CASE REPORTS

Pegfilgrastim-induced leukocytosis and hyperleukocytosis

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Received: November 12, 2020 **Accepted:** February 4, 2021 **Online Published:** March 22, 2021
DOI: 10.5430/crim.v8n1p5 **URL:** https://doi.org/10.5430/crim.v8n1p5

ABSTRACT

Objective: To report a case of leukocytosis (LCT) and hyperleukocytosis (HLCT) episodes post Pegfilgrastim (Neulasta) administration.

Case Summary: A 74-year-old female presented with several episodes of LCT and HLCT following administration of Pegfilgrastim while undergoing adjunct dose dependent chemotherapy for adenocarcinoma of the gallbladder. The patient had completed cycle 6, day 8 of chemotherapy and subsequently received Neulasta 48 hours later. Two days later, she presented to the ER with white blood cell (WBC) count of 110K. Prior to Neulasta administration, her WBC counts were within normal range and after each episode of leukocytosis, the patient's WBC count trended downward. Upon consultation, hematology considered Pegfilgrastim as a likely cause for this patient's WBC cycling and HLCT.

Discussion: Pegfilgrastim-induced HLCT occurs in less than 1% of patient cases. Dose-dependent chemotherapy combined with Pegfilgrastim treatment is an optimal treatment option to reduce the length of chemotherapy schedules and risk of febrile neutropenia. Following the dosing of Pegfilgrastim, the drug clearance is mediated by neutrophil receptors which results in a reduction of ANC values.

Conclusions: Further studies are needed to determine the optimum timing and dosage of Pegfilgrastim to offer maximum myeloprotective benefit while also minimizing the risks of adverse events such as leukocytosis and hyperleukocytosis experienced by our patient.

Key Words: Leukocytosis, Hyperleukocytosis, Neulasta, Pegfilgrastim, ANA, G-CSF

1. INTRODUCTION

Pegfilgrastim is an FDA approved granulocyte colony-stimulating factor (G-CSF) used to reduce adverse effects (AE) of myelosuppressive, dose-dependent chemotherapy.[1] Adjuvant therapies combining chemotherapy and G-CSF treatments are associated with improved overall and disease-free survival.[2] Clinically, Pegfilgrastim is used as a primary prophylactic agent to reduce the incidence of chemotherapy-induced febrile neutropenia (FN), a potentially life-threatening condition.[3,4] Additionally, Neulasta has its own side effects such as pain in the extremities, bone pain, and fatigue.[3] The recommended dose of 6 mg in adults is typically given 24 hours post chemotherapy to avoid adverse effects, but simultaneously protect patients from FN.[1,5] This FDA indicated dose can be reduced to further minimize AEs, but this is done on a case-by-case basis by evaluating additional parameters such as splenic function, history of sickle cell disorder, capillary leak syndrome, acute

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myeloid leukemia, and glomerulonephritis.[1,3]

Pegfilgrastim works by stimulating proliferation of hematopoietic stem cells and inducing differentiation into mature neutrophils.[6] Compared to other G-CSF drugs such as Filgrastim, Pegfilgrastim offers long-lasting stimulation.[2,6] However, this stimulation can also induce the mass proliferation of other white blood cell (WBC) types, resulting in leukocytosis (LCT) or a WBC > 11×10^9 cells/L. In some rare cases, patients may experience hyperleukocytosis (HLCT) or a WBC > 100×10^9 cells/L. In clinical trials conducted to bring Pegfilgrastim to market, HLCT was observed in less than 1% of the 932 patients.[1] Patients experiencing either LCT or HLCT may experience fever, bleeding or bruising, dizziness, fatigue, pain in proximal limbs and abdomen, dyspnea, and weight loss.[7] HLCT can further progress and result in leukostasis symptoms due to vascular obstruction in the lungs and CNS.[5] Given these sequelae, it is important to identify HLCT causes and minimize risks posed to patients.

We present a case of a 74-year-old female undergoing dose-dependent chemotherapy for treatment of advanced unresectable adenocarcinoma of the gallbladder who experienced transient hyperleukocytosis following Pegfilgrastim administration. What makes our case presentation so unique are the multiple episodes of HLCT experienced by a single patient and normalization of WBC counts between episodes. Moreover, this individual's advanced age suggests she would have about 30% cellularity in her bone marrow. As such, for her to mount a cytopenic white cell response at the levels required to classify as HLCT is remarkable.

2. Case presentation

A 74-year-old female with past medical history of hypertension, COPD, hepatitis C, rheumatoid arthritis, and recent diagnosis of adenocarcinoma of the gallbladder on chemotherapy presented to the ER by recommendation from her oncologist due to abnormally elevated WBC count and worsening of her chronic abdominal pain.

She was originally diagnosed with adenocarcinoma of the gallbladder in February 2020 after CT abdomen showed large heterogeneous mass in the gallbladder fossa region with hepatic infiltration and intrahepatic biliary dilatation. Subsequent fine needle aspiration of the liver was positive for malignancy. The tumor was determined to be unresectable and she was started on systemic treatment in March 2020 with Cisplatin and Gemcitabine on days 1 and 8 every 21 days of a chemotherapy cycle. She was also receiving Neulasta post-chemotherapy as primary prophylaxis to prevent myelosuppressive effects of chemotherapy.

The patient had completed cycle 6, day 8 of chemotherapy and subsequently received Neulasta 48 hours later. Two days later, she presented to the ER with WBC 110×10^3. She was afebrile and hemodynamically stable. Initial physical exam was unremarkable except for diffuse abdominal tenderness without peritoneal signs. Labs were significant for hemoglobin 8.3 g/dl, absolute neutrophil count 106.4×10^3/ul, procalcitonin 0.01 ng/ml, lactate 1.9 mmol/L, creatinine 1.48 mg/dl, total bilirubin 0.4 mg/dl, direct bilirubin 0.1 mg/dl, alkaline phosphatase 173 IU/L, AST 15 IU/L, ALT 30 IU/L. Urinalysis revealed moderate leukocyte esterase, negative nitrite and 6-10 WBC. Chest x-ray showed cardiomegaly. CT abdomen showed no significant change in the gallbladder fossa mass, however there was segmental wall thickening of the transverse colon and distal descending colon consistent with colitis. Patient was started on ceftriaxone for possible UTI and hematology was consulted for hyperleukocytosis.

Since starting chemotherapy and Neulasta, she had experienced similar episodes of leukocytosis and hyperleukocytosis following Pegfilgrastim administration. The WBC counts cycled between LCT/HLCT and normal values (see Figure 1). Episodes of HLCT peaked at 113×10^3 and 110×10^3 WBC. Prior to Neulasta administration, her WBC counts were within normal range and after each episode of leukocytosis, the patient's WBC count trended downward. Due to this pattern, the hematology consultant determined the hyperleukocytosis to likely be due to Neulasta. Blood cultures remained negative and antibiotics were discontinued. Her WBC trended down to 38×10^3 on discharge two days later and 23×10^3 one week later. Additionally, due to this robust reaction, a peripheral blood smear was ordered as an outpatient and the patient followed up in the oncology clinic for further management.

3. Discussion

Pegfilgrastim-induced HLCT occurs in less than 1% of patient cases.[3] HLCT is a life-threatening condition that has dangerous sequelae like leukostasis, where increases in blood viscosity can induce the formation of vascular obstruction in the lungs and CNS.[5] Interestingly, these patient experienced cycles of increased WBC count post-Pegfilgrastim dosing. These cycles were mainly categorized as LCT; however, this patient did experience two accounts of HLCT within the span of three months (see Figure 1). The patient was administered Pegfilgrastim 24 hours after chemotherapy, following FDA guidelines.[1] Interestingly, spikes of WBC counts were observed within 48 hours of the Pegfilgrastim administration. Our data shows that there may be a correlation between Pegfilgrastim administration and HLCT (p = .0034) since higher WBC counts were observed following administration.

During the remainder of the chemotherapy cycles, the patient exhibited normal WBC counts.

As a long-acting G-CSF, Pegfilgrastim is mainly eliminated through the kidney or internalized via cell surface receptors that endocytose and degrade Pegfilgrastim inside the cell.[1,6] The latter is a neutrophil-mediated clearance response to neutrocytosis and is the predominant elimination method for Pegfilgrastim. In our data, we found that there may be a correlation between Pegfilgrastim administration and ANC counts (P = .0168), like previously mentioned WBC counts (see Figure 2). After Pegfilgrastim administration, there was an initial ANC peak followed by a gradual decrease when excess neutrophils were cleared out (see Figure 2). After administration, the neutrophil clearance rate seemed to be modified causing a higher ANC count. Since Pegfilgrastim clearance is dependent on neutrophil receptors, if neutrophil clearance is affected, HLCT can result.[5]

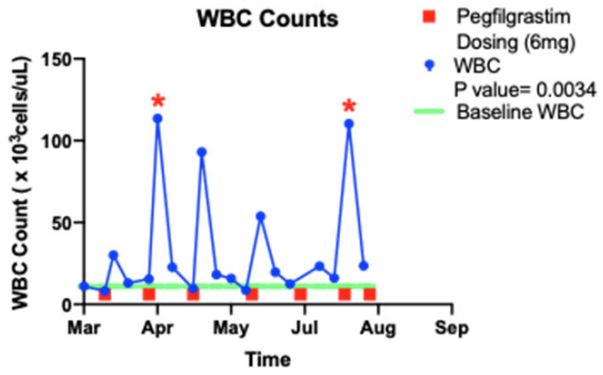

Figure 1. WBC Counts Changing Upon Pegfilgrastim Administration. It displays a chart that quantifies changes in WBC count post Pegfilgrastim dosing. The blue line represents changes in WBC count, with each point being a single measure of WBC count. The red boxes represent dates where the patient was administered Pegfilgrastim. The green line designates WBC counts = 11 $\times$ 10^3 cells/ul. Points above this line are dates where the patient experienced LCT or HLCT. Red Asterisks are representative of episodes of HLCT. A Welch's T test was performed and a p-value of 0.0034 was found. This value is considered significant under our studies parameters (p values $\leq$ .05 are significant).

Some recent studies suggest that in sensitive patients, timing of Pegfilgrastim dosing may be key in reducing elevated WBC counts–LCT or HLCT. Specifically, one study observed that delivering Pegfilgrastim off-label via a 72-hour post chemotherapy dose allows for G-CSF to administer its full myeloprotective potential.[2] In this dosing scheme, the study reports having reduced accounts of LCT and HLCT while maintaining protection against FN. Other studies have found that using a gradual dosing scale, where incremental increase in Pegfilgrastim dose over the span of a few treatment cycles can reduce risks of AEs.[4] These studies claim that since Pegfilgrastim is intrinsically a long-acting G-CSF, prophylactic scaled dosing can gradually increase neutrophil counts to protect against FN, but simultaneously maintain an optimal clearance rate. As such, these patients can avoid some Pegfilgrastim induced AEs, including LCT and HLCT. Moreover, literature also suggests that primary prophylaxis of Pegfilgrastim is recommended when using chemotherapy regimens that are associated with a high rate of FN onset.[8] In these cases, FN is considered immediately life-threatening and as such must be resolved first prior to assessment for LCT or HLCT.

This study is limited to single patient in which these patterns of cyclic WBC counts are observed. As such, a larger population study of the adverse events of patients taking Neulasta would garner a more supported statistical significance. Although, it is important to note that our patient did experience several episodes of LCT and HLCT.

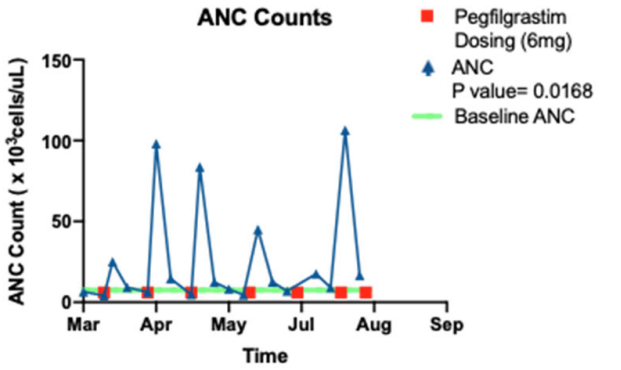

Figure 2. ANC Counts Changing Upon Pegfilgrastim Administration. It displays a chart that quantifies changes in ANC count post Pegfilgrastim dosing. The blue line represents changes in ANC count, with each point being a single measure of ANC count. The red boxes represent dates where the patient was administered Pegfilgrastim. A normal ANC value can range between 1.6 - 7.6 $\times$ 10^3 μl. The green line designates ANC = 7.6 $\times$ 10^3 cells/ul which is the higher end of normal range. Points above this line are dates where the patient experienced higher counts of ANC. A Welch's T test was performed and a p-value of .0168 was found. This value is considered significant under our studies parameters (p values $\leq$ .05 are significant).

4. Conclusion

Pegfilgrastim-induced leukocytosis (LCT) and hyperleukocytosis (HLCT) can result when maximum neutrophil receptor-mediated clearance is surpassed, as observed several times in our patient. Further studies to determine if a smaller dose of

Pegfilgrastim would exhibit the same myeloprotective benefits while also minimizing the risk of AEs such as LCT and HLCT can benefit our patient population. In addition, further trials to improve optimum timing of Pegfilgrastim dosing following each chemotherapy cycle can aid patients, as the current FDA approved timeline of 24 hours post chemo cycle may not be the most efficacious.

ACKNOWLEDGEMENTS

We would like to thank the University of Toledo Dana Cancer Center for helping with data acquisition and allowing for patient-centered studies. We would also like to acknowledge Mr. Eric Betka for confirming dates when the patient was given Pegfilgrastim. We would like to thank Dr. Grace Ning, MD for mentoring us during this project and answering our queries.

CONFLICTS OF INTEREST DISCLOSURE

The authors have declared no conflicts of interest.

REFERENCES

[1] Inc A. Neulasta Highlights of Prescribing Information. These highlights do not include all the information needed to use NEULASTA safely and effectively. U.S. Food and Drug Administration 2015.

[2] Lambertini M, Bruzzi P, Poggio F, et al. Pegfilgrastim administration after 24 or 72 or 96 h to allow dose-dense anthracycline- and taxane-based chemotherapy in breast cancer patients: a single-center experience within the GIM2 randomized phase III trial. Support Care Cancer. 2016; 24(3): 1285-94. PMid:26306520. https://doi.org/10.1007/s00520-015-2907-2

[3] Takuwa H, Tsuji W, Goto T, et al. Pegfilgrastim-induced fatigue and leukocytosis improved following dose reduction in a young patient with breast cancer: A case report. Mol Clin Oncol. 2019; 11(4): 371-5.

[4] Li L, Ma S, Wu M, et al. The prophylactic effects of long-acting granulocyte colony-stimulating factor for febrile neutropenia in newly diagnosed patients with epithelial ovarian cancer: a randomised controlled study. BMJ Support Palliat Care. 2019; 9(4): 373-80. PMid:31467066. https://doi.org/10.1136/bmjspcare-2019-001862

[5] Chavda R, Herrington JD. Pegfilgrastim-induced hyperleukocytosis leading to hospitalization of a patient with breast cancer. Proc (Bayl Univ Med Cent). 322019. p. 261-2. PMid:31191148. https://doi.org/10.1080/08998280.2018.1547873

[6] Wessels H, Lehnick D, Höfler J, et al. Pharmacodynamics, safety, and immunogenicity of Pelmeg(®), a pegfilgrastim biosimilar in healthy subjects. Pharmacol Res Perspect. 2019; 7(5): e00507. PMid:31417681. https://doi.org/10.1002/prp2.507

[7] Nancy Berliner. Leukocytosis and Leukopenia,. In: Editor(s): Lee Goldman AIS, editor. ISBN 9781437716047, 24th Edition ed: Willey; 2012. p. 170.

[8] Ohkura Y, Ueno M, Udagawa H. Risk factors for febrile neutropenia and effectiveness of primary prophylaxis with pegfilgrastim in patients with esophageal cancer treated with docetaxel, cisplatin, and 5-fluorouracil. World J Surg Oncol. 2019; 17(1): 125. PMid:31315622. https://doi.org/10.1186/s12957-019-1665-x