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ORIGINAL RESEARCH

Optimizing Dose-Adjusted EPOCH Chemotherapy with Long-Acting Granulocyte Colony-Stimulating Factor During the COVID-19 Epidemic

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Chong Wei
Yan Zhang
Wei Wang
Wei Zhang

Department of Hematology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, People's Republic of China

Introduction: Febrile neutropenia (FN) is a highly prevalent complication of chemotherapy. In this study, we aimed to evaluate the efficacy of polyethylene glycol recombinant granulocyte colony-stimulating factor (PEG-rhG-CSF) compared with short-acting rhG-CSF in the dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin (DA-EPOCH) regimen.

Patients and Methods: A total of 66 patients with newly diagnosed aggressive B-cell lymphomas who received the rituximab combined with DA-EPOCH regimen and G-CSF support after chemotherapy were included in this study, including 33 patients in the PEG-rhG-CSF group during coronavirus disease (COVID-19) epidemic and another 33 matched patients in short-acting rhG-CSF group as historic control.

Results: The incidence of FN and FN-related hospitalization was significantly lower in chemotherapy cycles using PEG-rhG-CSF than in those using short-acting rhG-CSF (FN incidence: 10.4% vs 20.2%, P=0.038; incidence of FN-related hospitalization: 1.7% vs 7.3%, P=0.042). Overall, the incidence of dose-escalation and dose-reduction of the DA-EPOCH regimen was similar between these two groups.

Conclusion: Our findings suggest that PEG-rhG-CSF as a substitute for short-acting rhG-CSF in the DA-EPOCH regimen significantly reduced the incidence of FN and FN-related hospitalization, while simplifying neutropenia management for both patients and healthcare providers.

Keywords: febrile neutropenia, granulocyte colony-stimulating factor, lymphoma, chemotherapy

Introduction

Febrile neutropenia (FN) is a common yet serious complication of chemotherapy, particularly among patients with hematologic malignancies treated with highly myelosuppressive regimens. FN may result in dose reduction, delay, or even discontinuation of chemotherapy, potentially compromising patient outcomes. Current guidelines recommend the granulocyte colony-stimulating factor (G-CSF) for primary prophylaxis after chemotherapy when the risk for FN is >20%.[1,2]

Two of the most widely used G-CSFs are short-acting rhG-CSF and long-acting polyethylene glycol rhG-CSF (PEG-rhG-CSF). Short-acting rhG-CSF is primarily cleared through the kidney and requires daily dosing to maintain effective blood

Correspondence: Wei Zhang
Department of Hematology, Peking Union Medical College Hospital, No. 1 Wangfujing Shuaifuyuan, Dongdan, Beijing, 100730, People's Republic of China
Tel +86 13681473557
Email vv1223@vip.sina.com

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concentration. By contrast, PEG-rhG-CSF consisting of rhG-CSF pegylated at the N terminus has significantly reduced renal clearance and requires only a single dose per chemotherapy cycle.[3] In clinical trials and in practice, PEG-rhG-CSF has a similar efficacy and safety profile to rhG-CSF and may be preferred by both patients and physicians due to improved adherence and convenience.[4]

Rituximab combined with dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin (DA-EPOCH-R) is a more intensive regimen compared to the standard rituximab combined with cyclophosphamide, epirubicin, vindesine, and prednisone (R-CHOP) regimen, which is commonly used in highly aggressive B-cell lymphomas, such as Burkitt lymphoma, high-grade B-cell lymphoma (HGBL), and primary mediastinal large B–cell lymphoma (PMBL).[5–8] In our center, patients with HGBL (HGBL, NOS and HGBL with double-hit), double expressing (DE) diffuse large B-cell lymphoma (DLBCL), and PMBL are treated with the DA-EPOCH-R regimen. Daily administration of G-CSF beginning on day 6 and continued until absolute neutrophil count (ANC) recovery is mandatory for this regimen.[5] During the coronavirus disease (COVID-19) epidemic, PEG-rhG-CSF has been widely used as a substitute for short-acting rhG-CSF to reduce patients' visits to the hospital in our center. In this retrospective study, we aim to evaluate the efficacy of PEG-rhG-CSF compared to short-acting rhG-CSF in the DA-EPOCH-R regimen.

Patients and Methods

Patients and Data Collection

This report is a single-center, observational, retrospective, propensity score matching study conducted at the Peking Union Medical College Hospital. Patients with newly diagnosed lymphoma who have received the DA-EPOCH-R regimen as first-line chemotherapy and G-CSF (either short-acting rhG-CSF or PEG-rhG-CSF) support after chemotherapy were identified and included. Other inclusion criteria were as follows: 1) histological findings consistent with DLBCL with DE, HGBL, NOS, HGBL with double-hit (DH), and PMBL according to the 2016 revision of the World Health Organization (WHO) classification of lymphoid neoplasms;[9] 2) Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2; 3) baseline ANC of at least 1×10^9/L and platelet count of at least 100×10^9/L; 4) regularly received DA-EPOCH-R chemotherapy and were followed up in our center.

Patients were divided into 2 groups: the short-acting rhG-CSF group and the PEG-rhG-CSF group. The PEG-rhG-CSF group included patients who received PEG-rhG-CSF support after the DA-EPOCH-R regimen during the COVID-19 epidemic from January to August 2020. Patients who were switched from short-acting rhG-CSF to PEG-rhG-CSF during this period were also assigned to the PEG-rhG-CSF group and only chemotherapy cycles using PEG-rhG-CSF were evaluated. Patients who received short-acting rhG-CSF after the DA-EPOCH-R regimen between January 2018 and December 2019 were matched to those in the PEG-rhG-CSF group at a ratio of 1:1. Propensity score matching based on the following baseline characteristics was used to control confounding factors: age, baseline ANC, and the proportion of bone marrow involvement. Patients who received both short-acting rhG-CSF and PEG-rhG-CSF in the same chemotherapy cycle were excluded from the analysis.

The patients' clinical data were obtained from our hospital's medical records, including patient demographics, histologic subtypes, Ann Arbor stage, baseline complete blood count (CBC), the International Prognostic Index (IPI) score,[10] and chemotherapy regimens. Variables including the number of chemotherapy cycles, number of dose-adjustments, nadir ANC values, records of FN, and FN-related hospitalization were extracted.

This study was conducted in accordance with the Declaration of Helsinki. Study protocols were approved by the institutional review board of the Peking Union Medical College Hospital. Written informed consent was obtained from all patients before the collection of patients' information.

Treatment

The DA-EPOCH-R regimen was administered as previously described.[5] In this regimen, the pharmacodynamic dose adjustment was based on the nadir platelet and ANC value, which was checked twice weekly. If the nadir platelet value was below 25×10^9/L or nadir ANC below 0.5×10^9/L on at least 3 measurements, doses were reduced by 20% in etoposide, doxorubicin, and cyclophosphamide for the next cycle. If nadir ANC was at least 0.5×10^9/L, doses were escalated by 20% in etoposide, doxorubicin, and cyclophosphamide for the next cycle. This regimen was repeated every 3 weeks. The second course of chemotherapy was initiated when the ANC was at least 1×10^9/L and the platelet count was at least 100×10^9/L.

For patients in the short-acting rhG-CSF group, rhG-CSF was administered according to the original standard

protocol of the DA-EPOCH-R regimen. Daily subcutaneous injection of rhG-CSF 5 μg/kg/day begun on day 6 and continued until the ANC was above 5×10^9/L post the nadir level. For patients in the PEG-rhG-CSF group, a single once-per-cycle injection of 6mg PEG-rhG–CSF was given 24–48 hours after chemotherapy. For all patients, CBC evaluation after chemotherapy was performed at a frequency of at least twice per week.

Drug source: the short-acting rhG-CSF injection (product name: Ji Sai Xin, produced by North China Pharmaceutical Company Ltd. China) is 150μg/0.5mL per vial; PEG-rhG-CSF injection (product name: Xin Rui Bai, produced by Qilu Pharmaceutical Company Ltd. China) is 3mg/mL per vial.

Definitions and End-Points

Grade 4 neutropenia was defined as ANC<0.5×10^9/L, according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 of the National Cancer Institute (NCI, https://evs.nci.nih.gov/ftp1/CTCAE/About.html). FN was defined as an oral temperature of >38.3°C or two consecutive readings of >38.0°C for 2 hours with an ANC of <0.5×10^9/L or an ANC expected to fall below 0.5×10^9/L. FN-related hospitalization referred to admission to the emergency room or inpatient department due to FN. The recovery time of ANC was defined as the time from the first day of chemotherapy until the time that ANC reached 0.5×10^9/L.

The primary endpoint was the incidence of FN. The secondary endpoints included the following: (1) the incidence of grade 4 neutropenia; (2) the recovery time of ANC; (3) FN-related hospitalization; (4) dose-reduction and dose-escalation in the subsequent chemotherapy cycles; (5) treatment discontinuation and treatment-related death due to infection during myelosuppression period. (6) G-CSF–associated bone pain which was evaluated using a visual analog scale (VAS) score of 0–10.

Statistical Analyses

Differences in patient demographics and clinical characteristics between the 2 groups were assessed using the χ^2 test for categorical variables and the *t*-test for continuous variables. On the other hand, differences in efficacy endpoint variables were evaluated using χ^2 test or if necessary, the Fisher's exact test for categorical variables and the Mann–Whitney *U*-test for continuous variables. *P* value < 0.05 was considered statistically significant. All analyses were performed using the SPSS 20.0 software (SPSS Inc., Chicago, IL, USA).

Results

Baseline Characteristics

Following propensity score matching, a total of 33 patients in the short-acting rhG-CSF group and 33 patients in the PEG-rhG–CSF group were included in this study, and the two groups had similar baseline clinical characteristics and distribution of propensity scores. The baseline characteristics of the patients are listed in Table 1. The median age at diagnosis was 48 (range: 18–77) years in the short-acting rhG–CSF group and 51 (range: 16–70) years in the PEG-rhG-CSF group, with a male-to-female ratio of 1.8:1 and 0.9:1. At the time of diagnosis, most patients (75.6% of patients in the short-acting rhG-CSF group and 69.7% in the PEG-rhG-CSF group) had stage IV disease. Bone marrow involvement was documented in 5 patients (15.2%) each for both groups. The histologic subtypes observed in the short-acting rhG-CSF group included DLBCL with DE in 13 (39.4%) patients, HGBL, NOS in 6 (18.2%) patients, HGBL with DH in 5 (15.2%) patients, and PMBL in 9 (27.3%) patients, whereas those in the PEG-rhG-CSF group were 12 (36.4%), 10 (30.3%), 5 (15.2%), and 6 (18.2%), respectively. No significant differences in demographics and clinical characteristics were found between the 2 groups.

Efficacy End-Points

The incidences of grade 4 neutropenia, FN, and FN-related hospitalization per chemotherapy cycle are listed in Table 2. A total of 124 chemotherapy cycles using short-acting rhG-CSF and 115 cycles using PEG-rhG-CSF were analyzed. The nadir ANC, hemoglobin level, and platelet count showed no significant difference between the two groups. One patient in each group received 2 units of red blood cell transfusion, and no platelet transfusion was documented in each group. Grade 4 neutropenia was observed in 70 (56.5%) cycles of chemotherapy using short-acting rhG-CSF and 52 (45.2%) cycles using PEG-rhG-CSF (*P*=0.083), whereas FN was observed in 25 (20.2%) and 12 (10.4%) cycles of chemotherapy in the 2 groups, respectively (*P*=0.038). A higher incidence of FN-related hospitalization was also documented in chemotherapy cycles using short-acting rhG-CSF compared to using PEG-rhG-CSF (7.3% vs 1.7%, *P*=0.042).

The proportion of patients with chemotherapy dose-reduction and dose-escalation was similar between the 2 groups (Table 3). Dose-escalation was observed in 10/33 patients (30.3%) in the short-acting rhG-CSF group and 9/33 patients (27.3%) in the PEG-rhG-CSF group (*P*=0.946). Dose-reduction was observed in 2 patients (6.1%) each for

Table 1 Baseline Patient Demographics and Clinical Characteristics

Characteristics	No. of Patients (%)		*P* value
	Short-Acting rhG-CSF Group (n = 33)	PEG-rhG–CSF Group (n = 33)	
Age, years			
Median (range)	48 (18–77)	51 (16–70)	0.970
>60	9 (27.3%)	7 (21.2%)	0.566
Sex, male	21 (63.6%)	16 (48.5%)	0.215
Histologic subtypes			0.650
DLBCL with DE	13 (39.4%)	12 (36.4%)	
HGBL with DH	6 (18.2%)	10 (30.3%)	
HGBL, NOS	5 (15.2%)	5 (15.2%)	
PMBL	9 (27.3%)	6 (18.2%)	
Baseline WBC ($\times 10^9$/L), median±SD	6.09±1.61	6.45±1.47	0.458
Baseline ANC ($\times 10^9$/L), median±SD	4.74±1.38	4.95±1.31	0.634
Baseline HGB (g/L), median±SD	115±17.1	113±19.5	0.873
Baseline PLT ($\times 10^9$/L), median±SD	273±35.2	245±25.7	0.624
Bone marrow involvement	5 (15.2%)	5 (15.2%)	1.000
B symptom present	17 (51.5%)	19 (57.6%)	0.621
Ann Arbor stage			0.555
I	2 (6.1%)	4 (12.1%)	
II	4 (12.1%)	2 (6.1%)	
III	2 (6.1%)	4 (12.1%)	
IV	25 (75.6%)	23 (69.7%)	
IPI score			0.263
0–1 (low risk)	7 (21.2%)	8 (24.2%)	
2 (intermediate-low risk)	12 (36.4%)	6 (18.2%)	
3 (high–intermediate risk)	10 (30.3%)	10 (30.3%)	
4–5 (high risk)	4 (12.1%)	9 (27.3%)	

Abbreviations: DLBCL, diffuse large B-cell lymphoma; DE, double-expressing; HGBL, high-grade B-cell lymphoma; DH, double-hit; PMBL, primary mediastinal large B-cell lymphoma; WBC, white cell count; ANC, absolute neutrophil count; HGB, hemoglobin; PLT, platelet; IPI, International Prognostic Index.

both groups. However, 2 patients in the short-acting rhG-CSF group experienced life-threatening FN and long ANC recovery time, leading to treatment discontinuation. Another patient in the short-acting rhG-CSF group experienced severe pulmonary infection and died of respiratory failure in the emergency room.

The main adverse event of G-CSF is bone pain. There appeared to be less G-CSF-associated bone pain in the short-acting rhG-CSF group compared with PEG-rhG-CSF group. However, the VAS score showed no significant difference, with a mean VAS score of less than 3 (Table 3). No other adverse events of G-CSF were reported in both groups.

Discussion

Current guidelines generally recommend the use of G-CSF for the prevention of chemotherapy-induced FN;[1] nevertheless, guidance for clinical practice regarding the choice between short- and long-acting G-CSF is still unclear. PEG-rhG-CSF is the most widely approved and commonly used long-acting G-CSF worldwide. In randomized controlled trials (RCTs) comparing the short-acting rhG-CSF with PEG-rhG–CSF, a similar efficacy and safety profile has been reported.[11–13] Most retrospective studies and meta-analyses suggested the superior efficacy of PEG-rhG-CSF vs short-acting rhG-CSF, which may have been a result of the underdosing of short-acting rhG-CSF in

Table 2 Comparison of End-Point Variables Between Chemotherapy Cycles Using Short-Acting rhG-CSF and PEG-rhG-CSF

Variables	Chemotherapy Cycles of Short-Acting rhG-CSF	Chemotherapy Cycles of PEG-rhG-CSF	*P* value
No. of cycles	124	115	
Nadir ANC value ($\times 10^9$/L), mean±SD	0.86±0.21	1.12±0.35	0.317
Recovery time of ANC (day), mean±SD	15±3.5	14±2.7	0.659
Nadir HGB value (g/L), mean±SD	95±15.6	87±17.9	0.254
Nadir PLT value ($\times 10^9$/L), mean±SD	148±37.5	157±27.9	0.175
Cycles with grade 4 neutropenia, n (%)	70 (56.5%)	52 (45.2%)	0.083
Cycles with FN, n (%)	25 (20.2%)	12 (10.4%)	0.038
Cycles with hospitalization for FN, n (%)	9 (7.3%)	2 (1.7%)	0.042

Abbreviations: FN, febrile neutropenia; ANC, absolute neutrophil count; HGB, hemoglobin; PLT, platelet; RBC, red blood cell.

Table 3 Comparison of End-Point Variables Between Patients in the Short-Acting rhG-CSF and PEG-rhG-CSF Groups

Variables	Patients in the Short-Acting rhG-CSF Group	Patients in the PEG-rhG-CSF Group	*P* value
No. of patients	33	33	
Patients with dose-reduction, n (%)	2 (6.1%)	2 (6.1%)	1.000
Patients with dose-escalation, n (%)	10 (30.3%)	9 (27.3%)	0.946
Treatment discontinuation, n (%)	2 (6.1%)	0	0.492
Treatment-related death, n (%)	1 (3.0%)	0	1.000
VAS score of G-CSF-associated pain, mean ±SD	2.7±2.3	2.9±2.0	0.374

real-world usage.[12,13] Regarding patients with lymphomas, RCTs and retrospective studies focusing on the prophylactic effect of PEG-rhG–CSF are limited.[14–16] Few studies have evaluated PEG-G-CSF as part of a high-dose chemotherapy such as DA-EPOCH. In our study, long-acting PEG-rhG-CSF was evaluated as a substitution for short-acting rhG-CSF in patients receiving the DA-EPOCH-R regimen. To the best of our knowledge, this is the first study that has evaluated PEG-rhG-CSF as part of a specific chemotherapy regimen and in patients with highly aggressive B-cell lymphomas.

In our study, PEG-rhG-CSF significantly reduced the incidence of FN compared to short-acting rhG-CSF. When PEG-rhG-CSF was used as a supporting regimen, the incidence of grade 4 neutropenia and FN was 45.2% and 10.4% per chemotherapy cycle. These findings are comparable to the 49–53% incidence of grade 4 neutropenia and 8–19% incidence of FN reported in the Phase 2 studies of the DA-EPOCH-R regimen.[5,8,17] FN-related hospitalization was also significantly reduced (7.3% for short-acting rhG-CSF vs 1.7% for PEG-rhG-CSF), with no treatment discontinuation and treatment-related deaths in the PEG-rhG-CSF group. The essence of the DA-EPOCH regimen was the dose-adjustment paradigm, which was designed to achieve maximum tolerable treatment intensity in the individual patient without excess toxicity. In our study, the proportion of patients with dose-escalation and dose-reduction was similar between the short-acting rhG-

CSF and PEG-rhG-CSF groups, indicating that similar treatment intensity has been achieved.

Based on convenience and patient adherence, PEG-rhG-CSF may be preferred over short-acting rhG-CSF. Short-acting rhG-CSF is always injected in the hospital or clinic, which requires daily hospital/clinic visit. In real world, not all patients have stringently received the short-acting rhG-CSF according to the dosing schedule of the DA-EPOCH regimen. This is particularly the case in elderly patients with limited mobility. In December 2019, an outbreak of COVID-19 began in Wuhan and spread widely in China. The patients undergoing the DA-EPOCH-R chemotherapy were switched from short-acting rhG-CSF to PEG-rhG-CSF during this period. Once-per-cycle dosing of PEG-rhG-CSF greatly reduced the inconvenience of frequent hospital visits and minimized the exposure of immunodeficient lymphoma patients to the hospital environment, which not only reduced their risk of COVID-19 infection, but also contribute to the control of COVID-19 transmission.

The application of PEG-rhG-CSF remarkably reduced the burden of lymphoma patients on the healthcare system during the COVID-19 pandemic. The pandemic had a huge impact on the healthcare system, including the exhaustion of medical workers, the shortage of healthcare infrastructures, and increased pressure on emergency services. The number of clinic visits and hospital beds of the hematological department in our hospital was also reduced by approximately 50% during this period. As a consequence, the routine delivery of care to lymphoma patients faced a great challenge. The utilization of PEG-rhG-CSF significantly reduced the frequency of hospital visits, the incidence of FN, and the possibility of FN-related hospitalization, which resulted in the reduced occupation of medical resources during the COVID-19 pandemic.

The cost-effectiveness of long-acting rhG-CSF has been evaluated in several studies.[18,19] In a cost-effectiveness analysis comparing pegfilgrastim vs filgrastim in lymphoma and myeloma patients undergoing high-dose chemotherapy and peripheral blood stem cell transplantation, no evidence of higher cost was found for pegfilgrastim.[19] The PEG-rhG-CSF used in our study is a biosimilar of pegfilgrastim and had been independently developed in China. The commonly used short-acting rhG-CSFs in China are also less expensive biosimilars of filgrastim. The cost of 6 mg PEG-rhG-CSF and 10 days' short-acting rhG-CSF (assuming a patient weight of 60 kg) are roughly the same. Nevertheless, the utilization of PEG-rhG-CSF not only relieved the pain and inconvenience of repeated injection, but also significantly reduced FN incidence and FN-related hospitalization, which reduced the total potential medical cost. Further health economic evaluations could provide a better insight into the cost-effectiveness of PEG-rhG-CSF.

The limitations of our study also need to be acknowledged. First, being a retrospective observational drug use evaluation, patients in the 2 groups were from different periods, which may have resulted in selection bias. Hence, our conclusions need further verification through prospective RCTs. Second, the superior efficacy results of PEG-rhG-CSF reported in our study may be partially due to the underdosing of short-acting rhG-CSF in real-world practice. Third, due to the dose-adjustment nature of this regimen, both the treatment intensity and the type of G-CSF may have affected the severity of neutropenia and its complications. However, we have attempted to provide a more comprehensive picture by reporting chemotherapy dose-reduction and dose-escalation, in addition to FN incidence.

In conclusion, PEG-rhG-CSF as a substitute of short-acting rhG-CSF in the DA-EPOCH regimen significantly reduced the incidence of FN and FN-related hospitalization in real-world clinical practice. Once-per-cycle administration of PEG-rhG-CSF simplifies the management of neutropenia for both patients and healthcare providers.

Ethical Approval

The study was done in accordance with the Declaration of Helsinki. The protocol was approved by our institutional review board.

Informed Consent

Informed consent was obtained from all individual participants included in the study.

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Disclosure

The authors declare that they have no conflict of interest.

References

1. Aapro MS, Bohlius J, Cameron DA, et al. 2010 update of EORTC guidelines for the use of granulocyte-colony stimulating factor to reduce the incidence of chemotherapy-induced febrile neutropenia in adult patients with lymphoproliferative disorders and solid tumours. *Eur J Cancer*. 2011;47(1):8–32.
2. Smith TJ, Bohlke K, Armitage JO. Recommendations for the use of white blood cell growth factors: American Society of Clinical Oncology clinical practice guideline update. *J Oncol Pract*. 2015;11(6):511–513. doi:10.1200/JOP.2015.006742
3. Yang BB, Savin MA, Green M. Prevention of chemotherapy-induced neutropenia with pegfilgrastim: pharmacokinetics and patient outcomes. *Chemotherapy*. 2012;58(5):387–398. doi:10.1159/000345626
4. Aapro M, Boccia R, Leonard R, et al. Refining the role of pegfilgrastim (a long-acting G-CSF) for prevention of chemotherapy-induced febrile neutropenia: consensus guidance recommendations. *Support Care Cancer*. 2017;25(11):3295–3304. doi:10.1007/s00520-017-3842-1
5. Wilson WH, Grossbard ML, Pittaluga S, et al. Dose-adjusted EPOCH chemotherapy for untreated large B-cell lymphomas: a pharmacodynamic approach with high efficacy. *Blood*. 2002;99(8):2685–2693. doi:10.1182/blood.V99.8.2685
6. Dunleavy K, Pittaluga S, Shovlin M, et al. Low-intensity therapy in adults with Burkitt's lymphoma. *N Engl J Med*. 2013;369(20):1915–1925. doi:10.1056/NEJMoa1308392
7. Howlett C, Snedecor SJ, Landsburg DJ, et al. Front-line, dose-escalated immunochemotherapy is associated with a significant progression-free survival advantage in patients with double-hit lymphomas: a systematic review and meta-analysis. *Br J Haematol*. 2015;170(4):504–514. doi:10.1111/bjh.13463
8. Dunleavy K, Pittaluga S, Maeda LS, et al. Dose-adjusted EPOCH-rituximab therapy in primary mediastinal B-cell lymphoma. *N Engl J Med*. 2013;368(15):1408–1416. doi:10.1056/NEJMoa1214561
9. Swerdlow SH, Campo E, Pileri SA, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. *Blood*. 2016;127(20):2375–2390. doi:10.1182/blood-2016-01-643569
10. International Non-Hodgkin's Lymphoma Prognostic Factors Project. A predictive model for aggressive non-Hodgkin's lymphoma. *N Engl J Med*. 1993;329(14):987–994. doi:10.1056/NEJM199309303291402
11. Huang W, Liu J, Zeng Y, et al. 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*. 2018;82(4):607–613. doi:10.1007/s00280-018-3639-z
12. Pfeil AM, Allcott K, Pettengell R, et al. Efficacy, effectiveness and safety of long-acting granulocyte colony-stimulating factors for prophylaxis of chemotherapy-induced neutropenia in patients with cancer: a systematic review. *Support Care Cancer*. 2015;23(2):525–545. doi:10.1007/s00520-014-2457-z
13. Cornes P, Gascon P, Chan S, et al. Systematic review and meta-analysis of short- versus long-acting granulocyte colony-stimulating factors for reduction of chemotherapy-induced febrile neutropenia. *Adv Ther*. 2018;35(11):1816–1829. doi:10.1007/s12325-018-0798-6
14. Vose JM, Crump M, Lazarus H, et al. Randomized, multicenter, open-label study of pegfilgrastim compared with daily filgrastim after chemotherapy for lymphoma. *J Clin Oncol*. 2003;21(3):514–519. doi:10.1200/JCO.2003.03.040
15. Chan A, Leng XZ, Chiang JY, et al. Comparison of daily filgrastim and pegfilgrastim to prevent febrile neutropenia in Asian lymphoma patients. *Asia Pac J Clin Oncol*. 2011;7(1):75–81. doi:10.1111/j.1743-7563.2010.01355.x
16. Ng JH, Ang XY, Tan SH, et al. Breakthrough febrile neutropenia and associated complications in Non-Hodgkin's lymphoma patients receiving pegfilgrastim. *Acta Haematol*. 2011;125(3):107–114. doi:10.1159/000321545
17. Dunleavy K, Fanale MA, Abramson JS, et al. Dose-adjusted EPOCH-R (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab) in untreated aggressive diffuse large B-cell lymphoma with MYC rearrangement: a prospective, multicentre, single-arm phase 2 study. *Lancet Haematol*. 2018;5(12):e609–e617. doi:10.1016/S2352-3026(18)30177-7
18. Miyake O, Murata K, Tanaka S, et al. Costs associated with febrile neutropenia in Japanese patients with primary breast cancer: post-hoc analysis of a randomized clinical trial. *Jpn J Clin Oncol*. 2018;48(5):410–416. doi:10.1093/jjco/hyy030
19. Perrier L, Lefranc A, Pérol D, et al. Cost effectiveness of pegfilgrastim versus filgrastim after high-dose chemotherapy and autologous stem cell transplantation in patients with lymphoma and myeloma: an economic evaluation of the PALM Trial. *Appl Health Econ Health Policy*. 2013;11(2):12. doi:10.1007/s40258-013-0011-7