

# Development and Implementation of a Risk Assessment Tool for Chemotherapy-Induced Neutropenia

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**Purpose/Objectives:** To evaluate a tool developed and implemented to help practitioners assess the risk of chemotherapy-induced neutropenia (CIN) and its complications in patients with nonleukemia cancer types.

**Design:** Retrospective survey of chart records.

**Setting:** Community-based oncology practice.

**Sample:** The medical records of 85 adult patients treated with new courses of chemotherapy, regardless of the cancer type or stage; 50 charts belonged to patients treated before the implementation of the tool and 35 to patients evaluated with the tool.

**Methods:** A risk assessment tool for CIN that was developed using risk factors from published studies and national guidelines was implemented. Patients who were found to be at increased risk for CIN were given colony-stimulating factor (CSF) support starting with the first chemotherapy cycle. The effectiveness of the tool was evaluated by comparing clinical outcomes before and after the implementation of the risk assessment tool.

**Main Research Variables:** Febrile neutropenia, IV antibiotic use, hospitalization for neutropenia, and chemotherapy dose reductions and delays.

**Findings:** Chemotherapy dose delays, febrile neutropenia, treatment with IV antibiotics, and hospitalization for neutropenia occurred less frequently in patients assessed with the tool and managed with the algorithm for CSF use than in those who were not assessed.

**Conclusions:** The Risk Assessment for Neutropenic Complications Tool is effective in helping practitioners determine which patients are at high risk for CIN and its complications.

**Implications for Nursing:** By using the tool to identify patients treated with chemotherapy who need growth factor support, nurses can help to reduce the incidence of neutropenia and its complications.

Neutropenia, the most common dose-limiting toxicity in patients with cancer treated with myelosuppressive chemotherapy, is associated with numerous negative consequences (Crawford, Dale, & Lyman, 2004). Patients with chemotherapy-induced neutropenia (CIN) are at increased risk for life-threatening infections, and the risk is greatest when the absolute neutrophil count (ANC) is less than  $500/\text{mm}^3$  (Bodey, Buckley, Sathe, & Freireich, 1966). Infection in patients with neutropenia often manifests only as fever (i.e., febrile neutropenia). Febrile neutropenia not only has negative clinical consequences, but it also has substantial economic effects and consequences on patients' quality of life (QOL). Because the rates of hospitalization for febrile neutropenia are high and the durations of hospitalization are long, febrile neutropenia puts a significant economic burden on the health-

## Key Points . . .

- ▶ Chemotherapy dose reductions and treatment delays can compromise treatment outcomes, whether the goal is cure, prolongation of survival, or palliation.
- ▶ Chemotherapy-induced neutropenia is one of the main reasons for dose modifications.
- ▶ Identifying patients at increased risk for chemotherapy-induced neutropenia with a risk assessment tool will help oncology nurses target appropriate supportive care to patients who are most likely to benefit from it.

care system (Caggiano, Stolshek, Delgado, & Carter, 2001; Kuderer, Cosler, Crawford, Dale, & Lyman, 2002). Studies also have found that QOL is impaired in patients with CIN (Fortner et al., 2002; Okon et al., 2002).

One method of managing or reducing the incidence of CIN is to reduce or delay doses of chemotherapy. Such dose modifications occur frequently in community oncology practices, and nationwide practice-pattern surveys of medical records have shown that 56% of patients with early-stage breast cancer and 53% with non-Hodgkin lymphoma were undertreated (Lyman, Dale, & Crawford, 2003; Lyman, Dale, Friedberg, Crawford, & Fisher, 2004). Dose reductions and delays, especially in curable tumors, can compromise treatment outcomes and long-term survival (Bonadonna & Valagussa, 1981; Budman et al., 1998; Epelbaum et al., 1990; Kwak, Halpern, Olshen, & Horning, 1990; Lepage et al., 1993). Another approach is to use supportive hematopoietic colony-stimulating factors (CSFs), which reduce the incidence, severity, and duration of CIN and

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facilitate the delivery of full, on-schedule chemotherapy doses (Crawford et al., 1991; Green et al., 2003; Holmes et al., 2002; Trillet-Lenoir et al., 1993).

The current American Society of Clinical Oncology (ASCO) guidelines, which were updated last in 2000, recommend the first-cycle use of CSFs only with chemotherapy regimens that have an expected 40% or higher incidence of febrile neutropenia (Ozer et al., 2000). The recently published guidelines for the use of myeloid growth factors from the National Comprehensive Cancer Network ([NCCN], 2005) define high risk as a greater than 20% risk for febrile neutropenia or other neutropenic events that could compromise the ability to deliver full-dose chemotherapy, and the routine use of CSFs starting in the first cycle is recommended for such patients. The NCCN definition of high risk is supported by recent clinical data that have shown reductions of more than 90% in febrile neutropenia, hospitalizations for febrile neutropenia, and IV antibiotic use with the use of first-cycle pegfilgrastim with a chemotherapy regimen in which the expected incidence of febrile neutropenia approaches 20% (Vogel et al., 2005).

According to the 2005 NCCN guidelines, the recommendation for the prophylactic use of CSFs is for treatment with curative intent, adjuvant therapy, or treatment expected to prolong survival and improve QOL. In patients receiving chemotherapy with a curative intent, the use of CSFs should be considered to allow chemotherapy doses and schedules to be maintained. Most importantly, the NCCN guidelines emphasized the evaluation of a patient's individual risk factors combined with the myelotoxicity associated with the prescribed chemotherapy regimen.

The investigator conducted the retrospective chart review described in this article to evaluate the effect of a tool that was developed and implemented to determine which patients with a variety of nonleukemia tumor types are at risk for CIN and its complications. An algorithm for using CSFs to manage neutropenia was developed in conjunction with the risk assessment tool. The purpose of the tool and algorithm is to help healthcare providers manage CIN and its complications effectively and to help improve patient outcomes. To that end, the tool and algorithm were designed to be simple to use and applicable to all nonleukemia tumor types and stages in adult patients.

## Methods

### Tool Development

Using the Evidence-Based Utilization Framework (based on the University of Pennsylvania's Nursing Committee Evidence-Based Practice Framework [Stricker & Sullivan, 2003]) as a guide, the author recognized that the significant clinical problem was the need to identify patients at risk for neutropenia and its complications. Guidelines for determining the risk of neutropenia with chemotherapy, such as those developed by ASCO (Ozer et al., 2000), were not inclusive enough for the needs of most practices.

Continuing to follow the framework, the author acquired additional relevant research through a literature search and determined it to be sufficient quality evidence (Stricker & Sullivan, 2003). By using those data, the investigator decided that a risk assessment tool would be developed and used with all patients treated with chemotherapy.

Potential risk factors for the assessment tool were extracted from studies that were found during the literature search. Risk

factors also were taken from the ASCO guidelines for the use of hematopoietic CSFs (Ozer et al., 2000) and the NCCN guidelines for managing fever and neutropenia (NCCN, 2004). The following risk factors were identified.

- Treatment with a chemotherapy regimen with at least a 40% risk of febrile neutropenia, according to criteria established by Beveridge et al. (2001)
- Patient age older than 70 years
- Bone marrow involvement or compromise
- Open wounds
- Occurrence of febrile neutropenia in a previous course of therapy
- Serum albumin level lower than 3.5 g/dl
- First-cycle ANC less than 500/mm<sup>3</sup>

The risk factors were incorporated into a simple checklist, the Risk Assessment for Neutropenic Complications Tool (see Figure 1). Only risk factors that were applicable to all nonleukemia cancer types, typically included in patient charts, and easily verified by either the practitioner or the nurse were chosen for inclusion in the tool. All involved medical personnel had to agree to use the tool, so the simplicity of the tool would make its use feasible.

### Tool Implementation

A medical professional on the patient care team (physician, nurse practitioner, or nurse) evaluated the risk of CIN and its complications in each patient by using the Risk Assessment for Neutropenic Complications Tool before the first cycle of chemotherapy, and patients were treated according to the algorithm for CSF support that was developed by the author (see Figure 2).

Patients were categorized as being at high risk for neutropenia and its complications if they had at least one of the risk factors listed. Patients classified as high risk were given CSF starting with the first cycle of chemotherapy. Patients treated with standard regimens with a cycle of more than 14 days were given the once-per-chemotherapy-cycle CSF, pegfilgrastim, and those treated with dose-dense regimens with a cycle of 14 days or fewer were given filgrastim.

Those who had no risk factors prior to the first course of chemotherapy were considered low risk and were monitored and

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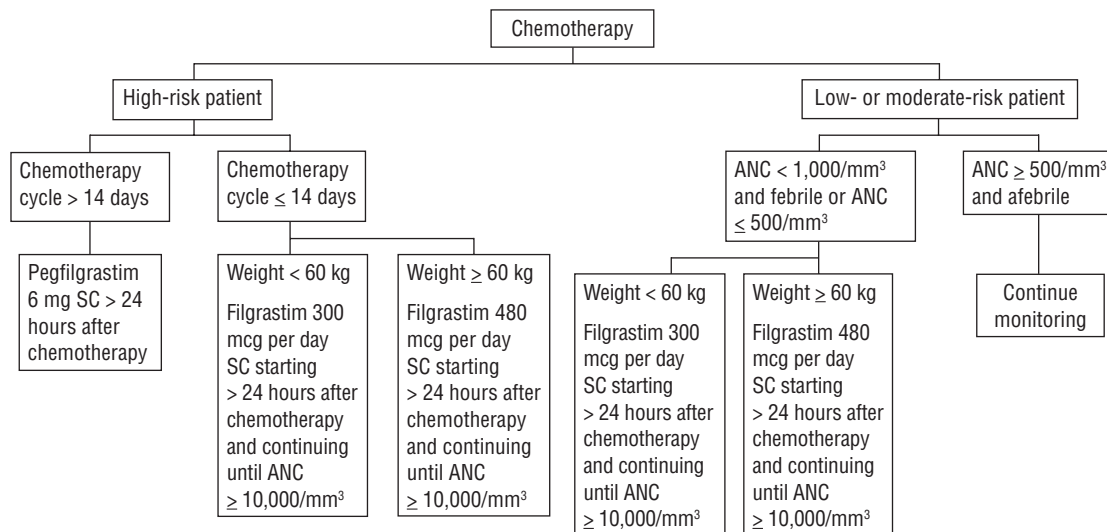
#### Risk Assessment for Neutropenic Complications

- On a chemotherapy regimen with  $\geq 40\%$  risk of febrile neutropenia
- Age  $\geq 70$  years with combination chemotherapy
- Bone marrow involvement or compromise
- Open wounds or infection
- Serum albumin  $\leq 3.5$  g/dl
- First-cycle absolute neutrophil count  $\leq 500$
- Preexisting occurrence of febrile neutropenia

*Note.* If any of the above is checked, the patient is at high risk for neutropenic complications (see Figure 2).

*Note.* The risk assessment is performed beginning with the first and all subsequent courses of therapy. Once considered high risk, a patient's risk is never lowered and no further risk assessment is required.

### Figure 1. Risk Assessment for Neutropenic Complications Tool



*Note.* After a patient's risk for neutropenia has been determined, this algorithm is used to guide patient management. A patient who is considered low or moderate risk and then becomes febrile with an ANC < 1,000/mm<sup>3</sup> will be considered high risk in all subsequent cycles.

ANC—absolute neutrophil count; SC—subcutaneously

**Figure 2. Algorithm for Colony-Stimulating Factor Support**

assessed for mid-cycle ANC nadir at all subsequent cycles of chemotherapy. If patients were found to be low risk prior to the first cycle, the tool then prompted assessment of the first-cycle ANC. With a first-cycle ANC of less than 500/mm<sup>3</sup>, or with an ANC of less than 1,000/mm<sup>3</sup> and development of a fever, patients were considered high risk and were treated with CSF support in all subsequent cycles, according to the algorithm.

Additionally, all patients were educated about neutropenic precautions such as proper hand washing, taking their temperatures, and when to contact their physicians or nurses.

### Study Population

This retrospective chart review was conducted in a community-based medical oncology practice that treats adult patients with all nonleukemia types of cancer. Data were abstracted from the charts of a convenience sample of 35 adult patients who were treated with new courses of chemotherapy from January–October 2003, regardless of the cancer type or stage, with whom the Risk Assessment for Neutropenic Complications Tool was used. The patients were treated following the established algorithm. The patients' clinical outcomes were compared with the outcomes obtained from a control group of the charts of patients (n = 50) who had been treated with chemotherapy at the practice from January–October 2000 without the use of the Risk Assessment for Neutropenic Complications Tool.

### Study Outcomes

The clinical outcomes abstracted from the medical records were the occurrence of febrile neutropenia, use of IV antibiotics, hospitalization secondary to febrile neutropenia, chemotherapy dose delays, and chemotherapy dose reductions.

### Data Analysis

Statistical significance was tested by using the Fisher exact test. All tests of significance were two-tailed. Because of the

small sample size, significant p values are considered hypothesis generating.

## Results

### Patient Characteristics

Patient characteristics were obtained from the charts (see Table 1). Patient demographics and malignancy types and stages were comparable between the two groups.

### Clinical Outcomes

The clinical outcomes are presented in Figure 3. The percentage of patients with chemotherapy dose delays was significantly lower in patients managed according to the tool and algorithm than in those managed without them (9% versus 32%; p = 0.01). Other outcomes also showed differences in patients managed according to the tool and algorithm, but the differences did not reach statistical significance. Reductions were observed in the proportions of patients with febrile neutropenia (14% versus 11%), treatment with IV antibiotics (28% versus 14%), hospitalizations secondary to febrile neutropenia (16% versus 11%), and chemotherapy dose reductions (10% versus 3%).

A significantly greater percentage of patients in the study group, who were managed with the Risk Assessment Tool and the algorithm, were treated with CSFs than those in the control group, who had been managed without the tool and algorithm three years earlier (72% versus 28%, p < 0.001). Because no other major changes in the management of neutropenia in the practice occurred during that period, the greater use of CSFs was attributed to the implementation of the tool.

## Discussion

Neutropenia and its complications are associated with negative clinical and economic consequences as well as decreases

**Table 1. Patient Demographics and Disease Characteristics**

Characteristic	2000—Before Risk Assessment Tool (N = 50)		2003—With Risk Assessment Tool (N = 35)	
	n	%	n	%
<b>Age (years)</b>				
$\bar{X}$	59.6		57.3	
SD	14.5		11.6	
<b>Characteristic</b>	<b>n</b>	<b>%</b>	<b>n</b>	<b>%</b>
<b>Gender</b>				
Male	10	20	8	23
Female	40	80	27	77
<b>Ethnicity</b>				
Caucasian	44	88	33	94
African American	6	12	2	6
<b>Diagnosis</b>				
Breast cancer	23	46	16	46
Lung cancer	7	14	6	17
Colon cancer	4	8	2	6
Non-Hodgkin lymphoma	4	8	2	6
Ovarian cancer	3	6	1	3
Other	9	18	8	23
<b>Cancer stage</b>				
I	1	2	1	3
II	17	34	12	34
III	5	10	1	3
IV	27	54	21	60

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

in patients' QOL (Crawford et al., 2004; Fortner et al., 2002, 2004; Kuderer et al., 2002; Okon et al., 2002). Being able to determine which patients are at high risk for neutropenia and its complications can help healthcare providers target appropriate supportive care to those who are most likely to benefit. Research has found that CSFs reduce the incidence of neutropenia and febrile neutropenia (Crawford et al., 1991; Green et al., 2003; Holmes et al., 2002; Trillet-Lenoir et al., 1993), and data support the idea that targeting CSF therapy in accordance with specified risk factors can be cost effective and clinically effective (Lyman, Kuderer, Crawford, & Dale, 2003; Timmer-Bonte et al., 2004). Administering CSFs according to an algorithm based on the presence of specified risk factors can help reduce the incidence of clinical complications and improve outcomes in patients treated with myelosuppressive chemotherapy.

Until now, a risk assessment tool that applies to different tumor types and is easily used has been lacking. This article details the improved clinical outcomes observed after the development and implementation of such a risk assessment tool and shows that the Risk Assessment for Neutropenic Complications Tool can help practitioners determine which patients are at high risk for CIN and its complications. Patients first were assessed using the tool prior to the initiation of chemotherapy; patients identified at high risk for CIN were given CSFs in accordance with the algorithm for managing neutropenia starting in the first cycle. Low-risk patients were monitored for mid-cycle ANC nadirs in all cycles; if the ANC nadir fell below 500/mm<sup>3</sup> or a fever developed with an ANC less than 1,000/mm<sup>3</sup>, a CSF was given in all subsequent cycles. A statistically significant lower rate of chemotherapy

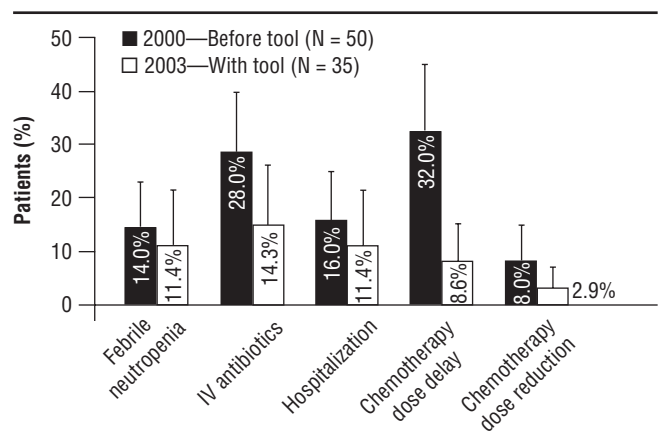
dose delays existed when the tool was used in conjunction with the algorithm for managing neutropenia with CSFs; the difference could not be explained by changes in the management of CIN in the practice. Indeed, many institutions have implemented protocols and guidelines for managing CIN and febrile neutropenia, and some have been associated with better outcomes (Glynn-Tucker, 2002; Maxwell & Winkler, 2002; White, Maxwell, Michelson, & Bedell, 2005). The features of the Risk Assessment for Neutropenic Complications Tool in the present study, however, that make it particularly attractive are its simplicity, applicability across nonleukemia tumor types, and ease and rapidity of use.

As part of the multidisciplinary oncology team, nurses are well positioned to use risk models to help guide decisions about patient care because they perform consistent and frequent clinical assessments (Houston, 1997; Ropka, Padilla, & Gillespie, 2005). Nurses are responsible for implementing orders for chemotherapy as well as providing supportive care for managing CIN and febrile neutropenia that affect patients' clinical outcomes. Furthermore, nurses can help to improve patients' QOL by proactively assessing them to prevent complications, optimizing the management of any complications that do occur, and educating patients and their caregivers about treatment and management options.

Implementation of the Risk Assessment for Neutropenic Complications Tool, as with any practice tool, requires that physicians in the practice agree with it and that the nursing staff use it. Physician support is necessary with all practice changes.

The nurse practitioner's role in the studied practice included establishing evidence-based protocols for all supportive care areas (e.g., nausea, diarrhea, mucositis, constipation, anemia, neutropenia). By using research-based data that support a proposed change and by being open to physician preferences when the options are comparable, consensus can be reached. Using data from studies that support the content of the Risk Assessment for Neutropenic Complications Tool was instrumental in securing physician support.

Another challenge in implementing the Risk Assessment for Neutropenic Complications Tool was obtaining buy-in from the nursing staff. Once the physician had agreed with the nurse practitioner about the content of the tool, the nurse practitioner



**Figure 3. Clinical Outcomes Using the Risk Assessment for Neutropenic Complications Tool**



explained the rationale for it to the nursing staff. The nurse practitioner found that asking the nurses how the tool best could be used was important. Once the nurse practitioner explained to the nursing staff how the tool was developed and how it could benefit patients and the practice, they accepted it and began to implement it. By making the implementation of the tool a team effort, the entire staff took ownership of it, thus ensuring its use.

## Limitations

Study limitations included the small number of subjects and the differences in patient care practices from 2000–2003, including possible differences in chemotherapy regimens, management of neutropenia, and availability of CSFs. Although the number of study participants was small, the participants were a true representation of the community in which the investigator practices, which is small. The limitation of differences in chemotherapy regimens at the study practice from 2000–2003 include notable differences in adjuvant treatment of breast cancer and treatment of metastatic colon cancer. In 2000, the predominant adjuvant breast cancer treatment was cyclophosphamide plus doxorubicin followed by paclitaxel (AC-T); in 2003, treatment was cyclophosphamide, epirubicin, and fluorouracil (CEF). The CEF regimen causes a much greater grade III–IV leukopenia or neutropenia than AC (86% versus 7%) (Beveridge et al., 2001). Treatment of metastatic colon cancer in 2000 was predominantly 5-fluorouracil and leucovorin (5-FU/LV), whereas in 2003, the regimen consisted of oxaliplatin, fluorouracil, and leucovorin (FOLFOX). The incidence of grade III–IV leukopenia or neutropenia in the 5-FU/LV regimen is 21%, versus 44% in the FOLFOX regimen (Beveridge et al., 2004). Therefore, the regimens used in 2003 have an increased incidence of leukopenia and neutropenia.

In considering ways in which neutropenia was managed in 2000 versus 2003, neutropenia management in 2000 was reactive: Physicians waited until an incident of febrile neutropenia or severe neutropenia occurred, then ordered a CSF for subsequent cycles. In 2000, the CSF ordered was filgrastim. After U.S. Food and Drug Administration approval of pegfilgrastim on January 31, 2002, the CSF was ordered according to the Algorithm for CSF Support and was either filgrastim or pegfilgrastim (see Figure 3). Because both of those CSFs have equal efficacy (Holmes et al., 2002), use of either CSF is appropriate and not considered a limitation. The use of the Risk Assessment for Neutropenic Complications Tool with the Algorithm for CSF Support has simplified the assessment and decision-making process regarding the appropriate CSF to use.

## Conclusion

Neutropenia and its complications have negative clinical and economic consequences, as well as detrimental effects on patients' QOL. The Risk Assessment for Neutropenic Complications Tool can help practitioners determine which patients are at high risk for CIN and its complications. When the tool is used in conjunction with the Algorithm for CSF Support, it can help to reduce the incidence of CIN and its consequences and may help in targeting supportive care to appropriate patients, ensuring maximum clinical benefits from chemotherapy treatment.

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## References

- Beveridge, R., Del Prete, S., Fausel, C., Leather, H., McFarland, H., & Valley, A. (Eds.). (2001). *Guide to the management of selected adverse events associated with cancer chemotherapy*. Thousand Oaks, CA: Amgen.
- Beveridge, R.A., Reitan, J.F., Fausel, C., Leather, H., McFarland, H., Rifkin, R.M., et al. (Ed.). (2004). *Guide to selected cancer chemotherapy regimens and associated adverse events* (5th ed.). Thousand Oaks, CA: Amgen.
- Bodey, G.P., Buckley, M., Sathe, Y.S., & Freireich, E.J. (1966). Quantitative relationships between circulating leukocytes and infection in patients with acute leukemia. *Annals of Internal Medicine*, 64, 328–340.
- Bonadonna, G., & Valagussa, P. (1981). Dose-response effect of adjuvant chemotherapy in breast cancer. *New England Journal of Medicine*, 304, 10–15.
- Budman, D.R., Berry, D.A., Cirincione, C.T., Henderson, I.C., Wood, W.C., Weiss, R.B., et al. (1998). Dose and dose intensity as determinants of outcome in the adjuvant treatment of breast cancer. The Cancer and Leukemia Group B. *Journal of the National Cancer Institute*, 90, 1205–1211.
- Caggiano, V., Stolshek, B., Delgado, D., & Carter, B. (2001). First and all cycle febrile neutropenia hospitalizations (FNH) and costs in intermediate grade non-Hodgkin's lymphoma (IGL) patients on standard-dose CHOP therapy [Abstract 1810]. *Blood*, 11, 431a.
- Crawford, J., Dale, D.C., & Lyman, G.H. (2004). Chemotherapy-induced neutropenia: Risks, consequences, and new directions for its management. *Cancer*, 100, 228–237.
- Crawford, J., Ozer, H., Stoller, R., Johnson, D., Lyman, G., Tabbara, I., et al. (1991). Reduction by granulocyte colony-stimulating factor of fever and neutropenia induced by chemotherapy in patients with small-cell lung cancer. *New England Journal of Medicine*, 325, 164–170.
- Epelbaum, R., Faraggi, D., Ben-Arie, Y., Ben-Shahar, M., Haim, N., Ron, Y., et al. (1990). Survival of diffuse large cell lymphoma. A multivariate analysis including dose intensity variables. *Cancer*, 66, 1124–1129.
- Fortner, B.V., Stolshek, B., Tauer, K.W., Okon, T.H., Durrence, H., White, H., et al. (2002). Final analysis: Chemotherapy induced neutropenia (CIN) is associated with lower quality of life (QoL) in patients (pts) with cancer [Abstract 640P]. *Annals of Oncology*, 13(5, Suppl.), 174.
- Fortner, B.V., Tauer, K., Zhu, L., Okon, T.A., Moore, K., Templeton, D., et al. (2004). Medical visits for chemotherapy and chemotherapy-induced neutropenia: A survey of the impact on patient time and activities. *BMC Cancer*, 4, 22.
- Glynn-Tucker, E. (2002, April). *A multidisciplinary performance improvement project for management of febrile neutropenia*. Presentation at the ONS 27th Annual Congress, Washington, DC.
- Green, M.D., Koelbl, H., Baselga, J., Galid, A., Guillem, V., Gascon, P., et al. (2003). A randomized double-blind multicenter phase III study of fixed-dose single-administration pegfilgrastim versus daily filgrastim in patients receiving myelosuppressive chemotherapy. *Annals of Oncology*, 14, 29–35.
- Holmes, F.A., O'Shaughnessy, J.A., Vukelja, S., Jones, S.E., Shogan, J., Savin, M., et al. (2002). Blinded, randomized, multicenter study to evaluate single administration pegfilgrastim once per cycle versus daily filgrastim as an adjunct to chemotherapy in patients with high-risk stage II or stage III/IV breast cancer. *Journal of Clinical Oncology*, 20, 727–731.
- Houston, D. (1997). Supportive therapies for cancer chemotherapy patients and the role of the oncology nurse. *Cancer Nursing*, 20, 409–413.
- Kuderer, N., Cosler, L.E., Crawford, J., Dale, D.C., & Lyman, G.H. (2002). Cost and mortality associated with febrile neutropenia in adult cancer

- patients [Abstract 998]. *Proceedings of the American Society of Clinical Oncology*, 21, 250a.
- Kwak, L.W., Halpern, J., Olshen, R.A., & Horning, S.J. (1990). Prognostic significance of actual dose intensity in diffuse large-cell lymphoma: Results of a tree-structured survival analysis. *Journal of Clinical Oncology*, 8, 963–977.
- Lepage, E., Gisselbrecht, C., Haioun, C., Sebban, C., Tilly, H., Bosly, A., et al. (1993). Prognostic significance of received relative dose intensity in non-Hodgkin's lymphoma patients: Application to LNH-87 protocol. The GELA (Groupe d'Etude des Lymphomes de l'Adulte). *Annals of Oncology*, 4, 651–656.
- Lyman, G.H., Dale, D.C., & Crawford, J. (2003). Incidence and predictors of low dose-intensity in adjuvant breast cancer chemotherapy: A nationwide study of community practices. *Journal of Clinical Oncology*, 21, 4524–4531.
- Lyman, G.H., Dale, D.C., Friedberg, J., Crawford, J., & Fisher, R.I. (2004). Incidence and predictors of low chemotherapy dose-intensity in aggressive non-Hodgkin's lymphoma: A nationwide study. *Journal of Clinical Oncology*, 22, 4302–4311.
- Lyman, G.H., Kuderer, N.M., Crawford, J., & Dale, D. (2003). Economic impact of pegfilgrastim use based on the risk of febrile neutropenia (febrile neutropenia) in NHL patients treated with CHOP [Abstract 2384]. *Proceedings of the American Society of Clinical Oncology*, 22, 593.
- Maxwell, C., & Winkler, J. (2002, April). *Nurse driven neutropenia management guidelines: Improving patient outcomes through evidence-based practice*. Presentation at the ONS 27th Annual Congress, Washington, DC.
- National Comprehensive Cancer Network. (2004). *NCCN clinical practice guidelines in oncology: Fever and neutropenia*. Retrieved July 12, 2005, from [http://www.nccn.org/professionals/physician\\_gls/PDF/fever.pdf](http://www.nccn.org/professionals/physician_gls/PDF/fever.pdf)
- National Comprehensive Cancer Network. (2005). *NCCN clinical practice guidelines in oncology: Myeloid growth factors in cancer treatment*. Retrieved June 30, 2005, from [http://www.nccn.org/professionals/physician\\_gls/PDF/myeloid\\_growth.pdf](http://www.nccn.org/professionals/physician_gls/PDF/myeloid_growth.pdf)
- Okon, T.A., Fortner, B.V., Schwartzberg, L., Tauer, K.T., Durrence, H., Kovacs, A., et al. (2002). Quality of life (QOL) in patients with grade IV chemotherapy-induced neutropenia (CIN) [Abstract 2920]. *Proceedings of the American Society of Clinical Oncology*, 21, 275b.
- Ozer, H., Armitage, J.O., Bennett, C.L., Crawford, J., Demetri, G.D., Pizzo, P.A., et al. (2000). 2000 update of recommendations for the use of hematopoietic colony-stimulating factors: Evidence-based, clinical practice guidelines. American Society of Clinical Oncology Growth Factors Expert Panel. *Journal of Clinical Oncology*, 18, 3558–3585.
- Ropka, M.E., Padilla, G., & Gillespie, T.W. (2005). Risk modeling: Applying evidence-based risk assessment in cancer nursing practice. *Oncology Nursing Forum*, 32, 49–56.
- Stricker, C.T., & Sullivan, J. (2003). Evidence-based oncology oral care clinical practice guidelines: Development, implementation, and evaluation. *Clinical Journal of Oncology Nursing*, 7, 222–227.
- Timmer-Bonte, J., Biesma, B., Smit, J., Wilschut, F., Akkermans, J., De Boo, G., et al. (2004). Prevention of chemotherapy-induced febrile neutropenia (febrile neutropenia) by antibiotics (AB) versus antibiotics plus granulocyte-colony stimulating factor (G-CSF) in small cell lung cancer (SCLC): A randomized phase III study [Abstract 8002]. *Proceedings of the American Society of Clinical Oncology*, 23, 726.
- Trillet-Lenoir, V., Green, J., Manegold, C., Von Pawel, J., Gatzemeier, U., Lebeau, B., et al. (1993). Recombinant granulocyte colony stimulating factor reduces the infectious complications of cytotoxic chemotherapy. *European Journal of Cancer*, 29A, 319–324.
- Vogel, C.L., Wojtukiewicz, M.Z., Carroll, R.R., Tjulandin, S.A., Barajas-Figuroa, L.J., Wiens, B.L., et al. (2005). First and subsequent cycle use of pegfilgrastim prevents febrile neutropenia in patients with breast cancer: A multicenter, double-blind, placebo controlled phase III study. *Journal of Clinical Oncology*, 23, 1178–1184.
- White, N., Maxwell, N., Michelson, J., & Bedell, C. (2005). Protocols for managing chemotherapy-induced neutropenia in clinical oncology practices. *Cancer Nursing*, 28, 62–69. 