for breast cancer dose intensive chemotherapy, most of

Table 3 Comparison of adverse reactions between PEG-rhG-CSF and rhG-CSF

Factors	PEG-rhG-CSF (*n* = 25) cycle		rhG-CSF (*n* = 20) cycle		χ^2	*P*
	n	%	*n*	%		
Bone pain	18	9	15	9.3	1.785	0.185
Pain in injection site	12	6	11	6.9	1.114	0.736
Fever	0	0	2	0.63	–	0.197
Palpitation	4	2	4	2.5	0.00	1.00
Rash	4	2	6	3.8	0.464	0.496
Fatigue and fatigue	24	12	28	17.5	2.176	0.140

which are single-center and single-arm studies [10]. The application of rhG-CSF can stimulate the release of bone marrow to the peripheral blood, reduce the incidence of infection caused by the suppression of bone marrow function after chemotherapy, and ensure the smooth progress of chemotherapy [11]. It is an effective drug for the prevention and treatment of neutropenia caused by chemotherapy and radiotherapy. However, due to its short half-life and frequent injection in clinical application, it brings inconvenience and pain to patients. In this study, 45 postoperative breast cancer patients who received CE followed by T-intensive adjuvant chemotherapy were divided into two groups. Among them, 25 patients in the treatment group were treated with PEG and 20 patients in the control group were treated with rhG-CSF. The incidence of neutropenia, granulocytic fever and antibiotic use in patients using PEG-rhG-CSF during non-chemotherapy was 12%, 6% and 6% lower than that of rhG-CSF, respectively. A study showed that early prophylactic administration of PEG-rhG-CSF can reduce the incidence of neutropenia by 94% and reduce the use of IV anti-infective drugs by 80% [6]. A retrospective study showed that prophylactic use of PEG-rhG-CSF can reduce the risk of granulocytic fever in tumor patients after chemotherapy by 50%, without affecting the efficacy and overall survival [12]. In order to avoid the pain for patients with venous blood every day, we have blood tests 1, 4, 7, 11, and 14 days after treatment. Blood tests 1 day (24 h) after drug blood granulocyte in the treatment group showed significantly higher granulocytes than that of the treatment group ($P < 0.05$), but after 4 and 7 days the two groups showed no statistical difference in granulocyte count ($P > 0.05$). After 7, 11 and 14 days, although average blood test were within the normal range, the granulocyte count in the treatment group was significantly higher than the control group ($P < 0.05$). This study showed that the experimental group maintained a higher granulocyte concentration than the control group. In this study, the main adverse reactions in the experimental group and the control group were bone pain, pain at the injection site, fever, and fatigue. Some patients exhibited rashes, palpitations, and chest tightness. The number of adverse reactions in the application cycle in the experimental group was lower than in the control group, but the difference between the two groups was not statistically significant ($P > 0.05$). The adverse reactions of PEG-rhG-CSF were mainly bone pain, but these were generally transient. Paracetamol or non-steroidal anti-inflammatory drugs could reduce the pain symptoms. All patients improved after symptomatic treatment, and the incidence of adverse reactions was low. If allergic phenomenon occurred, symptomatic treatment and consideration of reduction of dosage was required. If it occurred repeatedly, the drug was discontinued. No allergic patients were found in this experiment.

Patients with tumor radiation and chemotherapy after granulocyte depletion are the most common adverse reactions A lack of granulocytes can lead to infections in the respiratory tract, digestive tract, and urinary tract. It can also cause bacteremia, septic shock, and death. Granulocyte depletion can also cause fever, oral mucosa ulcer, and adverse reactions associated with peripherally inserted central catheter (PICC) removal. This will lead to the delay and reduction of chemotherapy, and affect the long-term effects of chemotherapy. In addition, it increases medical expenses, reduces quality of life and increases the risk of death. PEG-rhG-CSF has a significantly longer half-life (15–80 h) than traditional rhG-CSF. Therefore, the vast majority of patients with PEG-rhG-CSF can [13, 14]: be treated more conveniently, experience reduced the frequency of subcutaneous injection and venous blood pain, have improved compliance [15], and safety, ensure treatment is completed on time according to the dose chemotherapy cycle, and improve the long-term effectiveness of chemotherapy. This will be especially useful for intensive therapy to increase the granulocyte count and the efficacy of chemotherapy, and reduce the risk of secondary infection. Therefore, using PEG-rhG-CSF can ensure the smooth progress of intensive therapy, maximize the curative effect and safety of the treatment, reduce the risk of granulocytopenia, relieve the suffering of frequent injections and blood tests, and reduce the use of antibiotics.

Conflicts of interest

The authors declare no conflict of interest.

References

1. Forouzanfar MH, Forem an KJ, Delossantos AM, *et al*. Breastand cervical cancer in 187 countries between 1980 and 2010: asystematic analysis. Lancet, 2011, 378:1461–1484.
2. Jiang BQ, Li ZD, Zhuang ZG. Studies on clinical safety of two docetaxel regimens in treatment of breast cancer. Adverse Drug Reactions J, 2009, 11:165–169.
3. Russell N, Mesters R, Schubert J, *et al*. A phase 2 pilot study of pegfilgrastimand filgrastim for mobilizing peripheral blood progenitorcells in patients with non- Hodgkin's lymphoma receiving chemotherapy. Haematologica, 2008, 93: 405–412.
4. National Comprehensive Cancer Network. NCCN Guidelines Myeloid Growth Factors. Version 1. 2013.
5. He XX, Jiao AM, Xia YQ, *et al*. Study on the effectiveness and the dosage of rhG-CSF given in accordance with the level of leukopenia after chemotherapy. Chin J Clin Oncol Rehabil (Chinese), 2007, 14: 515.
6. Shi YK, Xu JP, Wu CP, *et al*. Multicenter postmarketing clinical study on using pegylated recombinant human granulocyte-colony stimulating factor to prevent chemotherapy-induced neutropenia. Chin J Clin Oncol (Chinese), 2017, 44: 679–684.
7. Chinese Society of Clinical Oncology (csco). Chinese expert consensus on the clinical application of peg-rhg-csf. Chin J Clin Oncol (Chinese), 2016, 43: 271–274.
8. Hübel K, Engert A. Clinical applications of granulocytecolony-stimulating factor: an update and summary. Ann Hematology, 2003, 82: 207–213.
9. Ma J. Chinese expert consensus on the clinical application of polyethylene glycol recombinant human granulocyte-stimulating factor (PEG-rhG-CSF). Chin Cancer Clin Oncol (Chinese), 2016, 43: 271–274.
10. Fernandes R, Mazzarello S, Stober C, *et al*. Optimal primary febrile neutropenia prophylaxis for patients receiving docetaxel-cyclophosphamide chemotherapy for breast cancer: a systematic review. Breast Cancer Res Treat, 2017, 161: 1–10.
11. Yang B, Kido A. Pharmacokinetics and pharmacodynamics of pegfilgrastim. Clin Pharmacokinetic, 2010, 50: 295–306.
12. Almenar D, Mayans J, Juan O, *et al*. Pegfilgrastim and daily granulocyte colony-stimulating factor: patterns of use and neutropenia-related outcomes in cancer patients in Spain- results of the LEARN Study. Eur J Cancer Care, 2009, 18: 280–286.
13. Molineux G. Pegylation: engineering improved pharmaceuticals for enhanced therapy. Cancer Treat Rev, 2002, 28 (Suppl A): 13–16.
14. Klastersky J, Awada A. Prevention of febrile neutropenia in chemotherapy-treated cancer patients: pegylated versus standard myeloid colonystimulating factors. Do we have a choice? Crit Rev Oncol Hematol, 2011, 78: 17–23.
15. Ling MS, Xu XY, Shi FX, *et al*. Study of polyethylene glycol increasing renaturation efficiency of recombinant human granule-mono colony stimulating factor. Pharm Biotechnol,1997, 4: 5–8.

DOI 10.1007/s10330-019-0350-0
Cite this article as: Qu SX, Qiu JN, Zhang YD, *et al*. Application of pegylated recombinant human granulocyte colony-stimulating factor (PEG-rhG-CSF) for the prevention of neutropenia in triple negative breast cancer patients older than 65 years during adjuvant chemotherapy. Oncol Transl Med, 2019, 5: 218–222.