Long-term effects of using pegylated recombinant human granulocyte colony-stimulating factor following chemotherapy: A real-world study on patients with ovarian cancer

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Abstract. Pegylated recombinant human granulocyte colony-stimulating factor (PEG-rhG-CSF) is recommended for the prevention of neutropenia during chemotherapy for gynecological tumors. However, its long-term safety is still worth exploring. The present study aimed to explore the long-term effects of the prophylactic use of PEG-rhG-CSF on neutrophils following the completion of first-line chemotherapy during poly(ADP-ribose) polymerase inhibitor (PARPi) maintenance therapy in patients with ovarian cancer. In the present retrospective cohort study, patients were categorized according to whether or not they received prophylactic injections of PEG-rhG-CSF at 24-48 h after the completion of first-line chemotherapy (prophylactic group vs. non-prophylactic group). The primary outcomes were changes in neutrophil and leukocyte levels in both groups. The Mann-Whitney U test with Benjamini-Hochberg correction was used to compare data between the two groups at different time points, and statistical significance for this analysis was defined as a corrected P-value below the adjusted significance threshold (leukocytes, P<0.08; neutrophils, P<0.06; hemoglobin, P<0.04; and platelets, P<0.02). Multivariate linear regression was used to analyze the independent factors influencing the primary outcomes, for which a two-sided P-value of <0.05 was considered statistically significant. The time points observed were at 1, 2, 3 and 6 months, and 1 year following the administration of PARPi. Of the 53 enrolled patients, 20 were in the prophylactic group and 33 were in the non-prophylactic group. Compared with those in the non-prophylactic group, the leukocyte counts in the prophylactic group were significantly lower at 2 months, 6 months and 1 year (P<0.08), the neutrophil counts in the were significantly lower at 3 months and 1 year (P<0.06), and the hemoglobin concentration was significantly lower at 6 months (P<0.04). Multivariate linear regression analysis revealed that parity, pathological type and the prophylactic injection of PEG-rhG-CSF following first-line chemotherapy were independent factors influencing neutrophil and leukocyte counts in the first year following the administration of PARPi (P<0.05). The prophylactic injection of PEG-rhG-CSF reduced neutrophil and leukocyte counts by $2.181x10^9$/l and $2.370x10^9$/l, respectively. On the whole, the present study demonstrates that the prophylactic injection of PEG-rhG-CSF following the completion of first-line chemotherapy may increase the risk of long-term myelosuppression; thus, the prophylactic use of PEG-rhG-CSF should be carefully considered in patients following the completion of first-line chemotherapy.

Introduction

Among the gynecological malignancies, ovarian cancer has the highest mortality rate and seriously threatens the lives and health of women. In 2022, there were an estimated 324,398 new cases of ovarian cancer and 206,839 related deaths worldwide (1). Currently, the first-line treatments for advanced-stage epithelial ovarian cancer include tumor reduction surgery, platinum-based chemotherapy and maintenance therapy with a poly(ADP-ribose) polymerase inhibitor (PARPi) (2,3). Neutropenia is the most common hematological toxicity observed during chemotherapy. The National Comprehensive Cancer Network guidelines recommend the use of pegylated recombinant human granulocyte colony-stimulating factor (PEG-rhG-CSF) for the prevention of chemotherapy-induced neutropenia (4). rhG-CSF binds to specific G-CSF receptors on the surface of granulocytes and

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stimulates the differentiation and proliferation of neutrophil progenitor cells. PEG-rhG-CSF is chemically modified with polyethylene glycol to increase its molecular weight and reduce the glomerular filtration rate, resulting in an extended half-life, enhanced water solubility, reduced immunogenicity and a prolonged action time within the body; some clinical studies have confirmed its efficacy and safety in the context of chemotherapy for malignant tumors (5-9). However, these studies only assessed the short-term efficacy of PEG-rhG-CSF and failed to observe long-term changes in neutrophils and leukocytes.

Studies have demonstrated that chemoradiotherapy can induce the aging of hematopoietic stem cells (10-12).The administration G-CSF following the repeated use of cytotoxic drugs appears to damage bone marrow hematopoietic function (13). This is related to the direct or indirect induction of stem cell differentiation into more lineage-committed hematopoietic cells by G-CSF, resulting in the depletion of bone marrow reserves (14,15). Patients with ovarian cancer may already have potential bone marrow damage after undergoing multiple cycles of chemotherapy. However, due to the administration of G-CSF, patients may still have normal blood cell counts in the short term despite reduced hematopoietic stem cell (HSC) reserves. Therefore, potential bone marrow damage is difficult to detect.

Patients with advanced-stage epithelial ovarian cancer usually undergo maintenance therapy with PARPi for 2-3 years following first-line chemotherapy. During this process, there is also a risk of developing neutropenia, with an incidence rate ranging from 16 to 58.8% (16). The mechanism is associated with the PARP1-mediated suppression of myeloid progenitor cell growth and the impaired ability to repair granulocyte DNA damage (17). However, the question of whether the prophylactic use of PEG-rhG-CSF following first-line chemotherapy for ovarian cancer will aggravate chemotherapy-induced long-term bone marrow damage, thus affecting patients with later PARPi maintenance treatment, has not yet been fully addressed. Thus, this is worthy of further investigation.

The present retrospective cohort study observed long-term changes in neutrophils and leukocytes in patients with ovarian cancer receiving prophylactic injections of PEG-rhG-CSF following the completion of first-line chemotherapy during maintenance therapy with PARPi. Furthermore, the present study explored the independent factors influencing neutrophils and leukocyte levels.

Patients and methods

Patients. The present study included 62 female patients with a median age of 54 years (range, 45-68 years). The inclusion criteria were as follows: i) Patients who were diagnosed with ovarian cancer pathologically; ii) stage II-IV disease [International Federation of Gynecology and Obstetrics (FIGO) staging system, 2014] (18); iii) patients who had received prophylactic PEG-rhG-CSF injections during the interchemotherapy interval; and iv) patients who had received PARPi maintenance therapy. The exclusion criteria were as follows: i) Tumors originating from other sites; ii) those for whom PARPi therapy could not be continued for severe side-effects or other reasons; and iii) cases where clinical data were missing as the patients were lost to follow-up.

Study design and treatment. A total of 62 patients with primary ovarian cancer who took niraparib/olaparib between March 2021 and January 2024 were included retrospectively. A total of 3 patients were excluded for economic reasons, and 2 patients were excluded due to refractory thrombocytopenia following treatment with PARPi. In addition, 4 patients were lost to follow-up. Thus, a total of 53 patients were included in the study. The patients were divided into the prophylactic group (n=20), receiving prophylactic PEG-rhG-CSF injections at 24-48 h after the completion of first-line chemotherapy, and the non-prophylactic group (n=33). The flow chart of the study is presented in Fig. 1.

PEG-rhG-CSF medication regimen. Patients in the prophylactic group were administered subcutaneously with 6 mg PEG-rhG-CSF at 24-48 h after the completion of first-line chemotherapy. The non-prophylactic group did not receive PEG-rhG-CSF following the completion of first-line chemotherapy. According to the Chinese expert consensus, when the neutrophil count of the patients was $<1x10^9$/l, 150 μg rhG-CSF were injected until it reached $\geq 2x10^9$/l (19). The carboplatin plus paclitaxel (TC) regimen is a chemotherapy regimen associated with a moderate risk of developing febrile neutropenia (FN) (20). If the patient had ≥1 risk factor, or if a FN or dose-limiting neutropenia event occurred in the previous cycle of chemotherapy without the prophylactic use of G-CSF, and the medication was agreed by the patient and their family, PEG-rhG-CSF would be administered prophylactically at 24-48 h after the completion of chemotherapy. The ensuing chemotherapy session needed to be at least 14 days apart from the PEG-rhG-CSF injection.

Chemotherapy medication regimen. Patients in both groups received platinum-based first-line chemotherapy, with the majority completing 6-8 cycles. The TC regimen was the most commonly used. Patients received paclitaxel at a dose of 175 mg/m^2 administered as a 3-h infusion, followed by carboplatin administered as a 1-h infusion with an area under the curve (AUC) of 5-6. The glomerular filtration rate (GFR) was estimated using creatinine clearance. The carboplatin dose was calculated with the Calvert formula: Carboplatin dose in milligrams=AUC x (GFR + 25). Courses were administered on a 21-day schedule. Prior to each medication, patients were administered 8 mg ondansetron to prevent vomiting and 10 mg dexamethasone to prevent allergic symptoms. At the same time, strict electrocardiographic monitoring was performed during the medication.

PARPi medication regimen. If patients achieved a complete response or partial response 1 month after the completion of first-line chemotherapy with stable blood and organ function tests, PARPi treatment was recommended for administration as soon as possible. The starting dose of olaparib was 300 mg twice daily, and the starting dose of niraparib was determined according to the weight and platelet level of the patient. The starting dose for patients with a body weight ≥77 kg or a baseline platelet count $\geq 150x10^9$/l was 300 mg once daily, while the starting dose for patients weighing <77 kg or with a baseline platelet count $<150x10^9$/l was 200 mg once daily. Following the initiation of PARPi treatment, routine blood samples were

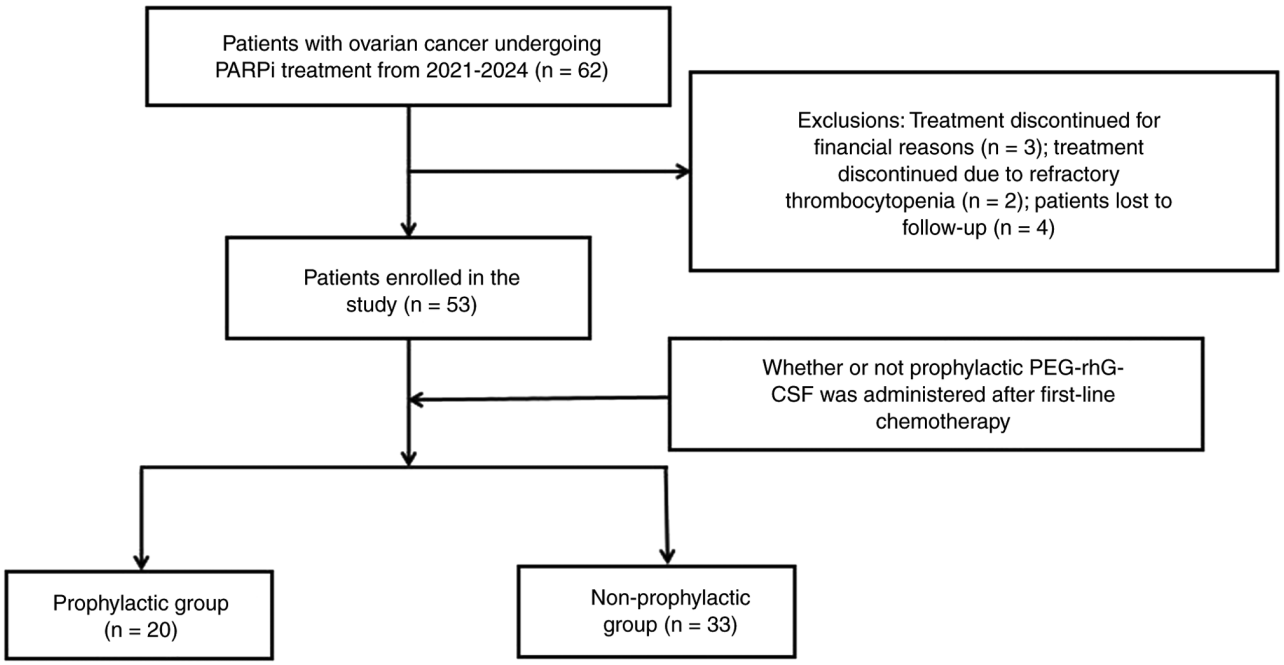

Figure 1. Flow chart of the overall study. PARPi, poly(ADP-ribose) polymerase inhibitor; PEG-rhG-CSF, pegylated recombinant human granulocyte colony-stimulating factor.

monitored weekly in month 1, then every month for year 1 and periodically thereafter. The drug dose was adjusted according to the degree of adverse hematological reactions observed, and the related symptoms were treated appropriately. PARPi was permanently discontinued if hematological toxicity did not resolve after a 28-day treatment interruption, and the patient should be referred to a hematologist for additional evaluation and treatment.

Outcomes. The primary study outcomes were the changes in neutrophils and leukocytes in the two groups. The secondary study outcomes were the changes in hemoglobin and platelet counts in the two groups. Multivariate linear regression was used to analyze the independent influencing factors of the primary outcome. The time points observed were 1, 2, 3 and 6 months, and 1 year following the administration of PARPi.

Statistical analysis. IBM SPSS Statistics 27.0 software (IBM Corp.) was used for the data analysis. For continuous data, the data were analyzed via the Mann-Whitney U test and are expressed as the median (Q1, Q3). For classified data, the measured data were analyzed using the χ^2 test and Fisher's exact test. The Mann-Whitney U test with Benjamini-Hochberg correction (false discovery rate=0.1) was conducted to compare repeated measurement indicators between the two groups. Statistical significance for this analysis was defined as a corrected P-value below the adjusted significance threshold, with the corrected P-values for each index as follows: Leukocytes, P<0.08; neutrophils, P<0.06; hemoglobin, P<0.04; and platelets, P<0.02. Multivariate linear regression analysis was performed to identify independent factors associated with the primary endpoint, for which two-sided P<0.05 was considered to indicate a statistically significant difference.

Results

In the present study, 62 patients with ovarian cancer treated between March 2021 and January 2024 were included, with a median age of 54.00 years (51.75-59.00 years) and a median body mass index (BMI) of 22.83 kg/m^2 (21.29-26.48 kg/m^2). Among these, 58.49% of the patients had the pathological type of high-grade serous carcinoma (HGSC), 92.45% had stage IIIA-IVB disease and 88.68% were treated with niraparib (Table I). As shown in Fig. 1, 2 patients could not continue PARPi treatment due to refractory thrombocytopenia, the treatment of 3 patients was discontinued for economic reasons and 4 patients were lost to follow-up; thus, 53 patients were ultimately included. Among these, 20 patients received the prophylactic injection of PEG-rhG-CSF following first-line chemotherapy (prophylactic group), and 33 did not (non-prophylactic group).

The baseline characteristics of the two groups before PARPi administration are summarized in Table I. The FIGO stages of the patients were as follows: 4 patients in the prophylactic group had stage IIA-IIB and 16 had stage IIIA-IVB, while all 33 patients in the non-prophylactic group had stage IIIA-IVB. There were no significant differences in gravidity, parity, age, BMI, pathological classification, type of PARPi, BRCA mutation, the complete removal of the macroscopic lesions (R0) status, the receipt of injections of rhG-CSF or the number of injections of PEG-rhG-CSF. Chemotherapy-related information is recorded in Table SI. There were no significant differences between the two groups in terms of the chemotherapeutic regimen, the number of chemotherapies, cumulative doses of paclitaxel and carboplatin, and the interval between the end of chemotherapy and PARPi treatment. There were no significant differences in leukocytes, neutrophils, hemoglobin and platelets between

Table I. Patient characteristics at baseline before PARPi administration in the prophylactic (n=20) and non-prophylactic (n=33) groups.

Characteristics	All patients	Prophylactic group	Non-prophylactic group	P-value
Median age (Q1, Q3), years	54.0 (51.8, 59.0)	54.5 (51.3, 58.8)	54.0 (50.0, 59.5)	0.934
Median gravidity (Q1, Q3)	3.0 (2.0, 4.0)	3.0 (2.0, 4.0)	4.0 (3.0, 5.0)	0.064
Median parity (Q1, Q3)	2.0 (1.0, 2.0)	2.0 (1.0, 2.0)	2.0 (1.0, 2.0)	0.732
Median BMI (Q1, Q3), kg/m^2	22.8 (21.3, 26.5)	21.9 (20.5, 25.4)	23.7 (21.6, 27.1)	0.061
Classification of diseases, n (%)				-
EOC	53 (100.0)	20 (100.0)	33 (100.0)	
Pathological type, n (%)				0.121
HGSC	31 (58.5)	9 (45.0)	22 (66.7)	
Others	22 (41.5)	11 (55.0)	11 (33.3)	
2014 FIGO staging, n (%)				0.017
IIA-IIB	4 (7.6)	4 (20.0)	0 (0.0)	
IIIA-IVB	49 (92.5)	16 (80.0)	33 (100.0)	
Type of PARPi, n (%)				0.269
Niraparib	47 (88.7)	16 (80.0)	31 (93.9)	
Olaparib	6 (11.3)	4 (20.0)	2 (6.1)	
BRCA mutation, n (%)				0.081
BRCA1/2	14 (26.4)	8 (40.0)	6 (18.2)	
Others	39 (73.6)	12 (60.0)	27 (81.8)	
R0 status				0.158
Yes	20 (37.7)	5 (25.0)	15 (45.5)	
No	33 (62.3)	15 (75.0)	18 (54.5)	
Received injections of rhG-CSF, n (%)				0.450
Yes	23 (43.4)	10 (50.0)	13 (39.4)	
No	30 (56.6)	10 (50.0)	20 (60.6)	
Number of injections of PEG-rhG-CSF, n (%)				0.093
≥5	26 (49.1)	13 (65.0)	13 (39.4)	
<5	27 (50.9)	7 (35.0)	20 (60.6)	
Routine blood (before PARPi)				
Median no. of leukocytes (Q1, Q3), x10^9/l	4.6 (3.9, 5.5)	4.36 (3.8, 4.9)	4.95 (3.9, 5.9)	0.233
Median no. of neutrophils (Q1, Q3), x10^9/l	2.8 (2.2, 3.5)	3.1 (2.2, 3.7)	2.8 (2.0, 3.5)	0.551
Median hemoglobin level (Q1, Q3), g/l	114.0 (106.0, 122.5)	111.5 (104.0, 123.8)	115.0 (107.5, 121.5)	0.274
Median no. of platelets (Q1, Q3), x10^9/l	159.0 (131.5, 204.5)	148.5 (120.0, 192.5)	162.0 (135.0, 209.5)	0.263

BMI, body mass index; BRCA1/2, BRCA1/2 DNA repair associated; EOC, epithelial ovarian cancer; HGSC, high-grade serous carcinoma; FIGO, International Federation of Gynecology and Obstetrics; PARPi, poly(ADP-ribose) polymerase inhibitor; R0, complete resection of the macroscopic lesions; PEG-rhG-CSF, pegylated human granulocyte colony-stimulating factor.

the two groups prior to chemotherapy and prior to treatment with PARPi (Tables I and SI).

The changes in neutrophils, leukocytes, hemoglobin and platelets following treatment with PARPi in both groups are presented in Table II. Compared with the non-prophylactic group, in the prophylactic group, the leukocyte counts decreased significantly at month 2, month 6 and year 1 (based on corrected P<0.08), the neutrophil counts decreased significantly at month 3 and year 1 (based on corrected P<0.06) and the hemoglobin level decreased significantly at month 6 (based on corrected P<0.04). There were no statistically significant differences in platelet counts between the two groups at any time point. The trajectory of the routine blood test results over time is illustrated in Fig. 2. To investigate the significant difference between the two groups in leukocyte and neutrophil counts at the 1-year, multiple linear regression models were constructed separately with these counts as dependent variables. Multivariate linear regression analysis revealed that at 1 year following PARPi treatment, whereas parity was positively associated with leukocytes and neutrophils (P<0.05) (Tables III and IV). Leukocytes in patients with HGSC decreased by 1.964x10^9/l, and the prophylactic injection of PEG-rhG-CSF following first-line chemotherapy reduced the leukocyte level by 2.370x10^9/l (P<0.05) (Table III). The

Table II. Changes in leukocytes, neutrophils, hemoglobin and platelets after poly(ADP-ribose) polymerase inhibitor administration in the prophylactic (n=20) and non-prophylactic group (n=33) groups.

A, First month

Routine blood	Prophylactic group	Non-prophylactic group	P-value (raw)	P(corr) (FDR=0.1)
Median no. of leukocytes (Q1, Q3), x10^9/l	3.9 (3.1, 5.0)	3.6 (3.4, 3.7)	0.246	0.10
Median no. of neutrophils (Q1, Q3), x10^9/l	2.5 (0.9, 2.9)	2.1 (1.5, 2.6)	0.484	0.10
Median hemoglobin level (Q1, Q3), g/l	108.5 (93.5, 118.8)	109.5 (105.8, 116.3)	0.367	0.04
Median no. of platelets (Q1, Q3), x10^9/l	136.5 (102.0, 174.3)	99.5 (87.3, 168.0)	0.646	0.04

B, Second month

Routine blood	Prophylactic group	Non-prophylactic group	P-value (raw)	P(corr) (FDR=0.1)
Median no. of leukocytes (Q1, Q3), x10^9/l	3.7 (3.3, 4.4)	4.9 (3.9, 10.7)	0.027	0.04
Median no. of neutrophils (Q1, Q3), x10^9/l	1.8 (1.6, 2.5)	2.8 (2.4, 8.2)	0.063	0.06
Median hemoglobin level (Q1, Q3), g/l	104.5 (91.3, 121.8)	112.5 (79.0, 113.8)	0.684	0.08
Median no. of platelets (Q1, Q3), x10^9/l	102.0 (75.8, 130.5)	114.0 (71.3, 355.5)	0.853	0.08

C, Third month

Routine blood	Prophylactic group	Non-prophylactic group	P-value (raw)	P(corr) (FDR=0.1)
Median no. of leukocytes (Q1, Q3), x10^9/l	4.1 (2.9, 4.6)	4.1 (3.0, 5.6)	0.119	0.08
Median no. of neutrophils (Q1, Q3), x10^9/l	1.8 (1.3, 2.6)	2.5 (1.7, 3.6)	0.048	0.04
Median hemoglobin level (Q1, Q3), g/l	99.5 (77.5, 132.0)	107.5 (94.5, 119.8)	0.594	0.06
Median no. of platelets (Q1, Q3), x10^9/l	129.0 (84.3, 144.0)	141.0 (80.5, 272.0)	0.075	0.02

D, Sixth month

Routine blood	Prophylactic group	Non-prophylactic group	P-value (raw)	P(corr) (FDR=0.1)
Median no. of leukocytes (Q1, Q3), x10^9/l	3.9 (3.7, 4.3)	4.7 (4.1, 6.5)	0.053	0.06
Median no. of neutrophils (Q1, Q3), x10^9/l	2.1 (1.6, 2.6)	3.0 (2.7, 4.0)	0.115	0.08
Median hemoglobin level (Q1, Q3), g/l	117.5 (109.8, 114.0)	123.0 (124.5, 265.5)	0.005	0.02
Median no. of platelets (Q1, Q3), x10^9/l	131.0 (100.3, 174.8)	107.0 (96.5, 141.5)	0.951	0.10

E, First year

Routine blood	Prophylactic group	Non-prophylactic group	P-value (raw)	P(corr) (FDR=0.1)
Median no. of leukocytes (Q1, Q3), x10^9/l	3.4 (3.1, 3.9)	7.6 (4.3, 9.5)	0.001	0.02
Median no. of neutrophils (Q1, Q3), x10^9/l	1.8 (1.5, 2.5)	5.2 (2.9, 6.8)	0.021	0.02
Median hemoglobin level (Q1, Q3), g/l	122.0 (107.0, 127.3)	105.0 (80.3, 140.3)	0.967	0.10
Median no. of platelets (Q1, Q3), x10^9/l	146.5 (115.3, 185.5)	177.5 (125.0, 401.8)	0.683	0.06

Corr, corrected.

number of neutrophils in patients with HGSC decreased by 1.816x10^9/l, and the prophylactic injection of PEG-rhG-CSF reduced the number of neutrophils by 2.181x10^9/l (P<0.05) (Table IV). In general, parity, pathological type and the prophylactic injection following the completion of first-line chemotherapy were significantly associated with lower levels

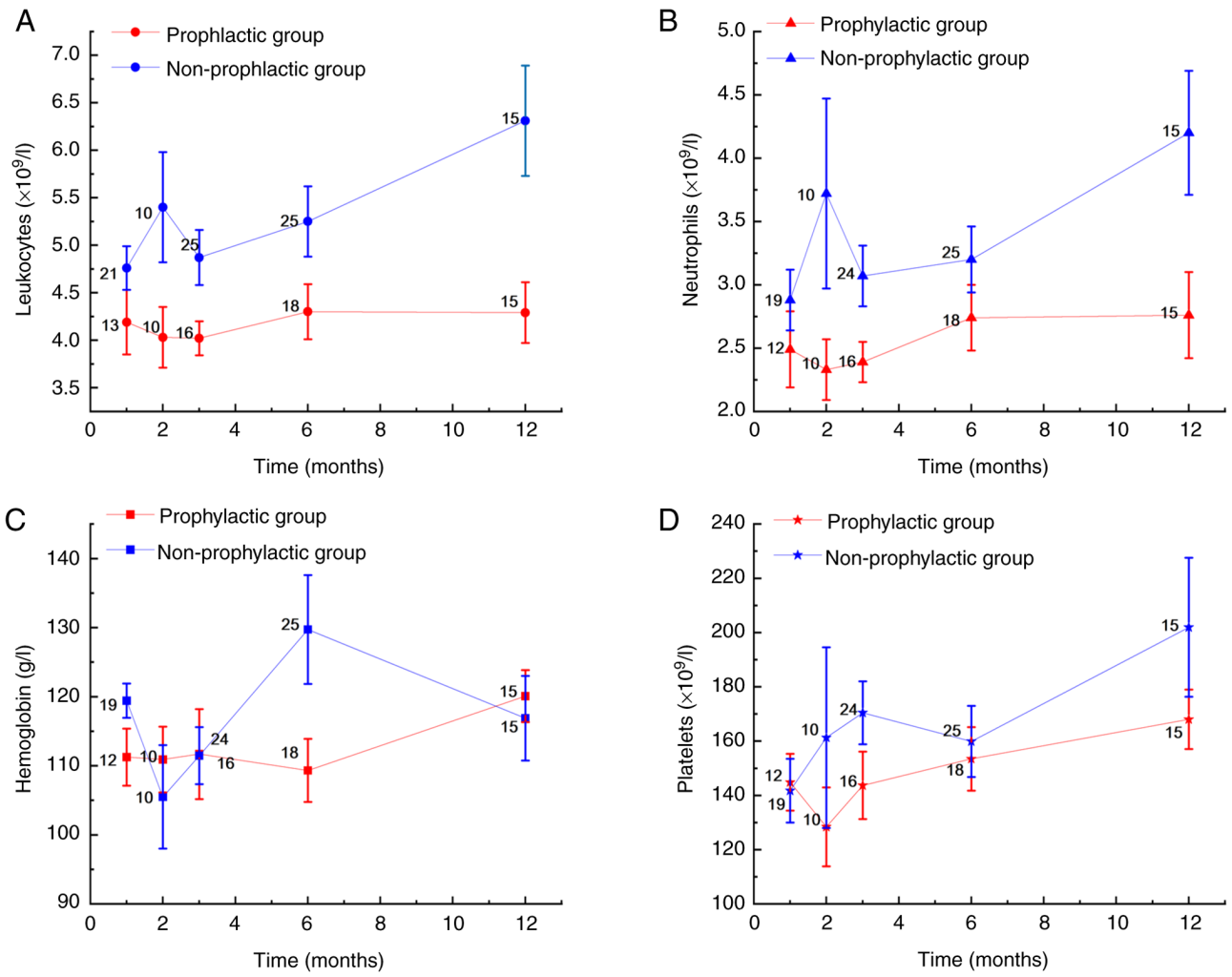

Figure 2. Changes in routine blood parameters in both groups. (A) Trajectory of neutrophils over time. (B) Trajectory of leukocytes over time. (C) Trajectory of hemoglobin over time. (D) Trajectory of platelets over time. Patient numbers at each time point are indicated in the line chart.

of leukocytes and neutrophils at 1 year following the administration of PARPi ($P<0.05$) (Tables III and IV).

Discussion

The present retrospective study investigated the long-term effects of the prophylactic use of PEG-rhG-CSF on routine blood parameters during PARPi maintenance therapy in patients with ovarian cancer. It was found that the low levels of neutrophils, leukocytes and hemoglobin in patients with ovarian cancer receiving PARPi maintenance therapy may be associated with the prophylactic injection of PEG-rhG-CSF following first-line chemotherapy. The mechanism may be associated with impaired bone marrow hematopoiesis.

As hematopoietic cells renew, long-term myelosuppression can be defined as myelosuppression persisting 3 months after the completion of chemotherapy, primarily characterized by neutrophil, platelet or hemoglobin levels below the normal ranges (21,22). The present study found that injecting PEG-rhG-CSF prophylactically following first-line chemotherapy was an independent influencing factor affecting neutrophils and leukocytes at 1 year following PARPi treatment. In other words, prophylactically injecting PEG-rhG-CSF following the completion of first-line chemotherapy may be associated with low levels of neutrophils and leukocytes, increasing the risk of long-term myelosuppression. Although PEG-rhG-CSF is widely used in clinical practice to prevent chemotherapy-induced myelosuppression, little is known about the combined effects of chemotherapy and PEG-rhG-CSF on the primitive stem cells responsible for long-term hematopoietic support. van Os *et al* (13) reported that G-CSF administered after multiple doses of cytotoxic agents appeared to impair long-term hematopoiesis and marrow stem cell reserves. Other studies have demonstrated that G-CSF combined with a cytotoxic agent can lead to HSC damage and the loss of the bone marrow reserves, and that this effect is more evident in animals with a damaged HSC compartment. The mechanism involved is associated with G-CSF directly or indirectly inducing stem cells to differentiate into more hematopoietic-oriented cells, leading to loss of the bone marrow reserve (14,15). These studies provide a theoretical basis for the possible bone marrow injury caused by G-CSF after multiple doses of chemotherapy. Platinum drugs and paclitaxel are common chemotherapeutics used to treat ovarian cancer, and they exert cytotoxic effects by inhibiting DNA replication and cell mitosis, respectively (23-25). Patients with ovarian cancer

Table III. Association between clinical characteristics and leukocytes 1 year after PARPi administration.

Variables	B	95% CI	P-value	VIF
Age	-0.006	(-0.109, 0.097)	0.907	1.873
BMI	-0.075	(-0.286, 0.137)	0.460	2.336
Gravidity	-0.563	(-1.334, 0.208)	0.140	3.092
Parity	1.239	(0.236, 2.242)	0.019	3.944
Pathology type	1.964	(0.509, 3.419)	0.012	1.691
2014 FIGO stage	-0.309	(-2.472, 1.853)	0.763	1.734
Received neoadjuvant chemotherapy	-0.208	(-1.807, 1.391)	0.785	1.970
R0 status	-0.459	(-2.065, 1.148)	0.550	1.740
Chemotherapy medication regimen	0.710	(-1.166, 2.586)	0.431	2.623
Received bevacizumab	0.122	(-1.866, 2.110)	0.897	1.762
Number of chemotherapy cycles	-0.024	(-0.758, 0.711)	0.946	1.915
Received injections of rhG-CSF	0.153	(-1.850, 2.156)	0.872	3.091
Number of PEG-rhG-CSF injections	-0.608	(-2.366, 1.150)	0.471	2.204
Injection of PEG-rhG-CSF after the last chemotherapy	2.370	(0.566, 4.173)	0.014	2.610
Type of PARPi	1.419	(-1.239, 4.076)	0.271	2.040

BMI, body mass index; FIGO, International Federation of Gynecology and Obstetrics; R0, complete removal of the macroscopic lesions; PEG-rhG-CSF, pegylated recombinant human granulocyte colony-stimulating factor; PARPi, poly(ADP-ribose) polymerase inhibitor; CI, confidence interval; VIF, variance inflation factor.

Table IV. Association between clinical characteristics and neutrophils after PARPi administration.

Variables	B	95% CI	P-value	VIF
Age	-0.006	(-0.095, 0.083)	0.882	1.873
BMI	-0.050	(-0.233, 0.133)	0.567	2.336
Gravidity	-0.618	(-1.284, 0.049)	0.067	3.902
Parity	1.104	(0.237, 1.971)	0.016	3.944
Pathology type	1.816	(0.558, 3.073)	0.008	1.691
2014 FIGO stage	-0.445	(-2.314, 1.423)	0.617	1.734
Received neoadjuvant chemotherapy	0.244	(-1.139, 1.626)	0.711	1.970
R0 status	-0.813	(-2.202, 0.576)	0.230	1.740
Chemotherapy medication regimen	0.560	(-1.061, 2.182)	0.471	2.623
Whether received bevacizumab	0.008	(-1.711, 1.726)	0.992	1.762
Number of chemotherapy cycles	-0.168	(-0.802, 0.467)	0.580	1.915
Received injections of rhG-CSF	-0.398	(-2.219, 1.334)	0.630	3.091
Number of PEG-rhG-CSF injections	-0.343	(-1.863, 1.176)	0.636	2.204
Injection of PEG-rhG-CSF after the last chemotherapy	2.181	(0.622, 3.740)	0.010	2.610
Type of PARPi	2.002	(-0.295, 4.299)	0.083	2.040

BMI, body mass index; FIGO, International Federation of Gynecology and Obstetrics; R0, complete removal of the macroscopic lesions; PEG-rhG-CSF, pegylated recombinant human granulocyte colony-stimulating factor; PARPi, poly(ADP-ribose) polymerase inhibitor; CI, confidence interval; VIF, variance inflation factor.

who are injected with PEG-rhG-CSF following the repeated use of cytotoxic drugs may experience the loss of the bone marrow stem cell reserve, with lower levels of neutrophils and leukocytes. Neutrophils are the most abundant type of granulocyte in the human body, accounting for 40-70% of white blood cells; they are a key component of the innate immune system and are mainly responsible for resisting extracellular pathogens and acute inflammatory reactions. Patients with neutropenia are susceptible to pathogen attacks and are at an increased risk of acquiring infections (26).

In addition, studies have reported that G-CSF stimulates neutrophil elevation, while causing the suppression of bone marrow erythropoiesis (27,28), which may be related with the results observed within the present study at 6 months after

PARPi treatment. This may be linked to the induction of the over-mobilization of bone marrow cells by G-CSF, leading to the disruption of the bone marrow microenvironment, which in turn leads to bone marrow dysfunction (29). Moreover, for patients requiring maintenance treatment, PARPi itself can also cause myelosuppression (16,30), and the overall incidence of anemia is 21.0-70.8%. In the event that the bone marrow stem cell reserve is already impaired prior to PARPi treatment, patients may be at a high risk of myelosuppression during PARPi maintenance therapy. Therefore, for patients with ovarian cancer requiring PARPi maintenance therapy, the use of prophylactic PEG-rhG-CSF following the completion of first-line chemotherapy needs to be reconsidered.

HGSC is the most common subtype of ovarian cancer, with a high degree of malignancy and a poor prognosis (31,32). In the present study, patients with HGSC had lower levels of neutrophils and leukocytes than those with other pathological types during subsequent PARPi maintenance therapy for ovarian cancer. Huang *et al* (22) reported that among patients with long-term myelosuppression and ovarian cancer, the proportion of patients with pathological grade 2-3 and stage IV disease was greater. The findings of the present study are consistent with these results. Notably, the present study also found that the parity of the patients was positively associated with neutrophil and leukocyte counts during PARPi treatment. The mechanism involved may be associated with the suppression of retrotransposons in HSCs during pregnancy, which activate cyclic GMP-AMP synthase and stimulator of interferon gene signaling and trigger the interferon response, thus promoting the activation of HSCs and increasing the production of neutrophils (33).

To reduce the incidence of severe myelosuppression and FN in patients during chemotherapy, PEG-rhG-CSF is increasingly being used for malignant tumors (34-36). However, only a limited number of studies have mentioned its effect on long-term myelosuppression in patients. For patients with advanced-stage epithelial ovarian cancer, PARPi can significantly prolong progression-free survival time (37-39). Therefore, the indications for the use of PEG-rhG-CSF following the completion of first-line chemotherapy should be strictly controlled to avoid affecting the subsequent maintenance therapy in patients with ovarian cancer. It is also critical to develop novel treatment methods and ensure the safety of patients administered medication during maintenance treatment.

The present study strictly followed clinical medication specifications. PEG-rhG-CSF was injected 24-48 h after the completion of chemotherapy, and the evaluation of whether to implement PARPi treatment began at least 14 days after the injection of PEG-rhG-CSF. This avoided the short intervals between chemotherapy, PEG-rhG-CSF injection and targeted therapy, which induce potential bone marrow suppression. However, the present study also has some limitations. First, the opportunistic, single-center, retrospective study design resulted in the cohort being established based on the available clinical data of patients treated over a specific 3-year period, rather than via prospective enrollment. The use of multivariate linear regression adds value; however, the relatively small sample, resulting from the low incidence of ovarian cancer and strict inclusion criteria requiring concomitant PEG-rhG-CSF and PARP inhibitor therapy, may limit statistical power and model stability. Second, although a detailed analysis of potential outcome-related factors (such as baseline bone marrow reserve, number of chemotherapy cycles, chemotherapy regimen, and chemotherapy dosage) was conducted, the complexity of clinical decision-making and the potential biases it may introduce may be unavoidable. For example, during PARPi therapy, patients may face treatment interruptions and dose adjustment. Third, the present retrospective study relied on previous medical records, and thus, data on some indicators may be lacking. Nonetheless, this pragmatic design was critical for investigating this specific clinical situation and offers a foundational real-world evaluation that can guide future, larger prospective studies. Additionally, the study planned to analyze the impact of neutropenia and FN on long-term myelosuppression. However, since patients with ovarian cancer have some risk factors for the occurrence of FN, most patients in the study received primary prevention according to expert consensus, resulting in an extremely low incidence of neutropenia and FN. Analyzing their impact on long-term myelosuppression was somewhat challenging. Therefore, further prospective studies or even multicenter studies are required in the future to explore the potential impact of the prophylactic injection of PEG-rhG-CSF during maintenance treatment in patients with ovarian cancer in order to expand the current findings and ensure the accuracy of the results. Further basic research is warranted to verify the findings presented, to determine whether patients with ovarian cancer already experience HSC aging following multiple rounds of chemotherapy and to determine whether the prophylactic injection of PEG-rhG-CSF following multiple rounds of chemotherapy can aggravate bone marrow damage.

In conclusion, myelosuppression may lead to the interruption of PARPi treatment, thereby affecting the treatment efficacy in patients with ovarian cancer. The present study found that low levels of neutrophils, leukocytes and hemoglobin in patients with ovarian cancer undergoing PARPi maintenance therapy may be associated with the prophylactic injection of PEG-rhG-CSF following first-line chemotherapy. Therefore, in order to improve the safety of PARPi therapy and reduce the risk of neutropenia and subsequent infection in patients with ovarian cancer, the prophylactic use of PEG-rhG-CSF following first-line chemotherapy needs to be carefully considered. Future initiatives should also concentrate on creating cutting-edge methods for managing and preventing neutropenia. Furthermore, in order to confirm these results and remove the inherent constraints of confounding by indication in retrospective investigations such as the present study, prospective, randomized controlled trials are necessary.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

YZ and MY contributed to the design of the study and revised the manuscript. WZ contributed to the analysis of data and drafted the manuscript. NT, YW and TF contributed to the acquisition, analysis and interpretation of data. WZ and YZ confirm the authenticity of all the raw data. All authors have read and approved the manuscript.

Ethics approval and consent to participate

The present retrospective cohort study was approved by the Ethics Committee of North Sichuan Medical College (Nanchong, China; approval no. 2025ER698-1). The committee granted a waiver of informed consent to participate as the study posed no more than minimal risk to participants and as the waiver did not adversely affect their rights or welfare.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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