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Exploring optimal administration timing of pegylated recombinant human granulocyte colony-stimulating factor for chemotherapy-induced neutropenia in early breast cancer treated with pharmorubicin and endoxan: a prospective randomized controlled clinical trial

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Abstract

Background Pegylated recombinant human granulocyte colony-stimulating factor (PEG-rhG-CSF) is a treatment for preventing febrile neutropenia (FN) in patients with early breast cancer. However, the optimal injection timing of PEG-rhG-CSF after chemotherapy is obscure. The trial was designed to explore the best administration timing of PEG-rhG-CSF when breast cancer patients could benefit most.

Methods Patients with early breast cancer were randomly assigned to receive a preventive injection on the 7th or 3rd day following chemotherapy. The experimental group ($n=80$) received PEG-rhG-CSF treatment on day 7 after chemotherapy, whereas the control group ($n=80$) received it on day 3. The occurrence of grades 3–4 neutropenia and FN in the first cycle was the primary endpoint. The secondary endpoint was the frequency of PEG-rhG-CSF dose reduction.

Results In comparison to the control group, the experimental group exhibited higher white blood cell count (WBC) and absolute neutrophil count (ANC) on the 9th and 13th days following chemotherapy ($P<0.05$). Additionally,

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the incidence of grade 3–4 neutropenia was significantly lower in the experimental group ($P=0.038$). Furthermore, a greater proportion of patients in the experimental group met the criteria for reducing the PEG-rhG-CSF dose compared to the control group (69.74% vs. 35.06%, $P<0.001$).

Conclusions In comparison with PEG-rhG-CSF injection on day 3 after chemotherapy, the incidence of grade 3–4 myelosuppression is lower, and the safety is more manageable after the injection on day 7. This approach potentially allows for a wider adoption of PEG-rhG-CSF dose reduction, leading to a consequential decrease in overall medical costs for patients.

Trial registration Clinical Trials: NCT04477616. Registered July 16, 2020.

Keywords Breast cancer, PEG-rhG-CSF, Chemotherapy, Neutropenia

Introduction

Breast cancer is the most common malignant worldwide and the second-leading cause of cancer-related deaths among women. For many years, the treatment of patients with breast cancer has been based on the chemotherapeutic regimen of anthracyclines, cyclophosphamide, and paclitaxel as inositol [1, 2]. The appropriate chemotherapy dose and treatment duration can greatly boost the recurrence-free and overall survival rates of patients with breast cancer [3, 4]. However, the toxicity brought on by chemotherapy will greatly affect the patient's tolerance, lowering the sustained relative dose intensity (RDI) of chemotherapy, reducing the dose and/or course of chemotherapy, and ultimately resulting in lower efficacy [5, 6]. Among them, the most significant dosage-limiting component in cytotoxicity caused by chemotherapy is myelosuppression [7]. Neutropenia, a particular type of myelosuppression characterized by an abnormally low level of neutrophils, could include an elevated risk of opportunistic infection and septicemia [8, 9]. Therefore, it is imperative to reduce the incidence of neutropenia through clinical interventions and help patients benefit most from chemotherapy.

Pegylated recombinant human granulocyte colony-stimulating factor (PEG-rhG-CSF), a modified form of granulocyte colony-stimulating factor, can ameliorate neutropenia and its complications by promoting the release of mature neutrophils and stimulating the production of neutrophil precursors [10]. In clinical practice, the administration time of PEG-rhG-CSF is typically 24–48 h after the completion of each chemotherapy cycle, which is aimed at supporting the recovery of neutrophil levels after the potential myelosuppressive effects of chemotherapy [11, 12]. However, the exact timing may vary based on the specific chemotherapy regimen and the individual patient's needs. By now, there have been few studies designed to investigate the optimal dosing timing for PEG-rhG-CSF. In addition, no evidence supports that patients benefit most from preventive injection of PEG-rhG-CSF 24–48 h after chemotherapy. Our preliminary research indicates that the nadir of white blood cell count occurs around the 10th day after chemotherapy and it is expected to recovery to normal or above-normal levels within three days after treatment of PEG-rhG-CSF according to the chemotherapy regimen used [13]. Therefore, this study aimed to identify the relatively optimal injection timing of PEG-rhG-CSF in patients with breast cancer following myelosuppressive chemotherapy and prospectively explore the possibility of dosage reduction and lowers patient medical costs.

Methods

Study design

Based on previous studies, the incidence of grade 3–4 neutropenia for the control group was assumed to be 40%, and we hypothesized that the incidence in the experimental group would be halved to 20%. Using a two-sided significance level (α) of 0.05 and a power of 80%, the calculated sample size for each group was 79 patients. Given the short duration of the study, we anticipate a low rate of loss to follow-up. As a result, we have decided to round up the sample size to 80 patients per group (160 patients in total).

This single-center, open-label, randomized controlled study was conducted in the First Affiliated Hospital of Nanjing Medical University. A total of 160 patients with breast cancer were randomly assigned (1:1) to the study (Fig. 1). To be more specific, 80 patients were randomized to the experimental group, wherein, on the 7th day of chemotherapy (with the initiation of chemotherapy designated as day 1), a single 6 mg dose of PEG-rhG-CSF was administered to each participant. Concurrently, the control group's 80 patients received same dose of PEG-rhG-CSF on the 3rd day following chemotherapy. On the 9th, 11th, and 13th days following chemotherapy, blood routine tests were performed on both groups. What is more, individuals who develop a fever during this period would promptly inform their doctor.

Patients in the experimental group experiencing febrile neutropenia (FN) in the first cycle will receive PEG-rhG-CSF treatment (6 mg) on day 3 (recommended by the label) in the second cycle of chemotherapy. Conversely, patients in the control group with FN will undergo a modification in their chemotherapy drug dosage. When

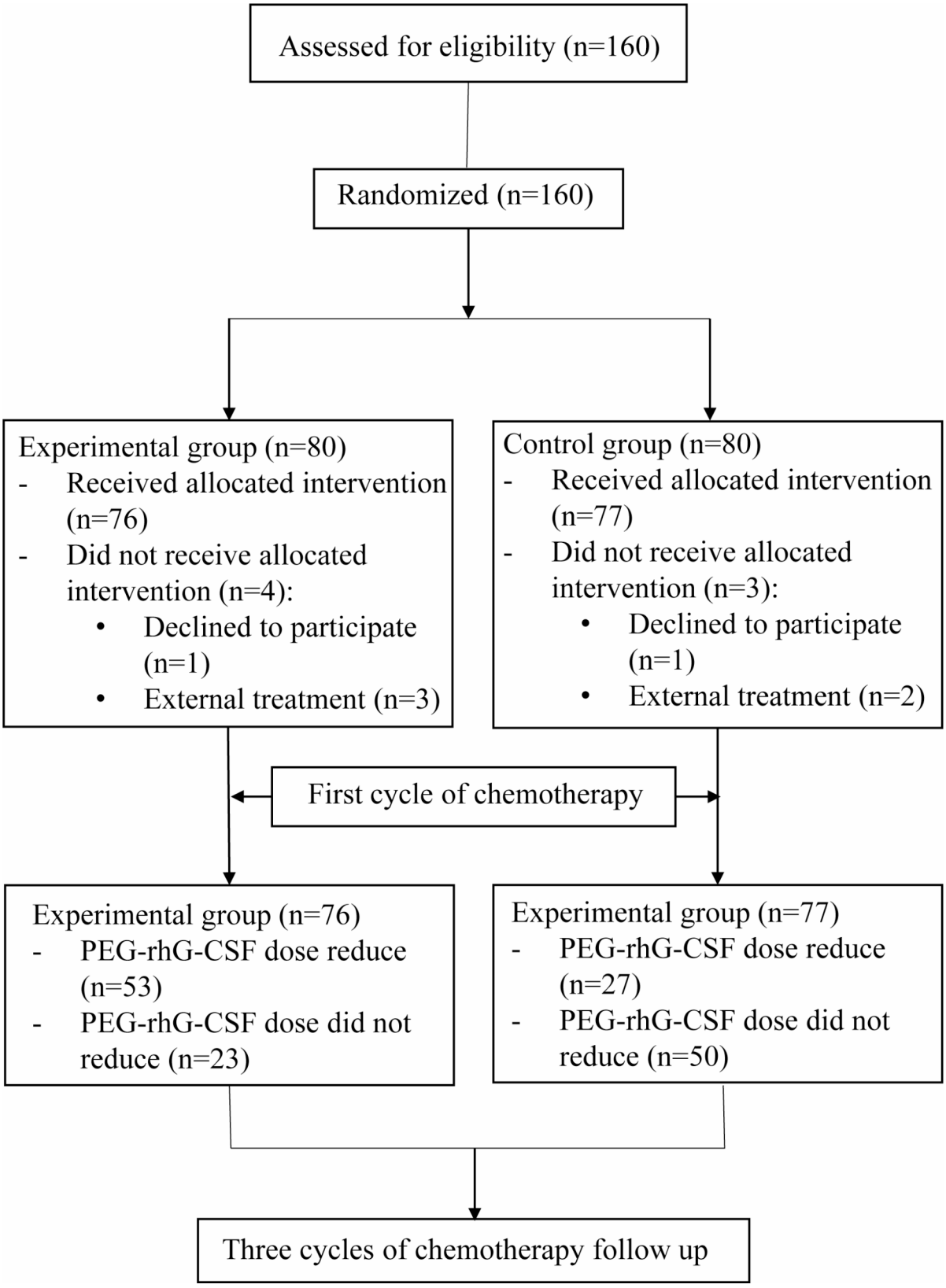

Fig. 1 The study flow diagram of enrolled patients. PEG-rhG-CSF (pegylated recombinant human granulocyte colony-stimulating factor

a patient (in experimental group or in the control group) fulfills the criterion of achieving three consecutive blood routine tests with white blood cell count (WBC) or absolute neutrophil count (ANC) exceeding the lower limit of the normal range (typically 4×10^9/L), and at least one of these measurements surpassing the upper limit of the normal range (typically 10×10^9/L), the dosage of PEG-rhG-CSF injection would modified to 3 mg.

This study was approved by the First Affiliated Hospital of Nanjing Medical University's Ethics and Research Committee, and the study was carried out in compliance with the institutional and national accountable committees on human experimentation. Our study adheres to CONSORT guidelines. Prior to the commencement of any treatment, informed consent was obtained from each patient. The study protocol was performed in accordance with the Declaration of Helsinki and was registered in ClinicalTrials.gov (Registration number: NCT04477616).

Randomization

Randomization was computer-generated with allocation concealment by opaque sequentially numbered sealed envelopes. Eligible participants were randomized to receive a single 6 mg dose of PEG-rhG-CSF on either 7th day of chemotherapy or on the 3rd day following chemotherapy, in a 1:1 allocation ratio. Outcome assessors were blinded to group allocation.

Study population

From July 2021 to September 2022, participants were sourced from Nanjing Medical University's First Affiliated Hospital. All patients received at least 4 cycles of EC (Pharmorubicin, 90 mg/m^2, day 1, every 21 days; and Endoxan, 600 mg/m^2, day 1, every 21 days). The inclusion criteria of the patients were as follows: (1) female patients, aged 20–70 years; (2) diagnosis of breast cancer; (3) did not receive chemotherapy before and plans to undergo ≥4 consecutive cycles of EC chemotherapy in accordance with the requirements of this study and had risk factors of FN; (4) physical condition (Karnofsky performance status) score of ≥70 points; (5) expected survival period of >3 months; (6) no other diseases of the blood except for mild anemia of iron deficiency anemia; (7) within 1.5 times the upper limit of the normal for aspartate aminotransferase and/or alanine aminotransferase; (8) within 1.5 times the normal upper limit for serum creatinine levels; and (9) the patient (or legal representative) signs the informed consent form.

The exclusion criteria were as follows: (1) uncontrollable infections or received systemic antibiotic treatment within 72 h before chemotherapy; (2) abnormal hematopoiesis except iron deficiency anemia, with a history of malignant hematopathy, and those who have received hematopoietic stem cell transplantation or organ transplantation; (3) radiotherapy within 4 weeks before enrollment or prepared to receive radiotherapy during the study; (4) other malignant tumors in the past but have not been cured or have metastasis; (5) a history of serious heart and lung diseases, or obvious electrocardiograph abnormalities; (6) allergy to PEG-rhG-CSF, rhG-CSF, and other preparations or proteins from *Escherichia coli*; (7) serious mental or nervous system disease, affecting the provision of informed consent and/or adverse reaction expression or observation, or uncooperativeness; (8) pregnancy or lactation or women of childbearing age who refused to take contraceptive measures; (9) participation in clinical trials of other drugs within 4 weeks before enrollment.

Assessment

The blood routine test, body temperature, ostealgia, arthralgia, myalgia, and other adverse events (AEs) in all the patients were documented after the first chemotherapy cycle. Only those who meet the criteria for dose reduction will be monitored throughout the subsequent three cycles of chemotherapy. The primary endpoints of this study were the incidence of grade 3 neutropenia (ANC$<1\times10^9$/L), grade 4 neutropenia (ANC$<0.5\times10^9$/L), and FN (an ANC$<0.5\times10^9$/L with an oral temperature of >38.3℃ or two consecutive readings>38.0℃ for 2 h) [14] in the first cycle. The secondary endpoint was the incidence of reducing the PEG-rhG-CSF dose from two groups. The Common Terminology Criteria for Adverse Events version 5.0 was used to assess safety including ostealgia, arthralgia, and myalgia.

Statistical analysis

Differences in the incidence of grade 3–4 neutropenia, FN, and dosage reduction were examined using the $\chi 2$ or Fisher's exact test. Data were examined utilizing IBM SPSS Statistics version 26 (IBM Corp., Armonk, NY, USA). $P<0.05$ were regarded as statistically significant. The forward method was used for both univariate and multivariate analysis.

Results

Baseline characteristics

The primary endpoints were achieved in 153 out of 160 patients (95.6% of the total) in the first cycle. Follow-up was completed by 77 (96.3%) and 76 (95.0%) individuals in the control and experimental group, respectively. Baseline characteristics of the two groups were well-balanced, as detailed in Table 1. Premenopausal patients constituted more than half of the population in the clinical trial. Additionally, over 50% of the patients underwent modified radical mastectomy.

Table 1 Baseline characteristics of patients

Characteristics	Statistics	Experimental group (*n* = 76)	Control group (*n* = 77)
Age (years)	mean (SD)	48.05 (10.17)	49.97 (9.88)
Weight (kg)	mean (SD)	59.23 (6.160	62.38 (8.93)
Height (cm)	mean (SD)	159.93 (4.73)	161.06 (4.00)
BMI (kg/cm^2)	mean (SD)	23.18 (2.44)	24.02 (3.17)
Menstrual status	n (%)		
Premenopausal		48 (63.2%)	40 (51.9)
Postmenopausal		28 (36.8)	37 (48.1)
Tumor	n (%)		
T0		1 (1.3)	1 (1.3)
T1		28 (36.8)	38 (49.4)
T2		47 (61.8)	34 (44.2)
T3		0 (0)	4 (5.2)
Node	n (%)		
N0		20 (26.3)	25 (32.5)
N1		44 (57.9)	40 (51.9)
N2		9 (11.8)	6 (7.8)
N3		3 (3.9)	6 (7.8)
Molecular subtypes	n (%)		
HR+/HER2−		52 (68.4)	46 (59.7)
HR+/HER2+		10 (13.2)	7 (9.1)
HR−/HER2+		3 (3.9)	5 (6.5)
HR−/HER2−		11 (14.5)	19 (24.7)
Surgeries	n (%)		
Breast-conserving surgery		24 (31.6)	24 (31.2)
Modified radical mastectomy		52 (68.4)	53 (68.8)
Baseline WBC (×10^9/L)	mean (SD)	6.00 (1.28)	5.88 (1.71)
Baseline ANC (×10^9/L)	mean (SD)	3.73 (1.05)	3.64 (1.36)

BMI: Body Mess Index; WBC, white blood count; ANC, absolute neutrophil count

Table 2 Univariate and multivariate analysis of enrolled patients

Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Age (years)	0.938 (0.905–0.972)	< 0.001*	0.974 (0.921–1.030)	0.352
Menstrual status	0.223 (0.112–0.443)	< 0.001*	0.318 (0.107–0.944)	0.039*
Injection time	4.033 (2.054–7.917)	< 0.001*	4.401 (2.067–9.371)	< 0.001*
Baseline WBC (×10^9/L)	1.449 (1.123–1.869)	0.004*	2.029 (1.118–3.683)	0.020*
Baseline ANC (×10^9/L)	1.393 (1.035–1.874)	0.029*	0.588 (0.282–1.224)	0.156

HR, Hazard Ratio; WBC, white blood count; ANC, absolute neutrophil count; *, *p*-value < 0.05

Univariate and multivariate analyses

Age, weight, height, body mass index, menstrual status, tumor stage, node stage, molecular subtypes, surgical method selection, baseline WBC, baseline ANC, and injection time were the variables identified in the univariate analysis. Moreover, in the multivariate analysis, menstrual status, injection time, and baseline WBC were identified as independent factors associated with dose reduction (Table 2).

Outcomes

The baseline WBC and ANC showed no statistically significant difference between the experimental and control groups (Table 1; Fig. 2a-b). However, the WBC and ANC in the experimental group were statistically significantly higher than those in the control group on the 9th and 13th day of chemotherapy ($P<0.05$). In comparison with the control group, the incidence of grade 3–4 neutropenia was substantially lower in the experimental group (15.79% vs. 29.87%, $P=0.038$, Table 3), While the incidence of grade 4 neutropenia exhibited no difference between the two groups (9.21% vs. 15.58%, $P=0.232$) (Table 3). Both groups had a lower incidence of FN (6.49% vs. 3.95%, $P=0.719$) (Table 3).

After the first chemotherapy cycle, we systematically tracked eligible patients for dosage reduction across the next three subsequent cycles. Among the experimental group, 53 out of 76 patients (69.7%) met the criteria for dose reduction, whereas in the control group, 27 out of 77 patients (35.1%) underwent dose reduction (Table 4). Thus, these patients with dose reduction were subjected to subsequent analysis (53 in the experimental group and 27 in the control group). On the 9th day after the second chemotherapy, patients with dose reduction in the experimental group had statistically higher WBC and ANC than the control group ($P<0.05$, Fig. 2c-d). Moreover, the WBC and ANC in the control group gradually increased during the follow-up of the 9th-13th day, whereas they reach a minimum in the experimental group on day 11 (Fig. 2c-d). The incidence of grade 3–4 neutropenia was lower in patients with dose reduction. Only one patient in each group had grade 4 neutropenia, and no FN occurred (Table 4).

Given the notably low occurrence of grade 3–4 neutropenia and FN among individuals who underwent a reduction in PEG-rhG-CSF dosage during the second cycle of chemotherapy, the schedule for the blood routine tests following the third and fourth cycles was modified to be conducted on the 9th day after chemotherapy. As we can see, the WBC and ANC were significantly greater than the lowest value within their normal range, and patients with dose reduction in the experimental group had higher WBC and ANC than the control group ($P<0.05$, Fig. 3). During the third and fourth cycles of chemotherapy, none of the patients with dose reduction experienced FN, and only one patient in the experimental group had grade 3 neutropenia (Table 5).

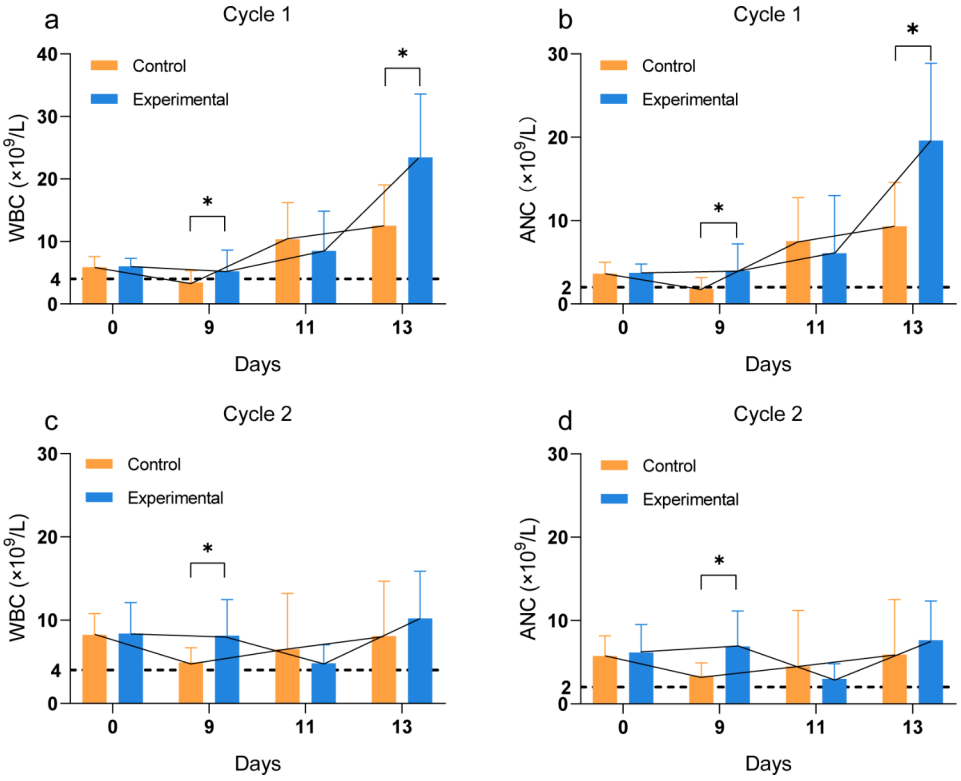

Fig. 2 The trend of neutrophils after the first and second cycle of chemotherapy. WBC, white blood cell count; ANC, absolute neutrophil count; *,$P<0.05$

Table 3 The incidence of grade 3–4 neutropenia and FN between the control group and experimental group after the first cycle of chemotherapy

Events	Experimental group ($n=76$), n (%)	Control group ($n=77$), n (%)	*P*-value
Grade 3–4 neutropenia			
Incidence (%)	12/76 (15.79)	23/77 (29.87)	0.038*
Grade 3 neutropenia			
Incidence (%)	5/76 (6.58)	11/77 (14.29)	0.119
Grade 4 neutropenia			
Incidence (%)	7/76 (9.21)	12/77 (15.58)	0.232
FN			
Incidence (%)	3/76 (3.95)	5/77 (6.49)	0.719

FN, febrile neutropenia; *, *p*-value < 0.05

Table 4 The incidence of grade 3–4 neutropenia, FN and dose reduction between the control group and experimental group after the second cycle of chemotherapy

Events	Experimental group ($n=76$), n (%)	Control group ($n=77$), n (%)	*P*-value
Dose reduction			
Yes	53 (69.74)	27 (35.06)	< 0.001*
No	23 (30.26)	50 (64.94)	
Grade 3–4 neutropenia			
Incidence (%)	5/53 (9.43)	3/27 (11.11)	1.000
Grade 3 neutropenia			
Incidence (%)	5/53 (9.43)	2/27 (11.11)	0.762
Grade 4 neutropenia			
Incidence (%)	0/53	1/27 (3.70)	0.337
FN			
Incidence (%)	0/53	0/27	

FN, febrile neutropenia; *, *p*-value < 0.05

Safety

During each chemotherapy cycle, we documented the frequency of ostealgia, arthralgia, myalgia, and other events. In general, the incidence of these events was slightly higher in the experimental group than in the control group. The incidence of grade 1 arthralgia during the first cycle of chemotherapy was statistically higher in the experimental group than in the control group (Fig. 4). All events were grade 1 and showed no significant difference during the follow-up chemotherapy.

Discussion

One of the primary causes of the decrease in chemotherapy dosage and extension of the treatment period is blood toxicity, particularly myelosuppression [15]. rhG-CSF was developed to lessen the chance of chemotherapy-induced myelosuppression and increase the safety of chemotherapy [16], which can lower the incidence of FN from 24–7-16% in patients receiving chemotherapy [17, 18]. Various chemotherapy regimens were employed depending on

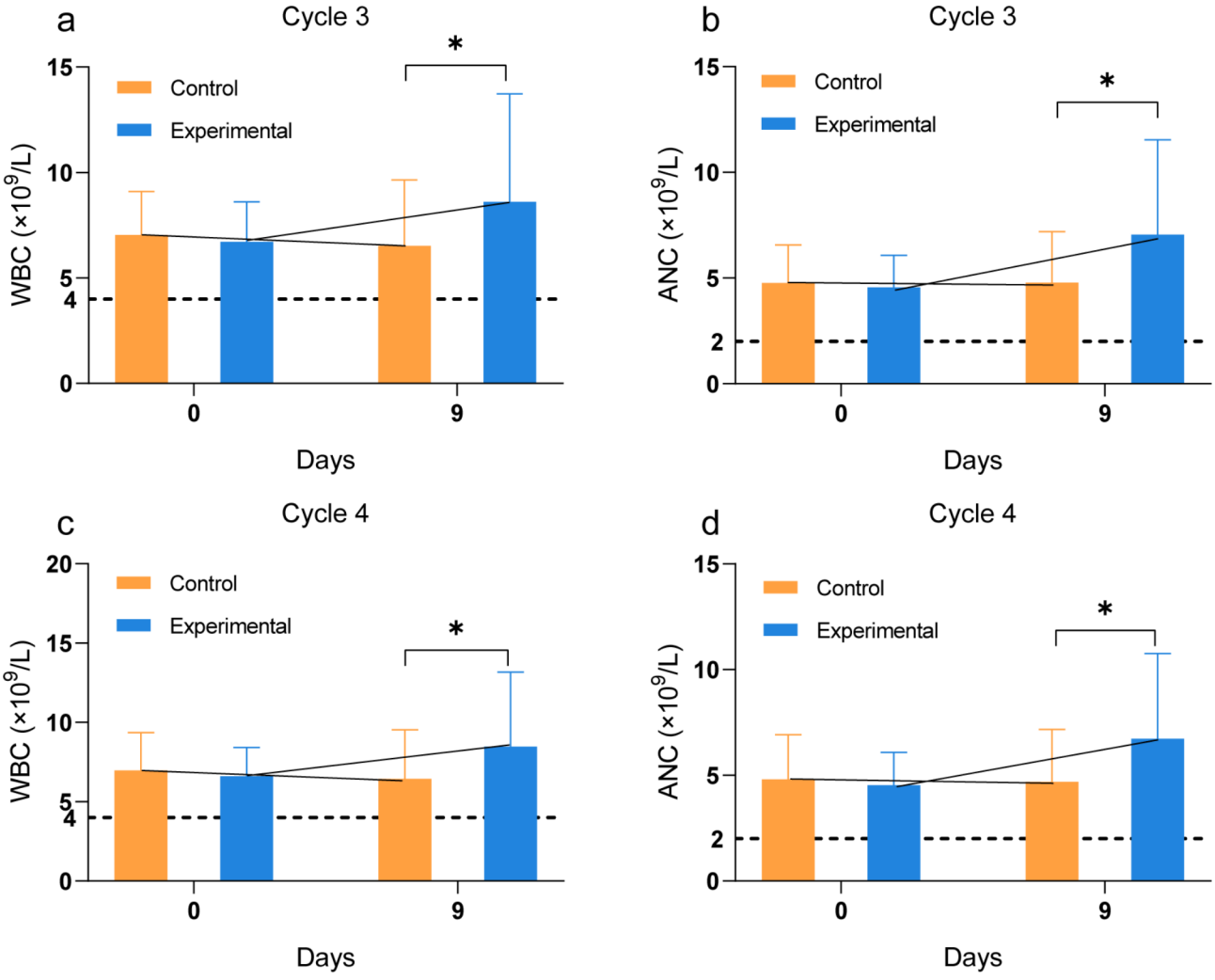

Fig. 3 The trend of neutrophils after the Third and fourth cycle of chemotherapy. WBC, white blood cell count; ANC, absolute neutrophil count; *,$P < 0.05$

Table 5 The incidence of grade 3–4 neutropenia and FN between the control group and experimental group after the third and fourth cycle of chemotherapy

Events	Experimental group ($n = 53$), n (%)	Control group ($n = 27$), n (%)	*P*-value
Grade 3–4 neutropenia			
Incidence (%)	1/53 (18.87)	0/27	1.000
Grade 3 neutropenia			
Incidence (%)	1/53 (18.87)	0/27	1.000
Grade 4 neutropenia			
Incidence (%)	0/53	0/27	
FN			
Incidence (%)	0/53	0/27	

FN, febrile neutropenia; *, *p*-value < 0.05

the molecular subtypes and stages of breast cancer. The chemotherapy regimen and dose intensity affect patient chemosensitivity [19, 20]. The myelosuppression rate increases with high-risk chemotherapy regimens (overall FN risk > 20%) and relative dosage intensity. Due to the development of PEG-rhG-CSF, each chemotherapy session now entails a standardized injection dose of 6 mg, eliminating the need for previous daily injections. This innovation significantly enhances patient convenience while maintaining equal efficacy and safety in preventing neutropenia and FN [21–23]. Two randomized controlled studies have shown that a single injection of PEG-rhG-CSF is as safe and effective as daily injections of rhG-CSF in reducing neutropenia and its complications. However, the injection time of PEG-rhG-CSF is based on rhG-CSF, and few studies have discussed the injection timing of PEG-rhG-CSF [24, 25]. To investigate the efficiency and safety of various PEG-rhG-CSF injection times, a prospective randomized controlled study was conducted. We further prospectively investigated the likelihood and safety of dose reduction in light of the high cost of PEG-rhG-CSF compared with rhG-CSF.

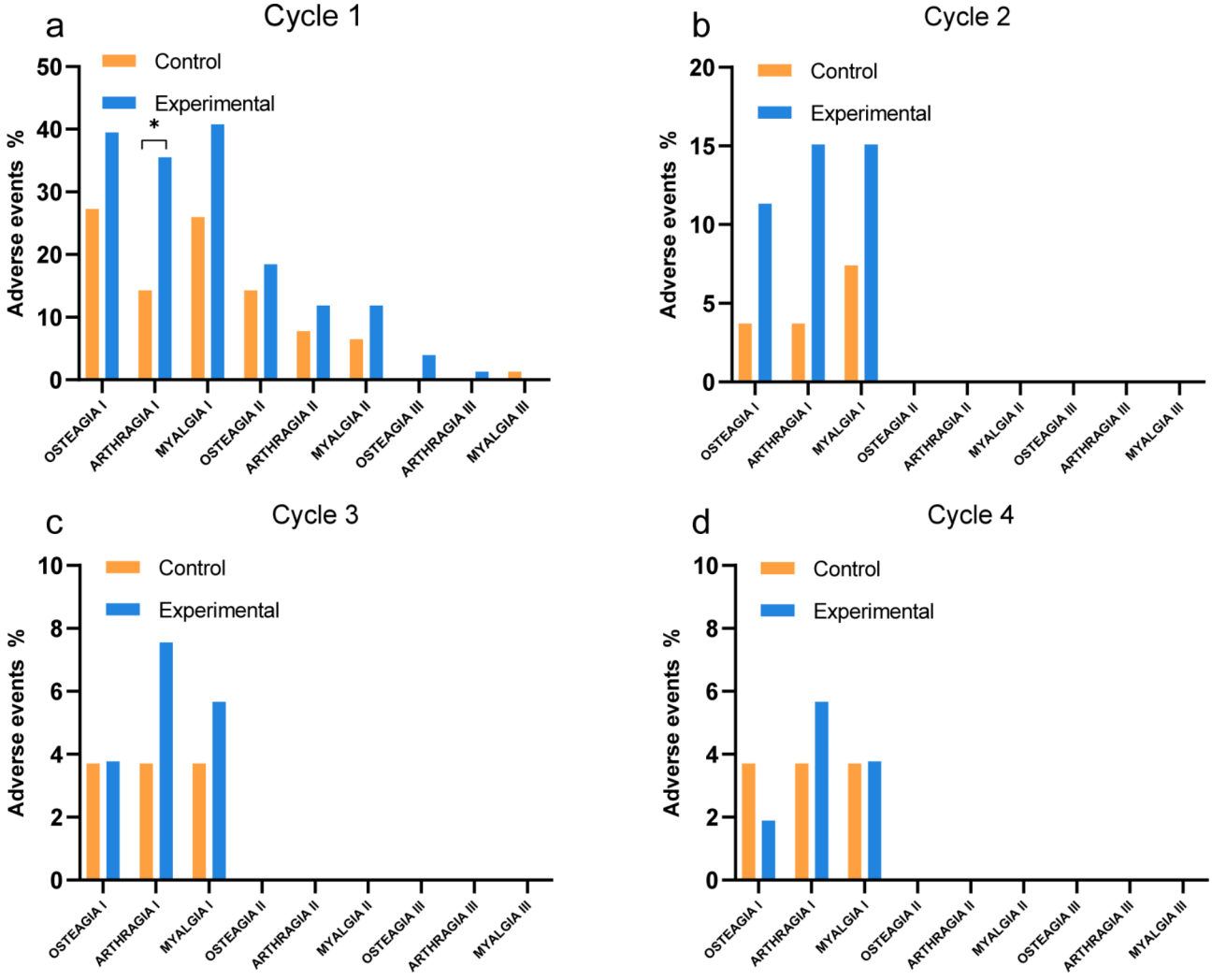

Fig. 4 Adverse events during four cycles of chemotherapy. *,$P < 0.05$

Our previous study discovered that the lowest WBC and ANC after chemotherapy often occur around 10th day after chemotherapy and that they can rise to above-normal levels within 3 days after PEG-rhG-CSF injection [13]. Therefore, PEG-rhG-CSF injections were administered on the 7th day following chemotherapy instead of the 3rd day as is customary. We hypothesized that PEG-rhG-CSF injection to stimulate granulocyte peak can lessen the effects of chemotherapy-induced granulocyte trough. After the first cycle of chemotherapy, 12 of 76 (15.79%) patients in the experimental group developed grade 3–4 neutropenia, whereas in the control group, 23 of 77 (29.87%), or twice as many cases of myelosuppression as the experimental group, developed grade 3–4 neutropenia, with a statistically significant *P*-value of 0.038. The incidence of FN was also lower in the experimental group (3.95%) than in the control group (6.49%). The WBC and ANC in the experimental group were statistically greater than those in the control group ($P<0.05$) on the 9th and 13th day following chemotherapy. These findings substantiate our initial hypothesis that administering PEG-rhG-CSF on the 7th day after chemotherapy may significantly enhance WBC and ANC, thereby mitigating the risk of grade 3–4 neutropenia. Most patients only have mild or moderate AEs [21, 26], with a statistically elevated probability indicating that the experimental group is prone to experiencing arthralgia I. Postponing PEG-rhG-CSF injection reduces the risk of myelosuppression, but it increases the likelihood of arthralgia I, this is a phenomenon not previously observed in prior studies. In general, administering PEG-rhG-CSF on the 7th day following chemotherapy results in great effectiveness and safety; However, the probability of mild arthralgia is heightened.

Given the fact that PEG-rhG-CSF has a substantial medical cost, we prospectively screened patients who qualified for injection dose reduction and then examined patients' safety and AEs [26]. Menstrual status, baseline

WBC, and injection time were three independent risk factors identified by both univariate and multivariate analyses. In other words, patients are predisposed to fulfill the criteria for PEG-rhG-CSF dose reduction if they are not in the menopausal period, receive an injection on the 7th day following chemotherapy, and have high basal WBC. In the second cycle of chemotherapy, a significantly higher proportion of patients in the experimental group (69.7%) met the criteria for PEG-rhG-CSF dose reduction compared to the control group, where only 35.1% met the criteria ($P<0.001$). The prevalence of grade 3–4 neutropenia in dose reduction group was extremely low, and no patient had FN. The WBC and ANC in the two groups were higher than their normal range on the 9th, 11th, and 13th day. Following PEG-rhG-CSF injection, mature granulocytes from bone marrow are first encouraged to be released into the peripheral blood; these granulocytes then gradually declined after consumption until PEG-rhG-CSF stimulates the differentiation of hematopoietic progenitor cells of the bone marrow granulocyte, at which point mature granulocytes enter the blood once more for a second peak [25]. Coincidentally, in our study, we found that the experimental group experienced a trough of WBC and ANC on day 11, which may have been connected to the two peaks of PEG-rhG-CSF, compared with the growing trend of the control group on days 9–13. Therefore, our findings support the fact that administering a 3 mg injection of PEG-rhG-CSF to patients who meet the criteria for dose reduction after the first cycle of chemotherapy is both effective and secure. As for AEs, the incidence was relatively low (<15%), and patients who met the dosage reduction requirements after the second chemotherapy experienced mild pains. The incidence of myelosuppression and AEs in these patients was further decreased in the third and fourth chemotherapy cycles, and only one patient in the experimental group experienced grade 3 neutropenia, which further validates the safety and efficacy of PEG-rhG-CSF dose reduction. In summary, our study indicates that administering PEG-rhG-CSF injection on the 7th day following chemotherapy not only reduces the risk of myelosuppression but also enhances the likelihood of dosage reduction, leading to lower patient medical costs.

This study has some limitations. First, the limited sample size and single-center design of this clinical investigation raise concerns about its dependability and potential for bias. Second, blood cell tests were not performed at the same hospital, which could have caused a little discrepancy. Third, an EC chemotherapy regimen was administered to all patients, and alternative chemotherapy regimens were not included for comparison. Therefore, further investigation is necessary.

Conclusion

This study compared the safety and efficacy of PEG-rhG-CSF injection on the 7th and 3rd day after chemotherapy. Despite a higher incidence of mild arthralgia, patients receiving PEG-rhG-CSF injections on day 7 demonstrated lower rates of myelosuppression and FN compared to those on day 3. Furthermore, PEG-rhG-CSF injection on the 7th day significantly increased the likelihood of dose reduction, leading to reduced healthcare costs for patients.

Abbreviations

AE	Adverse events
ANC	Absolute neutrophil count
FN	Febrile neutropenia
PEG	Polyethylene glycol
PEG-rhG-CSF	Pegylated recombinant human granulocyte colony-stimulating factor
RDI	Relative dose intensity
rhG-CSF	Recombinant human granulocyte colony-stimulating factor
WBC	White blood cell

Acknowledgements

Not applicable.

Author contributions

X.Z. and L.X. contributed to the conception and design of the study. Y.X. conducted the analysis. L.H. and J.W. drafted the manuscript. J.L. and J.H. interpreted the results and designed the presentation of the results. Y.W., W.Z. and R.C. collected the clinical data. X.H., X.W. and W.S. substantively revised the manuscript. All authors read and approved the final manuscript.

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Data availability

The datasets generated during the current study are not publicly available due to privacy or ethical restrictions but are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This study was approved by the First Affiliated Hospital of Nanjing Medical University's Ethics and Research Committee (2021-SR-072), and the study was carried out in compliance with the Helsinki Declaration's guidelines and the institutional and national accountable committees on human experimentation. Each patient's informed consent was acquired (every patient signed an informed consent form before receiving treatment).

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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