


Myelodysplastic syndrome and acute myeloid leukemia following adjuvant chemotherapy with and without granulocyte colony-stimulating factors for breast cancer

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Abstract Risk of myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) post-breast cancer treatment with adjuvant chemotherapy and granulocyte colony-stimulating factors (G-CSF) is not fully characterized. Our objective was to estimate MDS/AML risk associated with specific breast cancer treatments. We conducted a retrospective cohort study of women aged ≥ 66 years with stage I–III breast cancer between 2001 and 2009 using the Surveillance, Epidemiology, and End Results-Medicare database. Women were classified as receiving treatment with radiation, chemotherapy, and/or G-CSF. We used multivariable Cox proportional hazards models to estimate adjusted hazard ratios (HR) and 95 % confidence intervals (CI) for MDS/AML risk. Among 56,251 breast cancer cases, 1.2 % developed MDS/AML during median follow-up of 3.2 years. 47.1 % of women received radiation and 14.3 % received chemotherapy. Compared to breast cancer cases treated with surgery alone, those treated with chemotherapy (HR = 1.38, 95 %-CI 0.98–1.93) and

chemotherapy/radiation (HR = 1.77, 95 %-CI 1.25–2.51) had increased risk of MDS/AML, but not radiation alone (HR = 1.08, 95 % CI 0.86–1.36). Among chemotherapy regimens and G-CSF, MDS/AML risk was differentially associated with anthracycline/cyclophosphamide-containing regimens (HR = 1.86, 95 %-CI 1.33–2.61) and filgrastim (HR = 1.47, 95 %-CI 1.05–2.06), but not pegfilgrastim (HR = 1.10, 95 %-CI 0.73–1.66). We observed increased MDS/AML risk among older breast cancer survivors treated with anthracycline/cyclophosphamide chemotherapy that was enhanced by G-CSF. Although small, this risk warrants consideration when determining adjuvant chemotherapy and neutropenia prophylaxis for breast cancer patients.

Keywords Breast cancer · Myelodysplastic syndrome · Acute myeloid leukemia · Adjuvant chemotherapy · Granulocyte colony-stimulating factors

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Introduction

Myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) following cancer treatment with cytotoxic therapy with radiation and chemotherapy account for approximately 10–20 % of all cases of MDS/AML [1]. The clinical course of these cases is typically aggressive with worse prognostic features and survival compared to de novo MDS/AML [2]. Given the growing population of breast cancer survivors successfully treated with radiation and chemotherapy, uncommon but lethal iatrogenic MDS and AML (MDS/AML) are important concerns for oncologists and their patients [3].

Several studies report increased risk of MDS/AML in breast cancer patients after treatment with radiation and

adjuvant chemotherapy [4–8]. For some commonly used classes of breast cancer chemotherapy agents such as alkylating agents (i.e., cyclophosphamide) and anthracyclines (i.e., doxorubicin and epirubicin), an increased incidence of treatment-related leukemia with multiple signature chromosomal abnormalities has been observed [9, 10].

Another possible association with increased MDS/AML risk in breast cancer patients has been reported for granulocyte colony-stimulating factors (G-CSF) as prophylactic treatment following adjuvant chemotherapy [11–13]. G-CSF stimulates proliferation and differentiation of white blood cells and is used to prevent chemotherapy-induced neutropenia [14–17]. While G-CSF reduces the need for treatment delays or dose reductions, the anti-apoptotic effects of G-CSF could potentially spare some lineage-specific mutant stem cells resulting from cytotoxic therapy and permit survival in subsets of mature myeloid cells with chromosomal alterations [18]. Prior population-based studies of G-CSF use with adjuvant chemotherapy and MDS/AML risk among older women in the Surveillance, Epidemiology, and End Results (SEER)-Medicare linked database show mixed results with increased risk of MDS/AML reported in one study [12] and no association with risk of AML in another [4]. In the Cancer and Leukemia Group B 9741 phase III trial [19], patients randomized to dose-dense chemotherapy with filgrastim support had no increased risk of developing MDS/AML, but in a review of randomized clinical trials by Lyman et al. [13], chemotherapy patients treated with G-CSF had a doubling in risk of MDS/AML post-treatment.

Secondary treatment-related myeloid cancers are rare, and the overall number of cases following breast cancer is low. However, consideration of MDS/AML risk post-breast cancer treatment may be important for subgroups of patients susceptible due to age [20] and/or use of potentially leukemogenic therapies [21]. Our purpose is to evaluate current MDS/AML risk among women treated for invasive breast cancer in the SEER-Medicare linked database between 2001 and 2009, a period in which MDS became a reportable disease, new treatment regimens became standard and use of G-CSF increased [14, 15, 22].

Patients and methods

Study population

The SEER-Medicare database was developed by the National Cancer Institute and the Centers for Medicare and Medicaid Services. It contains information on more than 94 % of Medicare enrollees diagnosed with cancer in the SEER 18 reporting regions [23]. This includes

demographic information, clinical data, health care use and enrollment, provider claims and information on survival and development of multiple primary cancers. Extensive details of this data source are described elsewhere [24].

We conducted a retrospective cohort study of women aged ≥ 66 years diagnosed with invasive, American Joint Committee on Cancer (AJCC) [25] stage I–III breast cancer between January 2001 and December 2009. To minimize bias due to unobserved claims, the study population was restricted to women who were continuously enrolled in Medicare Part A and Part B 12 months prior to breast cancer diagnosis and through 12 months post-diagnosis of primary breast cancer. For our analysis, we excluded women if they had any of the following characteristics: breast cancer not first primary cancer; breast cancer diagnosis made at autopsy or death certificate; AJCC tumor stage 0 (in situ) or stage IV (metastatic); and unknown stage. We also excluded women enrolled in Medicare based on end-stage renal disease, those under age 65 with disability and those for whom Medicare was not primary payer (e.g., enrolled in a health maintenance organization).

A final analytic cohort of 56,251 women was included in the study (Supplemental Figure S1) after further excluding women who experienced the following either before 1 year post-breast cancer diagnosis or 120 days post last cancer-directed surgery, radiation, or chemotherapy: MDS/AML diagnosis ($n = 756$), other second primary cancer diagnosis ($n = 3504$) or death ($n = 3263$) [26]. This study was approved by the institutional review board of the Fred Hutchinson Cancer Research Center in November 2013.

Data sources

SEER-Medicare files used for this analysis included the patient entitlement and diagnosis summary file (PEDSF); medicare provider analysis and review (MEDPAR); carrier claims (NCH); outpatient (OUTPT); and durable medical equipment (DME).

SEER–PEDSF was the primary source of information for the incident primary breast cancer including diagnosis year, AJCC stage, lymph node status, hormone receptor status, tumor size and radiation treatment. Data on ICD-9 diagnostic codes and procedure claims in the Medicare inpatient and outpatient files were also used to calculate Charlson comorbidity index [27] scores adapted by Klabunde et al. [28] to adjust for baseline differences in comorbidity between groups in multivariable analyses.

Exposures

To identify treatment-related claims, we reviewed NCH, OUTPT, and DME files [29]. Chemotherapy exposure was identified from the Medicare files using ICD-9-CM

Procedural and current procedural terminology (CPT) healthcare common procedure coding system (HCPCS) codes from provider claims and revenue centers [24]. Exposure was defined as 2 or more HCPCS/CPT codes for a given chemotherapeutic agent within 12 months of diagnosis. We identified patients who received any chemotherapy (yes/no) and also collected information on specific chemotherapy agents which are grouped as follows: alkylating agents, antimetabolites, anthracyclines, platinum agents, taxanes, HER2-targeted chemotherapy (i.e., trastuzumab) and ‘other.’ We identified G-CSF use by specific agent (filgrastim or pegfilgrastim) from the same claims data.

Outcomes

SEER records on multiple primary cancers were our gold standard for the occurrence of second primary cancers, including MDS and AML. Considering that MDS is newly reportable to SEER registries [30] and the tendency toward under-ascertainment or under-reporting of MDS cases [31], we adapted an algorithm for identifying cases from SEER-Medicare using 2 or more ICD-9-CM claims to identify incident MDS and AML cases. Date of incident MDS/AML was defined as the earlier of 2 or more ICD-9-CM claims within 12 months of each other for MDS or AML; or date of SEER-reported second primary MDS/AML.

Statistical analysis

Women were followed from one year prior to breast cancer diagnosis until MDS/AML diagnosis, development of a second cancer, relapse with this cancer, death or end of study period on December 31, 2011. To differentiate the effects of first-line treatment and treatment for disease progression or breast cancer recurrence, women were censored at the time of relapse chemotherapy. Relapse/second-line chemotherapy treatment was defined as chemotherapy claims that occurred after a gap of 120 days or more following previous treatment.

Cox proportional hazards models were used to evaluate the association between breast cancer treatments and risk of MDS/AML. We estimated hazard ratios (HR) and 95 % confidence intervals (CI) while adjusting for potential confounders. We modeled time from the incident breast cancer diagnosis with a delayed entry (at risk time) at 1 year post-diagnosis or 120 days after the last of surgery, radiation, or chemotherapy (whichever was later). Women were considered at risk in the analysis until the earliest of MDS or AML diagnosis, end of the study period, or competing events including death, relapse chemotherapy and other second primary cancers. We tested hypotheses comparing: (i) women who received surgery/radiation,

surgery/chemotherapy and surgery/radiation/chemotherapy to surgery only patients; (ii) specific chemotherapy regimen patients to no chemotherapy patients; and (iii) among those who received chemotherapy, we compared G-CSF receipt yes/no, filgrastim yes/no and pegfilgrastim yes/no.

We examined associations in multivariable models including adjustment for: SEER registry; year of diagnosis; age at diagnosis (66–70, 71–75, 76–80, 81–85, 86+ years); AJCC stage (I, II, III); race (White, Black, Other, unknown); ethnicity (Non-Hispanic, Hispanic, unknown); hormone receptor status (ER-positive or PR-positive, ER/PR-negative, unknown); lymph node status (positive, negative, unknown); surgical procedure (mastectomy, breast-conserving surgery, surgery NOS); and Charlson score at diagnosis (0, 1, 2+).

We tested for interaction between the exposures of interest and the logarithm of follow-up time to evaluate proportional hazards assumptions. There was no evidence of violation of the proportionality assumption. All analyses were performed using SAS statistical software version 9.3 (SAS Institute Inc., Cary, North Carolina).

We performed additional analysis of risk among patients receiving specific adjuvant chemotherapy regimens (all AC-containing regimens, TC, CF or CMF and ‘other’) ($n = 8050$) stratified by G-CSF receipt (yes/no) and by filgrastim and pegfilgrastim to account for potential confounding by indication present with the administration of G-CSF in more neutropenia-inducing adjuvant chemotherapy regimens (>20 % risk) [15]. We also evaluated dose differences by comparing receipt of 1–5 and 6 or more doses of filgrastim or pegfilgrastim to none.

Results

Characteristics of the 56,251 incident stage I–III breast cancer patients included in our study are shown in Table 1. Median age was 75 years at breast cancer diagnosis and most were Non-Hispanic White (87 %) with Charlson comorbidity scores ≥ 1 (84 %). The majority of incident breast cancer was stage I (57 %) or stage II (34 %), lymph node-negative (74 %), estrogen/progesterone receptor positive (79 %), and treated with breast-conserving surgery (59 %).

The majority of breast cancer patients were treated with surgery only (46 %), with 40 % receiving surgery/radiation, 7 % surgery/chemotherapy and 7 % surgery/radiation/chemotherapy (Table 1). Among women receiving chemotherapy treatment, the most common regimen was anthracycline/cyclophosphamide/taxane (ACT) (28 %). Overall, 46 % of breast cancer patients receiving chemotherapy had AC-containing regimens. The remaining 56 % received taxane/cyclophosphamide (TC) (19 %), cyclophosphamide/fluorouracil +/- methotrexate (CF or

Table 1 Descriptive characteristics of female Medicare beneficiaries diagnosed with incident stage I–III breast cancer between 2001 and 2009 by subsequent primary MDS/AML status

	No MDS/AML (<i>n</i> = 55,596)	MDS/AML (<i>n</i> = 655)	<i>P</i> value ^a	All women (<i>N</i> = 56,251)
Age (years) at breast cancer diagnosis				
Median (interquartile range)	75 (70–81)	74 (70–80)	0.923	75 (70–81)
66–70	16,032 (28.8)	183 (27.9)	0.112	16,215 (28.8)
71–75	13,569 (24.4)	164 (25.0)		13,733 (24.4)
76–80	11,990 (21.6)	157 (24.0)		12,147 (21.6)
81–85	8628 (15.5)	96 (14.7)		8724 (15.5)
86–95	5377 (9.7)	55 (8.4)		5432 (9.7)
Race				
White	48,715 (87.6)	565 (86.3)	0.011	49,280 (87.6)
Black	4526 (8.1)	73 (11.1)		4599 (8.2)
Other ^b	2182 (3.9)	14 (2.0)		2196 (3.7)
Unknown				176
Hispanic ethnicity				
No	52,911 (95.2)	628 (95.9)	0.401	53,539 (95.2)
Yes	2685 (4.8)	27 (4.1)		2712 (4.8)
AJCC Stage				
I	31,858 (57.3)	307 (46.9)	<0.001	32,165 (57.2)
II	18,847 (33.9)	264 (40.3)		19,111 (34.0)
III	4891 (8.8)	84 (12.8)		4975 (8.8)
Lymph node status				
Negative	41,215 (74.1)	430 (65.6)	<0.001	41,645 (74.0)
Positive	14,040 (25.3)	220 (33.6)		14,260 (25.4)
Unknown				346
Hormone receptor status				
ER+ or PR+	43,829 (73.8)	469 (71.6)	<0.001	44,298 (78.8)
ER–/PR–	7523 (13.5)	121 (18.5)		7644 (13.6)
Unknown				4309 (7.7)
Charlson comorbidity index				
0	21,169 (38.1)	223 (34.0)	<0.001	21,392 (38.0)
1	22,611 (40.7)	287 (43.8)		22,898 (40.7)
2+	8162 (14.7)	141 (21.5)		8303 (14.8)
Missing				3658
Surgical procedure				
Mastectomy (including radical)	22,523 (40.5)	294 (44.9)	0.067	22,817 (40.6)
Breast-conserving	33,020 (59.4)	360 (55.0)		33,380 (59.3)
Unknown				54
Combined radiation and chemotherapy				
None	25,300 (45.5)	249 (38.0)	<0.001	25,549 (45.4)
Radiation only	22,422 (40.3)	230 (35.1)		22,652 (40.3)
Chemotherapy only	4138 (7.4)	83 (12.7)		4221 (7.5)
Radiation and chemotherapy	3736 (6.7)	93 (14.2)		3829 (6.8)
Chemotherapy type ^c				
Any chemotherapy	7874 (14.2)	176 (26.9)	<0.001	8050 (14.3)
All AC-containing regimens	3592 (45.6)	94 (53.4)		3686 (45.8)
AC	1180 (15.0)	37 (21.0)	<0.001	1217 (15.1)
ACT	2210 (28.1)	50 (28.4)		2260 (28.1)
TC	1473 (18.7)	18 (10.2)		1491 (18.5)
CF or CMF	1059 (13.4)	27 (15.3)		1086 (13.5)

Table 1 continued

	No MDS/AML (<i>n</i> = 55,596)	MDS/AML (<i>n</i> = 655)	<i>P</i> value ^a	All women (<i>N</i> = 56,251)
Other/non-standard ^d	1750 (22.2)	37 (21.0)		1787 (22.2)
Granulocyte colony-stimulating factors (G-CSF)				
None	3115 (5.6)	68 (10.4)	<0.001	3183 (5.7)
Yes (any) ^e	4759 (8.6)	108 (16.5)		4867 (8.7)
Filgrastim	1807 (38.0)	58 (53.7)	<0.001	1865 (23.2)
Pegfilgrastim	3491 (73.4)	63 (58.3)	<0.001	3554 (44.1)
Number of G-CSF doses				
1–5	2302 (48.4)	43 (39.8)	<0.001	2345 (29.1)
6+	2457 (51.6)	65 (60.2)		2522 (31.3)
Person-years of follow-up				
Median (interquartile range)	3.2 (2.1–5.3)	4.3 (2.7–6.7)	<0.001	3.2 (2.1–5.3)

MDS myelodysplastic syndrome, AML acute myeloid leukemia

^a To test for differences of characteristics between the 2 groups, we used χ^2 test for categorical variables and Wilcoxon rank-sum test for medians

^b Other ethnicity includes Asian/Pacific Islander, American Indian, and Alaskan Native

^c Chemotherapy agents: *A* anthracyclines (doxorubicin or epirubicin); *C* cyclophosphamide; *T* taxanes (docetaxel or paclitaxel); *F* fluorouracil; *M* methotrexate; chemotherapy regimens listed are mutually exclusive groups with or without trastuzumab; AC-containing regimens = AC, ACT, FAC

^d Other/non-standard = single-agent therapy or one of the regimens listed above and vinca alkaloids (vincristine, vinorelbine, or vinblastine), etoposide, bevacizumab, or azacitidine together or in combination

^e Use of G-CSF products not mutually exclusive

Table 2 MDS/AML cases and use of G-CSF products among female Medicare beneficiaries diagnosed with incident stage I–III breast cancer between 2001 and 2009 by chemotherapy regimen^a

	Any chemotherapy regimen <i>n</i> = 8050	All AC-containing regimens ^b <i>n</i> = 3686 (45.8 %)	TC <i>n</i> = 1491 (18.5 %)	CF or CMF <i>n</i> = 1086 (13.5 %)	Other ^c <i>n</i> = 1787 (22.2 %)
MDS/AMS cases	176 (2.2)	94 (2.6)	18 (1.2)	27 (2.5)	37 (2.1)
Any G-CSF ^d	4835 (60.1)	2552 (69.2)	1137 (76.3)	422 (38.9)	756 (42.3)
Filgrastim	1865 (23.2)	1025 (27.8)	276 (18.5)	263 (24.2)	301 (16.8)
Pegfilgrastim	3554 (44.1)	1865 (50.6)	960 (64.4)	192 (17.7)	537 (30.1)

^a Chemotherapy agents: *A* anthracyclines (doxorubicin or epirubicin); *C* cyclophosphamide; *T* taxanes (docetaxel or paclitaxel); *F* fluorouracil; *M* methotrexate; chemotherapy regimens listed are mutually exclusive groups with or without trastuzumab

^b AC-containing regimens = AC, ACT, FAC

^c Other/non-standard = single-agent therapy or one of the regimens listed above and vinca alkaloids (vincristine, vinorelbine, or vinblastine), etoposide, bevacizumab, or azacitidine together or in combination

^d Use of G-CSF products not mutually exclusive

CMF) (13.5 %) and other/non-standard regimens (22 %). Other non-standard regimens were single-agent therapies or one of the other listed regimens with vinca alkaloids, etoposide, bevacizumab, or azacitidine together or in combination. Sixty percent of those treated with chemotherapy received G-CSF treatment with 23 % receiving filgrastim and 44 % receiving pegfilgrastim (Table 2). Treatment with G-CSF varied by adjuvant chemotherapy regimen with TC regimen most often accompanied by G-CSF treatment (79 %) followed by the AC regimens (69 %).

Median follow-up was 3 years (interquartile range 2–7) and varied by diagnosis date with women diagnosed during the earlier study years having the longest follow-up: median 8 years for women diagnosed in 2001–2003, 6 years for 2004–2006, and 3 years for 2007–2009. Among the women in our study, 655 (1.2 %) developed MDS/AML (*n* = 515 MDS and *n* = 140 AML), including 38 MDS cases that were later diagnosed with AML. Age-adjusted cumulative hazards of MDS/AML are shown in Fig. 1. MDS/AML incidence varied by index breast cancer treatment; 2.4 % of women treated with surgery/radiation/

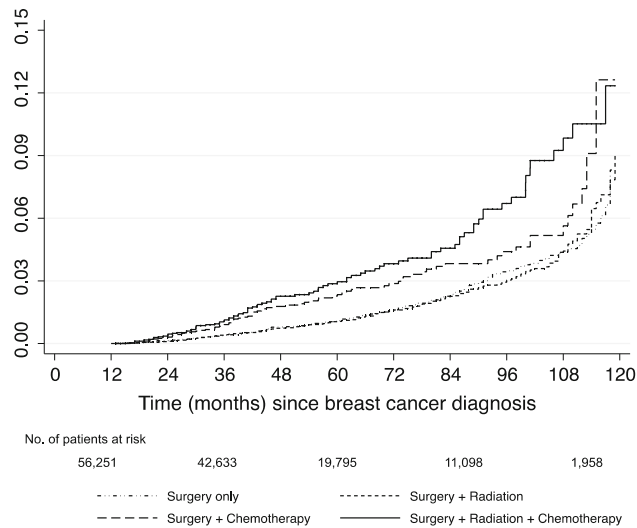


Fig. 1 Cumulative hazard of MDS/AML among female Medicare beneficiaries diagnosed with incident stage I–III breast cancer between 2001 and 2009 by initial breast cancer treatment

chemotherapy and 1.0 % of women treated with surgery only were diagnosed with MDS/AML during follow-up. Breast cancer patients with subsequent MDS/AML diagnosis were more likely to have breast cancer that was stage II or III, lymph node-positive, ER-negative/PR-negative, higher Charlson score and treated with chemotherapy and G-CSF (Table 1).

In analyses from multivariable Cox models, we observed a significant association between treatment with chemotherapy and risk of MDS/AML (Fig. 2). Compared to women who received surgery only, women who received chemotherapy (HR = 1.38, 95 % CI 0.98–1.93) and chemotherapy/radiation (HR = 1.77, 95 % CI 1.25–2.51) had increased MDS/AML risk. Risk was not significantly elevated among surgery/radiation only patients. Compared to women not treated with chemotherapy, women who received anthracycline/cyclophosphamide-containing regimens had higher risk of MDS/AML (HR = 1.86, 95 % CI 1.33–2.61). Patients in the other adjuvant chemotherapy

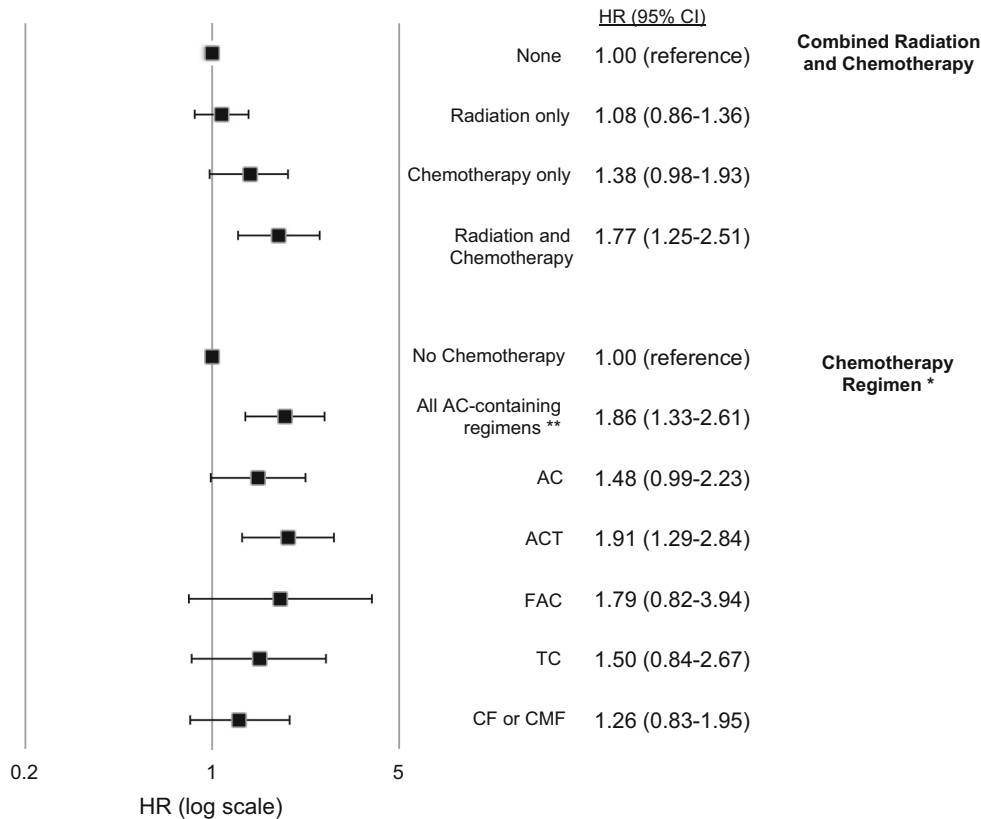


Fig. 2 Risk of MDS/AML among female Medicare beneficiaries diagnosed with incident stage I–III breast cancer between 2001 and 2009 in relation to primary breast cancer initial treatment and to chemotherapy regimen. Abbreviations: *MDS* myelodysplastic syndrome; *AML* acute myeloid leukemia; *HR* hazard ratio; *CI* confidence interval. Chemotherapy agents: *A* anthracyclines (doxorubicin or epirubicin); *C* cyclophosphamide; *T* taxanes (docetaxel or paclitaxel); *F* fluorouracil; *M* methotrexate. *Note* all hazard ratios are adjusted for age at diagnosis (66–70, 71–75, 76–80, 81–85, 86–95 years);

diagnosis year; race (White, Black, other, unknown); Hispanic ethnicity (yes, no, unknown); AJCC stage (I, II, III); hormone receptor status (ER-positive or PR-positive, ER-negative/PR-negative, unknown); surgical procedure (mastectomy, breast-conserving surgery, surgery NOS); Charlson comorbidity index score (0, 1, 2+); any granulocyte colony-stimulating factors received (yes/no). *Hazard ratios for chemotherapy regimens (AC, ACT, FAC, TC, CF, or CMF) are from a separate model adjusted for radiation therapy (yes/no). **AC-containing regimens = AC, ACT, FAC

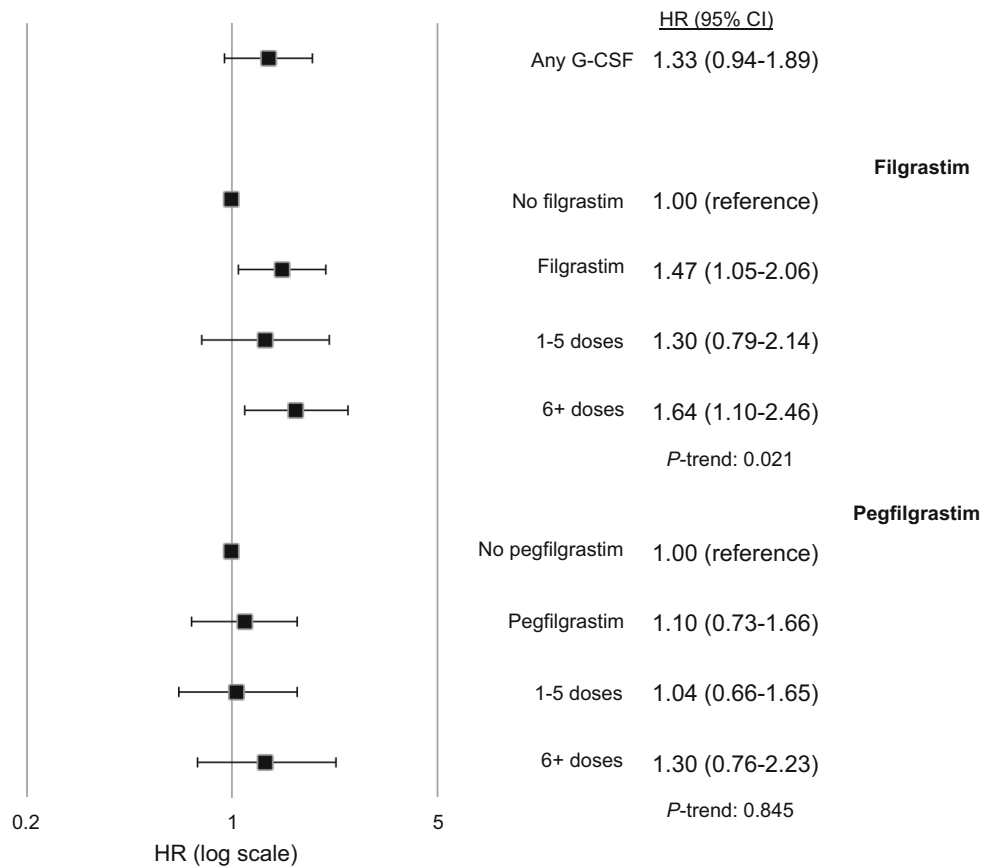


Fig. 3 Risk of MDS/AML among female Medicare beneficiaries diagnosed with incident stage I-III breast cancer between 2001 and 2009 that received chemotherapy in relation to G-CSF treatment. Abbreviations: *MDS* myelodysplastic syndrome; *AML* acute myeloid leukemia; *HR* hazard ratio; *CI* confidence interval; *G-CSF* granulocyte colony-stimulating factors. Note all hazard ratios are adjusted for age at diagnosis (66–70, 71–75, 76–80, 81–85, 86–95 years);

diagnosis year; race (White, Black, other, unknown); Hispanic ethnicity (yes, no, unknown); AJCC stage (I, II, III); hormone receptor status (ER-positive or PR-positive, ER-negative/PR-negative, unknown); surgical procedure (mastectomy, breast-conserving surgery, unknown); radiation (yes/no); Charlson comorbidity index score (0, 1, 2+); chemotherapy regimen received (AC, ACT, FAC, TC, CF or CMF, other)

regimen categories, TC and CF/CMF, did not have significantly increased risk of MDS/AML post-treatment.

G-CSF use increased over time during the study period, with use of pegfilgrastim surpassing filgrastim (Supplemental Figure S2). Adjusted for chemotherapy type, there was a non-significant increased risk of MDS/AML in women who received G-CSF with chemotherapy (HR = 1.33, 95 % CI 0.94–1.89) (Fig. 3). Stratified by G-CSF type, increased risk was observed with filgrastim use (HR = 1.47, 95 % CI 1.05–2.06) which when stratified by dosage was exclusive to the 6+ dose-category (HR = 1.64, 95 % CI 1.10–2.46) (log-linear dose–response trend, *P* = 0.021). Pegfilgrastim use was not associated with increased MDS/AML risk with any use or in dose-stratified analyses.

In analyses of G-CSF use stratified by chemotherapy regimen, we observed a significantly increased risk of MDS/AML post-treatment among AC-containing regimens with any G-CSF treatment (*n* = 2552, HR = 1.78,

95 % CI 1.07–3.02) and AC-containing regimens with filgrastim treatment (*n* = 1025, HR = 2.01, 95 % CI 1.23–3.27) but not with pegfilgrastim treatment (*n* = 1865, HR = 1.20, 95 % CI 0.67–2.15) (Table 2). In additional analyses of the AC-containing regimens with filgrastim treatment by dose (1–5 doses/6+ doses), risk was increased for both categories but only significant for the 6+ filgrastim dose-category (1–5 doses: HR = 1.82, 95 % CI 0.94–3.39; 6+ doses: HR = 2.70, 95 % CI 1.33–5.28, *P*-trend = 0.036). No increased risk was observed among any of the other chemotherapy regimens with G-CSF treatment or with filgrastim or pegfilgrastim individually (Table 3).

In sensitivity analyses, we evaluated changes in our results when criteria were varied for chemotherapy agent exposure by 1+, 2+, or 3+ HCPCS/ CPT codes, and MDS/AML diagnoses identified from Medicare claims (1+ or 2+ ICD-9 codes). Results were not substantively different in these analyses.

Table 3 Risk of MDS/AML in relation to G-CSF treatment among female Medicare beneficiaries diagnosed with incident stage I-III breast cancer between 2001 and 2009 by grouped chemotherapy regimens^a

	AC-containing regimens ^b N = 3686 n = 94 MDS/AML cases		TC N = 1491 n = 18 MDS/AML cases		CF or CMF N = 1086 n = 27 MDS/AML cases		Other N = 1787 n = 37 MDS/AML cases	
	HR	(95 % CI)	HR	(95 % CI)	HR	(95 % CI)	HR	(95 % CI)
G-CSF								
None	1.00	(Reference)	1.00	(Reference)	1.00	(Reference)	1.00	(Reference)
Any	1.78	(1.07–3.02)	1.37	(0.74–2.46)	1.05	(0.53–2.04)	0.98	(0.47–1.99)
Filgrastim								
None	1.00	(Reference)	1.00	(Reference)	1.00	(Reference)	1.00	(Reference)
Any	2.11	(1.29–3.30)	1.70	(0.75–3.77)	1.26	(0.59–2.84)	1.00	(0.50–2.17)
1–5 doses	1.82	(0.94–3.39)	2.32	(0.89–6.06)	1.20	(0.42–3.44)	1.05	(0.24–4.52)
6+ doses	2.70	(1.33–5.28)	4.46	(0.93–21.3)	1.45	(0.71–2.95)	1.67	(0.71–3.92)
P-trend	0.036		0.353		0.441		0.650	
Pegfilgrastim								
None	1.00	(Reference)	1.00	(Reference)	1.00	(Reference)	1.00	(Reference)
Any	1.21	(0.68–2.26)	0.80	(0.41–1.51)	0.90	(0.26–3.17)	1.05	(0.48–2.26)
1–5 doses	0.88	(0.39–2.37)	1.68	(0.42–6.73)	0.72	(0.30–1.73)	0.70	(0.15–3.29)
6+ doses	1.88	(0.63–4.96)	1.72	(0.18–15.9)	1.53	(0.65–3.64)	1.39	(0.43–4.55)
P-trend	0.305		0.838		0.286		0.622	

Chemotherapy regimen-specific hazard ratios are adjusted for age at diagnosis (66–70, 71–75, 76–80, 81–85, 86–95 years); diagnosis year; race (White, Black, Other, unknown); Hispanic ethnicity (yes, no, unknown); AJCC stage (I, II, III); hormone receptor status (ER-positive or PR-positive, ER-negative/PR-negative, unknown); surgical procedure (mastectomy, breast-conserving surgery, unknown); radiation (yes/no); Charlson comorbidity score at diagnosis (0, 1, 2+)

MDS myelodysplastic syndrome, AML acute myeloid leukemia, HR hazard ratio, CI confidence interval

^a Chemotherapy agents: A anthracyclines (doxorubicin or epirubicin); C cyclophosphamide; T taxanes (docetaxel or paclitaxel); F fluorouracil; M methotrexate

^b AC-containing regimens = AC, ACT, FAC

Discussion

In a large population-based cohort of older breast cancer patients, we found an association between chemotherapy treatment and increased risk of MDS/AML with evidence that the association may be exclusive to anthracycline/cyclophosphamide-containing regimens. In our analysis of G-CSF use by chemotherapy type and number of doses, we found increased risk of MDS/AML specific to filgrastim use and a possible dose–response effect. The MDS/AML incidence of 2.4 % among women treated with combined radiation and chemotherapy was more than double the incidence observed in women treated with surgery only and may represent a significant issue for elderly breast cancer patients. No significantly increased risk was observed among elderly patients treated with surgery and radiation only.

The absence of significant risk of MDS/AML among surgical patients treated with radiation without chemotherapy runs counter to our previous studies of MDS/AML post-treatment for breast cancer [7, 8]. However, the patients treated with chemotherapy and radiation

had a higher risk than surgical patients treated with chemotherapy and no radiation. This may be due to the restriction of our observations to elderly women only in whom the risk associated with radiation may be less than that of younger women [32].

Our findings of MDS/AML risk associated with chemotherapy align with findings from previous population-based studies [4, 33] and clinical trials [5, 34]. In a prior analysis of older women using SEER-Medicare linked data (1992–2002) [4], adjuvant chemotherapy with alkylating agents and anthracyclines was associated with increased risk of AML, but MDS was not included in the analysis. The absence of association between antimetabolites (i.e., fluorouracil, methotrexate) or taxanes with risk of MDS/AML has been reported previously [4, 35–38].

Concern for leukemogenesis with the use of cytokines has existed for some time [39–43]. In a SEER-Medicare database study of breast cancer cases between 1991 and 1999 [12], increased risk of MDS/AML was observed with use of G-CSF. Another SEER-Medicare study [4] of breast cancer cases from 1992 to 2002 found no increased risk of AML with use of G-CSF in breast cancer treatment, but

MDS was not included in that study. Studies in healthy stem cell donors that receive G-CSF have shown short-term induced DNA instability without increased risk of MDS/AML [44–47]. Patients with congenital chronic neutropenia (CCN) have a high risk of leukemic transformation which may increase with long-term exposure to G-CSF [40, 41, 43]. Touw et al. hypothesized that genomic instability, including G-CSF receptor mutations, is responsible for the high rate of leukemic transformation in CCN patients treated regularly with G-CSF [42]. Slovak et al. [48] conducted a small study of clonal hematopoiesis following neoadjuvant chemotherapy for breast cancer but did not observe changes suggesting MDS/AML development. Our observation of a possible leukemogenic effect of G-CSF may represent leukemogenesis potentiation in hematopoietic cells genetically damaged by chemotherapy.

In the current study, we observed an increased risk of MDS/AML with the use of filgrastim but not pegfilgrastim. During our study period, the pegylated form of recombinant human G-CSF analog filgrastim (i.e., pegfilgrastim) was introduced. G-CSF is administered differentially with pegfilgrastim given as a fixed dose once per chemotherapy cycle and filgrastim administered daily until absolute neutrophil counts increase [14–16]. Pegfilgrastim has different pharmacokinetics than filgrastim but a similar mechanism of action [49, 50].

Strengths of this study include use of a population-based cohort from the SEER-Medicare linked database. As elderly women are rarely included in clinical trials, information on treatment risks and surveillance for rare adverse events like MDS/AML are only answered by large population-based cohort studies like ours.

A limitation of our study is the identification of subsequent diagnoses of MDS and AML based on Medicare claims and SEER data. Concerns with misclassification of MDS/AML outcomes from claims data (ICD-9 codes) are based on the tendency for false-positive MDS/AML when based on a single claim. To minimize possible misclassification, we used a recommended case definition with high specificity [31]. Using SEER as the criterion measure, ascertainment of cases using classification of two or more ICD-9 codes had sensitivity and specificity of 90.1 % and 99.2 %, respectively, for MDS; 89.3 % and 99.7 %, respectively, for AML in our study. We conducted stratified analysis to adjust for the potential confounding effect of simultaneous indication for adjuvant chemotherapy and G-CSF treatment to prevent neutropenia, both with possible leukemogenic effects. The presence of elevated risk in both the adjusted multivariable model and the stratum-specific categories supports our findings.

American Society of Clinical Oncology guidelines recommend G-CSF treatment before adjuvant chemotherapy if a 20 % or greater chance of neutropenia exists [15].

Growth factor products (G-CSF) continue to be among the top 15 drug expenditures in the United States [22]. The benefits of adjuvant chemotherapy made possible with G-CSF outweigh the risk of MDS/AML in patients with high risk of breast cancer relapse [8, 17, 51–54].

It is unclear why a differential risk of MDS/AML between filgrastim and pegfilgrastim was observed. Confirming and understanding possible differences in long-term safety of G-CSF by product are extremely important. Further studies of MDS/AML risk post-breast cancer treatment with G-CSF and adjuvant chemotherapy need to include all age groups to characterize risk attributable to specific therapies and identify patient groups that may be at greater leukemic risk.

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Author Contributions G.S.C., J.A.M., S.M.S., and H.G.K. conceived and designed the study; G.S.C., J.A.M., W.J.L., and S.M.S. collected and assembled the data, developed the algorithms, and performed the statistical analyses; all authors interpreted the results and read and commented on the article.

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Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

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