Pegfilgrastim-induced hyperleukocytosis leading to hospitalization of a patient with breast cancer

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ABSTRACT

In patients receiving dose-dense chemotherapy, adverse effects such as neutropenia can be reduced by colony-stimulating factors. Pegfilgrastim, a colony-stimulating factor, has associated adverse effects, including bone pain, fever, and, rarely, hyperleukocytosis. We describe a 45-year-old woman with breast cancer receiving dose-dense Adriamycin and cyclophosphamide chemotherapy. She presented with hyperleukocytosis after receiving pegfilgrastim, which resulted in hospitalization. This case report reviews the strategy to minimize the risk of hyperleukocytosis from pegfilgrastim administered in dose-dense chemotherapy.

KEYWORDS Breast cancer; granulocyte colony-stimulating factor; hyperleukocytosis; leukocytosis; pegfilgrastim

Neutropenia is a major cause of morbidity and mortality in more than 20% of patients with breast cancer receiving anthracycline-based dose-dense chemotherapy.¹ Severe neutropenia or febrile neutropenia can cause significant delays and/or chemotherapy dose reductions.^{1,2} Disease-free survival as well as overall survival are affected by the number of delayed cycles as well as reduction in relative dose intensity.³ The administration of a granulocyte colony-stimulating factor (G-CSF), such as pegfilgrastim, minimizes the duration and extent of neutropenia.³ However, there are associated adverse effects from G-CSF such as bone pain and fever.^{4,5} G-CSF acts on hematopoietic cells, stimulating proliferation, thus adding risk for hyperleukocytosis.^{4,6,7} This case report reviews the case of a patient with breast cancer receiving pegfilgrastim alongside dose-dense chemotherapy, leading to hospitalization due to hyperleukocytosis.

CASE REPORT

A 45-year-old woman presented to a local emergency department with weakness, pain, nausea, and vomiting after receiving cycle 4 of breast cancer chemotherapy 3 days prior to her presentation. She was recently diagnosed with *HER*-negative, progesterone receptor–negative, estrogen receptor–negative

grade III (T4N2Mx) invasive ductal carcinoma. Her treatment plan included dose-dense Adriamycin + cyclophosphamide (ddAC) followed by dose-dense paclitaxel. Each cycle was followed by pegfilgrastim 6 mg subcutaneously given after chemotherapy (*Figure 1*).

Tests revealed a white blood cell (WBC) count of $123 \times 10^9/L$ with a left shift of 13% bands. Her WBC was repeated with a result of $>105 \times 10^9/L$, with 2% bands, 94% segmented neutrophils, and 3% lymphocytes. The patient was evaluated for systemic inflammatory response syndrome; the workup included a peripheral smear, blood cultures, urine culture, sputum cultures, procalcitonin level, lactate dehydrogenase level, creatine kinase level, and chest x-ray. The procalcitonin level was 0.41 ng/mL, lactate dehydrogenase was 450 IU/L, and chest x-ray displayed patchy bibasilar pleural-parenchymal opacities. The patient was started on intravenous normal saline and antibiotics and admitted to the hospital for possible pneumonia. On day 2 of her hospitalization, she remained afebrile and the WBC count decreased to $60.8 \times 10^9/L$. All cultures were negative, and she was discharged with 5 days of oral levofloxacin 750 mg. Following this hospitalization, the patient was seen by her outpatient oncologist and completed the rest of her dose-dense chemotherapy without documented recurrence of hyperleukocytosis. The patient had return of complete blood

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Figure 1. Dose-dense chemotherapy and pegfilgrastim administration schedule for cycles 1 to 4. The blue dashed line represents white blood cell (WBC) levels on different cycle days of dose-dense doxorubicin + cyclophosphamide (ddAC).

count to normal limits and no bone marrow biopsy was performed to identify any underlying myeloproliferative disorder.

DISCUSSION

Dose-dense chemotherapy is an effective treatment that allows for a shorter time interval between treatment cycles and requires the use of pegfilgrastim.⁸ After pegfilgrastim administration, neutrophil receptor-mediated clearance of the drug occurs as the absolute neutrophil count recovers gradually. Hyperleukocytosis (described with WBC $>100 \times 10^9/L$) can occur if the clearance is affected, which can present asymptotically or symptomatically.⁴ Hyperleukocytosis can cause leukostasis. Neurologic or pulmonary symptoms that arise from leukostasis include somnolence, dizziness, stupor, headache, ataxia, coma, hypoxemia, dyspnea, tachypnea, and lung failure.⁹ These symptoms are a result of vascular obstructions primarily within the lung parenchyma and the central nervous system. In this case report, the presenting symptoms were primarily of neurologic, pulmonary, or musculoskeletal origin. With a negative infectious workup, the presenting symptoms of this patient were likely due to pegfilgrastim's adverse effects.

As demonstrated in *Figure 1*, ddAC cycle 4 pegfilgrastim was administered 24 hours after ddAC infusions. The prescribing information for pegfilgrastim instructs avoiding pegfilgrastim within 24 hours after infusion or 14 days before receiving the next round of chemotherapy due to a potential for an increase in excessive cytopenias.^{4,10} This is a concern when pegfilgrastim is administered within 14 days of the next cycle, as seen with dose-dense chemotherapy. This issue was addressed in a retrospective study that evaluated the safest timing of administration of pegfilgrastim in patients with breast cancer receiving dose-dense chemotherapy. The researchers compared pegfilgrastim administration at 24, 72, and 96 hours after chemotherapy. This study indicated that the chances of leukocytosis (defined as $>50 \times 10^9/L$) in at

least one cycle in the 24-, 72-, and 96-hour cohorts were 75%, 50%, and 66.7%, respectively.⁸ Patients receiving pegfilgrastim 24 hours after ddAC therapy had a higher incidence of leukocytosis.⁸ There was no significant difference among the cohorts in the incidence of adverse events, such as leukopenia or neutropenia.⁸ Delayed administration of pegfilgrastim is prohibited by the prescribing information restriction from administering G-CSF within 14 days before receiving the next chemotherapy.

As appreciated in this case, hyperleukocytosis adds a burden to the patient that may lead to an increase in health care system and provider visits. Further prospective trials are needed to support a change in the pegfilgrastim administration time to 72 hours after dose-dense chemotherapy. These alterations may lead to less hyperleukocytosis while maintaining favorable protection from leukopenia and neutropenia in patients receiving ddAC.

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