

Quality management of potential chemotherapy-induced neutropenic complications: evaluation of practice in an academic medical center

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Abstract

Goals Management of the risk of potential chemotherapy-induced neutropenic complications such as febrile neutropenia (FN) and severe neutropenia (SN) is a quality of care priority. How frequently does care at our institution conform to established guidelines?

Materials and methods This retrospective chart review study included a random sample of 305 cancer patients receiving care at a single US academic medical center. Abstracted data included demographics, risk factors, and outcome variables (e.g., development of FN/SN, administration of myeloid growth factors). To evaluate quality of care, we assessed conformance between actual practice and established clinical practice guidelines for the use of myeloid growth factors from the National Comprehensive Cancer Network (NCCN).

Main results Of the 305 cases reviewed, 8% were classified as low risk (<10%), 48% as intermediate risk (10–20%), and 44% as high risk (>20%), using the risk classifications in the NCCN guidelines modified to accommodate illness

and other risk factors. Thirty-four percent received prophylactic administration of myeloid growth factors. Half of the cases had adequate documentation of mid-cycle absolute neutrophil count to determine whether FN/SN developed. Among these cases with adequate documentation, 21% developed FN/SN. Use of growth factors did not conform to established quality guidelines. Overall, 77 of 133 (58%) high-risk cases received myeloid growth factors, whereas six of 25 (24%) low-risk cases received myeloid growth factors.

Conclusions Routine clinical practice in this academic oncology setting was poorly aligned with established guidelines; there is substantial opportunity to standardize clinical strategies and increase conformance with evidence-based guidelines.

Keywords Neutropenia (MeSH) · Fever (MeSH) · Neoplasms (MeSH) · Quality of health care (MeSH)

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Introduction

Neutropenia occurs when chemotherapy decimates neutrophils [1], a primary function of which is to combat bacterial infections. Without neutrophils, the patient is at risk for life-threatening infections such as sepsis or pneumonia. Severe neutropenia (SN) is defined as an absolute neutrophil count (ANC) of <500 cells/mm³ or of <1,000 cells/mm³ with expected decrease to 500 cells/mm³ [1]. Febrile neutropenia (FN) has the same ANC parameters but includes a temperature >101°F or a persistent fever >100.4°F [1].

Approximately half of patients receiving cancer chemotherapy experience FN or SN as a significant

adverse drug effect, with exact risk of these complications determined by patient factors including tumor type, renal function, age, and previous exposure to chemotherapy. Risk also varies by diagnosis. Reported prevalence of FN/SN in non-small cell lung cancer (NSCLC) is 7.4%, whereas in breast cancer, it is 30.2% [2]. FN and SN are closely inter-related; approximately 40% of patients with SN develop FN, with risk increasing daily as SN prolongs [3]. Development of fever elevates the patient's risk of a life-threatening infection; when antibiotics are not administered, FN carries a 45–58% risk of death [4, 5]. Comorbid conditions also increase risk for patients with FN. The overall inpatient mortality rate associated with neutropenia is 9.5%; for patients with one comorbidity, mortality risk increases to 10.3% and, with two comorbidities, to >21.4% [6]. Most patients with FN stay over a week in the hospital receiving intravenous antibiotics and awaiting neutrophil recovery. FN and SN are often considered together when evaluating risk of neutropenic complications and their sequelae [12].

Colony stimulating factors, such as granulocyte colony-stimulating factor (G-CSF, filgrastim, pegfilgrastim, and lenograstim) and granulocyte macrophage CSF (sargramostim) stimulate production of granulocytes via bone marrow. These myeloid growth factors are administered soon after chemotherapy to decrease the risk of neutropenic complications, especially when the risk of FN is perceived to be >20% [7]. A systematic review found filgrastim and pegfilgrastim to be clinically effective and cost-effective if used according to best practice guidelines [8, 9].

Guideline-based management of patients at risk for chemotherapy-induced neutropenic complications

Based on evidence from two recent randomized trials [10, 11], the American Society of Clinical Oncology (ASCO) in 2006 updated its clinical practice guideline, “Recommendations for the Use of White Blood Cell Growth Factors: An Evidence-Based Clinical Practice Guideline,” to indicate primary prophylaxis with CSFs when risk of FN is $\geq 20\%$ [12]. Both ASCO and the European Association for Research and Treatment of Cancer (EORTC) currently recommend that patients who are at >20% risk for FN receive prophylactic treatment with myeloid growth factors [13]. The National Comprehensive Cancer Network (NCCN) in the USA also endorses this 20% risk threshold [14] (Table 1). These guidelines concur that, when risk of FN is 10–20%, prophylaxis with myeloid growth factors should be carefully considered, and when risk is <10%, use of myeloid growth factors is not recommended. A more conservative approach is proposed by the Multinational Association of Supportive Care in Cancer (MASCC), which has developed

the MASCC risk-index score based on seven independent factors present at onset of febrile neutropenia [15, 16].

Purpose of the study

Appropriate management of the risk for chemotherapy-induced neutropenic complications is a quality of care priority in oncology; yet, in this field, the urgency of treating disease can overshadow common but complex tasks such as predicting risk of FN/SN and appropriately administering myeloid growth factors. Approaches to FN/SN risk management that are not evidence- or guideline-based potentially compromise patient safety and/or result in excessive, unnecessary costs.

This study sought to answer a key question related to quality of care, where quality care was defined as care that conforms to best practice guidelines promoted by ASCO, EORTC, and NCCN: How frequently do cancer patients at our institution receive care in alignment with established guidelines for managing risk of chemotherapy-induced neutropenic complications? Through generating a better understanding of current practices, the study was intended to help determine whether physician adherence to evidence-based guidelines is adequate or requires improvement. Additionally, it offers a case study of a quality assessment approach to supportive oncology.

Materials and methods

Overview of design

This retrospective chart review included data from patients who received chemotherapy at Duke University Medical Center (Duke) in Durham, NC, from January 1, 2004 to December 31, 2006. Its objectives were to describe, in a single institution's population, the incidence of FN/SN and FN/SN risk factors, myeloid growth factor utilization, and conformance of actual practice with the NCCN Myeloid Growth Factor Clinical Practice Guideline [14]. The NCCN guideline was selected as the representative document, since it could be operationalized easily into specific steps and corresponding metrics.

Participants

The study population was randomly selected from the Duke Tumor Registry. Lists were generated of all adult patients with lymphoma and lung, breast, colorectal, and ovarian cancers who received chemotherapy at Duke during the study timeframe. After lists of potential cases

Table 1 NCCN and ASCO recommendations for myeloid growth factor (CSF) use to prevent febrile neutropenia (FN) during adjuvant chemotherapy

	Clinical factors to consider in determining risk	FN prophylaxis	FN risk
NCCN	Chemotherapy regimen Individual patient risk	CSF recommended	High (>20%)
	Neutropenic complication in the immediate previous cycle Chemotherapy regimen Individual patient risk	CSF should be considered	Intermediate (10%-20%)
	Chemotherapy regimen Individual patient risk	No CSF. Consider CSF only if patient is at significant risk for serious FN consequences	Low (<10%)
ASCO: primary prophylactic CSF	First and subsequent cycle use Age Medical history Disease characteristics Myelotoxicity of chemotherapy regimen Age >65 Years Poor performance status Previous FN Poor nutritional status Open wounds or active infections More advanced cancer Extensive prior treatment, incl. large XRT ports Administration of combined chemo-radio therapy Cytopenias due to bone marrow involvement by tumor Other serious comorbidities	CSF supported	High (>20%)
	Experienced a neutropenic complication from a prior cycle of chemotherapy for which primary prophylaxis was not received, in which a reduced dose may compromise disease-free or overall survival or treatment outcome	CSF often appropriate	<20%
ASCO: secondary prophylactic CSF	Patients with neutropenia who are afebrile Adjunctive treatment with antibiotic therapy for patients with fever and neutropenia	CSF should NOT be routinely used	
	Patients with FN who are at high risk for infection-associated complications Patients who have prognostic factors that are predictive of poor clinical outcome	CSF should be considered	

were randomized, the top cases were selected in a distribution reflecting the relative incidences of cancer types in the Duke population. We sought to identify at least 300 eligible cases and ultimately included 305 cases. Since patients could have received more than one chemotherapy regimen and prior chemotherapy was a potential risk factor for neutropenic complications, we randomized the regimen of focus (e.g., first-line,

second-line, etc.). Data were abstracted on the first cycle of the selected chemotherapy regimen only; the study required that the first cycle was received at Duke.

Study procedures

Data on demographics, disease characteristics, and outcome variables were abstracted from paper or

electronic case notes onto a case report form (CRF). CRFs were completed using electronic pens by two trained research nurses, a pharmacist, and two physicians. All CRFs were over-read by a second abstractor. Data from the electronic pens automatically populated a Microsoft Access 2003 database (Microsoft, Seattle, WA, USA). Validation and error checking software highlighted potential errors on electronic CRFs for secondary review and approval before data were permanently entered into the final study dataset (Mi-Co Mi-Forms version 6.1.2.2, Research Triangle Park, NC, USA). Once data were permanently written to the database, the record was de-identified. Identifying patient information was held in a separate “master” dataset at a different location; the main study dataset was completely de-identified and linked to the master dataset by a unique study linkage variable. All analyses were conducted with de-identified data.

A third physician independently reviewed the chemotherapy administered in all cases and mapped it to the NCCN Guideline risk categories of low (<10%), intermediate (10–20%), and severe (>20%), using the v1.2008 version of the published guideline [14], with the ASCO 2006 guideline as back-up [7]. Dose-dense regimens were assigned a risk score of >20%. When the regimen was not listed in either guideline document, the original clinical trial report was consulted to determine risk for the regimen. The assigned risk level is named the “Guideline-based Risk” in this review.

Both the NCCN and ASCO guideline documents recommend elevating the assigned risk level to a higher category when certain clinical factors are present. The lists of factors to consider differ somewhat between the two guidelines (e.g., the ASCO guideline includes age as a risk factor while the NCCN guideline does not); however, the majority of factors are similar. Consultation with practicing medical oncologists at Duke suggested that clinicians routinely modified their assessment of risk for neutropenic complications depending on the presence/absence of these factors. We therefore defined a “Modified Guideline-based Risk” level in which we increased the patient’s risk category if his/her chart indicated any of the following factors: age >65, poor performance status (Eastern Cooperative Oncology Group score ≥ 2), prior chemotherapy or radiotherapy, diabetes, metastatic cancer (stage IV or metastatic), Charlson Comorbidity Index Score >3, or poor renal function (glomerular filtration rate <50). If a patient had one or two risk factors, the Guideline-based risk was increased by one level. If a patient had three or more risk factors, the guideline-based risk was increased by two levels. Maximum risk for any patient was three. This approach was designed to approximate the manner

in which oncologists actually apply guideline recommendations in clinical practice.

Analyses

Basic descriptive statistics were employed to characterize the study population (Table 2) and to report the frequency of missing variables and outcomes. Clinical practice at this institution was compared to recommendations of best practice guidelines, using (1) the intact NCCN Myeloid Growth Factor Clinical Practice Guideline [14], and (2) the NCCN Guideline modified to incorporate additional risk factors (Tables 3 and 4, respectively). In each risk category (low, intermediate, and high), we calculated the frequency of disease type, documentation of mid-cycle ANC, delivery of myeloid growth factors, and development of FN/SN. To evaluate quality of care in this area, we created three metrics that reflect the recommendations of the NCCN Myeloid Growth Factor Clinical Practice Guideline [14] (Table 5):

1. For any patient whose risk of FN/SN was assessed as $\geq 10\%$, documentation of assessment of mid-cycle ANC
2. For patients with >20% risk of FN/SN, delivery of myeloid growth factors
3. For patients with <10% risk of FN/SN, no delivery of growth factors

Conformance to quality metrics was calculated as the proportion of evaluable cases that met the pre-defined metric. Univariate predictors of the likelihood of documenting mid-cycle laboratory studies were assessed using chi-squared tests; $p < 0.05$ was considered statistically significant (Table 6).

Ethical approval

The study was approved by the Duke University Health System Institutional Review Board.

Results

Three hundred five cases (305) were reviewed (Table 2). The distribution of cancer types was 44% breast, 18% colorectal, 26% lung, 9% lymphoma, and 5% ovarian. Majority of the patients in cases were female (73%), consistent with this tumor type distribution. Mean age was 55 (SD, 13); 74% of the patients were white. Overall, 34% of patients received prophylactic administration of myeloid growth factors. Half of the cases had adequate documentation of mid-cycle ANC to determine whether a FN/SN neutropenic complication developed; neutropenic complications were identified in 21% of these cases.

Table 2 Demographic and medical characteristics of the cohort

Characteristics	n=305
Age (years): mean (SD) [range]	55 (13) [23–89]
Male	83 (27%)
Race/ethnicity	
White	226 (74%)
Black/African American	63 (21%)
Other	9 (3%)
Unknown	7 (2%)
Type of cancer	
Breast	133 (44%)
Colorectal	55 (18%)
Non-small cell lung cancer	66 (22%)
Small cell lung cancer	11 (4%)
Ovarian	15 (5%)
Non-Hodgkin's lymphoma	20 (7%)
Hodgkin's lymphoma	5 (2%)
Stage of cancer	
Stage1	41 (13%)
Stage2	75 (25%)
Stage3	73 (24%)
Stage4	68 (22%)
Missing/Unknown	48 (16%)
History of prior chemotherapy	68 (22%)
Current chemotherapy regimen	
Anthracycline-based regimen	128 (42%)
Number of myelosuppressive agents	
1	57 (19%)
2	199 (65%)
3	45 (15%)
4	4 (1%)
Planned relative dose intensity	
<85% of standard	29 (10%)
>85% of standard	272 (89%)
Unknown	4 (1%)
Primary G-CSF prophylaxis	103 (34%)

Documentation of mid-cycle ANC

Laboratory tests that determine mid-cycle ANC are critical to the identification of high-risk patients who require prevention or management of subsequent FN/SN episodes. Hence, documentation of a mid-cycle ANC report was considered a major quality indicator. Cases counted as having mid-cycle assessments were those patients whose mid-cycle ANC was assessed and documented at Duke facilities or patients whose mid-cycle ANC was assessed at non-Duke facilities and documented in the Duke medical record. If no documentation of mid-cycle ANC existed, the case was counted as not meeting the metric.

Overall, documentation of mid-cycle ANC was only available for 50% of cases. When risk of chemotherapy-induced neutropenia was assigned solely according to chemotherapy regimen, i.e., guideline-based risk, more

low-risk patients than high-risk patients had ANC documented (58% vs. 41%, Table 3). The trend was less dramatic when we modified the chemotherapy-induced risk based upon patient or disease factors, i.e., modified guideline-based risk (56% vs. 52%, Table 4). In both cases, low-risk patients were most likely to have ANC documented, although that group needed ANC follow-up the least. Documentation of ANC for intermediate- and high-risk patients—the quality metric—was present for 44% of cases using the guideline-based risk assessment approach and for 49% of cases using the modified guideline-based risk assessment approach (Table 5).

The quality assessment may have been biased by scenarios that systematically led to less frequent documentation of mid-cycle ANC. For example, clinicians might have requested mid-cycle studies less frequently when they planned to administer myeloid growth factor regardless of lab result. We therefore examined the effect of various clinical factors on the presence/absence of a mid-cycle ANC. Cancer type emerged as the only identified predictor of ANC assessment (Table 6), with breast cancer patients being more likely to *not* have a documented ANC and lung cancer and lymphoma patients being more likely to have a documented ANC.

Conformance with myeloid growth factor administration guidelines

Guideline-based risk

When we assigned risk based upon the categories presented in the NCCN guideline, 41% of cases were classified as low risk, 32% as intermediate risk, and 27% as high risk (Table 3). Myeloid growth factor was administered in 34% of cases, ranging from 21% of low-risk to 67% of high-risk cases.

Assessment of the impact of conformance with guidelines could only be conducted for cases with documented mid-cycle ANC or some other assessment of presence/absence of FN/SN ($n=151$; Table 2). Of 73 cases in the low-risk category, 18 (25%) received myeloid growth factor. This treatment practice is inconsistent with the guidelines. Among the 55 low-risk cases where growth factor was not administered, six (11%) developed documented neutropenic complications. Low-risk patients who received growth factor had the same rate of neutropenic complications (11%), suggesting that prophylactic administration of growth factors to low-risk patients did not improve outcomes, although numbers are small.

Among the 34 high-risk cases with documented mid-cycle ANC, only 15 (44%) had documentation of myeloid growth factor delivery. Of the 19 high-risk cases where growth factor was not administered, six (32%) developed

Table 3 Guideline-based risk: assessment of risk for chemotherapy-induced neutropenic complications based upon type of chemotherapy received only (as per NCCN guideline)

Total cases=305	Low risk (<10% risk of FN/SN), n=126		Intermediate risk (10–20% risk of FN/SN), n=97		High risk (>20% risk of FN/SN), n=82	
Type of cancer						
Breast	21 (17%)		60 (62%)		52 (63%)	
Colorectal	49 (39%)		6 (6%)		0 (0%)	
Non-small cell lung cancer	38 (30%)		5 (5%)		23 (28%)	
Small cell lung cancer	3 (2%)		7 (7%)		1 (1%)	
Ovarian	13 (10%)		2 (2%)		0 (0%)	
Non-Hodgkin's lymphoma	2 (2%)		13 (13%)		5 (6%)	
Hodgkin's lymphoma	0 (0%)		4 (4%)		1 (1%)	
Mid-cycle ANC documented						
Yes	73 (58%)		44 (45%)		34 (41%)	
No	53 (42%)		53 (55%)		48 (59%)	
Myeloid growth factor administered						
Yes	27 (21%)		21 (22%)		55 (67%)	
No	99 (79%)		76 (78%)		27 (33%)	
Neutropenic complications developed						
FN ^a	1		2		2	
SN ^b	4		6		5	
Physician note only ^c	3		8		1	
Yes—any FN/SN above	8 (6%)		16 (16%)		8 (10%)	
No	65 (52%)		28 (29%)		26 (32%)	
Unknown	53 (42%)		53 (55%)		48 (59%)	
Among cases with mid-cycle ANC documented (n=151)						
			Myeloid growth factor administered			
Developed FN/SN						
Yes	2 (11%)		6 (11%)		4 (31%)	
No	16 (89%)		49 (89%)		19 (61%)	
Total	18 (25%)		55 (75%)		13 (30%)	
					31 (70%)	
					15 (44%)	
					19 (56%)	

Figures in italics indicate cases for which quality of care would have improved with appropriate risk level assessment and, based on that risk, adherence to the NCCN guideline. Boldface type indicates cases for which appropriate care, per the NCCN guideline, was documented

^a Met full criteria for febrile neutropenia: documented laboratory test with ANC <500 cells/mm³ or <1,000 cells/mm³ with expected decrease to 500 cells/mm³, and documented temperature >101°F or a persistent fever >100.4°F

^b Met full criteria for severe neutropenia: documented laboratory test with ANC <500 cells/mm³ or <1,000 cells/mm³ with expected decrease to 500 cells/mm³

^c Physician notes documented FN or SN, although not all criteria were fully met in chart note

documented neutropenic complications, whereas in the 15 cases where growth factor was administered, only two (13%) developed documented FN/SN.

Neutropenic complications developed in each risk category in relatively stable proportions. When assessing risk using the NCCN guidelines (Table 3), FN developed in one (1%), two (2%), and two (2%) of low, intermediate, and high risk patients, respectively ($n=126$, 97, and 82, respectively); SN developed in four (3%), six (6%), and five (6%) of low, intermediate, and high risk patients, respectively. When assessing risk using the modified guideline-based method (Table 3), FN developed in one (4%), one (1%), and three (2%) of low, intermediate, and high risk patients, respectively ($n=25$, 147, and 133, respectively); SN developed in one (4%), four (3%), and

ten (8%) of low, intermediate, and high risk patients, respectively.

Modified guideline-based risk

Risk categories shifted substantially when the risk level was elevated to account for the presence of risk factors noted by clinicians and in the NCCN and/or ASCO guidelines as potentially increasing risk of chemotherapy-induced neutropenic complications. This risk adjustment better accommodates the characteristics of the sick referral population seen in an academic tertiary care cancer center (Table 4). With this modification, 8% of cases were assessed as low risk ($n=25$), 48% as intermediate risk ($n=147$), and 44% as high risk ($n=133$). Myeloid growth factor was administered

Table 4 Modified guideline-based risk: assessment of risk for chemotherapy-induced neutropenic complications based upon type of chemotherapy received and patient factors (age >65, poor performance

status, prior chemotherapy or radiotherapy, diabetes, metastatic cancer, comorbidities, or poor renal function)

Total cases=305	Low risk (<10% risk of FN/SN), n=25		Intermediate risk (10–20% risk of FN/SN), n=147		High risk (>20% risk of FN/SN), n=133	
Type of cancer						
Breast	10 (40%)		58 (39%)		65 (49%)	
Colorectal	4 (16%)		43 (29%)		8 (6%)	
Non-small cell lung cancer	5 (20%)		25 (17%)		36 (27%)	
Small cell lung cancer	0 (0%)		4 (3%)		7 (5%)	
Ovarian	6 (24%)		8 (5%)		1 (1%)	
Non-Hodgkin's lymphoma	0 (0%)		7 (5%)		13 (10%)	
Hodgkin's lymphoma	0 (0%)		2 (1%)		3 (2%)	
Mid-cycle ANC documented						
Yes	14 (56%)		68 (46%)		69 (52%)	
No	11 (44%)		79 (54%)		64 (48%)	
Myeloid growth factor administered						
Yes	6 (24%)		20 (14%)		77 (58%)	
No	19 (76%)		127 (86%)		56 (42%)	
Developed neutropenic complications						
FN ^a	1		1		3	
SN ^b	1		4		10	
Physician note only ^c	0		7		5	
Yes—any FN/SN above	2 (8%)		12 (8%)		18 (14%)	
No	12 (48%)		56 (38%)		51 (38%)	
Unknown	11 (44%)		79 (54%)		64 (48%)	
Among cases with mid-cycle ANC documented (n=151)						
	Myeloid growth factor administered					
Developed FN/SN	Yes	No	Yes	No	Yes	No
Yes	0 (0%)	2 (15%)	2 (14%)	10 (19%)	6 (19%)	12 (32%)
No	1 (100%)	11 (85%)	12 (86%)	44 (81%)	25 (81%)	26 (68%)
Total	1 (7%)	13 (93%)	14 (21%)	54 (79%)	31 (45%)	38 (55%)

Figures in italics indicate cases for which quality of care would have improved with appropriate risk level assessment and, based on that risk, adherence to the NCCN guideline. Boldface type indicates cases for which appropriate care, per the NCCN guideline, was documented

^aMet full criteria for febrile neutropenia: documented laboratory test with ANC <500 cells/mm³ or <1,000 cells/mm³ with expected decrease to 500 cells/mm³, and documented temperature >101°F or a persistent fever >100.4°F

^bMet full criteria for severe neutropenia: documented laboratory test with ANC <500 cells/mm³ or <1,000 cells/mm³ with expected decrease to 500 cells/mm³

^cPhysician notes documented FN or SN, although not all criteria were fully met in chart note

in 24% of low-risk, 14% of intermediate-risk, and 58% of high-risk cases.

After modification of risk level, assessment of the impact of conformance with guidelines was conducted for the 151 cases with adequate documentation. Of 14 cases in the modified low-risk category with documented mid-cycle ANC, one (7%) received myeloid growth factor, reflecting a practice that is inconsistent with guidelines. Of the 13 low-risk cases where growth factor was not administered, two (15%) developed documented neutropenic complications.

Of 69 cases in the modified high-risk category with documented mid-cycle ANC, only 31 (45%) had documentation of myeloid growth factor delivery. Of the 38 high-risk cases where growth factor was not administered, 12

(32%) developed documented neutropenic complications, whereas in the 31 cases where growth factor was administered, only six (19%) developed documented neutropenic complications.

Quality assessment

Conformance with the myeloid growth factor guidelines was defined as quality practice. Actual practice was compared to guideline-based practice using both the unmodified and modified risk classifications (Table 5). All metrics demonstrate substantial opportunity for improvement, with conformance <70% for both documentation of mid-cycle ANC and administration of myeloid growth factor to high-risk patients. Of note, although there was

Table 5 Summary of myeloid growth factor quality metrics for the cohort of 305 cases

	Cases evaluable	Cases meeting quality metric	Conformance to quality metric (%)
Guideline-based risk method			
For any patient where the risk of FN/SN was assessed as $\geq 10\%$, documentation of mid-cycle ANC	179	78	44
For patients with $>20\%$ risk of FN/SN, delivery of myeloid growth factors	82	55	67
For patients with $<10\%$ risk of FN/SN, no delivery of growth factors	126	99	79
Modified guideline-based risk method			
For any patient where the risk of FN/SN was assessed as $\geq 10\%$, documentation of mid-cycle ANC	280	137	49
For patients with $>20\%$ risk of FN/SN, delivery of myeloid growth factors	133	77	58
For patients with $<10\%$ risk of FN/SN, no delivery of growth factors	25	19	76

great discussion locally about the need to modify risk classifications for patient and disease factors, retrospective application of these modifications did not reveal better quality prescribing.

Discussion

Comparing actual practice to guidelines for preventing chemotherapy-induced neutropenia, this study raises questions about quality of care at an academic medical center. These findings may pertain to other institutions and warrant further investigation.

Thresholds defining risk categories clearly affect evaluations of quality. The modified risk assessment method elevated risk scores, resulting in more high-risk patients and lower conformance to guidelines. Though the threshold for high risk remains somewhat controversial, we believe that overestimating risk, with possible overtreatment of intermediate/high-risk patients, is preferable to underestimating risk because under-treatment places patients at potential risk for FN/SN.

This exercise illustrates a systematic approach to assessing and improving quality of care. The first step is evaluation: Does clinical practice conform to evidence-based recommendations? Consensual guidelines provide a standard against which to evaluate practice. We reviewed local clinical practice against consensus guidelines, after assessing risk based on (1) chemotherapy regimen alone and (2) chemotherapy regimen, modified to incorporate additional risk factors. With risk assessed by chemotherapy alone, 33% of high-risk patients did not receive myeloid growth factors; with modified risk, 42% of high-risk patients did not receive myeloid growth factors. Simultaneously, clinicians seemed to overprescribe for low-risk patients. In the unmodified and modified risk analyses, respectively, 21% and 24% of low-risk patients received myeloid growth factors.

The second step in quality assessment/improvement is the exploration of divergence from evidence-based recommendations: Why does actual practice deviate from guidelines? We first considered reasons for erratic documentation of mid-cycle laboratory studies determining ANC. Approximately half of the cases were missing this documentation, though standard clinical practice includes a mid-cycle ANC after the first cycle of a new chemotherapy regimen. If mid-cycle ANC identifies SN, myeloid growth factors are

Table 6 Predictors of likelihood to document mid-cycle laboratory studies (ANC) and occurrence of neutropenic complications after the first cycle

Characteristic	Mid-cycle ANC documented <i>n</i> =151	Mid-cycle ANC not documented <i>n</i> =154	P value for the difference between ANC documentation (chi-square test)
Type of cancer			
Breast	34 (26%)	99 (74%)	<0.0001
Colorectal	23 (42%)	32 (58%)	
Lung cancer (any type)	64 (83%)	13 (17%)	
Ovarian	10 (67%)	5 (33%)	
Lymphoma (any type)	20 (80%)	5 (20%)	
Guideline-based risk group			
Low	73 (48%)	53 (34%)	0.041
Intermediate	44 (29%)	53 (34%)	
High	34 (23%)	48 (31%)	
Modified guideline-based risk group			
Low	14 (9%)	11 (7%)	0.511
Intermediate	68 (45%)	79 (51%)	
High	69 (46%)	64 (42%)	
Myeloid growth factor administered			
Yes	46 (30%)	57 (37%)	0.227
No	105 (70%)	97 (63%)	

recommended for subsequent cycles [14]. Missing ANC data could be attributable to laboratory tests not performed or failure to transfer results of tests conducted elsewhere. Failure to perform, or to document, ANC compromises patient care by leaving the clinician without data upon which to base subsequent decisions. Alternatively, clinicians may have proactively identified high-risk patients, administered myeloid growth factors, and not ordered mid-cycle ANC as they could predict results. Since differential baseline risk did not predict missing ANC data, a more likely explanation lies in systematic differences between groups of providers. Cancer type was the only predictor of missing ANC; thus, we hypothesize that adherence to standards differs across provider groups. If so, quality improvement should target group, as well as individual, practices.

Planning for change is a third step in quality assessment/improvement: What measures will help align actual practice with guidelines? Our study highlights a need to educate clinicians about evidence-based guidelines and risks of inappropriate prescribing. Growth factors are expensive; the cost of preventive delivery must outweigh the expense incurred if a patient develops FN/SN. Dale et al. [17] evaluated the economic advantage of using G-CSF by four groups: (1) no G-CSF, (2) primary G-CSF usage, (3) secondary G-CSF usage, and (4) high-risk. Incremental costs relative to group 4 were \$642, \$1,685, and \$1,832 for groups 1, 2, and 3, respectively; the cost of a 10-day hospitalization averaged \$17,500 [18]. A meta-analysis of randomized controlled trials of CSFs for chemotherapy-induced FN found that G-CSF reduces hospitalization time and neutrophil recovery period [19]. Our results indicate that myeloid growth factors may currently be misdirected toward low-risk patients, incurring unnecessary expense, rather than toward high-risk patients to exploit their cost-containing benefit.

Quality improvement can leverage new approaches to refine risk assessment and better target therapy. Risk assessment requires integration of multiple patient-, disease- and treatment-specific characteristics, with differing levels of importance. Lyman et al. [2] conducted a systematic review of risk factors for neutropenia and neutropenic complications and proposed a risk model that includes >20 variables [12]. They prospectively enrolled a registry of 4,466 patients to test the model [20]. The model provided predictive accuracy to calculate FN/SN risk: c statistic 0.817 (95% CI, 0.789–0.846), sensitivity 88.3% (95% CI, 83.8–91.7), and specificity 59.4% (95% CI, 56.2–62.5). Routine integration of such a model into clinical practice could support better targeting of growth factors to high-risk patients. Computer software that accomplishes this complex calculation with minimal clinician burden might facilitate better clinical practice. Lyman et al. are

refining this risk model to improve its performance, and incorporating it into an electronic decision support platform that will streamline data entry and make it convenient for clinicians.

The final quality assessment/improvement steps are to implement new quality improvement approaches and to measure their impact: Are change strategies resulting in better quality of care? Meaningful pre- and post-measures should reflect current guidelines. The metrics presented in this paper could provide an entry point to this conversation.

Principal limitations of this study include its retrospective nature and missing data. The high proportion of exclusions raises the possibility of bias, particularly in results requiring information about the FN/SN outcome. Some charts provided this information in physician notes; reliance on these charts may introduce systematic bias. Most data included in this study pertained to patients treated prior to publication of the relevant ASCO/NCCN guidelines (2006); arguably, it is unfair to evaluate the quality of care that clinicians provided if quality is defined by conformance to recommendations that were not yet available. Quality of care may have appeared higher if evaluated against different criteria for use of myeloid growth factors, such as the MASCC Risk Index, with higher risk thresholds. The low incidence of FN and SN in the total population (five and 15 patients, respectively) precludes definitive claims about risk, quality of care, and outcomes; nevertheless, the distribution of FN/SN, rather than total numbers, is interesting to note and suggests that prescribing practices do not correspond to risk. Despite its limitations, this study is consistent with usual chart audit approaches and provides insight into current practices, benchmarks, and opportunities for improvement.

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