

Use of prophylactic growth factors and antimicrobials in elderly patients with cancer: a review of the Medicare database

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Abstract

Purpose Growth factors and antimicrobials can reduce complications of chemotherapy-induced myelosuppression. Their prophylactic use in elderly patients is important given the associated comorbidity in this age group. There is a developing trend by payers to include supportive care agents in chemotherapy care bundles, which could affect clinical practice. We examined whether the febrile neutropenia (FN) risk categories can be used to describe utilization in the Centers for Medicare & Medicaid fee-for-service system in older adults. **Methods** We conducted a retrospective cohort study using the Medicare 20% sample data to describe growth factor and antimicrobial use patterns in patients receiving chemotherapy for breast cancer, lung cancer, and non-Hodgkin lymphoma (NHL).

Results The highest percentage of patients receiving granulocyte colony-stimulating factor (GCSF) within the first 5 days of a chemotherapy cycle were on high-FN-risk regimens, particularly for cycle 1 (73.7%, breast cancer; 61.5%, NHL) and cycle 2 (75.9%, breast cancer; 77.5%, NHL). Chemotherapy

regimens for lung cancer are less myelotoxic, and growth factor use was more likely with latter cycles. Antibiotic use was lower at 15% within a cycle and appeared to be in response to complications.

Conclusion Practitioners use GCSF and antibiotics for elderly patients treated with potentially toxic chemotherapy, while comorbidity burden plays a role for patients treated with less myelotoxic regimens. The complexity of these choices in clinical practice should be considered in the proposed reimbursement changes being piloted by Medicare and private insurance companies seeking treatment cost reductions, as altered use could affect safety and efficacy.

Keywords Antimicrobials · Chemotherapy · Febrile neutropenia · Granulocyte colony-stimulating factor

Introduction

Febrile neutropenia (FN) is a well-known complication of myelosuppressive chemotherapy. Hospitalizations for FN often result in chemotherapy treatment delays or dose reductions in subsequent cycles, reducing the efficacy of chemotherapy and increasing diagnostic and treatment costs [1, 2]. Use of supportive care agents has reduced complications from chemotherapy-induced myelosuppression. Primary prophylaxis with granulocyte colony-stimulating factor (GCSF), a biological agent that regulates the proliferation and survival of myeloid cells, successfully reduces the time of neutropenia and decreases FN incidence [3, 4]. Prophylactic antimicrobials, though not commonly used in the primary prophylaxis setting, reduce the number and severity of infectious episodes in patients with leukemia and lymphoma [5–7].

Several cancer consortiums, such as the National Comprehensive Cancer Network (NCCN), American

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Society of Clinical Oncology, and European Organization for Research and Treatment of Cancer, endorse the use of GCSFs and antibiotics to minimize adverse events associated with cancer therapy. In this study, we used NCCN guidelines to assign patients to one of three risk categories for development of FN and need for GCSF based on chemotherapy regimen and patient risk factors: high risk (>20%), intermediate risk (10–20%), and low risk (<10%) [8]. Consensus recommendations center on significant reduction of FN following primary GCSF prophylaxis when the FN risk is >20% [9]. Furthermore, some studies have demonstrated a significant reduction in FN with GCSF prophylaxis in patients with breast cancer receiving intermediate-risk chemotherapy when comorbidity increased the risk of infection [10]. Use of prophylactic antibiotics [11, 12] during chemotherapy is recommended in patients with anticipated neutropenia (absolute neutrophil count <1000) for longer than 7 days. Prophylactic antibiotic use is limited in solid tumor patients. Use of antivirals and antifungals is reserved for patients with prolonged neutropenia (>7–10 days), typically experienced by patients with hematologic malignancies or undergoing stem cell transplant. Use of supportive care therapies has gained attention as the Centers for Medicare & Medicaid Services (CMS) develops alternative payment models to contain the increasing cost of cancer treatments. Policy makers, insurers, and CMS have looked at alternative payment models. CMS is currently testing a 6-month chemotherapy period pilot payment model assessing total expenditures in a risk model (<https://innovation.cms.gov/initiatives/Oncology-Care/>). Because supportive care agents are an expensive component of chemotherapy care, we investigated how these services are used in routine clinical care and if the proposed FN risk systems can adequately describe utilization in the CMS fee-for-service system. We studied elderly patients treated for one of three cancer types: breast cancer, lung cancer, and non-Hodgkin lymphoma (NHL).

Methods

We conducted a retrospective cohort study using the Medicare 20% sample data for all Medicare beneficiaries between January 1, 2007, and December 31, 2011. The database, maintained by CMS, includes the annual denominator file (information on demographics and enrollment in Medicare for each beneficiary) and the annual claims-based standard analytic files (SAFs). The SAFs contain Part A institutional, Part B physician/supplier, and Part D oral prescription drug claims. These claims-based files include information on diagnoses, procedures performed, chemotherapeutic and GCSF agents administered in outpatient settings, dates of service, and oral antimicrobials prescribed and filled.

Patients were eligible for the study if they started a chemotherapy course between July 1, 2007, and November 30, 2011, to treat breast cancer, lung cancer, or NHL at age 65 years or older; were continuously enrolled in Medicare Part A and Part B from 6 months before the start of the chemotherapy course to the last day of the course; and had Medicare Part D coverage from 30 days before the start of the course to the last day of the course or the sixth cycle end date, whichever came first. Patients were excluded who were enrolled in managed care organizations or who had any medical claims for stem cell transplant during the period from 6 months before the start of the chemotherapy course to the last day of the course.

Patients with breast cancer, lung cancer, or NHL were identified using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis codes (breast cancer, 174.xx, 175.xx; lung cancer, 162.xx–163.xx; NHL, 200.xx, 202.xx). Chemotherapy was identified using billing codes for chemotherapy administration and/or agents (Supplementary Table S1). Chemotherapy course and cycle were defined following the algorithm used by Choi et al. [13]. A chemotherapy course began at the first chemotherapy claim (index date) between January 1, 2007, and December 31, 2011, and ended at the last chemotherapy claim with a gap of less than 60 days between two consecutive claims. The first chemotherapy cycle was defined as beginning with the index date and ending with the next chemotherapy claim that occurred at least 20 days after the index date. Subsequent cycles were defined using similar rules up to a maximum of 6 cycles (including the first). For patients with two or more chemotherapy courses identified between July 1, 2007, and November 30, 2011, only the first was used in this study.

According to NCCN guidelines for myeloid growth factors use [8], we classified chemotherapy regimens as high (>20%) and intermediate (10–20%) FN risk based on the chemotherapeutic agents on the claims. Regimens not defined as high or intermediate FN risk were combined into an unclassified FN risk category. To further evaluate unclassified FN risk regimens, we identified the number of chemotherapeutic agents by level of myelosuppression (high, low, none) according to the definition from a prior study by Wecker and colleagues [14]. For each cycle, we categorized patients into one of the following four groups in descending hierarchical order: (1) two or more high myelosuppressive agents, (2) exactly one high myelosuppressive agent, (3) one or more low myelosuppressive agents in the absence of high myelosuppressive agents, and (4) none (mainly biologic agents, for example, rituximab). Patient-cycles were excluded if information on myelosuppression level was not available for every agent used in the cycle.

We defined comorbid conditions 6 months before the start of chemotherapy using one or more Medicare Part A inpatient, skilled nursing facility, or home health agency claims or two or more Medicare Part A outpatient or Part B claims at least 30 days apart with qualifying ICD-9-CM diagnosis codes

(Supplementary Table S2). We also defined lengths of hospital stays and cause-specific hospitalizations, including cardiovascular disease, infectious disease, and other. The follow-up period was from the course start date to the earliest of the following: death; change in Medicare enrollment status for Parts A, B, and D; the last day of the sixth cycle; or the course end date.

For each cycle, we identified supportive treatment with GCSF and oral antimicrobial use. Administration of GCSF was identified using HCPCS codes (filgrastim: J1440 and J1441; pegfilgrastim: J2505; sargramostim: J2820) in Medicare Part A outpatient or Part B claims. Primary prophylactic use of GCSF was defined as first GCSF administered from cycle start date (day 0) to day 5. Oral antimicrobial agents including antibacterials, antivirals, and antifungals were identified in Medicare Part D claims using National Drug Codes (Supplementary Table S3). Part D claims for oral medications represent the date of prescription fill, which may not indicate the date of first use. Thus, for prescription fills during 5 days before day 0, use was considered to begin on day 0 for potential infection prophylaxis, and these fills were included in the definition of oral antimicrobials used during cycle days 0 through 5. For each patient, only the first prescription fill for any antimicrobial in each cycle was considered.

For each chemotherapy cycle, we illustrated supportive treatment with GCSF and oral antimicrobials from day 0 through day 5 of the cycle by chemotherapy regimen FN risk category. For patients receiving unclassified FN risk regimens, we further examined primary prophylactic use of GCSF by category of myelosuppression level of agents used within the cycle. For patients receiving GCSF anytime during the cycle, we described timing of GCSF initiation relative to the beginning of the cycle overall and by agent type for each day from day 0 through day 5 and over the entire period from day 6 to the end of the cycle. For patients with oral antimicrobial prescription fills anytime during the cycle, we examined timing of first prescription fill by each day during the period from 5 days before day 0 to the end of the cycle. Descriptive statistics (count and proportion) are reported. The analyses were repeated for each cycle up to 6 cycles for each cancer type. An exploratory analysis was performed to describe the type and duration of antimicrobial use for the first cycle of chemotherapy only. All analyses were performed using SAS, version 9.2 (SAS Institute Inc.).

Results

Patient characteristics and chemotherapy regimens

The study cohort included 9110 patients with breast cancer, 12,032 with lung cancer, and 6306 with NHL, treated with chemotherapy between July 1, 2007, and November 30, 2011. Most chemotherapy regimens were unclassified to FN risk:

breast cancer, 80%; lung cancer 57%; NHL, 83%. The proportion of patients on FN risk regimens classified as high and intermediate varied greatly across the three cancer types. Supplementary Table S4 summarizes the most commonly used regimens based on cancer type and FN risk classification.

Patient characteristics at baseline varied by cancer type and chemotherapy regimen FN risk category (Table 1). Breast cancer patients on high FN risk regimens were younger (82% aged 65–74 years) and less likely to have comorbid conditions, prior infectious hospitalization, or long hospital stays (≥ 4 days). NHL patients on high FN risk were younger (48 vs. 41% aged 65–74 years) and less likely to have congestive heart failure or long hospital stays. Differences in lung cancer patients by regimen category were less profound.

Supportive treatment utilization in first 5 days of chemotherapy cycle

Figure 1 shows the patterns of GCSF and oral antimicrobial use in the first 5 days of a chemotherapy cycle by regimen FN risk category for each tumor type and chemotherapy cycle. In general, the highest percentage of patients receiving GCSF within the first 5 days of a chemotherapy cycle were on high FN risk regimens, particularly for cycle 1 (73.7%, breast cancer; 61.5%, NHL) and cycle 2 (75.9%, breast cancer; 77.5%, NHL). During the subsequent cycles, GCSF use steadily decreased to 34.0% in cycle 6 for breast cancer but remained stable at about 80% for NHL. In general, patients on intermediate FN risk regimens were less likely to receive GCSF; however, we noted an interesting increased pattern of use for lung cancer patients: 20% in cycle 1 to 40% in the last 3 cycles. A substantial proportion of patients on unclassified FN risk regimens received GCSF: approximately 20–40% for cycles 3–6 for all three tumors. Compared with GCSF use, oral antimicrobial agent use from day 0 to day 5 of a chemotherapy cycle was considerably lower (<15%), regardless of cancer type and regimen FN risk category.

Among patients treated with unclassified FN risk regimens, use of myelosuppressive agents for breast cancer, lung cancer, and NHL occurred in 93.1, 96.8, and 56.9% of total patient-cycles, respectively. Primary prophylactic GCSF use was minimal in patients who received no myelosuppressive agents or low myelosuppressive agents only but greatly increased in patients who received high myelosuppressive agents, particularly those receiving two or more (Table 2).

Timing of supportive treatment utilization

Among all patients treated with chemotherapy, 24 to 54% received GCSF, depending on cancer type and cycle (Table 3). Among patients who received GCSF anytime during the first cycle, the most common GCSF agent used was pegfilgrastim (74–84%), followed by filgrastim (14–23%) and

Table 1 Baseline patient characteristics, by cancer type and febrile neutropenia risk category of chemotherapy regimen

Patient characteristics	Breast cancer (<i>n</i> = 9110)			Lung cancer (<i>n</i> = 12,032)			Non-Hodgkin lymphoma (<i>n</i> = 6306)		
	Risk of FN			Risk of FN			Risk of FN		
	High	Intermediate	Unclassified	High	Intermediate	Unclassified	High	Intermediate	Unclassified
Total patients	923	908	7279	37	5130	6865	1035	24	5247
Age, years									
65–69	48.1	27.6	28.9	48.6	26.7	26.1	19.9	*	20.7
70–74	33.8	28.6	28.9	32.4	32.7	29.6	27.7	*	20.5
75–80	14.4	21.9	20.0	*	23.9	22.7	24.9	45.8	20.9
≥80	3.7	21.8	22.2	*	16.7	21.6	27.4	*	38.0
Race									
White	85.6	84.3	87.3	91.9	88.9	87.3	89.6	91.7	92.1
African American	9.5	11.1	8.5	*	7.5	7.8	4.3	*	3.8
Other	4.9	4.6	4.1	*	3.5	4.9	6.1	*	4.1
Sex									
Male	1.6	*	1.0	40.5	48.2	48.0	43.3	54.2	42.3
Female	98.4	98.9	99.0	59.5	51.8	52.0	56.7	45.8	57.7
Comorbid conditions ^a									
ASHD	6.3	12.2	12.7	*	27.4	24.8	19.2	*	18.3
CHF	2.2	6.7	6.7	*	9.4	10.0	6.4	*	10.3
CVA/TIA	2.0	4.0	3.3		7.1	5.6	4.8	*	4.4
Dysrhythmia	5.7	13.0	11.3	*	18.1	19.1	15.3	*	16.9
PVD	5.1	7.7	8.1	*	15.1	14.7	11.0	*	10.3
Other CVD	6.8	7.7	8.2	*	9.9	10.6	11.7	*	9.5
Anemia	7.4	14.8	14.8	35.1	18.2	20.5	25.0	*	26.5
CKD	2.9	6.8	6.3		9.2	8.9	11.9	*	11.7
COPD	10.0	12.1	13.1	32.4	55.0	47.2	12.3	*	11.0
Diabetes	21.6	23.1	23.6	*	23.6	22.6	25.1	*	21.6
Osteoarthritis	10.8	10.7	11.4		10.4	10.4	12.1	*	9.8
Thyroid disease	13.9	16.2	15.8	*	11.3	11.8	14.8	*	11.4
Other cancer	1.7	6.5	8.9	*	7.0	8.9	11.6	*	16.7
Primary cause of hospitalization ^a									
Infectious disease	1.6	4.8	4.0	*	7.0	8.2	5.0	*	5.3
CVD	*	3.9	3.9		7.7	7.1	4.8	*	5.6
Other	37.2	34.4	30.6	*	41.0	36.8	34.4	*	21.0
Hospitalization LOS, days ^a									
0	61.1	61.7	65.1	70.3	50.5	54.8	60.7	58.3	72.3
1–3	28.6	18.8	15.6	*	8.5	8.1	7.8	*	5.7
4–6	6.7	9.3	8.7	*	14.5	12.8	9.9	*	7.6
≥7	3.6	10.2	10.5	*	26.4	24.2	21.6	*	14.4

ASHD atherosclerotic heart disease, CHF congestive heart failure, CKD chronic kidney disease, COPD chronic obstructive pulmonary disease, CVA/TIA cerebrovascular accident/transient ischemic attack, CVD cardiovascular disease, FN febrile neutropenia, GI gastrointestinal, LOS length of stay, PVD peripheral vascular disease

^a Defined based on 6 months prior to chemotherapy initiation

^b Values for cells with ten or fewer patients are suppressed

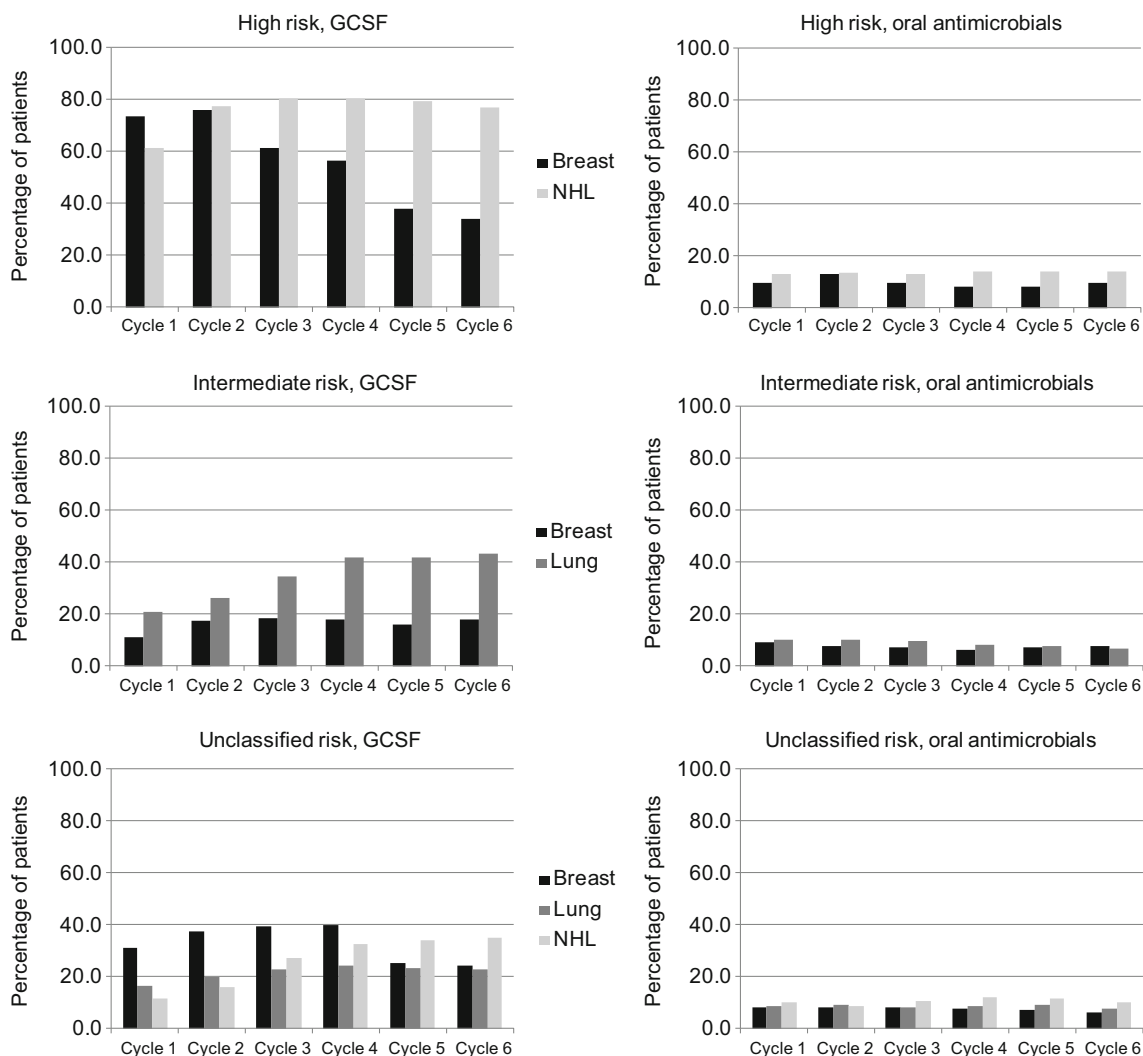


Fig. 1 Percentage of patients receiving a supportive treatment during days 0 to 5 of the chemotherapy cycle, by febrile neutropenia risk category of chemotherapy regimen and treatment type. *GCSF* granulocyte colony-stimulating factor, *NHL* non-Hodgkin lymphoma

sargramostim (3–4%). During the first cycle, timing of any GCSF use relative to the cycle start date was varied. For breast cancer and NHL, GCSF use peaked on the day after the beginning of the cycle (breast cancer, 66.2%; NHL, 39.5%) and greatly decreased from day 2 (breast cancer, 5.9%; NHL, 17.6%) to day 5 (breast cancer, 0.6%; NHL, 3.1%). For lung cancer, however, GCSF use peaked on day 1 (30.9%) and day 3 (19.2%). About 3 to 6% of GCSF was given on the cycle start date. More pegfilgrastim was given on days 0 through 5 and more filgrastim after day 5. Use patterns were similar by agent type and for the subsequent cycles.

About 20 to 31% of patients had at least one prescription fill for an oral antimicrobial agent during the chemotherapy cycle, depending on cancer type and cycle (Table 3). For breast cancer patients, the first prescription fill during the first cycle occurred in the 5 days before the start of the first cycle for 13.9% of patients; days 0–5, 17.6%; and after day 5, 68.6%. Peak days for first prescription fill were days 0, 7, and 14 of the first

chemotherapy cycle (Fig. 2). Similar patterns occurred for subsequent cycles and for patients with lung cancer and NHL.

Of the overall prescriptions for antimicrobials filled during the first cycle, most were for antibacterial agents; 77% of patients with NHL and 86% of patients with breast cancer filled antibacterial agents. Antifungals were the second most filled antimicrobial for breast cancer (10%) and lung cancer (11%) patients, and antivirals were the second most filled antimicrobial for NHL patients (13%). Median length of antimicrobial treatment during the first cycle of chemotherapy was 1 week for antibacterials and antifungals across all cancer types.

Discussion

In this study, we used the Medicare database to assess use of supportive care agents, specifically GCSF and antimicrobials,

Table 2 Percentage of patients receiving prophylactic GCSF by chemotherapy cycle and myelosuppression level of agents used in the cycle among patients who were treated with regimens not classified as high or intermediate risk of febrile neutropenia based on the NCCN guideline

Cancer Type and Cycle	Myelosuppression Level							
	None		≥1 Low, No High		1 High		≥2 High	
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
Breast cancer								
1	870	*	705	*	1545	4.8	3798	56.8
2	465	*	633	3.6	1366	6.2	3592	62.2
3	296		618	2.3	1316	13.9	3185	62.4
4	168		593	2.9	1260	17.1	2738	62.9
5	125		686	3.5	1183	16.8	1200	53.7
6	96	*	726	2.3	971	14.9	983	55.6
Lung cancer								
1	309	*	580	*	2323	7.4	3435	26.4
2	182	*	487	5.1	2164	11.0	3213	29.9
3	121	*	433	7.2	1914	12.5	2693	33.6
4	83		376	8.0	1624	14.2	2198	35.9
5	102		299	7.7	1348	16.6	1363	36.7
6	105		261	8.8	1161	15.8	1018	39.1
Non-Hodgkin lymphoma								
1	2941	0.9	113	*	1350	22.8	480	45.0
2	2368	1.0	85	*	1321	29.9	494	51.4
3	660	2.4	70	*	1195	32.5	428	57.9
4	350	4.6	61	19.7	1011	36.1	343	61.8
5	263	5.7	53	24.5	796	37.6	254	64.2
6	181	*	40	*	632	39.9	206	63.6

Patient-cycles were excluded if information on myelosuppression level was not available for every agent used in the cycle

GCSF granulocyte colony-stimulating factor, NCCN National Comprehensive Cancer Network

^a Values for cells with ten or fewer patients are suppressed

associated with cancer therapy in the elderly population. We explored utilization patterns of GCSF and antibiotics to help understand how these supportive care agents may be affected under a new CMS payment system (<https://innovation.cms.gov/initiatives/Oncology-Care/>).

We searched the Medicare 20% sample database for regimens associated with high, intermediate, and low risk for FN, as determined by NCCN guidelines. We found that patients with breast cancer or NHL were more frequently treated with high-risk regimens than were lung cancer patients, who primarily received intermediate-risk regimens. As anticipated, most GCSF use occurred in patients treated with high-risk regimens, with more than 60% of breast cancer patients and 80% of NHL patients receiving GCSF support at any given therapy cycle. Interestingly, while GCSF use remained constant through all cycles in NHL patients, use in breast cancer patients declined after cycle 2, a possible extrapolation from clinical trials in breast cancer [10, 15, 16] that observed the highest risk of FN occurring during the first 2 cycles of chemotherapy. Recent data suggest that primary GCSF use

throughout all chemotherapy cycles minimizes episodes of FN among patients with early breast cancer treated with high- and intermediate-risk regimens [17]. An analysis of subsequent years would be informative to determine how practitioners are applying the new evidence to supportive care.

In lung cancer patients, our data demonstrate greater use of GCSF with later cycles of chemotherapy. These patients have several comorbid conditions, such as coronary artery disease and chronic obstructive pulmonary disease, possibly associated with cigarette use (Table 1) [18]. Increasing GCSF use as cycles progress suggests a pattern in which complications early in the treatment course lead to increased supportive care measures in subsequent cycles to prevent complications and treatment delays. Our analysis demonstrates that in addition to chemotherapy-associated risk of FN, physicians also use patient risk factors to determine the need for growth factor support. Recent studies suggest that chemotherapy risk factor alone is not sufficient to predict the need for growth factor support [19, 20], and that a history of chronic comorbid conditions increases the risk of FN [19]. Thus far, the NCCN guidelines have

Table 3 GCSF use during a chemotherapy cycle and timing of GCSF relative to the beginning of the cycle for selected cycles, by cancer type

	Breast cancer			Lung cancer			Non-Hodgkin lymphoma		
	Cycle 1 (<i>n</i> = 9110)	Cycle 3 (<i>n</i> = 7275)	Cycle 5 (<i>n</i> = 4691)	Cycle 1 (<i>n</i> = 12,032)	Cycle 3 (<i>n</i> = 8874)	Cycle 5 (<i>n</i> = 4712)	Cycle 1 (<i>n</i> = 6306)	Cycle 3 (<i>n</i> = 3497)	Cycle 5 (<i>n</i> = 2226)
GCSF use during the cycle, <i>n</i> (% total)	3591 (39.4)	3275 (45.0)	1489 (31.7)	3223 (26.8)	3148 (35.5)	1721 (36.5)	1535 (24.3)	1644 (47.0)	1196 (53.7)
GCSF use by agent type, <i>n</i> (%)									
Pegfilgrastim	3000 (83.5)	2734 (83.5)	1143 (76.8)	2372 (73.6)	2341 (74.4)	1242 (72.2)	1278 (83.3)	1424 (86.6)	1041 (86.6)
Filgrastim	484 (13.8)	470 (14.4)	301 (20.2)	732 (22.7)	690 (21.9)	407 (23.7)	218 (14.2)	182 (11.1)	128 (10.7)
Sargramostim	97 (2.7)	71 (2.2)	45 (3.0)	119 (3.7)	117 (3.7)	72 (4.2)	39 (2.5)	38 (2.3)	27 (2.3)
GCSF use, by cycle day (%)									
0 (cycle start date)	6.2	7.4	6.9	3.4	4.6	4.7	5.1	5.5	6.9
1	66.2	68.9	62.1	30.9	35.1	36.9	39.5	52.5	53.7
2	5.9	5.7	6.0	7.0	7.7	8.2	17.6	16.2	17.5
3	4.4	4.0	5.0	19.2	23.0	22.7	10.4	9.4	8.7
4	0.9	1.3	1.3	2.9	3.1	2.9	5.7	3.3	2.8
5	0.6	1.0	1.0	4.1	3.3	3.7	3.1	2.4	1.5
6 to cycle end date	15.8	11.7	17.6	32.5	23.2	20.9	18.7	10.8	8.9
Pegfilgrastim use, by cycle day (%)									
0	7.1	8.0	7.3	4.4	4.8	5.4	4.9	5.3	6.4
1	74.9	75.6	69.8	37.9	38.6	40.4	44.6	56.3	57.5
2	5.9	5.6	6.4	8.5	8.3	8.9	19.0	16.8	18.0
3	4.6	3.9	4.2	24.2	27.1	27.0	11.9	10.1	9.3
4	0.7	0.9	1.0	3.0	3.0	3.1	5.3	2.7	2.9
5	0.4	0.4	*	4.6	3.5	3.7	3.0	2.1	1.4
6 to cycle end date	6.4	5.6	10.9	17.5	14.7	11.4	11.3	6.8	4.4
Filgrastim use, by cycle day (%)									
0	*	4.5	6.0	*	4.2	2.9	6.0	*	9.4
1	19.4	32.8	36.9	11.2	24.8	28.3	11.5	28.6	29.7
2	5.1	6.0	4.3	2.5	5.8	6.4	8.3	8.8	12.5
3	2.8	4.3	7.6	4.8	10.4	10.6	*	6.0	*
4	*	3.6	*	2.3	3.5	*	7.3	7.7	*
5	*	4.0	*	2.7	2.8	3.4	*	*	*
6 to cycle end date	68.2	44.9	39.5	76.0	48.6	45.9	60.1	40.1	39.1
Prescription filled for oral antimicrobial agent during the cycle, <i>n</i> (% total)	2378 (26.1)	1611 (22.1)	940 (20.0)	3398 (25.5)	2231 (25.1)	1127 (23.9)	1663 (26.4)	1042 (29.8)	688 (30.9)
Prescription filled, by cycle day (%)									
5 days before day 0	13.9	14.5	14.2	14.4	14.5	14.1	17.3	12.9	15
Day 0 to day 5	17.6	22.5	21.6	18.1	20.6	21.7	22.8	25.1	24.7
Day 6 to the end of the cycle	68.5	62.9	64.3	67.5	65.0	64.2	59.9	62.0	60.3

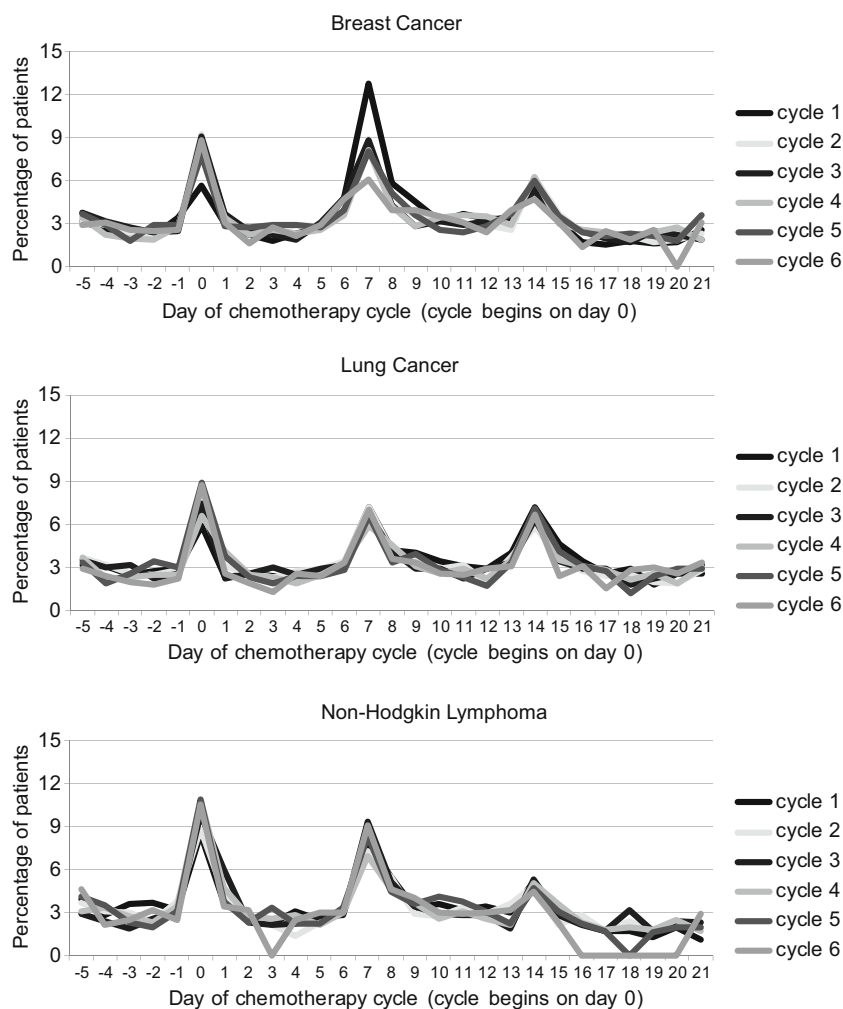
^a Values for cells with ten or fewer patients are suppressed

endorsed clinical latitude to practitioners in prescribing GCSF to patients in clinical scenarios outside of chemotherapy-associated risk. This will most likely create challenges under a bundling system, as there is no algorithm to predict necessity using comorbid conditions. These results support the need for monitoring systems that address safety in anticipated changes in

practice, with an emphasis on the efficacy of ancillary care interventions to prevent infectious complications.

Use of prophylactic antimicrobials is not currently recommended for solid tumors [21]. Consistent with this recommendation, we found that prophylactic antimicrobial use was less frequent than GCSF use (Table 3 and Fig. 1). Overall,

Fig. 2 Percentage of patients with first oral antimicrobial prescription filled during the chemotherapy cycle by day of cycle for each cancer type



antimicrobials were used only 10–15% of the time across different cancer types. Prophylactic antimicrobials were more likely to be used in patients with NHL treated with highly myelosuppressive regimens, as expected due to the greater potential for neutropenia associated with NHL regimens [22]. Antimicrobial prescription data revealed two distinct peaks across cycles: at day 0 and day 7 (Fig. 2) for all cancer types. These could reflect providers' anticipated or actual treatment for infection during the myelosuppressive period. Day 0 may reflect prophylactic use of antimicrobials or physicians providing antibiotic prescription in anticipation of potential febrile complications; day 7 likely represents empiric use for a febrile episode consistent with expected neutropenia 7–10 days after chemotherapy administration. Our interpretation is limited as we were able to gather information only on fill dates and not on actual compliance with oral administration. However, given the low frequency of use, this is unlikely to affect our interpretation of the data.

The greatest strength of this study is that it provides a realistic representation of supportive care drug use in the elderly population with cancer in the USA, as most patients in this

country aged older than 65 years are covered by Medicare, making our database a reliable gauge of practice patterns in the elderly population. Our intent was to describe utilization in the CMS fee-for-service system of the use of growth factors and antibiotics based on a risk stratification system that utilized chemotherapy risk as defined by NCCN [8]. An anticipated limitation is that most chemotherapy regimens used in the Medicare population are not included in the examples provided by the NCCN and had to be labeled as "unclassified" in our study. We compensated for this by using a sensitivity analysis to examine whether the drug combinations in the unclassified risk category included highly myelosuppressive agents. We employed a method previously described by Weycker et al. [14]. By using this method, we found that in both breast and lung cancer, several patients in the unclassified risk category receiving GCSF were treated with one or more agents considered highly myelosuppressive (Supplementary Table S4), thus providing justification for the use of growth factor support.

An important extrapolation of our data revealed that in addition to chemotherapy myelosuppressive risk, practitioners integrate patient comorbid conditions in their assessment of

FN risk and need for GCSF administration. The guidelines do not provide a clear formula for how to predict the risk of neutropenia based on patient comorbidity and leave this to physician discretion. Clearly, comorbid conditions, tumor-related characteristics, and the combination of agents and dosing all play important roles in FN risk. Studies attempting to correlate the risk of FN as assessed by physicians when compared with a validated multivariate model revealed a weak association, supporting the need to develop algorithms incorporating patient characteristics that reliably predict benefit of supportive care agents [23].

Our assessment of provider practice patterns for supportive care data assessment should inform physicians under the new CMS-proposed payment model that diversity of treatment is complex. A simple risk model relying on NCCN chemotherapy risk guidelines is not sufficient. The Oncology Care Model (OCM), a new payment model launched on July 1, 2016, requires and pays for care coordination at \$160/month for participating patients based on a 6-month period of cancer chemotherapy and care coordination. Total services are assessed from all Medicare Part A, B, and D claims retrospectively during the chemotherapy-defined period of care. This model leaves the existing service billing system intact but assesses the total care expenditures billed. The proposed CMS total savings approach lets providers select the various care delivery options over a longer time period. Performance measures discussed by CMS include supportive and palliative care options. Interestingly, specifics related to hospitalization for infection were lacking. This may be important since FN and hospitalizations for infection are among the costliest complications of cancer therapy. Growth factor support is an effective yet costly therapy that reduces FN complications. Oral prophylactic antibiotic use is less costly but whether it has equivalent benefit to growth factor support is unclear, especially regarding solid tumors in the elderly population.

In conclusion, use of GCSF and antibiotics during chemotherapy for breast, lung, and NHL cancers is complex and not easily determined in a simple risk model that uses only chemotherapy-associated FN risk. Our data demonstrate that supportive care is individualized in the elderly/Medicare population based on the diverse comorbidity burden and intensity of chemotherapy. Unfortunately, there are no existing algorithms to predict benefit based on this combination of chemotherapy and patient risk factors; hence, we rely on physician discretion to anticipate supportive care needs. This may prove to be challenging under the proposed CMS OCM, as there are no models to help us predict clinical outcomes of FN based on both chemotherapy intensity and patient comorbidity. There may be a tendency to either withhold supportive care drugs to minimize immediate costs or to overprescribe these medications to avoid complications of hospitalization. The period-of-care payment system continues to allow providers to make therapy choices while assessing total costs. Ongoing

assessments of the new payment system will be important to determine whether physician practices change under the new OCM and whether patient outcomes are comparable or better than under the traditional fee-for-service system, particularly related to infection complications.

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Compliance with ethical standards

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