Pegfilgrastim-Induced Pain in Patients With Lymphoma

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A

56-year-old Caucasian woman named Ms. P was diagnosed with diffuse large-cell lymphoma with aggressive features. Her presenting symptoms included fever, weight loss, and drenching night sweats, with disease present in mesenteric, inguinal, and axillary lymph nodes as well as in her bone marrow. Ms. P has multiple comorbidities including diabetes, hypertension, gout, osteoarthritis, and hyperlipidemia. Ms. P presented to the clinic to discuss treatment options. Her oncologist recommended chemotherapy with rituximab, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin (R+EPOCH) for six cycles with intrathecal chemotherapy prophylaxis and pegfilgrastim support. Ms. P agreed with the treatment plan and was admitted to receive chemotherapy. She tolerated the treatment well without any significant side effects or adverse events. She was discharged and returned to clinic after 24 hours to receive the pegfilgrastim.

Ms. P did well until two days later when she developed severe bilateral flank pain. She called her sister, who told her that she might have kidney stones. Ms. P took tramadol 50 mg orally to ease her pain but had no relief. She was taken to a local emergency room for evaluation. Her vital signs upon arrival were a temperature of 99.8°F, blood pressure of 140/90 mmHg, pulse of 120 bpm, oxygen saturation level of 95% on room air, and respirations of about 20 breaths per minute. Physical examination revealed clear lungs, a nontender abdomen, and no flank tenderness. She had no evidence of trauma and was neurologically intact. Ms. P was given hydromorphone 2 mg via IV, but received minimal relief. Urinalysis, urine culture, basic metabolic panel, and complete blood count were obtained, as well as chest x-ray, bilateral renal ultrasonography, IV pyelography, and computed tomography of the abdomen and pelvis with attention to the kidneys, ureters, and bladder. Urinalysis and microscopy revealed no infection or crystals. The basic metabolic panel revealed normal electrolytes but with slightly elevated uric acid (7.5 mg/dl). The complete blood count revealed a hematocrit of 9.3 g/dl, platelet count of 85 K/mcl, and white blood cell count of 25.5 K/mcl. All imaging studies revealed no acute process. Because of the elevated white blood cell count, blood cultures were obtained and broad-spectrum antibiotics were ordered. Ms. P was kept overnight for observation. The pain persisted and a pain service was consulted. After obtaining additional history, the pain consultant determined that the location of Ms. P’s pain was the bilateral iliac crests and was related to the pegfilgrastim. Ms. P was given a dose of ibuprofen and, after a few hours, she reported improvement of her pain. She was later discharged home.

Ms. P returned to her oncologist for clinical evaluation prior to the second cycle of chemotherapy. She reported her “bad experience” and said that she was “scared to death” about taking another dose of pegfilgrastim. Her oncologist reassured her that preventative measures can be taken to prevent the bone pain. After the oncologist explained to her how pegfilgrastim works, why it causes pain, and how the pain can be prevented, Ms. P agreed to take it. He also explained that the use of ibuprofen is not recommended for her subsequent cycles of chemotherapy because of its effects on platelets and that it can mask fevers. Ms. P was admitted to the hospital for her second cycle of chemotherapy but, this time, she was started on ceftriaxone the day she received pegfilgrastim and took 10 mg orally daily for 10 days. She had no further significant pain related to pegfilgrastim.

Pegfilgrastim

Pegfilgrastim is indicated to decrease the incidence of infection as manifested by febrile neutropenia in patients with nonmyeloid malignancies receiving myelosuppressive chemotherapy associated with a clinically significant incidence of febrile neutropenia (Amgen Inc., 2011). The American Society of Clinical Oncology and the National Comprehensive Cancer Network (NCCN) recommend first- and subsequent-cycle colony-stimulating factors for myelosuppressive chemotherapy regimens with about a 20% or greater risk of febrile neutropenia (NCCN, 2013; Smith et al., 2006). Treatment- and patient-related risk factors for febrile neutropenia include:

• Chemotherapy with a 20% or greater risk of febrile neutropenia
• Being older than age 65 years
• Having comorbidities such as chronic lung disease, diabetes, and cardiac disease
• Being diagnosed with advanced-stage cancer
• Having a poor performance status
• Having concurrent renal or liver dysfunction or concurrent infection, wound, or surgery
• Undergoing prior radiation or myelosuppressive therapy
• Having preexisting neutropenia or bone marrow involved with tumor (NCCN, 2013).
Neutropenia is one of the dose-limiting toxicities of myelosuppressive chemotherapy agents (Pinto et al., 2007) and a significant risk factor for infection (Gregory, Schwartzberg, Mo, Sierra, & Vogel, 2010). It also is one of the reasons for dose-reductions or delays of treatment that can affect patient outcomes. The administration of growth factors, such as pegfilgrastim or filgrastim, has contributed greatly to the reduction of the incidence, duration, and severity of chemotherapy-related neutropenia (Pinto et al., 2007). It also has helped clinicians administer myelosuppressive agents at full doses without delays and dose-dense chemotherapy regimens, both of which have increased long-term survival (Citron et al., 2003; Kirshner et al., 2012; Kummel et al., 2006).

**Pegfilgrastim-Induced Pain**

Pegfilgrastim acts on hematopoietic cells by binding to specific cell surface receptors, thereby stimulating proliferation, differentiation, commitment, and end-cell functional activation. Pegfilgrastim has a half life of 15–80 hours after subcutaneous injection (Amgen Inc., 2011).

An unwanted side effect of pegfilgrastim and filgrastim treatment is bone pain. The exact mechanism of filgrastim or pegfilgrastim-induced pain (PIP) is unknown, but Walbridge (2012) speculated that bone pain is caused by histamine-related inflammation. Bone pain has been reported in 26%–37% of patients in early clinical trials; however, in clinical practice, the incidence of pain seems to be significantly higher (Kirshner et al., 2012). Kirshner et al. (2012) reported (N = 510) an overall incidence of 59% of patients reporting pain, with 24% of patients experiencing severe bone pain. According to the results of early clinical trials, no risk factors have been identified to predict patients who might experience pain after pegfilgrastim or filgrastim administration (Kirshner et al., 2012; Kirshner, Hickok, & Hofman, 2007; Pinto et al., 2007).

Findings from a retrospective analysis conducted by Gregory et al. (2010) from clinical trials suggested that any grade bone pain may be more common in younger patients (younger than age 65 years) than in older patients (age 65 years and older) who are receiving chemotherapy. In non-small cell lung cancer, grade 3/4 bone pain was high and may be caused by the use of carboplatin and paclitaxel. In addition, bone pain of any grade appeared more common in patients who received taxanes than those who did not receive taxanes. Unfortunately, PIP is unpredictable and refractory to many analgesics, particularly opioids (Kirshner et al., 2007).

**Clinical Presentation**

Bone pain is a common side effect of treatment of growth factors such as filgrastim and pegfilgrastim (Amgen Inc., 2011). Pain is mainly noted in the bones, but pain also can be noted in joints and muscles and may manifest as headaches. Bone pain can present in the back, rib cage, sternum, upper and lower extremities, and hips. Pain in the sternum and rib cage may present as chest pain and may lead to a work-up for acute myocardial infarction. Pain in the hip or lower back also can lead patients to think that they have kidney stones, as illustrated in the case study. The pain can be severe at times, to the point that patients seek urgent care. No difference exists between the incidence and the severity of pain with either filgrastim or pegfilgrastim (Kubista et al., 2003). PIP also is unpredictable and it can occur immediately after the administration of the growth factor or a few days later. It also can occur with either the first or subsequent cycles (Gregory et al., 2010).

**Pain Management**

Nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen and naproxen seem to provide the most relief for this pain (Kirshner, Heckler, Reichel, & Morrow, 2010). However, not every

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patient with cancer can take NSAIDs because they can interfere with platelet function, which can be dangerous for patients who are thrombocytopenic or have a history of bleeding. In addition to anecdotal reports, clinical trials have shown that antihistamines, such as loratidine, reduced PIP when given the morning of the initial dose of pegfilgrastim and continued for 5–8 days (Kirshner, Heckler, Reichel, McAuliffe, & Morrow, 2011). The mechanism of action for antihistamines and anti-inflammatory drugs to reduce PIP is not well understood, but they may reduce histamine-related inflammation (Walbridge, 2012). Because the loratidine did not completely alleviate the pain in Kirshner et al. (2011), researchers currently are looking at the combination of loratidine and naproxen to manage PIP. A pilot study of the loratidine and naproxen combination showed that these drugs were safe when used to prevent PIP, but did not appear to be more effective than either drug used alone (Kirshner et al., 2010). However, the pilot study had a small sample, and a larger study is warranted to further evaluate the efficacy and toxicity of these drugs. Anecdotal reports mention second-generation antihistamines, such as cetirizine, that also relieve or even prevent bone pain. However, no clinical trials have been conducted yet to provide such evidence. A need also exists to study the combination of opioid analgesics with antihistamines and/or anti-inflammatory drugs.

Nursing Implications

Recognizing the variable presentation of growth-factor–associated pain is very important for nurses to ensure appropriate treatment and management of pain. Proper management of PIP can prevent unnecessary discontinuation of the medication and also prevent unnecessary visits to the emergency department and hospitalization. This is a concern, because, if patients refuse pegfilgrastim, clinicians will not be able to administer the optimal dose of chemotherapy, possibly decreasing response to treatment and long-term survival (Citron et al., 2003; Kummel et al., 2006). Therefore, nurses must be aware of the side effects of growth factors and educate their patients. Nurses must pay particular attention to a patient’s history and include a review of medications when encountering patients with cancer with complaints of acute pain. A thorough assessment of pain is critical (Wood, 2008).

Patients should be aware of the common side effects of growth factors so they will not be alarmed when they experience it. They need education about what preventative measures to take to minimize PIP. In addition, PIP is unpredictable and refractory to opioids, but medications are available to alleviate the pain. Although no strong evidence exists that antihistamines help in alleviating the pain caused by growth factors, they may be helpful in patient management.

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References


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