Nursing Management of Sustained Rigors and Recurrent Fever as Symptoms of Filgrastim Hypersensitivity: A Case Report

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A 36-year-old man presented to an emergency room with fever, fatigue, and severe rectal pain. He was subsequently found to be pancytopenic with a perirectal abscess. A bone marrow examination revealed 58% blasts consistent with acute myeloid leukemia. The patient was initiated on clofarabine, idarubicin, and cytarabine therapy. The first cycle of therapy was complicated by neutropenic fever, bacteremia, and pneumonia. The second cycle was complicated by delayed platelet recovery. As a result, the patient was referred for possible stem cell transplantation. The patient was enrolled in a phase III trial using standard of care double umbilical cord blood transplantation with myeloblative conditioning to include fludarabine and melphalan, with rabbit antithymocyte globulin. Filgrastim injections were initiated at 600 mcg daily.

The patient's post-transplantation phase was complicated by sustained rigors and recurrent febrile episodes. The patient experienced 1–6 episodes of rigors daily. During this period, the patient also reported severe lower back pain with a majority of the episodes of rigor. The patient then developed neutropenic fever on Day 17 with persistent fever daily ranging from 38.1°–39.5°C through Day 50, with only six days in which he was afebrile. Filgrastim injections were administered at 4 pm daily, and the febrile episodes were noted to occur primarily in the early to late evening hours, with rigors preceding the febrile events by about 30–60 minutes. By Day 30, the patient's engraftment had plateaued with a white blood cell count of 1.2 and an absolute neutrophil count of 0.89. As a result, the filgrastim dose was increased to 600 mcg twice daily.

Diagnostic Workup

Because of the ongoing symptoms associated with neutropenic fever, including rigors, and pain, an infectious disease consult was obtained on Day 8. Anticipating an infectious etiology corresponding with the neutropenic period, a complete infectious disease work-up was conducted (see Table 1). The patient developed diarrhea on Day 3 post-transplantation, which was positive for *Clostridium difficile,* and was resolved with metronidazole followed by oral vancomycin.

Diagnostic imaging studies including X-rays, and computed tomography (CT) scans of the chest, abdomen, and pelvis were negative. However, a positron-emission tomography (PET)/CT scan revealed multiple enlarged mediastinal and bilateral hilar lymph nodes. Flexible video bronchoscopy with endobronchial ultrasound and ultrasound-guided transbronchial fine needle aspiration (FNA) of the lymph node, as well as a bronchoalveolar lavage, were completed. Culture results were negative for a complete bacterial, viral, and fungal examination. Pathology revealed no malignant cells, no viral changes, fungal stains were negative, as was staining for pneumocystis. The FNA specimens also were negative. The patient's central venous catheter also was removed and the tip was sent for bacterial and fungal cultures, which returned negative for central line-associated bloodstream infection. Since the patient was not exhibiting symptoms of viral encephalitis or meningitis, lumbar puncture was not completed.

A bone marrow biopsy and aspiration was completed on Day 34 with no evidence of acute leukemia. All cultures, including cytomegalovirus, human herpesvirus 8 (HHV8), herpes simplex virus, adenovirus, varicella zoster virus, parvovirus, fungal cultures, and bacterial cultures also were negative. HHV6 was positive in the peripheral blood on Day 29, as well as in the bone marrow study on Day 34 (less than 183 DNA copies/ml), but improved with foscarnet therapy. Despite improvement of HHV6 in the blood, the patient's symptoms persisted. An immunoglobulin-G level was obtained on Day 34, which returned low at 572 mg/dl and was replaced with IV immunoglobulin 50 g daily for four doses. Throughout the course of the rigors and febrile events, the patient received various IV and/or oral antimicrobial, antifungal, antiviral, and an aminoglycoside (amikacin) therapy with limited improvement in the frequency and severity of symptoms.

Identifying Hypersensitivity

As infectious sources were ruled out, the attending physician turned his attention to evaluating the potential for hypersensitivity to the pharmacologic regimen. Agents were systematically tapered to observe for changes in symptom severity. The patient also began to voice concerns regarding the filgrastim injections and, as a result of limited improvement in neutrophil recovery, it was decided to reduce the dose on Day 50. The following day, the patient's fever curve and symptoms of rigors and pain were reduced with the dose reduction of filgrastim. The medication was discontinued on Day 51, with no other febrile

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events noted, and full symptom resolution within 48 hours of discontinuation.

Etiology

Sustained rigors with or without fever in various pathologic conditions have been reported and occur for a variety of reasons including, but not limited to, infection, inflammation, pain, anxiety, drug interactions, and immunoglobulin infusion (Leach, Gilbert, Evans, & van Boxel, 2011; Pierce & Jain, 2003; Smack Gregoor, van Saase, Weimar, & Kramer, 1995; Tal et al., 1997). Rigors are one of the most commonly reported adverse events after immunoglobulin administration in the U.S. Food and Drug Administration's MEDWATCH passive surveillance system (Pierce & Jain, 2003). In the event of infection-associated rigors, bacterial rather than viral infections are most commonly the culprit (Tal et al., 1997). In addition, medication hypersensitivity also has been reported to be responsible for rigors and fever (Smack Gregoor et al., 1995).

Pathophysiology

The pathophysiology of fever and rigors emerges within the thermoregulatory center located in the hypothalamus. The literature suggests a variety of pyrogens (e.g., bacteria, cytokines) stimulate release of metabolites such as prostaglandins from endothelial cells of blood vessels surrounding the hypothalamus (Boulant, 1997). When these metabolites cross the blood-brain barrier and diffuse into the thermoregulatory center of the hypothalamus, several signaling cascades occur, which lead to an increase in the temperature set point. Consequently, the hypothalamus sends sympathetic signals to cause vasoconstriction of peripheral blood vessels and decrease heat loss through the skin. If these pathophysiological changes do not generate enough heat to match the new temperature set point, the motor nervous system stimulates shivering to occur to increase heat production (Boulant, 1997). In the case of noninfectious conditions, the pathophysiology of rigor could be different. For example, immunoglobulin infusion, commonly used in the stem cell setting, is known to cause immediate or delayed rigors with or without fever. The proposed mechanistic factors in the literature for immunoglobulin-associated rigors are antigen-antibody reaction, aggregate formation, sodium content, and pH of the immunoglobulin (Palabrica, Kwong, & Padua, 2013; Stiehm, 2013). However, exact mechanistic information on rigors in most of the conditions remains fairly unknown.

Table 1. Diagnostic Workup of a Patient With Sustained Rigors and Recurrent Fever Post-Transplantation

Days After Transplantation	Test Ordered	Result
+3	C-reactive protein	Normal limits
+4	*Clostridium difficile*	**Positive**
	Blood cultures via central venous catheter and peripheral blood	Negative
	Cytomegalovirus by antigenemia and PCR	Negative
+7	Urine cultures with urinalysis	Negative
	Influenza A	Negative
	Influenza B	Negative
	Parainfluenza types 1, 2, 3	Negative
	Respiratory syncytial virus	Negative
	Varicella zoster virus	Negative
+19	Adenovirus by PCR	Negative
	Aspergillus antigen	Negative
	Human metapneumovirus	Negative
+29	Human herpesvirus 6 by PCR	**Positive**
+31	Parvovirus by PCR	Negative
+33	John Cunningham virus by PCR	Negative
+34	Toxoplasmosis by PCR	Negative
+44	Serum cryptococcal antigen	Negative
+46	*Pneumocystis carinii*	Negative
	Legionella	Negative

PCR—polymerase chain reaction

Note. The table reflects the first time each respective test was carried out following transplantation.

Filgrastim-Associated Fever and Rigors

Filgrastim, an integral part of cancer symptom management, is a commercially available recombinant human granulocyte–colony-stimulating drug. Filgrastim has been approved for neutrophil recovery in patients undergoing stem cell transplantations and also to mobilize hematopoietic progenitor cells from the bone-marrow into the peripheral blood of stem cell donors (Welte, 2014). The most common side effects associated with filgrastim are bone pain (90%) and headache (17%) among stem cell donors (de la Rubia et al., 1999). More severe reactions to filgrastim, including splenic rupture and anaphylactic-like reactions, have been reported in the literature (Tholpady, Chiosea, Lyons, Baird, & Leitman, 2013).

Filgrastim-associated sustained episodes of rigors with or without fever have not been reported in the literature. However, fever of unknown origin without rigors has been reported in a randomized clinical trial comparing safety and efficacy of single dose of pegfilgrastim versus daily filgrastim in pediatric patients undergoing autologus stem cell transplantation (Cesaro et al., 2013). Other studies of adult patients undergoing stem cell transplantation also report fever as one of the reversible adverse events associated with filgrastim administration (Orciuolo et al., 2011). Mechanistic information on filgrastim-associated febrile episodes also has been emerging. The non-glycosylated form

Nursing Management of Filgrastim Hypersensitivity

- Filgrastim is an approved drug used for both stem cell mobilization in donors and for neutrophil recovery in stem cell transplantation recipients (Welte, 2014).
- The incidence of filgrastim hypersensitivity exhibited as anaphylactic-like reaction, although rare, has been reported in both stem cell donors and patients (Adkins, 1998).
- Febrile episodes have been reported in filgrastim recipients, particularly in the presence of non-glycosylated filgrastim (Orciuolo et al., 2011).
- Fever with shivering can contribute to increased oxygen consumption and require oxygen support (Henker, Kramer, & Rogers, 1997).
- Oncology nurses should be aware of the potential for hypersensitivity to filgrastim, particularly in the presence of symptoms often associated with infectious sources during the neutropenic period.
- The Naranjo Adverse Drug Reaction Scale can be used to assess the likelihood of a pharmacologic sensitivity (Naranjo et al., 1981).
- Oncology nurses play an integral role in the management of hypersensitivity symptoms, providing supportive care and appropriate patient education.

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of filgrastim has been reported to be associated with increased incidence of febrile episodes compared to glycosylated filgrastim (Orciuolo et al., 2011). Febrile episodes could be attributed to an impairment of neutrophils during exposure to non-glycosylated filgrastim (Ribeiro et al., 2007).

A few cases of filgrastim hypersensitivity have been reported in the literature, but no conclusive patterns or symptoms emerged. Two cases have reported severe systemic anaphylactic-like hypersensitivity during filgrastim administration in allogenic donors (Adkins, 1998; Tholpady et al., 2013). Anaphylactic reaction associated with filgrastim also has been reported in patients with malignancies (Batel-Copel et al., 1995). Delayed hypersensitivity reaction manifested by skin rash one week after pegfilgrastim administration was reported for a patient with breast cancer (Dadla, Tannenbaum, Yates, & Holle, 2014).

Nursing Management

Recipients of stem cell transplantation often are prescribed filgrastim post-transplantation to enhance cell recovery and engraftment, particularly true for allogeneic transplantation recipients undergoing partially matched transplantations from haploidentical and cord-blood sources for whom neutrophil recovery may be delayed, thereby necessitating prolonged use of filgrastim. During the period of neutropenia, patients also are predisposed to infection, the symptoms of which could mirror the hypersensitivity symptoms with which the patient in the case study presented. Although infectious sources are most often the cause of fever, and potentially rigors, this case study illustrates the need for nurses to be aware of the potential for hypersensitivity reaction to filgrastim, as well as other agents, for which presenting symptoms may be similar.

Symptom Management

Nursing management of the patient with fever and rigors consists of attention to both the symptoms themselves as well as those symptoms arising from pharmacologic management. Meperidine is a commonly prescribed agent because of its ability to act on kappa-receptors to reduce shivers (Ikeda et al., 1997). However, meperidine is associated with sedative effects, severe hypotension (Atalay, Aksoy, Aksoy, Dogan, & Kursad, 2010), and the potential for nausea and vomiting (Anaraki & Mirzaei, 2012). Nurses should be attentive to hemodynamic monitoring and proactive response with antiemetic therapies. Complementary therapies, including warm blankets, have demonstrated a synergistic effect with meperidine, reducing the shivering threshold by lowering vasoconstriction (Kimberger et al., 2007).

The occurrence of fever presents several challenges, including increased physiologic stress resulting from increases in cell metabolism, heart rate, and cardiac output. In the presence of fever with shivering, oxygen consumption may increase by 100%–200% (Henker, Kramer, & Rogers, 1997). This increased demand for oxygen could necessitate the need for oxygen via nasal cannula, as occurred in this case study. Fever is also associated with cytokine release, contributing to weight loss, weakness, and nitrogen imbalance by triggering muscle catabolism. Mental changes such as delirium and seizures could also occur with increase in physiological stress (Gelfand & Dinarello, 1998). Nurses caring for such patients should be aware about underlying physiological changes associated with fever and rigors to initiate appropriate nursing interventions. For management of fever, acetaminophen and hydrocortisone were prescribed for the patient in the case study; however, these agents may be precluded based on chemotherapy regimens for which agents (e.g., busulfan) compete for metabolic pathways.

Pain and anxiety are additional symptom management considerations. Filgrastim-associated back pain should be managed with appropriate analgesic support. Anti-anxiolytics in conjunction with complementary therapies may be used to effectively manage anxiety and pain. In the case study, dilaudid was used for pain management, lorazepam

Table 2. Naranjo Adverse Drug Reaction Scale to Determine Filgrastim Hypersensitivity

No.	Question	Answer	Points
1	Are there previous conclusive reports on this reaction?	No	0
2	Did the adverse events appear after the suspected drug was given?	Yes	2
3	Did the adverse reaction improve when the drug was discontinued or a specific antagonist was given?	Yes	1
4	Did the adverse reaction appear when the drug was readministered?	N/A	0
5	Are there alternative causes that could have caused the reaction?	No	2
6	Did the reaction reappear when the placebo was given?	N/A	0
7	Was the drug detected in any body fluid in toxic concentration?	N/A	0
8	Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	Yes	1
9	Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	N/A	0
10	Was the adverse event confirmed by any objective evidence?	No	0

Note. From "A Method for Estimating the Probability of Adverse Drug Reactions," by C.A. Naranjo, U. Busto, E.M. Sellers, P. Sandor, I. Ruiz, E.A. Roberts, . . . D.J. Greenblat, 1981, *Clinical Pharmacology Therapeutics, 30,* p. 240. Copyright 1981 by John Wiley and Sons, Ltd. Adapted with permission.

for anxiety, and music therapy was integrated as the patient enjoyed music and played an instrument.

Discussion

The occurrence of fever and rigors in an immunocompromised patient after stem cell transplantation usually indicates neutropenic fever and underlying infectious etiology. Sensitivity reactions to filgrastim are rare; however, in this case, the occurrence was masked because of the patient's physiologic status and the multi-drug regimen prescribed related to the transplantation process. Ultimately, tapering drugs individually to identify how symptoms change in severity or resolve after discontinuation of a certain medication contributes to the identification of medication hypersensitivity.

The Naranjo Adverse Drug Reaction (ADR) scale is a tool that may be effectively used to identify the potential for medication hypersensitivity (Naranjo et al., 1981). In this case, the Naranjo score is 6 (see Table 2), which indicates a possible filgrastim-induced adverse event. The occurrence of recurrent fever and sustained rigors could be clinical manifestations of possible filgrastim hypersensitivity.

Although the focal symptoms in the patient in the case study were fever and rigors, the patient also concurrently reported bone pain. Although bone pain is an expected symptom of filgrastim administration, the episodes of rigors in this patient increased from Day 31 to Day 37 as the filgrastim dose was increased. Retrospectively, this could have been an additional indicator that the patient was experiencing hypersensitivity to filgrastim.

With widespread use of filgrastim both for stem cell donors and recipients, healthcare providers could be confronted with filgrastim-associated adverse events and hypersensitivity reactions. As observed in the case study, these adverse events can mimic other conditions and, as a result, differential diagnosis may be problematic. Oncology nurses and their interprofessional colleagues should, therefore, be aware of the potential for filgrastim-associated hypersensitivity and assess for its occurrence early and often during filgrastim administration. The ability to track and trend symptoms of hypersensitivity for this and other agents may contribute significantly to patients' physiologic and quality-of-life outcomes during cancer treatment.

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