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ORIGINAL ARTICLE

Time trends in utilization of G-CSF prophylaxis and risk of febrile neutropenia in a Medicare population receiving adjuvant chemotherapy for early-stage breast cancer

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Abstract
Purpose The purpose of this study is to assess temporal trends in the use of granulocyte colony-stimulating factor (G-CSF) prophylaxis and risk of febrile neutropenia (FN) among older women receiving adjuvant chemotherapy for early-stage breast cancer.
Methods Women aged ≥ 66 years with diagnosis of early-stage breast cancer who initiated selected adjuvant chemotherapy regimens were identified using the SEER-Medicare data from 2002 to 2012. Adjusted, calendar-year-specific proportions were estimated for use of G-CSF primary prophylaxis (PP) and secondary prophylaxis and FN risk in the first and the second/subsequent cycles during the first course of chemotherapy, using logistic regression models. calendar-year-specific mean probabilities were estimated with covariates set to modal values.
Results Among 11,107 eligible patients (mean age 71.7 years), 74% received G-CSF in the first course of chemotherapy. Of all patients, 5819 (52%) received G-CSF PP, and among those not receiving G-CSF PP, only 5% received G-CSF secondary prophylaxis. The adjusted proportion using G-CSF PP increased from 6% in 2002 to 71% in 2012. During the same period, the adjusted risk of FN in the first cycle increased from 2% to 3%; the adjusted risk increased from 1.5% to 2.9% among those receiving G-CSF PP and from 2.3% to 3.5% among those not receiving G-CSF PP.
Conclusion The use of G-CSF PP increased substantially during the study period. Although channeling of higher-risk patients to treatment with G-CSF PP is expected, the adjusted risk of FN among patients treated with G-CSF PP tended to be lower than among those not receiving G-CSF PP.

Keywords G-CSF · Febrile neutropenia · Prophylaxis · Breast cancer · Chemotherapy · Time trends

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Introduction

Breast cancer is the most commonly occurring cancer among women in the United States (US), with an estimated 246,660 new cases expected in 2016 [1]. Approximately 95% of all invasive breast cancers in older women in the US are nonmetastatic (stages I, II, or III) at initial presentation [2]. These patients are treated with combinations of surgery, radiation, chemotherapy, hormonal therapy, or human epidermal growth factor receptor 2 (HER2)-targeted therapy according to tumor stage, hormone receptor status, and level of HER2 expression [3]. For larger tumors (> 1 cm), treatment with adjuvant chemotherapy is often recommended [3].

Patients treated with myelosuppressive chemotherapy frequently experience febrile neutropenia (FN), a dose-limiting toxicity characterized by a low neutrophil count (< 500/mm^3) with a single oral temperature ≥ 101 °F or a sustained temperature ≥ 100.4 °F for ≥ 1 hour [4]. Febrile neutropenia events disrupt planned chemotherapy administration (e.g., delays, dose reduction) and may necessitate hospitalization, which can be prolonged and costly [5–7] and may adversely affect patients' quality of life [8]. Clinical trials have shown that FN occurs in 3–24% of patients receiving adjuvant chemotherapy for early-stage breast cancer (ESBC) [9–12].

Traditionally, intravenous antimicrobial therapy has been used for the management of chemotherapy-induced FN and related infectious complications [4]. In addition, granulocyte colony-stimulating factors (G-CSFs), such as filgrastim and pegfilgrastim, have been shown to effectively decrease the risk of FN by stimulating the production of neutrophils. Previous recommendations from the American Society of Clinical Oncology (ASCO) for prophylactic use of CSFs supported their use only in patients with a high risk of developing FN, defined as a ≥ 40% likelihood of FN at the start of treatment (primary prophylaxis [PP]) or when FN had already occurred but chemotherapy dose reduction was not considered appropriate for subsequent cycles (secondary prophylaxis [SP]) [13, 14]. Randomized clinical trials conducted in the last 2 decades, however, have provided new evidence for the efficacy of prophylactic G-CSFs for patients whose primary risk of FN is lower [15–17]. The ASCO CSF Update Committee revised its guidelines, in 2006, to recommend use of CSFs when the risk of FN is ≥ 20%, and no other equally effective but less myelosuppressive chemotherapy regimen is available [18].

The efficacy of G-CSFs in reducing FN risk is now well established; however, real-world data on trends in prophylactic utilization of G-CSFs and incidence of FN in recent years are lacking. In this study, we assessed population-level temporal trends in (1) the use of G-CSF PP and SP and (2) the risk of FN in chemotherapy cycles during the first course of chemotherapy among older women receiving selected adjuvant chemotherapy regimens for ESBC.

Methods

Data source

Data for this retrospective study were taken from the Surveillance, Epidemiology, and End Results (SEER)-Medicare linked database, comprising primarily patients ≥ 65 years with incident cancer who were enrolled in the US Medicare program. The linked SEER-Medicare data provide information on cancer diagnoses (e.g., site, stage, tumor size) and longitudinal Medicare claims data on healthcare service utilization including diagnoses, treatments, and procedures that patients received before and after their cancer diagnosis. The SEER-Medicare data available at the initiation of this study included information on patients with a diagnosis of incident cancers through 2011 and their linked Medicare claims through 2013 [19].

Patient selection

Women with incident ESBC diagnosed from 1994 to 2011 were first identified (N = 552,509) through a SEER-reported International Classification of Diseases for Oncology, Third Edition (ICD-O-3) topography code in the range of C50.0 to C50.9. Extent of disease (stages I, II, or III) was categorized by the SEER Adjusted American Joint Committee on Cancer staging system. Patients were included if ESBC was the first or only primary cancer and if they initiated adjuvant chemotherapy (study index date) within 6 months after incident ESBC diagnosis. The study population was further restricted to patients aged ≥ 66 years at the index date, with age as reason for Medicare eligibility, and who had continuous enrollment in both Medicare Part A and Part B plans (with no enrollment in health maintenance organization) for ≥ 12 months prior. Additionally, ≥ 1 month of enrollment after the index date was required to ensure receipt of the first cycle of treatment. Patients with evidence of a nonbreast second malignancy between the initial ESBC diagnosis and the index date were excluded.

We studied the period after introduction of pegfilgrastim in 2002 and focused our analysis on a group of patients with substantial risk of FN by restricting it to chemotherapy regimens with cycle length ≥ 2 weeks that prompted G-CSF PP in > 15% of patients in the study population. The chemotherapy regimens selected for analysis therefore included AC, TC, AC ➔ T, TP, A, FAC, TAC, AT, and FEC ➔ T, where A = anthracycline (doxorubicin or epirubicin), C = cyclophosphamide, T = taxane (docetaxel or paclitaxel), P = platinum agent (cisplatin, carboplatin, or oxaliplatin), F = fluorouracil, and E = epirubicin. To further explore trends in utilization of chemotherapy regimens, we classified these regimens into three broader classes: (a) "anthracycline, no taxane," (b) "taxane, no anthracycline," and (c) both anthracycline and taxane ("anthracycline/taxane").

Study follow-up

Patients were followed from the index date through (the earliest of) end of the first course of chemotherapy, disenrollment from Medicare Part A and/or Part B, HMO enrollment, incidence of second primary cancer, or death.

Study outcomes

Calendar-year-specific estimates of G-CSF utilization and FN risk were derived as study outcomes for the purpose of assessing population-level time trends. The definitions used to determine G-CSF prophylaxis and FN risk on a cycle-specific basis during the first course of chemotherapy were based on previously published population-based studies [20–24]:

- *G-CSF PP*: First administration of G-CSF between chemotherapy cycle day 1 and day 6, inclusive, in the first cycle of a patient's chemotherapy.
- *G-CSF SP*: First administration of G-CSF between chemotherapy cycle day 1 and day 6, inclusive, in the second or a subsequent cycle among those not receiving G-CSF PP, but with ≥ 1 episode of FN that occurred in the immediately preceding cycle.
- *FN risk*: Measured from chemotherapy cycle day 7 through the end of the cycle.

Episodes of FN observed in an inpatient setting were identified based on hospital admissions with a principal or secondary diagnosis code for neutropenia, fever, or infection. FN episodes requiring only outpatient care were identified from ambulatory encounters with an applicable diagnosis code and evidence of intravenous antimicrobial therapy on the same date. Diagnosis and procedure codes are provided in Supplemental Table S1 (online only).

Baseline measures and risk factors

We tabulated data on patient demographics (e.g., age, race, SEER registry location), calendar year of index chemotherapy, and tumor characteristics (e.g., stage, grade, size, hormonal status) and the presence of select chronic comorbidities (e.g., cardiovascular disease, diabetes, liver disease, lung disease, renal disease, osteoarthritis, rheumatoid disease, thyroid disorder). We used the Klabunde adaptation of the National Cancer Institute's Combined Index (NCICI) to obtain a measure of patients' overall pretreatment comorbidity burden during the 12-month period before the index date [25]. The Klabunde adaptation of NCICI is an extension of the Charlson Comorbidity Index [26], which has been used in several recent retrospective studies among cancer populations [27–30].

In addition, we took into account data on risk factors that predispose patients to receive or not receive G-CSF and also influence the risk of FN. Specifically, we documented recent use of hospice and skilled nursing facilities (proxy for poor health status); recent use of hospital bed, supplemental oxygen, walking aid, and wheelchair (proxy for poor physical functioning); recent infection, antibiotic use, sargramostim use; recent hospitalization; recent radiation or chemotherapy; and evidence of other diagnostic risk factors during the baseline period (hypertension, poor renal function, liver dysfunction, chronic lung disease, osteoarthritis, rheumatoid disease). Refer to Table 1 footnote for the observation window specified in defining "recent" use or history of corresponding risk factor.

Data analysis

Descriptive analyses were conducted for the utilization of G-CSF PP and SP in the overall study population and by calendar year of index chemotherapy. The number and percentage of patients with FN in the first cycle and in the second/subsequent cycles were described. We fit multivariable logistic regression models to estimate adjusted, calendar year-specific proportions of patients receiving G-CSF PP and SP. For estimating adjusted, calendar year-specific risks of FN in cycle 1, we used three distinct logistic regression models to assess risks (1) in the overall study population, (2) in patients receiving G-CSF PP, and (3) in patients not receiving G-CSF PP. The adjusted, calendar year-specific risks of FN in the second/subsequent cycles were assessed only in the overall study population. Linear, quadratic, and cubic terms for calendar year of index chemotherapy were included in all models to account for nonlinearity in trends over time. All models controlled for key risk factors (listed in Table 1). To estimate calendar year-specific proportions for patients receiving G-CSF and calendar year-specific risk of FN, mean probabilities and 95% confidence intervals (CIs) were estimated, while treatment regimen was set to AC ➔ T and all other model covariates were set to modal values following a previously published work [31] and a validation study confirming that prediction at modes yield valid results [32]. We also conducted an analysis of calendar year-specific proportions in models stratified by chemotherapy regimen class (anthracycline, no taxane; taxane, no anthracycline; anthracycline/taxane) rather than controlling for specific regimens in the regression models. All analyses were performed using SAS statistical software, version 9.4.

Results

Baseline characteristics

A total of 11,107 women with a diagnosis of ESBC met the study inclusion/exclusion criteria (Fig. 1). Their average age was 71.7 years (SD = 4.3), and 84% were white. Baseline

Table 1 Baseline characteristics of patients with early-stage breast cancer treated with select myelosuppressive chemotherapy regimens

Baseline measure	*N* (%)
Total patients	11,107 (100%)
Demographics	
Age	
Mean (SD)	71.7 (4.3)
Median	70.8
Q1, Q3	68.2, 74.3
Min, max	66.0, 92.0
Race[a]	
White	9357 (84.2%)
Black	1092 (9.8%)
Other	651 (5.9%)
Location of residence	
Big metropolitan	5634 (50.7%)
Metropolitan	3468 (31.2%)
Urban	721 (6.5%)
Less urban	1043 (9.4%)
Rural	241 (2.2%)
Year of index chemotherapy	
2002	1037 (9.3%)
2003	1010 (9.1%)
2004	1123 (10.1%)
2005	1102 (9.9%)
2006	1133 (10.2%)
2007	1194 (10.8%)
2008	1214 (10.9%)
2009	1122 (10.1%)
2010	1008 (9.1%)
2011	969 (8.7%)
2012	195 (1.8%)
Tumor characteristics (at incident ESBC diagnosis)	
Stage	
Stage I	2339 (21.1%)
Stage II	5778 (52.0%)
Stage III	2990 (26.9%)
Tumor size (cm)	
Mean (SD)	2.7 (2.4)
Median	2.2
Q1, Q3	1.5, 3.2
Min, max	0.1, 95.0
Number with unknown tumor size	201 (1.8%)
Grade	
Grade I (well differentiated)	1017 (9.2%)
Grade II (moderately differentiated)	4145 (37.3%)
Grade III (poorly differentiated)	5320 (47.9%)
Grade IV (undifferentiated)/unknown	625 (5.6%)
Positive ER/PR status	7100 (63.9%)
Positive HER2 status[a]	392 (3.5%)
Positive regional lymph nodes	6891 (62.0%)
Comorbidity burden	
NCI combined index score	
Mean (SD)	0.3 (0.5)
Median	0.0
Q1, Q3	0.0, 0.45
Min, max	0.0, 4.5
Components of NCI Combined Index[b]	
Myocardial infarction	39 (0.4%)
Old myocardial infarction	163 (1.5%)
Congestive heart failure	346 (3.1%)
Peripheral vascular disease (diagnosis)	213 (1.9%)
Cerebrovascular disease	319 (2.9%)
COPD	1386 (12.5%)
Dementia	21 (0.2%)
Paralysis	23 (0.2%)
Diabetes	2493 (22.5%)
Diabetes with sequelae (e.g., renal manifestations)	386 (3.5%)
Chronic renal failure	227 (2.0%)
Various cirrhodites	24 (0.2%)
Ulcer	68 (0.6%)
Ulcer with hemorrhage	19 (0.2%)
Rheumatoid disease	294 (2.7%)
Risk factors for FN (measured during the 12-month pre-index period)	
Radiation[c]	2121 (19.1%)
Chemotherapy	51 (0.5%)
Infection[d]	1365 (12.3%)
Antibiotic use[d]	1777 (16.0%)
Hypertension	8489 (76.4%)
Poor renal function	356 (3.2%)
Liver dysfunction	318 (2.9%)
Chronic lung disease	4023 (36.2%)
Osteoarthritis	3763 (33.9%)
Rheumatoid arthritis	471 (4.2%)
Hospitalization[d]	1443 (13.0%)
SNF admission	181 (1.6%)
Oxygen use	131 (1.2%)
Wheelchair use	143 (1.3%)
Walking aid use	327 (2.9%)
Hospital bed use	65 (0.6%)

COPD chronic obstructive pulmonary disease, *ER* estrogen receptor, *ESBC* early-stage breast cancer, *FN* febrile neutropenia, *HER2* human epidermal growth factor receptor 2, *NCI* National Cancer Institute, *PR* progesterone receptor, *Q1* first quarter, *Q3* third quarter, *SD* standard deviation, *SEER* Surveillance, Epidemiology, and End Results, *SNF* skilled nursing facility

[a] Measured for patients with HER-2 indicator recorded in the SEER-Medicare data (i.e., patients with dia gnosis of ESBC in 2010 and 2011)

[b] In accordance with a requirement of the SEER-Medicare data use agreement, categories with cell size 1 through 10 are not presented

[c] Measured during the period between breast cancer diagnosis and the study index date

[d] Measured during the 1-month period before the study index date

demographics and clinical characteristics are presented in Table 1.

Descriptive results

The most frequent chemotherapy regimens included AC (32%), TC (25%), and sequential AC ➔ T (23%), which were used regularly in all calendar years over the duration of study period (Table 2). We found that "anthracycline, no taxane" was the most common regimen class from 2002 to 2006. The use of "taxane, no anthracycline" increased from 2006 and was the most common regimen class from 2008 through the study end. The percentage of patients receiving each regimen class by calendar year is presented in Supplemental Fig. S1 (online only).

Overall, nearly three quarters of patients (n = 8235 [74.1%]) received G-CSF in the first course of chemotherapy. Pegfilgrastim was the most commonly used G-CSF agent (77%) with an increasing trend observed over time

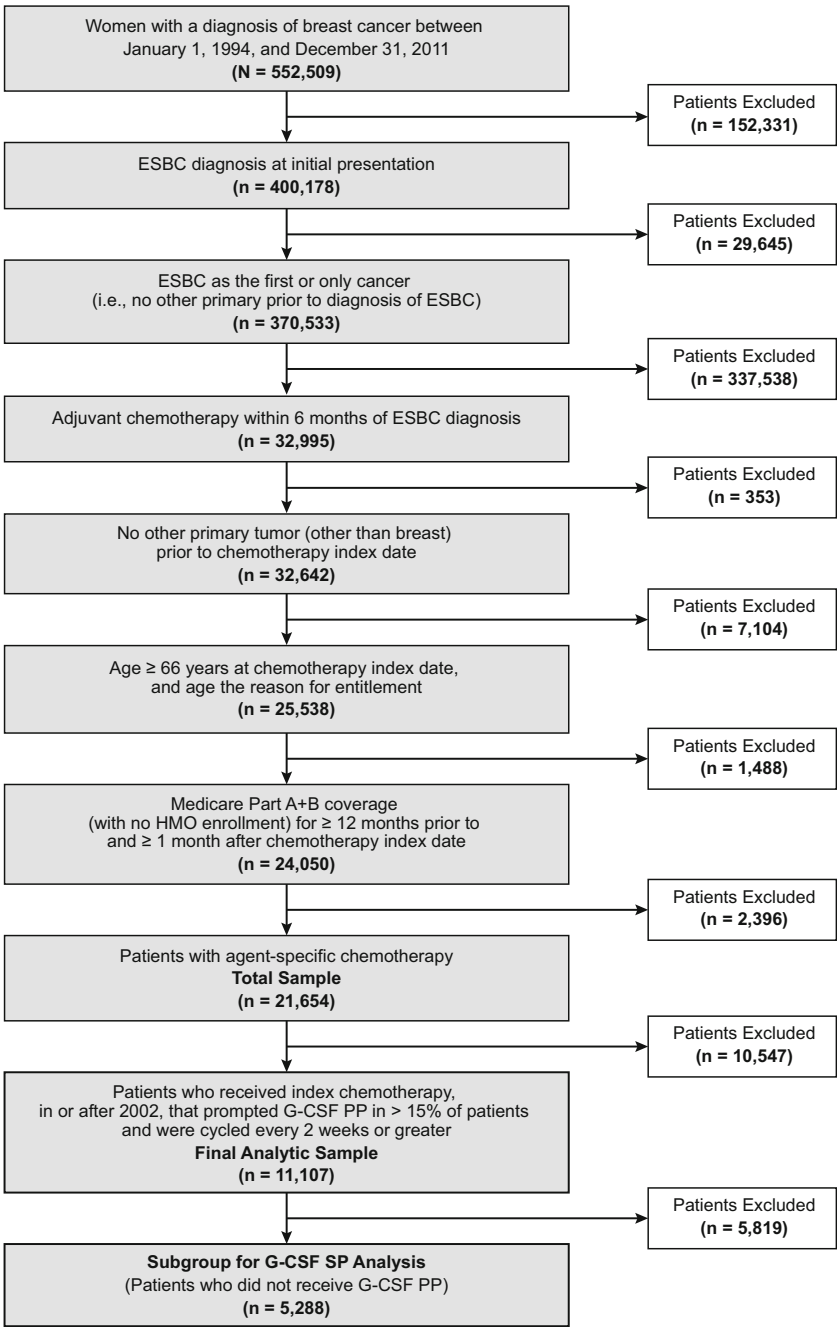

Fig. 1 Study population attrition flowchart. ESBC early-stage breast cancer, G-CSF granulocyte colony-stimulating factors, HMO health maintenance organization, PP primary prophylaxis, SP secondary prophylaxis

(Supplemental Fig. S2 (online only)). Of all patients, only about half received G-CSF PP in the first cycle (n = 5819 [52%]) (Table 3). Of 5288 patients who did not receive G-CSF PP, only 5% received G-CSF SP. Nearly 9% of patients in the overall population received G-CSF in the first cycle and 20% in the second/subsequent cycles for nonprophylactic reasons (reactive or therapeutic).

Adjusted, calendar-year-specific estimates

The adjusted proportion of patients receiving G-CSF PP increased from 6% (95% CI = 4.9–8.2%) in 2002 to 71% (95% CI = 64.9–76.8%) in 2012 (Fig. 2). Trends in the utilization of G-CSF PP across the three regimen classes (Supplemental Fig. S3) were similar to the trend for the overall study population (Fig. 2). The calendar-year-specific adjusted risk of FN in the first cycle for the overall population increased from 2.0% (95% CI = 1.3–3.1%) to 3.0% (95% CI = 1.7–5.2%) during the study. Among those receiving G-CSF PP, the adjusted risk of FN increased from 1.5 to 2.9% from 2002 to 2012 (Fig. 3). Among those not receiving G-CSF PP, the adjusted risk of FN increased from 2.3 to 3.5%. From models stratified by the three regimen classes, the difference in risk of FN between G-CSF PP and no G-CSF PP groups was greatest

Table 2 Frequency of patients with early-stage breast cancer treated with select myelosuppressive chemotherapy regimens, by calendar year

Regimen	Total *N*	Frequency of patients, by calendar year of index chemotherapy[a]										
		2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
AC	3508	625	546	561	445	420	317	190	122	136	120	26
TC	2734	N/A	12	18	N/A	127	311	567	569	536	479	101
AC ➔ T	2540	185	250	339	409	355	331	197	178	121	149	26
TP	872	N/A	N/A	N/A	11	34	101	168	194	160	158	N/A
CAF/FAC	559	160	116	87	66	49	29	25	N/A	N/A	N/A	N/A
A	369	25	49	66	83	64	28	15	N/A	12	15	N/A
TAC	360	N/A	23	29	54	60	57	33	27	23	30	N/A
AT	62	17	N/A	14	N/A	N/A	N/A	N/A	–	N/A	–	N/A
FEC ➔ T	103	–	–	N/A	17	N/A	N/A	N/A	N/A	N/A	N/A	–
Total	11,107	1037	1010	1123	1102	1133	1194	1214	1122	1008	969	195

For this analysis, we used a broader definition that combines multiple agents represented in a given therapy class (with the exception of FEC ➔ T), and therefore, the acronyms do not necessarily conform to their conventional usage

A anthracycline (doxorubicin or epirubicin), *C* cyclophosphamide, *E* epirubicin, *F* fluorouracil, *P* platinum agent (carboplatin or cisplatin), *N/A* not applicable, *T* taxane (docetaxel or paclitaxel)

[a] In accordance with a requirement of the SEER-Medicare data use agreement, data on categories with cell sizes 1 through 10 are suppressed and indicated as N/A. A number of categories with size > 10 are also suppressed and indicated as N/A where it was possible to derive other frequencies ≤ 10 using the row or column totals

for patients in the "taxane, no anthracycline" class (adjusted proportion [95% CI] = 0.010 [0.003–0.047]) in G-CSF PP group vs. adjusted proportion [95% CI] = 0.049 (0.024–0.098) in no G-CSF PP group (Supplemental Table S2).

The adjusted proportion of patients who received G-CSF SP increased from 2.2% (95% CI = 1.2–4.0%) in 2002 to 5.2% (95% CI = 2.3–11.3%) in 2012. For patients treated with G-CSF SP, the calendar-year-specific adjusted risk of FN in

Table 3 Observed utilization of G-CSF prophylaxis and incidence of febrile neutropenia, by calendar year, among patients with early-stage breast cancer treated with select myelosuppressive chemotherapy regimens

Year of index chemotherapy date	Patients treated with chemotherapy[a]		G-CSF PP		G-CSF SP		FN in cycle 1						FN in cycle 2+	
	Overall		Overall		Overall		Overall		G-CSF PP		No G-CSF PP			
	N	Col %	*N*	Row %	*N*[b]	Row %	*N*	Row %	*N*[b]	Row %	*N*[b]	Row %	*N*[b]	Row %
2002	1037	9.3%	65	6.3%	28	2.7%	49	8.6%	N/A	N/A	N/A	N/A	77	7.4%
2003	1010	9.1%	193	19.1%	38	3.8%	57	7.2%	N/A	N/A	N/A	N/A	74	7.3%
2004	1123	10.1%	531	47.3%	38	3.4%	65	6.3%	27	4.5%	38	3.8%	46	4.1%
2005	1102	9.9%	642	58.3%	17	1.5%	47	4.6%	28	4.0%	19	2.3%	35	3.2%
2006	1133	10.2%	701	61.9%	25	2.2%	52	4.9%	19	2.5%	33	4.3%	34	3.0%
2007	1194	10.8%	757	63.4%	25	2.1%	76	7.1%	45	5.6%	31	4.5%	33	2.8%
2008	1214	10.9%	775	63.8%	24	2.0%	73	6.8%	41	5.0%	32	4.8%	41	3.4%
2009	1122	10.1%	701	62.5%	29	2.6%	71	7.2%	32	4.3%	39	6.2%	30	2.7%
2010	1008	9.1%	649	64.4%	27	2.7%	53	6.0%	20	2.9%	33	6.3%	28	2.8%
2011	969	8.7%	672	69.4%	22	2.3%	72	8.0%	41	5.8%	31	7.1%	22	2.3%
2012	195	1.8%	133	68.2%	N/A	N/A	13	7.0%	N/A	N/A	N/A	N/A	N/A	N/A

FN febrile neutropenia, *G-CSF* granulocyte colony-stimulating factor, *N/A* not applicable, *PP* primary prophylaxis, *SP* secondary prophylaxis

[a] Includes index chemotherapy regimens, initiated in or after 2002, that prompted G-CSF PP in > 15% of patients and were cycled every 2 weeks or greater

[b] In accordance with a requirement of the SEER-Medicare data use agreement, data on categories with cell size 1 through 10 are suppressed and indicated as N/A. A number of categories with size > 10 are also suppressed and indicated as N/A where it was possible to derive other frequencies ≤ 10 using the row totals

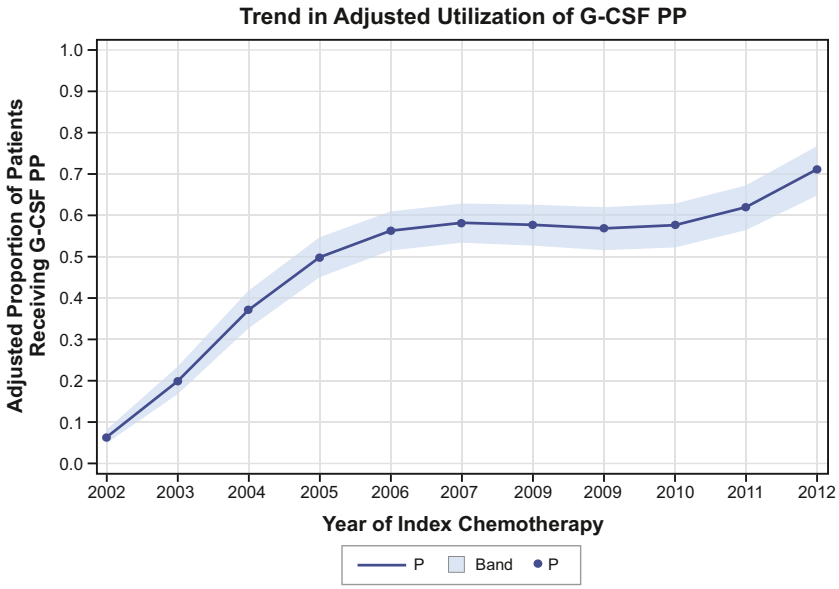

Fig. 2 Trend in adjusted utilization of G-CSF primary prophylaxis among patients with early-stage breast cancer treated with select myelosuppressive chemotherapy regimens. G-CSF granulocyte colony-stimulating factor, NCICI National Cancer Institute's Combined Index, P adjusted proportion, PP primary prophylaxis. Adjusted proportions were derived for the patients with ESBC with the following characteristics: white, age group 75–84 years, residing in big metropolitan area, stage II, tumor size 2–5 cm, grade III, chemotherapy regimen AC ➔ T, regimen cycled every 3 weeks, no baseline comorbid conditions as included in the NCICI, and no recent history of the following—radiation, chemotherapy, infection, antibiotic use, sargramostim use, hypertension, poor renal function, liver dysfunction, chronic lung disease, osteoarthritis, rheumatoid disease, hospitalization, skilled nursing facility admission, use of wheelchair, oxygen, walking aid, and hospital bed

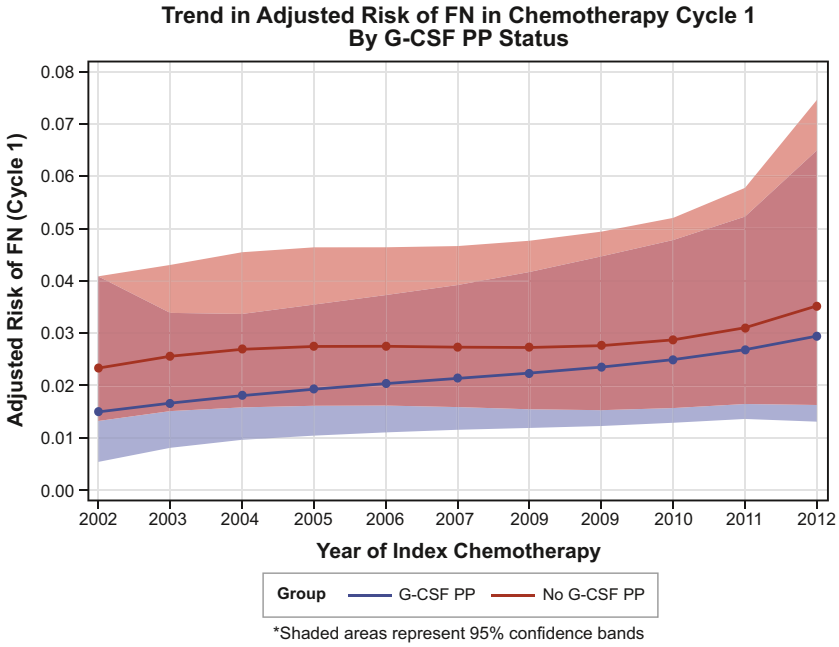

Fig. 3 Trend in adjusted risk of febrile neutropenia in cycle 1 among patients with early-stage breast cancer treated with select myelosuppressive chemotherapy regimens, by G-CSF primary prophylaxis status. G-CSF granulocyte colony-stimulating factor, NCICI National Cancer Institute's Combined Index, P adjusted proportion, PP primary prophylaxis. Adjusted proportions were derived for the patients with ESBC with the following characteristics: white, age group 75–84 years, residing in big metro area, stage II, tumor size 2–5 cm, grade III, chemotherapy regimen AC ➔ T, regimen cycled every 3 weeks, no baseline comorbid conditions as included in the NCICI, and no recent history of the following—radiation, chemotherapy, infection, antibiotic use, sargramostim use, hypertension, poor renal function, liver dysfunction, chronic lung disease, osteoarthritis, rheumatoid disease, hospitalization, skilled nursing facility admission, use of wheelchair, oxygen, walking aid, and hospital bed

the second/subsequent cycles did not change meaningfully as it varied from 6.2% (95% CI = 3.9–9.7%) in 2002 to 5.8% (95% CI = 2.8–11.6%) in 2012.

Discussion

We found a substantial increase in the use of G-CSF PP during the period 2002 through 2012, especially during the first few years. The increasing proportion of patients receiving G-CSF may be related to the changes in guidelines and the introduction of pegfilgrastim in 2002, which offered a more convenient, fixed-dose alternative to filgrastim. We controlled for the chemotherapy regimen in our modeling to limit confounding by the degree of myelosuppression associated with specific regimens. Nevertheless, some of the observed increasing trend in use of G-CSF may reflect a residual trend of increasing myelosuppressiveness of the regimens used during later study years.

No similar rapidly increasing trend in G-CSF use was observed for SP. The adjusted utilization of G-CSF SP increased only modestly, from approximately 2% in 2002 to 5% in 2012. The low observed utilization of G-CSF SP may be related to a stringent definition of secondary prophylaxis in this study requiring evidence of an episode of FN in the immediately preceding cycle. In practice, a low neutrophil nadir in a preceding cycle may prompt SP even if no FN event occurred, but since neutrophil counts are not available in SEER-Medicare data, we were unable to explore the use of such an alternative definition of G-CSF SP. In an exploratory analysis, we observed that a substantial proportion of patients received G-CSF for other (reactive or therapeutic) reasons, which is inconsistent with guideline recommendations. The proportion observed in this study is lower than those reported in some previous studies [33, 34]. The reactive or therapeutic utilization of G-CSF in the present study decreased from 2002 to 2012 (data not presented), which is probably related, at least in part, to the increasing trend in the use of G-CSF PP.

Despite substantially increasing use of G-CSF PP, the adjusted, calendar-year-specific risk of FN in the first cycle also increased over time (from 1.5% in 2002 to nearly 3% in 2012). These findings, which may appear to be contradictory, could be related to an increasing trend in the myelosuppressiveness of chemotherapy regimens. Increased use of the "taxane, no anthracycline" regimen class, which we found is associated with substantially higher risk of FN (in the absence of G-CSF PP than the other two regimen classes [see Supplemental Fig. S4] (online only)), may contribute to the upward slope of the G-CSF PP use curve during later years of the study. Increased use of "taxane, no anthracycline" occurred largely after 2006, when results of a phase 3 trial in women with ESBC were reported indicating that adjuvant treatment with docetaxel/cyclophosphamide resulted in improved disease-free survival compared with doxorubicin/cyclophosphamide [35]. Also, the relative decline in use of anthracycline-containing regimens during later years of the study is likely related to physicians' preference to avoid cardiac toxicity when alternative, more effective regimens became available.

It is possible that there is residual confounding in the adjusted estimates of FN risk even though the use of various chemotherapy regimens was controlled in our analyses. We did not attempt more elaborate adjustment of the model for FN risk based on the doses of chemotherapy agents actually administered, and it is possible that the risk for a patient developing FN was not fully predicted by the variables we included as covariates. Nevertheless, our finding that the adjusted risk of FN in the first cycle tended to be lower among patients who received G-CSF PP than among those who did not is consistent with the findings from clinical trials reporting a lower proportion of patients experiencing FN in the G-CSF group versus the group with no G-CSF [13–15].

The findings of this study should be interpreted in the context of limitations. First, several study measures were defined using diagnosis and procedure codes available in the claims data, and coding inaccuracy and the absence of specific billing codes may introduce some misclassification, which is likely to dampen the magnitude of observed associations. Second, confounding by indication is an inherent limitation of such studies because patients with high risk of FN are more likely to receive G-CSF prophylactically; we were not able to assess the baseline level of risk for developing FN, and hence, concordance with the guideline recommendations for use of G-CSF. Furthermore, we could not analyze the dosing of the G-CSF agent and whether the timing and duration of G-CSF use was suboptimal. We did adjust for chemotherapy regimens by taking into account the drugs administered and the cycle length. The comparatively small number of patients included in calendar year 2012 is related to the small proportion of patients whose ESBC was diagnosed late in 2011 and the occurrence of their subsequent date of chemotherapy initiation in the calendar year 2012. While we do not consider the smaller number of patients for this year to be a major issue, some bias may be present if the reduced number of patients is not simply an artifact of the data cutoff but is instead related to changes in G-CSF utilization or FN risk. We also conducted sensitivity analyses (for the different endpoints) by leaving out 2012 data, and the results were not substantially different from the main analyses (results not presented). Finally, our study population is restricted to women aged > 65, who were enrolled in the US Medicare program; these findings may or may not apply to women aged < 65 with ESBC.

In conclusion, we found that the use of G-CSF PP increased substantially from 2002 to 2012 in patients with ESBC. This increase may reflect the introduction of a single-administration agent, pegfilgrastim, in 2002, as well as changes in treatment guidelines for G-CSF PP and breast

cancer adjuvant therapy, including an increased utilization of taxane-based, nonanthracycline-containing regimens that are more myelotoxic than older regimens. We also observed a smaller increasing trend in the utilization of G-CSF SP. Finally, we found that the risk of FN increased during the study period. Nevertheless, despite expected channeling of higher-risk patients to treatment with G-CSF PP, the adjusted risk of FN in the first cycle among patients receiving G-CSF PP tended to be lower than among those not receiving G-CSF PP.

Compliance with ethical standards

Conflict of interest RKG, KJR, SDC, and JAK are employees of RTI Health Solutions. RTI Health Solutions is a unit of RTI International, an independent, nonprofit, research organization that does work for government agencies and private companies. ST is an employee of and shareholder in Amgen Inc.

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