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Neutropenic Fever Following Chemotherapy in a Patient With Lymphoma

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C.L., a 72-year-old woman diagnosed with stage II diffuse large B-cell lymphoma, had a medical history of hypertension and hypothyroidism, which was treated with lisinopril 20 mg daily and levothyroxine sodium 0.125 mg daily. Her treatment plan consisted of six cycles of rituximab 375 mg/m^2 IV on day 1, cyclophosphamide 750 mg/m^2 IV on day 1, doxorubicin 50 mg/m^2 IV on day 1, vincristine 1 mg IV on day 1, and prednisone 100 mg orally on days 1–5, followed by 30 Gy of radiation therapy. C.L. had a teaching session with the nurses in the infusion center at her hematologist's office one week prior to chemotherapy to help her understand the treatment, the expected side effects, and when to contact a healthcare provider.

Following the teaching session, C.L. continued with her preparation for chemotherapy. Her complete blood count revealed that hematocrit was 39.2% (normal range = 35%–47%), hemoglobin was 13 g/dl (normal range = 12–15 g/dl), white blood cell count was 6,000/mm^3 (normal range ≥ 1,500/mm^3), absolute neutrophil count was 3,000/mm^3 (normal range = 1,500–4,500/mm^3), and platelet count was 250,000/mm^3 (normal range = 150,000–400,000/mm^3). Chemistry panel results were within normal limits. C.L. had a Hickman catheter placed before beginning chemotherapy. She received her first dose of chemotherapy without complications at the infusion center in her hematologist's office. She received a pegfilgrastim injection 24 hours later to prevent severe neutropenia.

C.L. returned to see the nurses at the infusion center one week after her chemotherapy. She reported nausea (relieved by oral metoclopramide 10 mg) in the first two days after treatment. Her hematocrit was 37.8%, hemoglobin was 12 g/dl, white blood cell count was 4,000/mm^3, absolute neutrophil count was 1,500/mm^3, and platelet count was 230,000/mm^3. An absolute neutrophil count of 1,000–1,500/mm^3 is classified as grade 2 neutropenia (Cancer Therapy Evaluation Program, 2006). C.L.'s vital signs were stable, and her electrolytes were within normal limits. The hematologist prescribed ciprofloxacin 500 mg orally twice daily for prophylaxis against gram-negative and gram-positive infections (Zitella et al., 2005). The hematologist and nurses reviewed neutropenic precautions with C.L. and instructed her to call if she had any signs or symptoms of infection. C.L. said that she understood.

C.L. returned to the infusion center for a nurse evaluation the next week. Her hematocrit was 37.2%, hemoglobin was 11.9 g/dl, white blood cell count was 2,900/mm^3, absolute neutrophil count was 400/mm^3, and platelet count was 230,000/mm^3. An absolute neutrophil count of less than 500/mm^3 is defined as grade 4 neutropenia (Cancer Therapy Evaluation Program, 2006). C.L.'s temperature was 101°F, and her heart rate was 100 beats per minute. She reported that her temperature was 100.5°F the prior evening and 100.8°F an hour before her arrival at the office. She did not report either temperature because of the scheduled office visit. C.L. felt fatigued but had no other signs or symptoms of infection. The hematologist admitted her to the inpatient oncology unit for management of neutropenic fever.

How is the condition assessed and what are the interventions?

C.L.'s condition began to deteriorate after admission. Her temperature rose to 101.5°F, her heart rate was 110 beats per minute, and her blood pressure was 90/50 mmHg. C.L.'s nurse drew two sets of blood cultures, one from the Hickman catheter and one from a peripheral vein. She also collected a urine sample. C.L.'s absolute neutrophil count continued to drop to a nadir of 100/mm^3. C.L. received cefepime 2 g IV and normal saline 500 ml bolus after which continuous normal saline at a rate of 125 ml per hour was initiated. C.L. continued to receive IV cefepime and oral ciprofloxacin every 12 hours. In an effort to prevent cephalosporin-induced *Clostridium difficile*, C.L. began oral saccharomyces boulardii. Her vital signs improved after the antibiotics and IV fluids, and a chest x-ray ruled out pneumonia. An infectious disease consultation was requested, leading to the initiation of vancomycin 500 mg IV every 12 hours.

The urine culture and chest x-ray were negative. The blood cultures from the Hickman catheter and peripheral vein site were positive for *Staphylococcus aureus*. Vancomycin therapy was increased to 1 g every 12 hours. C.L.'s Hickman catheter was removed by an interventional radiologist, and she continued to receive antibiotics through a peripheral vein.

Do You Have an Interesting Clinical Experience to Share?

Clinical Challenges provides readers with a forum to discuss creative clinical solutions to challenging patient care issues. Case studies or descriptions may be submitted with or without discussion or solutions. References, tables, figures, and illustrations can be included. Materials or inquiries should be directed to *Oncology Nursing Forum* Associate Editor Susan Moore, RN, MSN, ANP, AOCN®, at smoore46@yahoo.com, or Nancy Jo Bush, MN, MA, RN, AOCN®, at nancyjobushrn@aol.com.

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C.L. was on neutropenic precautions during her hospitalization, and nurses taught C.L. and her husband about this classification. Verbal lessons were given, and a neutropenic precautions sign was placed on C.L.'s door. But the staff soon discovered that C.L. and her husband did not have a good understanding when sons, daughters-in-law, and grandchildren came to visit. C.L.'s toddler grandchildren were seen running and crawling around her hospital room. The nurse realized that more patient education was needed and again met with C.L. and her husband to assess their learning needs and reading abilities. Written and verbal information about neutropenic precautions and hand hygiene was presented, and the nurse emphasized the risk to C.L. of holding her grandchildren after they crawled on the floor in her room. After the session, C.L.'s husband became diligent about neutropenic precautions and limited C.L.'s visitors to himself and their two adult sons.

The hospital staff ensured that C.L. had good personal hygiene and that no flowers were present in her room. C.L. was permitted to use an alcohol-free mouthwash, and her only diet restrictions were to eat fully cooked meats, wash all fruits and vegetables, and drink pasteurized beverages (Marrs, 2006). C.L. was started on fluconazole for oral candidiasis prophylaxis and acyclovir to prevent herpes (Zitella et al., 2005). C.L. had received influenza and pneumococcal vaccines two months prior to the hospitalization, so they were not repeated.

C.L. was in the hospital for two weeks, and her blood counts improved during that time. C.L. learned more about neutropenia and the complications associated with the condition. An interventional radiologist placed a Port-a-Cath® (Smiths Medical) prior to discharge so that C.L. could continue receiving a vesicant chemotherapy agent through a central line. After C.L.'s infection resolved, the hematologist gave her a second cycle of chemotherapy in the inpatient setting but reduced the dose by 20%. She received pegfilgrastim 24 hours after chemotherapy to prevent recurrence of neutropenic fever. At the time of discharge, C.L. had an absolute neutrophil count of 3,000/mm^3 and was taking lisinopril 20 mg daily, levothyroxine sodium 0.125 mg daily, ciprofloxacin 500 mg orally twice per day, and allopurinol 300 mg twice per day. C.L. saw her hematologist in the office two days after discharge and had a nurse evaluation in the office a week later. C.L. said she felt much better after the second cycle of chemotherapy. At her nadir, C.L.'s white blood cell count was 2,000/mm^3 and her absolute neutrophil count was 1,600/mm^3. She tolerated subsequent cycles of dose-reduced chemotherapy without complications.

The inpatient and outpatient nurses who cared for C.L. decided to evaluate the education being provided to patients about neutropenia after chemotherapy. Concerned about too many instruction papers and that the reading level was too high, the nurses decided to streamline the education and create a one-page, easy-to-read handout in English and Spanish describing neutropenic precautions and signs and symptoms of infection. Magnets in both languages that said, "call if temperature is greater than 100.4°F" also were created. The nurses' efforts decreased the morbidity and mortality of neutropenic infections.

What is the definition of and criteria for neutropenic fever?

Neutropenic fever occurs when a patient's immune system is suppressed by illness or immunosuppressant medication(s), the patient's oral temperature is at least 100.4°F sustained for at least one hour, and the patient has an absolute neutrophil count less than 500/mm^3. Two major factors lead to increased risk of neutropenic fever: an absolute neutrophil count below 100/mm^3 and prolonged neutropenia (Poznansky & Vianello, 2008).

What is the pathogenesis?

Individuals with neutropenia are lacking the first line of defense against infection. Neutrophils make up 50%–70% of the total white blood cell count (Tefferi, Hanson, & Inwards, 2005). Fever often is the only sign or symptom of infection. The lack of white blood cells prevents the usual signs and symptoms of infection from being displayed. Neutropenia is classified into four grades (see Table 1), and individuals with a higher-grade neutropenia have a greater chance of developing an infection.

What are the risk factors?

The primary risk factor for neutropenic fever is a weakened immune system through disease or treatment. The following increase a patient's chance of developing neutropenic fever: chemotherapy, IV or implanted devices, hypogammaglobulinemia, defects in cell-mediated immunity, glucocorticoid therapy, and disruption of normal anatomic structures (Poznansky & Vianello, 2008). Individuals with compromised immune systems who are in crowds, in a hospital or skilled nursing facility, or exposed to someone who is ill with an infection are at a higher risk for developing fever and infection.

How is neutropenic fever diagnosed?

Neutropenic fever is diagnosed by evaluating the complete blood count and absolute neutrophil count. An absolute neutrophil count of less than 1,500/mm^3 is indicative of neutropenia (Tefferi et al., 2005). Body temperature of 100.4ºF or higher in the presence of an absolute neutrophil count less than 1,500/mm^3 confirms neutropenic fever (Hughes et al., 2002).

Are there any measures to prevent the development of neutropenic fever?

Individuals with neutropenia should avoid people who have active infections or feel ill, crowds, and small children and practice diligent personal hygiene—hand hygiene is essential to preventing infection (Zitella et al., 2005). Colony-stimulating factors, such as filgrastim and pegfilgrastim, are used to stimulate white blood cell production. Oral hygiene also is important to prevent infection (Larson & Nirenberg, 2004). Healthcare providers should avoid the use of suppositories and enemas to avoid disruption of protective mucosal barriers (Poznansky & Vianello, 2008). Influenza and 23-valent polysaccharide pneumococcal vaccines should be administered to prevent infection (Zitella et al., 2005). If neutropenia is anticipated, patients should receive influenza and pneumococcal vaccines before taking the immunosuppressive agent. Antifungal, antibacterial, and antiviral prophylaxis can be used for high-risk patients. A special diet for patients with neutropenia is not recommended; however, meat and fish should be thoroughly cooked and produce should be washed well (Zitella et al., 2006).

Table 1. Grades of Neutropenia

Grade	Neutrophil Count
1	> 1,500/mm^3
2	1,000–1,500/mm^3
3	500–1,000/mm^3
4	< 500/mm^3

Note. Courtesy of National Cancer Institute, 2006.

How is neutropenic fever managed?

Neutropenic fever is a medical emergency that, if not treated promptly, can lead to sepsis and death. Patients with neutropenic fever should be cultured for infections, including blood, urine, sputum, and fecal cultures. Chest x-rays should be performed. After cultures are collected, patients should receive broad-spectrum antibiotics immediately (Poznansky & Vianello, 2008). Once culture results are obtained, antimicrobial medication adjustments may need to be made. Aggressive IV hydration is used to prevent hypovolemic shock if patients progress to sepsis. Vasopressive agents and intubation may be necessary if a patient does not respond to hydration (National Comprehensive Cancer Network [NCCN], 2008).

Guidelines for prevention and treatment of cancer-related infections are available through the NCCN at www.nccn.org/professionals/physician_gls/PDF/infections.pdf. The Oncology Nursing Society (ONS) has published a Putting Evidence Into Practice® (PEP) card for prevention of infection. Copies are available through ONS or by downloading the PDF document at www.ons.org/outcomes/volume1/prevention/pdf/InfectionPEPCard.pdf.

Neutropenic fever can be life-threatening if not treated promptly. In addition to assessing and treating patients' conditions, nurses also need to evaluate patients' understanding

of the teaching that has been provided. Anxiety, language barriers, and in ability to read all are barriers to patient education. Repeating and presenting material in new ways are a vital part of nursing care.

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Clinical Highlights: Neutropenic Fever Following Chemotherapy

Definition

Neutropenic fever is defined as the presence of an oral temperature of 100.4°F or higher for at least one hour when the absolute neutrophil count is less than 500/mm^3 (Hughes et al., 2002).

Pathophysiology

Neutrophils make up 50%–70% of the total white blood cell count (Tefferi, Hanson, & Inwards, 2005). Infection and fever can result when a patient has neutropenia below 500/mm^3 for several weeks. Individuals may lack other signs and symptoms of infection because of the decreased white blood cell count (Poznansky & Vianello, 2008).

Risk Factors

Any patient with neutropenia, particularly when prolonged, is at risk for neutropenic fever. More specific risk factors include receiving chemotherapy, presence of an IV or implanted central line, having a hematologic malignancy, receiving glucocorticoid therapy, and disruption of normal anatomic structures (Poznansky & Vianello, 2008). Any patient with neutropenia who is exposed to an infectious agent is susceptible to infection.

Prevention

Patients with neutropenia should avoid crowds and contact with individuals who have an infection. Hand and oral hygiene (Larson & Nirenberg, 2004; Zitella et al., 2005) is important. Colony-stimulating factors such as filgrastim and pegfilgrastim can be used to stimulate white blood cell production. Influenza and pneumococcal vaccines should be given to prevent infection (National Comprehensive Cancer Network [NCCN], 2008; Zitella et al., 2005). Antifungal, antibacterial, and antiviral prophylaxis can be used for high-risk patients. Thorough cooking of meat and fish and carefully washing produce are recommended (Zitella et al., 2006).

Clinical Findings

Patients who present with an oral temperature of 100.4°F or higher accompanied by a neutrophil count of less than 500/mm^3 should be evaluated for infection. Although most patients with neutropenia have no signs or symptoms of infection other than fever, other presenting factors may include cough, aching, arthralgia, purulent discharge, burning or pain during urination, and erythematous skin lesions (NCCN, 2008; Zitella et al., 2005).

Differential Diagnoses

Patients who present with an elevated body temperature and neutropenia following a course of immunosuppressive chemotherapy should be assumed to have neutropenic fever until proven otherwise. Fever and neutropenia in a patient with cancer who is not receiving immunosuppressive chemotherapy can be caused by bone marrow replacement, neoplastic fever, or autoimmune disorders (Zell & Chang, 2005).

Treatment

Neutropenic fever is a medical emergency. A chest x-ray and blood, urine, sputum, stool, and wound cultures (if applicable) should be ordered. After cultures are collected, patients should receive broad-spectrum antibiotics immediately (Poznansky & Vianello, 2008). Antiviral and antifungal agents can be added if antibiotic therapy does not work and evidence exists of a viral or fungal infection. Colony-stimulating factors should be used for the duration of neutropenia.

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