Importance of Risk Factors for Febrile Neutropenia Among Patients Receiving Chemotherapy Regimens Not Classified as High-Risk in Guidelines for Myeloid Growth Factor Use

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Abstract

Background: Clinical practice guidelines recommend prophylaxis in patients with cancer receiving a colony-stimulating factor (CSF) when the risk of febrile neutropenia (FN) is high (>20%). For patients receiving chemotherapy regimens not documented as high-risk, the decision regarding CSF prophylaxis use can be challenging, because some patients may be at high risk based on a combination of the regimen and individual risk factors. **Methods:** A retrospective cohort design and US private health care claims data were used. Study subjects received chemotherapy regimens classified as “low” or “intermediate,” or unclassified, in terms of FN risk, and were stratified by cancer and regimen. For each subject, the first chemotherapy course, and each cycle and FN episode within the course, were identified. FN incidence proportions were estimated by the presence and number of risk factors and chronic comorbidities. **Results:** Across the 17 tumor/regimen combinations considered (n=160,304 in total), 74% to 98% of patients had 1 or more risk factor for FN and 41% to 89% had 2 or more. Among patients with 1 or more risk factor, FN incidence ranged from 7.2% to 29.0% across regimens, and the relative risk of FN (vs those without risk factors) ranged from 1.1 (95% CI, 0.8–1.3) to 2.2 (95% CI, 1.5–3.0). FN incidence increased in a graded and monotonic fashion with the number of risk factors and comorbidities. **Conclusions:** In this retrospective evaluation of patients with cancer receiving chemotherapy regimens not classified as high-risk for FN in US clinical practice, most patients had 1 or more FN risk factor and many had 2 or more. FN incidence was found to be elevated in these patients, especially those with multiple risk factors. (J Natl Compr Canc Netw 2015;13:979–986)

Background

Neutropenia is a common side effect of myelosuppressive chemotherapy that increases the risk of infection, which is typically signaled by fever. When neutropenic patients develop fever (ie, febrile neutropenia [FN]), the likelihood of infection and serious consequences often necessitates

hospitalization.¹ FN can lead to chemotherapy dose delays, dose reductions, and/or discontinuation, interfering with the delivery of treatment and possibly adversely affecting patient outcomes.^{1–5}

For adult patients receiving chemotherapy for solid tumors or nonmyeloid malignancies, NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines)

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for Myeloid Growth Factors⁶ recommend prophylaxis against FN with a colony-stimulating factor (CSF) when risk, based on the chemotherapy regimen and patient risk factors, is “high” (>20%) (to view the most recent version of these guidelines, visit NCCN.org). For patients whose risk is high based on the chemotherapy regimen alone, the decision to administer CSF prophylaxis is relatively straightforward. For patients receiving a regimen classified as “intermediate” (FN risk, $\geq 10\%$ to $\leq 20\%$), or even “low” (FN risk, $< 10\%$), however, careful consideration must be given to patient risk factors when calculating overall FN risk and deciding whether to administer CSF prophylaxis.^{1,5–14} Available evidence suggests that these patients are not rare; it has been estimated that approximately 50% of all adults receiving low- or intermediate-risk regimens have an FN risk greater than 20% when taking into account their (ie, patient) risk factors.^{1,15–20} Available evidence also suggests that it is important to consider not only whether risk factors are present but also the number and type of risk factors present.^{11,14}

Because of the many exclusion criteria used in clinical trials, patients in real-world clinical practice are likely to differ from trial subjects in significant ways. In addition, other factors, such as use of supportive care and chemotherapy dose delays and dose reductions during the treatment course, may lead to variation in FN risk profiles and events seen in the clinical trial and clinical practice settings. Understanding these risks in routine clinical practice, especially among patients receiving low- and intermediate-risk regimens, is thus important for treatment decision-making at the patient level and policy decision-making at the population level.

One source of data on the real-world complications of patients undergoing cancer chemotherapy is health care claims (or administrative) databases. Although lacking clinical richness, these databases provide access to the health care experience of millions of persons over a multiyear period, and thus contain information on large numbers of patients with specific cancer diagnoses who are treated with specific chemotherapy regimens.^{21–25} We thus undertook one of the first comprehensive evaluations to estimate the prevalence of risk factors for FN among patients with cancer receiving chemotherapy regimens not

classified as high-risk for FN in US clinical practice, and the risk of FN based on the presence and number of risk factors. The cancers and myelosuppressive chemotherapy regimens considered in the analyses described herein represent those commonly found in US clinical practice and for which the occurrence of FN is frequent, including breast cancer, colorectal cancer, lung cancer, and non-Hodgkin’s lymphoma (NHL).^{3,6–10}

Methods

Study Design and Data Source

A retrospective cohort design and data from 2 large integrated US health care claims repositories were used. The 2 repositories—the Truven Health Analytics MarketScan Commercial Claims and Encounters and Medicare Supplemental and Coordination of Benefits databases, and the IMS LifeLink PharMetrics Health Plan Claims database—comprise medical and outpatient pharmacy claims from a large number of private US health plans. Data for the current study spanned January 1, 2003, through December 31, 2012. The study databases were deidentified, and their use for health services research is fully compliant with the HIPAA Privacy Rule and federal guidance on Public Welfare and the Protection of Human Subjects.²⁶ A detailed description of the data sources is provided in [supplemental eAppendix 1 \(available with this article at JNCCN.org\)](#).

Source and Study Populations

The source population comprised all patients aged 18 years or older who initiated 1 or more courses of chemotherapy for a single primary cancer from July 1, 2003, to June 30, 2012. For each patient in the source population, all unique observed courses of chemotherapy were identified, as were all cycles within each of these courses. Patients in the source population were stratified into subgroups based on primary cancer type, presence of metastatic disease, and chemotherapy regimen.

From the source population, patients with primary cancers who initiated treatment with chemotherapy regimens classified as “low” or “intermediate” or unclassified in terms of FN risk in guidelines for CSF use were selected for inclusion in the study population.^{1,6,16} Regimen-specific subgroups with small sample sizes (<3500 patients,

the minimum number needed for adequately powered analyses [$\beta=0.80$]) were excluded from consideration. Only the first course of chemotherapy with an eligible (ie, low-risk, intermediate-risk, or unclassified) regimen was considered in analyses. A complete description of methods used to identify cancer type and the presence/absence of metastatic disease, and to characterize chemotherapy courses, cycles, and regimens, is provided in [supplemental eAppendices 2–4](#).

Study Outcomes

FN was ascertained on a cycle-specific basis, from day 6 of the chemotherapy cycle (ie, beginning on the 6th day after administration of the first chemotherapy agent during that cycle) to the last day of the chemotherapy cycle. FN was identified by the setting of care (inpatient vs outpatient) in primary analyses, using the diagnosis codes for neutropenia (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] code 288.0), infections ([see supplemental eAppendix 5](#)), and fever (ICD-9-CM 780.6); the presence of any of these codes (ie, those for neutropenia or infection or fever)—per the algorithms presented herein—was considered evidence of FN.^{22–25}

Inpatient FN was identified based on acute care facility admissions with a principal or secondary diagnosis code for FN (as mentioned previously). Outpatient FN was ascertained based on encounters in an ambulatory setting with a diagnosis code for FN (as mentioned previously) and, on the same date, evidence of intravenous (Health Care Common Procedure Coding System [HCPCS] level II codes) or oral (National Drug Codes [NDCs]) antimicrobial therapy. Outpatient encounters that preceded or followed a hospitalization during the same cycle of chemotherapy were not considered as separate outpatient FN episodes. Alternative definitions for FN were used in sensitivity analyses, including using only intravenous antimicrobial therapy for outpatient FN, using only the diagnosis code for neutropenia, and using only intravenous antimicrobial therapy for outpatient FN and the diagnosis code for neutropenia.

Risk Factors for FN and Other Variables

Risk factors for FN consisted of those listed in clinical practice guidelines and those reported to increase the risk of FN in published literature, including age of 65 years or older, presence of selected chronic comorbidities,

underweight and malnutrition; proxies for poor performance status (use of hospice care, skilled nursing facility, hospital bed, supplemental oxygen, walking aid, or wheel chair), use of immunosuppressive drugs, and history of selected blood-related disorders, infection, surgery (recent), and radiation therapy.^{1,3,6–14,27–34} Age was assessed based on the first day of the first cycle of chemotherapy in the course. All other risk factors (except for recent surgery and radiation therapy) were assessed during the 12-month period before the first day of the chemotherapy course; recent surgery was assessed during the 30-day prechemotherapy period, and radiation therapy during the 6-month prechemotherapy period.

Other variables ascertained included the use of CSF, filgrastim, pegfilgrastim, and sargramostim, as prophylaxis in the first cycle of chemotherapy, which was defined as receipt on or before cycle day 5. A detailed description of methods used to define FN risk factors (including all chronic comorbidities and blood-related disorders) and CSF use are provided in [supplemental eAppendix 6](#).

Statistical Analyses

The percentage of subjects in each cancer- and regimen-specific subgroup with each of the individual risk factors and 1 or more risk factors was calculated, as was the distribution of subjects by the number of risk factors (ie, 0, 1, 2, 3, ≥ 4). Incidence proportions for FN during the chemotherapy course were calculated within cancer- and regimen-specific subgroups, for patients with 1 or more risk factors and patients without risk factors, respectively; the relative risk (RR) of FN (ie, for patients with ≥ 1 vs 0 risk factors) and corresponding 95% CIs were also estimated. FN risk and corresponding RRs also were estimated by the number of risk factors present (ie, for patients with 1, 2, 3, or ≥ 4 vs 0 risk factors) and the number of chronic comorbidities (ie, those that are included among the list of risk factors). Analyses were conducted separately when considering the primary and alternative definitions of FN, only FN episodes requiring inpatient care, and only FN episodes occurring in the first cycle of chemotherapy.

Results

A total of 160,304 patients received myelosuppressive chemotherapy with a regimen not classified as high risk for FN and met all other

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inclusion/exclusion criteria (including $n \geq 3500$), and thus were included in analyses; patients were stratified into 17 cancer- and regimen-specific subgroups (see supplemental eTable 1). The most common risk factors across the 17 subgroups were age of 65 years or older (11%–55% of subjects), cardiovascular disease (15%–54%), diabetes (10%–39%), osteoarthritis (5%–17%), thyroid disorder (6%–14%), and recent history of anemia (10%–66%), infection (30%–57%), or surgery (3%–37%) (Table 2). Most subjects within each subgroup had 1 or more risk factor, ranging from

74% (nonmetastatic breast cancer, AC/AC-T [doxorubicin, cyclophosphamide, $\pm$ docetaxel]) to 98% (metastatic lung cancer, carboplatin + paclitaxel) (Table 3), and many had 2 or more risk factors (range, 41%–89%) (see supplemental eFigure 1). Use of CSF prophylaxis in cycle 1, on an overall basis, varied substantially across regimens, and ranged from 0.3% (nonmetastatic colorectal cancer, 5-FU) to 63% (NHL, R-CHOP [rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone] every 3 weeks/every 4 weeks).

Incidence of FN, based on the broad definition,

Table 2 Prevalence of Risk Factors in Study Population, by Cancer Type and Chemotherapy Regimen

	Nonmetastatic Breast Cancer (%)			Colorectal Cancer (%)			Lung Cancer (%)	
				Nonmetastatic		Metastatic	Nonmetastatic	
	TC (n=26,266)	TCH (n=9,105)	AC/AC-T (n=15,522)	FOLFOX (n=16,130)	5-FU (n=8,427)	FOLFOX (n=5,626)	CAR+PAC (n=14,010)	CIS+ETO (n=6,669)
Age ≥ 65 y	15.1	11.5	11.4	23.6	25.5	22.3	51.9	30.7
Chronic comorbidities								
Autoimmune disease	1.1	0.8	1.2	1.5	1.4	1.2	0.7	0.9
Cardiovascular disease	16.8	14.6	16.6	33.8	25.8	40.5	53.7	45.2
Diabetes	11.8	10.2	11.1	18.9	17.2	17.3	19.2	15.5
HIV/AIDS	0.1	0.0	0.1	0.1	0.4	0.2	0.2	0.1
Liver disease	1.9	2.2	2.0	7.6	5.7	24.1	3.6	4.3
Lung disease	6.9	5.7	6.1	8.3	7.1	9.1	50.9	44.9
Renal disease	1.3	0.9	1.0	3.2	2.8	3.4	4.2	1.7
Osteoarthritis	7.0	6.1	6.0	5.5	4.8	5.1	8.7	9.1
Peptic ulcer disease	0.2	0.2	0.2	1.4	0.8	1.2	0.7	0.7
Rheumatoid disease	1.0	1.0	1.1	0.6	0.7	0.6	1.8	1.3
Thyroid disorder	13.0	11.9	10.6	7.6	6.1	7.4	6.7	7.6
Number of comorbidities								
0	56.7	60.6	58.9	42.3	51.3	32.4	19.7	25.0
1	30.0	28.4	29.5	34.6	30.8	36.9	32.6	34.9
2	10.2	8.5	9.2	17.2	13.1	21.1	30.5	27.4
3	2.4	1.9	2.1	4.7	3.7	7.5	13.1	9.7
≥ 4	0.7	0.5	0.4	1.3	1.0	2.1	4.2	3.0
Underweight or malnourished	0.2	0.1	0.1	2.9	1.5	5.1	1.2	1.0
Proxies for poor performance status								
Hospice care or skilled nursing facility	0.3	0.2	0.2	1.3	1.0	1.7	1.5	0.7
Physical function								
Use of hospital bed	0.1	0.1	0.1	0.2	0.2	0.6	0.3	0.1
Use of supplemental oxygen	1.0	0.6	0.8	1.6	1.4	2.1	12.4	6.9
Use of walking aid	0.2	0.2	0.2	0.5	0.5	1.1	0.6	0.5
Use of wheel chair	0.2	0.1	0.2	0.4	0.4	0.4	0.7	0.4
Any of above	1.4	0.9	1.1	2.5	2.3	3.9	13.3	7.6
Any of above	1.6	1.0	1.2	3.6	3.1	5.4	14.3	8.1
Use of immunosuppressive drugs	6.9	8.2	3.1	2.0	1.7	2.5	8.1	5.6
Prechemotherapy conditions/events								
Anemia	11.2	10.3	11.0	44.0	26.8	45.0	20.0	16.0
Neutropenia	5.7	5.1	4.9	5.3	2.8	7.1	5.4	6.4
Infection	32.0	30.5	30.1	42.1	29.9	46.4	53.0	53.5
Hospitalized for neutropenia, fever, infection	3.1	3.3	3.1	21.4	9.4	25.6	21.1	18.3
Recent surgery	20.0	21.0	22.3	16.6	5.7	22.1	3.7	3.4
Radiation therapy	7.6	4.1	3.3	8.3	78.8	6.3	51.5	59.6

(continued)

Abbreviations: 5-FU, fluorouracil; AC/AC-T, doxorubicin + cyclophosphamide (once q3wk or q4wk) $\pm$ subsequent docetaxel or paclitaxel; BOR, bortezomib; CAR, carboplatin; CIS, cisplatin; ETO, etoposide; FOLFOX, folinic acid + fluorouracil + oxaliplatin; GEM, gemcitabine; MM, multiple myeloma; PAC, paclitaxel; R-CHOP, cyclophosphamide + doxorubicin + vincristine + prednisone with rituximab (once q3wk or q4wk); R-COP, cyclophosphamide + vincristine + prednisone with rituximab; TC, docetaxel + cyclophosphamide; TCH, docetaxel + cyclophosphamide + trastuzumab.

Febrile Neutropenia With Non-High-Risk Regimens

during the chemotherapy course among patients with risk factors ranged from 7.2% (nonmetastatic colorectal cancer, 5-FU) to 29.0% (NHL, R-CHOP every 3 weeks/every 4 weeks), and FN incidence was generally higher among patients with risk factors than among those without (RR, range, 1.1–2.2 [95% CI, 0.8–1.3 and 1.5–3.0, respectively]) (Table 3). FN incidence increased in a graded and monotonic fashion with the number of risk factors present. For example, in patients with nonmetastatic breast cancer receiving TC (docetaxel + cyclophosphamide)—the largest cancer/regimen subgroup, of whom 56.6%

received first-cycle CSF prophylaxis—FN incidence among those without risk factors was 10.1%, and increased to 11.6% (RR, 1.1; 95% CI, 1.0–1.3) with 1 risk factor, to 13.9% (RR, 1.4; 95% CI, 1.3–1.5) with 2 risk factors, to 15.7% (RR, 1.6; 95% CI, 1.4–1.7) with 3 risk factors, and to 22.7% (RR, 2.2; 95% CI, 2.0–2.5) with 4 or more risk factors. Corresponding values of FN incidence and RRs by the number of chronic comorbidities were as follows: no comorbidities, 14.1%; 1 comorbidity, 18.3% (RR, 1.3; 95% CI, 1.2–1.4); 2 comorbidities, 20.8% (RR, 1.5; 95% CI, 1.4–1.6); 3 comorbidities, 22.0% (RR, 1.6; 95% CI,

Table 2 Prevalence of Risk Factors in Study Population, by Cancer Type and Chemotherapy Regimen (cont.)

	Lung Cancer (%)			NHL (%)		Ovarian Cancer (%)		Pancreatic Cancer (%)	
	Nonmetastatic	Metastatic	MM (%)	R-CHOP	R-COP	Nonmetastatic	Metastatic	Nonmetastatic	Metastatic
	CAR+ETO (n=4,886)	CAR+PAC (n=7,307)	BOR (n=7,009)			CAR+PAC (n=5,587)	CAR+PAC (n=6,295)	GEM (n=6,697)	GEM (n=4,452)
Age ≥65 y	54.6	35.1	50.0	33.1	46.7	24.0	27.2	48.0	37.4
Chronic comorbidities									
Autoimmune disease	0.8	1.0	1.4	1.6	1.2	1.2	0.8	1.1	1.4
Cardiovascular disease	50.1	34.8	32.4	33.0	24.9	38.1	38.5	41.4	32.4
Diabetes	23.8	21.3	17.9	17.9	11.4	12.9	39.2	37.1	17.9
HIV/AIDS	0.1	0.1	0.9	0.1	0.1	0.0	0.2	0.2	0.9
Liver disease	5.5	5.4	7.4	4.9	4.8	9.6	21.5	39.8	7.4
Lung disease	50.1	38.9	10.9	9.7	11.0	7.2	8.4	10.8	10.9
Renal disease	6.3	28.7	5.3	5.5	2.2	3.4	4.7	4.7	5.3
Osteoarthritis	10.3	16.7	9.7	9.7	6.3	8.4	9.4	10.2	9.7
Peptic ulcer disease	0.8	1.1	2.6	2.0	0.4	0.8	3.3	3.6	2.4
Rheumatoid disease	1.6	1.5	1.9	1.9	1.0	1.2	0.9	1.0	1.9
Thyroid disorder	8.0	9.5	11.0	9.5	13.0	14.4	8.8	9.8	11.0
Number of comorbidities									
0	20.1	21.5	31.1	40.6	43.3	50.4	38.4	25.7	17.7
1	30.3	33.6	30.5	32.2	30.4	32.5	35.8	32.9	33.6
2	29.6	28.4	22.1	17.4	16.3	12.9	17.4	24.6	28.2
3	13.9	12.6	11.0	7.0	7.2	3.3	6.2	12.5	14.1
≥4	6.1	3.9	5.3	2.8	2.9	1.0	2.1	4.4	6.4
Underweight or malnourished	1.2	1.9	1.8	2.0	1.0	1.7	5.3	6.8	6.1
Proxies for poor performance status									
Hospice care or skilled nursing facility	2.6	2.1	3.7	1.6	2.3	1.6	3.3	2.8	2.2
Physical function									
Use of hospital bed	0.3	1.0	1.5	0.3	0.3	0.2	1.0	0.7	0.9
Use of supplemental oxygen	13.0	9.3	3.3	2.3	2.8	1.7	2.8	2.5	2.7
Use of walking aid	0.8	1.6	1.4	0.7	0.8	0.7	1.4	1.0	1.1
Use of wheel chair	0.9	1.5	2.0	0.4	0.8	0.4	0.4	0.6	0.7
Any of above	14.0	11.8	6.7	3.4	4.1	2.7	5.0	4.3	4.8
Any of above	15.7	13.4	9.4	4.7	5.6	4.0	7.7	6.7	6.7
Use of immunosuppressive drugs	6.5	20.7	18.4	9.3	8.7	6.4	7.1	2.5	3.1
Prechemotherapy conditions/events									
Anemia	19.9	21.2	65.6	31.8	30.2	25.1	29.3	27.1	27.8
Neutropenia	7.4	7.1	16.8	19.3	12.8	6.2	8.3	7.0	7.3
Infection	57.2	53.4	43.4	43.8	39.6	41.3	50.7	42.9	44.3
Hospitalized for neutropenia, fever, infection	24.2	25.0	17.7	14.7	11.0	14.1	22.9	20.2	21.7
Recent surgery	2.7	6.1	6.2	5.9	3.3	28.3	37.4	3.7	6.6
Radiation therapy	20.0	64.7	9.6	2.4	3.3	0.4	1.0	16.6	7.9

Abbreviations: 5-FU, fluorouracil; AC/AC-T, doxorubicin + cyclophosphamide (once q3wk or q4wk) +/- subsequent docetaxel or paclitaxel; BOR, bortezomib; CAR, carboplatin; CIS, cisplatin; ETO, etoposide; FOLFOX, folinic acid + fluorouracil + oxaliplatin; GEM, gemcitabine; MM, multiple myeloma; PAC, paclitaxel; R-CHOP, cyclophosphamide + doxorubicin + vincristine + prednisone with rituximab (once q3wk or q4wk); R-COP, cyclophosphamide + vincristine + prednisone with rituximab; TC, docetaxel + cyclophosphamide; TCH, docetaxel + cyclophosphamide + trastuzumab.

Table 3 Incidence Proportions for FN, by Presence/Absence of ≥1 Risk Factor

	% of Patients With ≥1 FN Risk Factor	% of Patients With Cycle 1 CSF Prophylaxis	Incidence Proportions for FN		
			≥1 FN Risk Factor	0 FN Risk Factors	Relative Risk (95% CI)
Breast cancer					
Nonmetastatic					
TC (n=26,266)	79.0	56.6	17.4	12.9	1.3 (1.2, 1.5)
AC/AC-T, q3wk/q4wk (n=15,522)	74.4	43.3	20.0	12.9	1.6 (1.4, 1.7)
TCH (n=9,105)	75.2	58.2	19.5	15.1	1.3 (1.2, 1.4)
Colorectal cancer					
Nonmetastatic					
FOLFOX (n=16,130)	90.2	10.2	12.6	8.7	1.4 (1.2, 1.7)
5-FU (n=8,427)	96.6	0.3	7.2	6.3	1.2 (0.7, 1.8)
Metastatic					
FOLFOX (n=5,626)	93.5	9.7	11.3	6.1	1.9 (1.2, 2.8)
Lung cancer					
Nonmetastatic					
CAR + PAC (n=14,010)	97.3	12.9	18.0	11.3	1.6 (1.2, 2.1)
CIS + ETO (n=6,669)	96.6	18.1	23.2	14.9	1.6 (1.1, 2.1)
CAR + ETO (n=4,886)	94.9	39.4	24.1	15.5	1.6 (1.2, 2.1)
Metastatic					
CAR + PAC (n=7,307)	97.9	18.3	20.4	10.6	1.9 (1.2, 3.1)
Multiple myeloma					
BOR (n=7,009)	95.4	1.2	20.8	9.6	2.2 (1.5, 3.0)
Non-Hodgkin's lymphoma					
R-CHOP, q3wk/q4wk (n=12,324)	87.5	62.7	29.0	17.5	1.7 (1.5, 1.9)
R-COP (n=3,992)	86.5	29.6	17.4	9.3	1.9 (1.4, 2.5)
Ovarian cancer					
Nonmetastatic					
CAR + PAC (n=5,587)	87.0	22.8	12.6	10.6	1.2 (1.0, 1.5)
Metastatic					
CAR + PAC (n=6,295)	93.7	23.2	17.3	10.4	1.7 (1.2, 2.2)
Pancreatic cancer					
Nonmetastatic					
GEM (n=6,697)	93.3	1.6	18.3	12.0	1.5 (1.2, 2.0)
Metastatic					
GEM (n=4,452)	94.6	23.1	23.1	21.9	1.1 (0.8, 1.3)

Abbreviations: 5-FU, fluorouracil; AC/AC-T, doxorubicin + cyclophosphamide (once q3wk or q4wk) +/- subsequent docetaxel or paclitaxel; BOR, bortezomib; CAR, carboplatin; CIS, cisplatin; CSF, colony-stimulating factor; ETO, etoposide; FN, febrile neutropenia; FOLFOX, folinic acid + fluorouracil + oxaliplatin; GEM, gemcitabine; PAC, paclitaxel; R-CHOP, cyclophosphamide + doxorubicin + vincristine + prednisone with rituximab (once q3wk or q4wk); R-COP, cyclophosphamide + vincristine + prednisone with rituximab; TC, docetaxel + cyclophosphamide; TCH, docetaxel + cyclophosphamide + trastuzumab.

1.3–1.8); and 4 or more comorbidities, 40.1% (RR, 2.8; 95% CI, 2.4–3.4) ([see supplemental eAppendix 7](#)). Results were generally comparable across the 17 cancer/regimen-specific subgroups, and results were similar when using the alternative definitions for FN, when only FN episodes requiring inpatient care were considered, and when only FN episodes occurring in the first chemotherapy cycle were considered.

Discussion

NCCN Guidelines⁶ recommend prophylactic CSF for patients who, based on their chemotherapy

regimen and risk factors, are at high-risk of FN. This recommendation, however, is based largely on findings from clinical trials, which may not be reflective of the population experience in clinical practice, on an overall basis (ie, for a given regimen), or within subgroups defined therein based on patient risk factors. Understanding these risks in this population is important for making informed treatment decisions at the patient level, because many patients receiving low- or intermediate-risk regimens may be at high risk of FN based on their risk factors.^{1,16,17,20} Understanding these risks is also important for making informed policy decisions at the population level, especially in light of

recent publications suggesting the widespread use of CSF prophylaxis, which is inconsistent with guideline recommendations.^{15,17,35,36}

We therefore undertook one of the first comprehensive evaluations to estimate the prevalence of risk factors for FN among patients with cancer receiving chemotherapy regimens not classified as high risk for FN in US clinical practice, and the RR of FN for patients with (vs without) risk factors and by the number of risk factors. We found that most patients (74%–98% across regimens) had 1 or more risk factor for FN and that many (42%–88%) had 2 or more risk factors. Most importantly, we also found that FN risk was higher among patients with (vs without) a risk factor, especially among those with multiple risk factors.

Among the 5 most common cancer/regimen combinations, FN risk was 30% to 70% higher among those with 1 or more risk factor (vs no risk factors), and absolute FN risk was close to or exceeded the 20% threshold for most of these subgroups, suggesting that many patients with risk factors receiving low/intermediate-risk regimens are appropriate candidates for CSF prophylaxis. Among patients with NHL receiving R-CHOP, for example, absolute FN risk exceeded 20% for all patients with risk factors, increasing from 21.9% among those with a single risk factor to 36.9% among those with 4 or more risk factors. Taken collectively, these findings underscore the importance of evaluating patient risk factors, both the type and number, in addition to the chemotherapy regimen when projecting FN risk and deciding whether to administer CSF prophylaxis. Such a personalized approach to cancer care and personal FN risk assessment is necessary to ensure optimization of patient outcomes. We note that, although estimates of FN risk—based on our operational algorithm for identifying FN episodes—may be somewhat different from true risks of FN, we believe that the magnitude of any bias resulting from imperfect case ascertainment is similar across subgroups and, accordingly, that it should not adversely impact our estimates of RRs.²³ We also note that study results (ie, estimates of relative risk) were largely robust when using the alternative definitions for FN.

A few additional potential biases and limitations vis-à-vis patient (treatment) selection and outcome measurement deserve mention. Compared with subjects enrolled in clinical trials of low/intermediate-

risk regimens, patients receiving these regimens in clinical practice may have a worse underlying risk profile, which may yield higher estimates of FN risk. On the other hand, these patients may be more likely to receive CSF or antimicrobial prophylaxis in clinical practice, which would lower the risk; dose reductions, regimen changes, and other FN-related actions during the chemotherapy course may also impact study results. FN risk was estimated for each chemotherapy regimen considering all patients in that subgroup, irrespective of receipt of CSF prophylaxis. For this reason, study results may not necessarily reflect the true underlying risk of FN for a given regimen (ie, in the absence of supportive care).

We thus reported use of CSF prophylaxis to put study results into context. Although FN risk can be evaluated among the subset of patients who did not receive CSF prophylaxis, given that this subgroup is undoubtedly systematically different in terms of their FN risk profile, such analyses would inherently suffer from selection bias. For this reason, we decided not to conduct analyses limiting attention to patients who did not receive CSF prophylaxis.

Because FN rarely occurs within the first 5 days of a cycle, and this period was used to identify prophylactic CSF use, the follow-up period for ascertainment of FN began on cycle day 6. However, to the extent that some patients actually experienced FN during the first 5 days of the cycle (<1% of patients in exploratory analyses using our broad definition), FN risks may be somewhat underestimated.

Because the accuracy of algorithms/variables capturing the presence of acute and chronic conditions is less than perfect, and because histories are left-truncated, some patients may be misclassified in terms of their risk factor profile.

Although not validated within the context of this study, measures of disability (ie, use of hospice care, skilled nursing facility, hospital bed, supplemental oxygen, walking aid, and wheel chair) have been found in previous evaluations to be predictive of performance status.^{29,31}

Finally, because the study population comprised (principally) patients with cancer who were younger than 65 years with coverage from private US health plans, the study population may not reflect patients treated in clinical practice across the United States.

Conclusions

The results of this study suggest that most patients with cancer receiving chemotherapy regimens who are not classified as high risk for FN have 1 or more risk factors, and many have 2 or more. The results of this study also suggest that FN risk is elevated in these patients, especially those with multiple risk factors. For these reasons, and because patients with risk factors may also be at risk for more severe consequences of FN, careful consideration should be given to fully evaluating each patient's overall risk of FN, based on a combination of the chemotherapy regimen and risk factors, so that those at elevated risk may be appropriately targeted for preventive measures.^{3,34}

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