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Emergency Department Waiting Times for Patients With Cancer With Febrile Neutropenia: A Pilot Study

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Purpose/Objectives: To determine the time frame for evaluation and treatment of adult patients with febrile neutropenia in the emergency department (ED).

Design: Prospective, descriptive survey.

Setting: ED in a large, urban, academic health center.

Sample: 19 patients with febrile neutropenia during 23 ED visits in eight months.

Methods: Demographic and treatment variables and durations of time were recorded from ED and medical records.

Findings: Patients had fevers a mean of 21 hours (range = 1–72 hours) before seeking treatment. Median waiting time from ED admission to examination was 75 minutes, 210 minutes before antibiotics were given, and 5.5 hours to hospital admission. Patients with more comorbidities and more extensive cancer waited significantly longer than those at lower risk ($p < 0.002$).

Conclusions: Although the standard of care is to treat febrile neutropenia as an oncologic emergency, patients waited prolonged periods prior to receiving treatment. Studies are indicated to examine early intervention for febrile neutropenia and to determine whether early intervention improves clinical outcomes.

Implications for Nursing: Nurses may repeat this study at other settings and with other populations of people with cancer. Other studies may provide evidence that clinical outcomes are dependent on rapid intervention for febrile neutropenia in the cancer population or evaluate the efficacy of education that oncology nurses deliver to people with cancer and febrile neutropenia.

Key Points . . .

- Febrile neutropenia is considered to be an oncologic emergency.
- People with cancer and febrile neutropenia waited at home with a fever before coming to the healthcare facility.
- Participants with extensive cancer waited the longest time before being seen and treated for this oncologic emergency.

Fever and neutropenia are among the most common side effects related to cancer treatment. Patients with febrile neutropenia are at risk for developing life-threatening sepsis and septic shock. To prevent the development of sepsis, prompt initiation of empiric antibiotics is the standard of care for this patient population. Because most cancers are treated in the community setting, patients with febrile neutropenia as a result of cancer therapy frequently must use the emergency department (ED) to receive treatment for this complication. The purpose of this study was to determine the time frame for the evaluation and treatment of adult patients with cancer with febrile neutropenia who sought care in the ED of an academic healthcare center. The components of an ED visit that were measured were time from onset of fever to a patient's presentation in the ED, time from the patient's ED admission to assessment and initiation of therapy, occurrence of sepsis and septic shock, and duration of time that the patient was febrile and neutropenic.

Literature Review

Patients with cancer with febrile neutropenia constitute a heterogeneous population with a variable risk for development of serious medical complications (Paesmans, 2000). When the neutrophil count decreases to less than 1,000 cells/mm^3, increased susceptibility to infection can be expected, with frequency and severity inversely proportional to neutrophil count (Hughes et al., 2002). Patients with hematologic malignancies receiving remission-induction chemotherapy or bone marrow or stem cell transplants are at greatest risk because of frequent prolonged neutropenia (Forrest, Schimpff, & Cross, 2002).

About 70%–75% of deaths from acute leukemia and 50% of deaths in patients with solid tumors are related to infection secondary to neutropenia (Barber, 2001). At least half of neutropenic patients who become febrile have an established or occult infection, and at least one-fifth of patients with neutrophil counts of less than 100 cells/mm^3 have bacteremia (Hughes et al., 2002). Significant advancements in supportive care for neutropenic patients have been made in the past decade. Despite these achievements, infection continues to be the major cause of morbidity and mortality in this population (Barber). Advancements have resulted in response rates to initial antimicrobial therapies that exceed 70%, and fewer than 10% of patients with cancer with febrile neutropenia die as a result of their infections (Elting & Cantor, 2002).

The American Society of Clinical Oncology developed guidelines for the use of hematopoietic growth factors in 1994 and updated them in 2000 (Ozer et al., 2000). The recommendations include initiating treatment with colony-stimulating factors

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Digital Object Identifier: 10.1188/04.ONF.711-715

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(CSFs) 24 hours after chemotherapy administration. A meta-analysis of published studies regarding the impact of oncology clinical practice guidelines showed moderate success in reducing hospital length of stay and possibly improved treatment outcomes when such guidelines were used (Smith & Hillner, 2001). In addition, a predictive model proposed that prophylactic use of CSFs would be associated with a reduction in complications and treatment costs (Lyman, 2000).

Patients who are at high risk for complications from febrile neutropenic events include those who have damage to the skin or gastrointestinal mucosa, central venous access devices, and poor nutritional status (Ellerhorst-Ryan, 2000; Rolsten, 1999). Concurrent conditions, including hypotension; dehydration; renal, hepatic, and respiratory insufficiency; altered mental status; hypercalcemia; and uncontrolled bleeding, also are considered to put patients at high risk for developing serious infections (Talcott, Siegel, Finberg, & Goldman, 1992). However, the symptoms and signs of inflammation may be minimal or absent in severely neutropenic patients, especially when anemia is present (Hughes et al., 2002).

Patients who are at low risk for developing complications from febrile neutropenia include those being treated for solid tumors with conventional chemotherapy regimens (Klastersky et al., 2000). Studies have shown that such patients can be treated with oral antibiotics after prompt initial evaluation and hospitalization for initiation of parenteral antibiotics (Freifeld et al., 1999; Rapoport et al., 1999). Treating these patients outside the hospital setting results in decreased hospital stays, thereby potentially decreasing the risk of nosocomial infections.

People with cancer with febrile neutropenia frequently are seen in the ED and then hospitalized to receive immediate empiric treatment with broad-spectrum IV antibiotics until neutropenic events are resolved. As more cancer treatment is shifted to the ambulatory setting and most patients with cancer are treated in community settings, the need to establish a means of instituting rapid diagnosis and initiating treatment for patients with cancer with febrile neutropenia who present to the ED is critical.

The professional oncology community has made great strides in providing patients with cancer and their families the education needed to identify and report complications. The problem is that many of these patients must go to the ED of a local hospital when febrile events occur at night or on weekends, when ambulatory cancer treatment facilities typically are closed. There, patients may have to wait for long periods of time to be evaluated and begin treatment.

According to Shelton (1999), rapid identification of patients at high risk for developing sepsis and prompt initiation of treatment are the most important management strategies. Oncology clinicians recognize that delays in starting antibiotic therapy in patients with febrile neutropenia can lead to life-threatening infections with sometimes fatal consequences (Koh & Pizzo, 2002). Unfortunately, however, no published research supports that belief. Because progression of infection in neutropenic patients can be rapid and difficult to detect symptomatically, empirical antibiotic therapy should be administered promptly at the onset of fever (Hughes et al., 2002).

Methods

The current project was a prospective, descriptive survey of patients with cancer with febrile neutropenia seen in an ED over a period of eight months.

Sample and Setting

Adult patients (older than 18 years) who presented to an ED in a large, academic, urban tertiary care center in New York, NY, between January 28, 2002, and October 31, 2002, with a chief complaint of fever greater than 38.3°C and presumed neutropenia; had a cancer diagnosis; were receiving chemotherapy or radiation therapy; were outpatients of the Medical Hematology/Oncology Faculty Practice Division; and had no known active infection were included in the study. Patients were excluded if they were allogeneic bone marrow transplant recipients, newly diagnosed with acute leukemia (because such patients may present to the ED with fever and pancytopenia caused by the disease rather than by chemotherapy), or patients of physicians who were not members of the Faculty Practice Division.

Study visits took place in the ED at night (6 pm–8 am), on weekends (from 6 pm Friday through 8 am Monday), or during 24-hour holidays, beginning 6 pm the night before a holiday and ending at 8 am the morning after a holiday or when the ambulatory infusion unit was closed. Nights, weekends, and holidays were studied because sick patient visits typically are handled during the day in the oncology clinic and patients were most likely to be seen in the ED when the oncology clinic was closed.

Instruments

A **Data Capture Form (DCF)** was developed for this study and used to collect data from ED and medical records on each patient encounter. The principal investigator (PI) and a research assistant (RA) conferred and reviewed each DCF at the initiation of the study and throughout the data-collection period to ensure inter-rater agreement. Elements included in the form were

- Time from onset of fever to a patient's arrival at the ED
- Time (measured in minutes) from ED admission (triage) until
  - Patient assessment
  - Laboratory results posted
  - Initiation of therapy (e.g., IV antibiotics)
  - Admission of patient to oncology unit or intensive care unit
- Evidence of sepsis or septic shock
- Time until patient was afebrile and no longer neutropenic
- Descriptive characteristics such as type of cancer, stage of disease, chemotherapy protocol, radiation therapy, comorbidities, concomitant medications, and sociodemographic characters such as age, gender, marital status, race, and insurance status.

Procedures

Standardized protocols were used in this study for assessment and treatment of this patient population. Talcott's Risk Assessment Model (RAM) (Talcott et al., 1992) was used to predict the medical risk of patients with febrile neutropenia. The four categories are

- Group I: patients who already were hospitalized (not applicable in this study)
- Group II: outpatients with significant concurrent comorbidity
- Group III: outpatients without serious concurrent comorbidity but with extensive cancer
- Group IV: outpatients with neither comorbidities nor extensive cancer.

The standardized febrile neutropenia protocol consisted of physical examination, complete blood count (CBC), cultures

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of blood and urine samples, complete chemistry profile (including liver function and creatinine), and chest x-ray.

Institutional review board approval was granted, and patients who were included in the study signed consent forms. Prior to initiation of the study, the ED staff was informed of the general nature of the study, but the specific variables to be measured were not discussed. When a potential study patient was expected or arrived in the ED, the medical oncology fellow on call notified the PI. The PI obtained informed consent, and the RA collected data from ED and medical records. To determine whether the researchers were being notified of all eligible patients, reports from answering service records, which document all patient telephone calls, also were monitored throughout the study period.

Data Analysis

Initially, demographic and clinical data were summarized. Analysis of variance and a student's t test or the equivalent nonparametric tests (Kruskall-Wallis or Mann-Whitney) were used to test for differences in mean waiting times in the ED among those with different cancer stages and risk categories. The Fisher's Exact Test was used to examine relationships among categorical variables such as the presence of bloodstream infection or central venous device.

Results

During the study period, 33 episodes of febrile neutropenia were presented in the ED. However, only 23 of the episodes occurred in patients of physicians in the Faculty Practice Division. All eligible patients agreed to participate. Hence, the study included 23 febrile neutropenia episodes in 19 patients who were seen in the ED during nights, holidays, or weekends during the study period. Patients were 29–73 years old ($\overline{X}$ = 56 years), 3% were male, 47% were Caucasian, 47% were married, 79% had private insurance, and 74% received care from a family member. Most patients had multiple myeloma or a solid organ tumor (e.g., breast, lung, testicular, head and neck) at stage 3 or 4 and were receiving cytoxan and colony-stimulating factors. None had a previous history of sepsis, but six (2%) had a previous history of neutropenia. Demographic and clinical variables of the 19 patients are summarized in Table 1.

At the time of the febrile neutropenia episodes, patients had experienced fever for a mean of 21 hours (range = 1–72 hours), and most (52%, 12 of 23 visits) were in the group III risk category. Seven patients (30%) were noted to have mucositis at ED admission. During 11 febrile neutropenia episodes, 48% of the participants had one or more central venous access devices in place, and four (17%) had other indwelling devices such as stents or endoprostheses. Treatment history and laboratory values of patients at the time of ED admission are summarized in Table 2.

In the ED, the median waiting time from admission to examination was 75 minutes. Median time before antibiotics were given was 210 minutes. All patients with febrile neutropenia were admitted from the ED to the hospital, and the mean time in the ED was 330 minutes (5.5 hours) (range = 2.0–11.6 hours). Researchers recorded a median of 2 days from ED admission to a patient becoming afebrile and 3.5 days before a normal white blood cell (WBC) count was achieved (see Table 3).

Time between ED admission and posting of laboratory values was significantly longer for patients in higher risk categories: Those in RAM group II (with comorbidities) waited a mean of 539.8 minutes compared with 236.3 minutes and 250.8 minutes in groups III (extensive cancer) and IV (neither comorbidity nor extensive cancer), respectively (F = 9.2, p = 0.002). Furthermore, time between ED admission and administration of antibiotics was significantly longer for those with more extensive cancer (stages 3 and 4) as compared with those who had stage 1 or 2 disease (276.4 versus 139.5 minutes; t value = –3.4, p = 0.006). No significant differences were found in time to normal WBC count or time until afebrile by either cancer stage or risk category. Mean WBC counts for patients with and without sepsis were 0.65 and 0.17 X 10^9/l, respectively (p = 0.17).

Table 1. Sample Demographic and Clinical Characteristics

Characteristic	n	%
Male	10	53
Caucasian	9	47
Married	9	47
Insurance type		
Private	15	79
Medicaid or Medicare	2	11
Unknown	2	11
Caregiver status		
Self-care	5	26
Family member support	14	74
History of neutropenia	5	26
Comorbidities		
Cardiovascular disease	14	74
Diabetes	2	11
Other cancer	2	11
Autoimmune disease	4	21
Other disease	6	32
Current cancer diagnosis		
Multiple myeloma	7	37
Solid organ tumor	6	32
Non-Hodgkin lymphoma	3	16
Other	3	16
Cancer stage		
1–2	3	16
3	8	42
4	2	11
Missing	6	32

N = 19

Note. Because of rounding, percentages may not total 100.

Discussion

The study institution specializes in hematologic malignancies, and the study population is reflective of this. Such patients are considered to be at greater risk for developing complications related to febrile neutropenia because of prolonged periods of neutropenia and delayed hematologic recovery (Garcia-Carbonero et al., 2001). Although the Infectious Disease Society of America guidelines do not recommend routine administration of antibiotics for this patient population (Hughes et al., 2002), 9 of 19 (47%) of the study patients were receiving prophylactic antibiotics at the time of the ED visit. A study of early-stage breast cancer therapy has shown that a patient who experiences an episode of febrile neutropenia has a greater risk of developing febrile neutropenia with subsequent chemotherapy treatments (Silber et al., 1998). In the current study, 5

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Table 2. Treatment and Laboratory Values of Patients on Admission to Emergency Department

Treatment	n	%
Immunotherapy	8	35
Radiotherapy	6	26
Chemotherapy		
High-dose cyclophosphamide	7	30
Cyclophosphamide	9	39
With platinum	3	13
With doxorubicin or taxane	3	13
Other agents	1	4
Growth factor		
Granulocyte–colony-stimulating factor	7	30
Other or combination	11	48
None	5	22
Antibiotic	9	39
Antiviral agent	1	4
Antifungal agent	4	17
Analgesics	8	35

Laboratory Value	$\bar{X}$	Range
White blood cell count	0.59 X 10^9/l	0.1–2.3
Hemoglobin	9.04 g/dl	4.5–13.5
Hematocrit	28%	13.0–40.6
Platelets	70.3 X 10^9/l	10–238
Neutrophils	32%	0–76
Lymphocytes	42%	0–91
Monocytes	11%	0–50
Eosinophils	3%	0–14
Basophils	2%	0–14
Absolute neutrophil count	400	0–980
Creatinine	1.5 mg/dl	0.5–6.1
Bilirubin	0.74 mg/dl	0.2–1.9
Albumin	3.5 g/dl	2.7–4.2
Lactate dehydrogenase	181.8 U/l	95–385

N = 23 patient visits

of 23 (22%) encounters had a history of prior episodes of febrile neutropenia.

Education for people with cancer includes a review of problems and side effects that require patients to call oncology healthcare providers from home. Fever higher than 38.3°C is emphasized as a major side effect that necessitates immediate medical assessment. Despite this, the study patients experienced fever for a mean of 21 hours prior to ED assessment. Most of these patients were in RAM group III (extensive cancer) and, therefore, at greater risk for developing febrile neutropenia complications. This result surprised the researchers and suggests several areas for future intervention and study. Patient and family education may be improved by thoroughly explaining the risks of febrile neutropenia and ensuring that patients understand the reasons related to early intervention for this potentially life-threatening complication. As a seasoned oncology clinician, the PI has heard from patients and families a multitude of reasons for not calling with problems. Some of the reasons include the desire to avoid an ED visit and hospitalization and reluctance to "bother" healthcare providers. Research to identify patient and family rationale for calling or not calling for fever may provide better means of educating patients with cancer and their families regarding the importance of early prevention and management of side effects of cancer therapy.

The major aim of this study was to measure ED waiting times for patients with cancer with febrile neutropenia. Patients were directed to the waiting area after being seen by a triage nurse for a median of 75 minutes before being evaluated for history of present illness and physical examination. During that time, no intervention was performed and the patients waited in the same waiting area as all other ED patients. After evaluation, median time before the first administration of IV antibiotics was 3.5 hours. This is an inordinately long time to wait for treatment to be delivered for an oncologic emergency. In addition, patients who had extensive cancer (stages 3 and 4) waited significantly longer to receive IV antibiotics than those with less extensive disease. Reasons for the longer wait are unclear but may be associated with the longer time required for a provider to perform a history and physical examination, or perhaps no treatments were initiated until results of laboratory tests were known.

Time between ED admission and posting of laboratory values for the patients in RAM group II (comorbidities) was significantly longer than those in other groups. More laboratory tests may have been done for this group, or perhaps they had interventions for other symptoms and specimens were delayed in being sent. Whatever the reasons, the fact that patients at highest risk waited the longest to receive treatment seems inappropriate.

Although the researchers did not find any literature to confirm the commonly held belief that initiating treatment for febrile neutropenia within two hours of presenting to the hospital makes a difference in terms of outcomes, the oncology community has embraced that belief as a standard of care (National Comprehensive Cancer Network, 2001). To that end, the oncology nursing staff at Dartmouth Hitchcock Cancer Center in Lebanon, NH, initiated a quality-improvement project in an attempt to decrease the length of time that patients with febrile neutropenia wait to receive definitive treatment for febrile neutropenia (Baltic, Schlosser, & Bedell, 2002). The project included multidisciplinary team development of febrile neutropenia diagnostic and treatment guidelines. The guidelines were disseminated to all hospital areas that received patients with febrile neutropenia: the ED, oncology unit, and clinic. Evaluation of the project reported that six patients who were seen in the ED had antibiotics administered within 107 minutes, considerably less than in the current study.

Since the inception of the current study, the ED staff instituted a procedure whereby patients with cancer with fever and presumed neutropenia would be triaged as urgent, be brought to the ED treatment area, and have all blood samples (CBC, chemistry profile, blood cultures, and other preadmission requirements) drawn and IV fluids started immediately.

Table 3. Time Intervals From Emergency Department Admission for Patients With Febrile Neutropenia Episodes

Event	Median Time	Range
Minutes until physical examination	75.0	1–230
Minutes until laboratory results posted	259.5	120–807
Minutes until antibiotics given	210.0	87–520
Minutes until admission to hospital unit	330.0	120–696
Days until afebrile	2.0	1–8
Days until normal white blood cell count	3.5	1–9

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Limitations of the Study

One limitation of the study is that voluntary attending physicians who were not part of the institution's Faculty Practice Division and gynecologic oncologists take their own night calls; hence, their patients were not included in the study. Because the study was conducted at only one academic institution that treats a large number of patients with hematologic malignancies, it may not reflect care in the community or at other institutions. This specific study population and the small sample size mean that caution must be used when making inferences and recommendations based on this study.

Implications

To the authors' knowledge, this study is the first to assess the experience of patients with cancer with febrile neutropenia in terms of time from fever event to treatment in the ED. Most cancer treatment in the United States is rendered in the community, and patients must use community resources not necessarily geared toward their needs, so this study has important implications for improvements in patient care. Future research might include improving interventions so that patients with cancer are treated more rapidly in the ED or at alternative care sites. Future studies might determine what, if any, impact rapid treatment may have on reducing febrile neutropenia complications, length of hospital stays, and cost of treating febrile neutropenia.

Although oncology nurses emphasize to patients the importance of calling immediately when they have a fever, the average time between the onset of fever and the actual time that the patient was seen in the ED was 21 hours in this study. Hence, a better job of educating patients and their caregivers is warranted. Exploring reasons why adult patients with cancer do not call about fever and possibly other oncologic emergencies that may have negative effects on their clinical conditions also seems indicated. In addition, the authors recommend a study to assess pediatric patients with cancer to determine whether parents of febrile children with cancer seek care more quickly and whether patient outcomes are similar.

Conclusion

In this pilot study, acutely ill patients with cancer with febrile neutropenia waited prolonged periods of time before seeking treatment and spent prolonged periods in the ED before treatment was initiated. Based on these results, studies are indicated to examine early intervention for febrile neutropenia and determine whether it improves clinical outcomes.

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For more information . . .

- Neutropenia Support Association Inc.
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