Acute Myeloid Leukemia or Myelodysplastic Syndrome Following Use of Granulocyte Colony-Stimulating Factors During Breast Cancer Adjuvant Chemotherapy

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Background Recently, increasing numbers of women receiving adjuvant chemotherapy for breast cancer have also received granulocyte colony-stimulating factors (G-CSFs) or granulocyte–macrophage colony-stimulating factors (GM-CSFs). Although these growth factors support chemotherapy, their long-term safety has not been evaluated. We studied the association between G-CSF use and incidence of leukemia in a population-based sample of breast cancer patients.

Methods Among women aged 65 years or older in the Surveillance, Epidemiology, and End Results–Medicare database who were diagnosed with stages I–III breast cancer from January 1, 1991, to December 31, 1999, we identified those who received G-CSF or GM-CSF concurrently with chemotherapy. We used Cox proportional hazards models to estimate hazard ratios for the association of treatment with G-CSF or GM-CSF and subsequent (through December 31, 2003) diagnosis of acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS). All statistical tests were two-sided.

Results Of 5510 women treated with chemotherapy, 906 (16%) received G-CSF or GM-CSF therapy, and 64 (1.16%) were subsequently diagnosed with either MDS or AML before a cancer recurrence. Use of G-CSF and GM-CSF was associated with more recent diagnosis, younger age, urban residence, fewer comorbidities, receipt of radiation therapy, positive lymph nodes, and cyclophosphamide treatment. Of the 906 patients who were treated with G-CSF, 16 (1.77%) developed AML or MDS; of the 4604 patients not treated with G-CSF, 48 (1.04%) developed AML or MDS. The hazard rate ratio for AML or MDS among those treated with G-CSF or GM-CSF compared with those who were not was 2.14 (95% confidence interval [CI] = 1.12 to 4.08). AML or MDS developed within 48 months of breast cancer diagnosis in 1.8% of patients who received G-CSF or GM-CSF but only in 0.7% of patients who did not (hazard ratio = 2.59, 95% CI = 1.30 to 5.15).

Conclusions The use of G-CSF was associated with a doubling in the risk of subsequent AML or MDS among the population that we studied, although the absolute risk remained low. Even if this association is confirmed, the benefits of G-CSF may still outweigh the risks. Meanwhile, however, G-CSF use should not be assumed to be risk free.

J Natl Cancer Inst 2007;99:196–205

A number of cytokines have been used in the past two decades to reduce the complications of neutropenia for patients who receive chemotherapy (1–6). The hematopoietic colony-stimulating factors were approved by the US Food and Drug Administration in 1991 and are increasingly used among breast cancer patients (7). The prophylactic use of granulocyte colony-stimulating factors (G-CSFs) has been shown to reduce the need for chemotherapy dose reductions and delays due to myelosuppression that may limit chemotherapy dose intensity, thereby increasing the potential for prolonged disease-free and overall survival in the curative setting (8). G-CSFs have also been administered to healthy donors who undergo peripheral stem cell mobilization procedures as part of allogeneic peripheral blood transfusions.

In the early years of the use of G-CSFs and granulocyte–macrophage colony-stimulating factors (GM-CSFs) to treat

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See "Notes" following "References."

DOI: 10.1093/jnci/djk028

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malignancies, the possibility was raised that these cytokines might induce acute myeloid leukemia (AML) (9). Chemotherapy given for a specific cancer may induce otherwise lethal mutations in a myeloid stem cell or progenitor cell, but the antiapoptotic effect of G-CSF or GM-CSF saves the mutant cell from destruction, thereby permitting it to develop into a myeloid cancer (10). In addition, it has been shown that de novo DNA synthesis in the white blood cell population of healthy donors increased with G-CSF administration but returned to baseline levels 6 weeks after completion of therapy (11). Using a combined multiparametric cell-scanning system to assess the effects of G-CSF administration to normal donors, Kaplinsky et al. (12) demonstrated that up to 0.6% of myeloid cells, but not purified $CD34^+$ stem progenitor cells, became tetraploid, indicating that G-CSF may induce alterations of chromosomal numbers in small subsets of mature myeloid cells in G-CSF–mobilized normal donors.

In 2003, a study of 412 children treated on two consecutive acute lymphocytic leukemia (ALL) protocols from 1991 to 1998 found that patients who had been treated with topoisomerase II inhibitors and G-CSF had a higher risk of developing myeloid leukemia after therapy than other patients (13). Later that year, using pooled data from six clinical trials, the National Surgical Adjuvant Breast and Bowel Project (NSABP) reported on the 5-year cumulative incidence of leukemia (43 case subjects) among 8563 patients with operable breast cancer who had received adjuvant doxorubicin and cyclophosphamide (14). The incidence of leukemia in the six trials ranged from 0.3% to 1.2%. Higher risk was associated with greater dose intensity and with the receipt of radiation therapy. Of the 1694 subjects assigned to trials that included treatment with G-CSF, 18 subjects (1.0%) developed either AML or myelodysplastic syndrome (MDS), and higher doses of G-CSF were associated with higher risks of AML and MDS. The relative risk of AML or MDS among patients treated with G-CSF who did not develop recurrent breast cancer was 2.34 (95% confidence interval [CI] = 0.72 to 7.55), but, due to the small sample size, this association was not statistically significant; it was reported as hypothesis generating (14). Excess AML and MDS have also been reported among children with acute lymphocytic leukemia treated with G-CSF (13), among patients with severe chronic neutropenia treated with G-CSF (15–17), among breast cancer patients treated with G-CSF (18), and even in healthy donors after G-CSF stimulation for a peripheral blood stem cell harvest (19,20). However, the association has not been found consistently, and strong evidence for causality is lacking (8,21,22).

Adjuvant chemotherapy for early-stage breast cancer has substantially increased the number of long-term breast cancer survivors (23). As a result, it is increasingly necessary to weigh the survival benefits of treatments against the risks of delayed toxicity that these treatments may entail. We therefore analyzed the association of G-CSF and GM-CSF with second primary AML or MDS among women treated with adjuvant chemotherapy for early-stage breast cancer.

CONTEXT AND CAVEATS

Prior knowledge

The cytokines granulocyte colony-stimulating factors (G-CSFs) and granulocyte macrophage colony stimulating factors (GM-CSFs) are used increasingly to avoid the myelosuppressive effects that would otherwise limit the chemotherapy dose in women with breast cancer. However, in vitro and epidemiologic evidence suggests that these cytokines may increase the risk of acute myelocytic leukemia (AML) or myelodysplastic syndrome (MDS).

Study design

Women included in a SEER–Medicare population-based database who received G-CSF or GM-CSF concurrently with chemotherapy for breast cancer were followed for the subsequent development of AML or MDS.

Contribution

Women with breast cancer who received either cytokine concurrently with chemotherapy had about a 2% risk of developing AML or MDS, whereas women who received chemotherapy alone had a subsequent AML or MDS risk of about 1%.

Implications

G-CSF and GM-CSF support may be associated with an increase in the risk of subsequent AML or MDS. However, the absolute risk was low, and the benefits may still outweigh any risks.

Limitations

The database includes only women 65 years of age and older, so the findings may not be generalizable to younger women. The claims data in the SEER—Medicare database may be incomplete. Information on dose and dose intensity was not available for individual women, and differences could have confounded the analysis. Additional studies will be required to determine whether the association is causal.

Patients and Methods

Study Database

We used a database that was codeveloped by the US National Cancer Institute (NCI) and the Centers for Medicare and Medicaid Services (CMS). The Surveillance, Epidemiology, and End Results (SEER) program, sponsored by NCI, is a network of tumor registries covering a growing proportion of the US population (14% during the period of this analysis). The CMS-sponsored Medicare program covers hospital services, physician services, and some drug therapy for more than 97% of persons aged 65 years and older. The linked SEER–Medicare database contains clinical, demographic, and medical claims data on patients aged 65 years and older who have been diagnosed with cancer since 1990. This unique population-based, longitudinal database has been described comprehensively elsewhere (24).

Patient Selection Criteria

We conducted a retrospective cohort study of women, aged 65 years or older and participating in Medicare, who were diagnosed with breast cancer from January 1, 1991, through December 31, 1999, and received chemotherapy within 12 months of their diagnosis. We excluded women who were enrolled in a health maintenance organization during any month of the study period because data were unavailable for these periods; women who did not participate in both Medicare Parts A and B during any month of the study period because data were partially unavailable; women diagnosed with American Joint Committee on Cancer

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Table 1. Baseline characteristics of breast cancer chemotherapy recipients by G-CSF status*

	Treated with G-CSF						
	Yes (N = 906)		No (N = 4604)		Total (N = 5510)		
Variable	**N**	**%**	**N**	**%**	**N**	**%**	***P* value†**
Year of diagnosis							<.0001
1991	0	0.0	465	10.1	465	8.4	
1992	0	0.0	566	12.3	566	10.3	
1993	36	4.0	465	10.1	501	9.1	
1994	86	9.5	447	9.7	533	9.7	
1995	96	10.6	454	9.9	550	10.0	
1996	119	13.1	423	9.2	542	9.8	
1997	141	15.6	535	11.6	676	12.3	
1998	188	20.8	640	13.9	828	15.0	
1999	240	26.5	609	13.2	849	15.4	
Age at diagnosis (y)							.002
65–69	348	38.4	1724	37.4	2072	37.6	
70–74	329	36.3	1580	34.3	1909	34.6	
75–79	178	19.6	896	19.5	1074	19.5	
80–85	48	5.3	302	6.6	350	6.4	
>85	3	0.3	102	2.2	105	1.9	
Race/ethnicity							.30
White	817	90.2	4072	88.4	4889	88.7	
Black	43	4.7	269	5.8	312	5.7	
Other	46	5.1	263	5.7	309	5.6	
Marital status							.08
Married	407	44.9	2177	47.3	2584	46.9	
Other	489	54.0	2339	50.8	2828	51.3	
Unknown	10	1.1	88	1.9	98	1.8	
AJCC breast cancer stage‡							<.0001
I	129	14.2	1054	22.9	1183	21.5	
II	568	62.7	2840	61.7	3408	61.9	
III	209	23.1	710	15.4	919	16.7	
Hormone receptor status							.15
ER+ or PR+	381	42.1	2059	44.7	2440	44.3	
ER−/PR−	376	41.5	1891	41.1	2267	41.1	
Unknown	149	16.4	654	14.2	803	14.6	
Tumor size (cm)							.006
<2	315	34.8	1701	36.9	2016	36.6	
2–5	431	47.6	2262	49.1	2693	48.9	
>5	129	14.2	472	10.3	601	10.9	
Unknown	31	3.4	169	3.7	200	3.6	
Positive lymph nodes							<.0001
0	206	22.7	1521	33.0	1727	31.3	
1–3	293	32.3	1317	28.6	1610	29.2	
≥4	406	44.8	1763	38.3	2169	39.4	
Unknown	1	0.1	3	0.1	4	0.1	
Comorbidity score							.02
0	691	76.3	3630	78.8	4321	78.4	
1	175	19.3	727	15.8	902	16.4	
≥2	40	4.4	247	5.4	287	5.2	
Treated with							
Radiation	565	62.4	2300	50.0	2865	52.0	<.0001
Doxorubicin	521	57.5	1066	23.2	1587	28.8	<.0001
Cyclophosphamide	781	86.2	2589	56.2	3370	61.2	<.0001
Duration of chemotherapy (days)							<.001
<90	245	27.0	1575	34.2	1820	33.0	
90–180	433	47.8	2124	46.1	2557	46.4	
>180	228	25.2	905	19.7	1133	20.6	
Urban residence							<.0001
Yes	865	95.5	4069	88.4	4934	89.5	
No	41	0.5	535	11.6	576	10.5	

(Table continues)

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Table 1 (continued).

Variable	Treated with G-CSF: Yes (N = 906) N	%	No (N = 4604) N	%	Total (N = 5510) N	%	*P* value†
Teaching hospital							.69
Yes	758	83.7	3876	84.2	4634	84.1	
No	148	16.3	728	15.8	876	15.9	

* G-CSF = granulocyte colony-stimulating factor; AJCC = American Joint Committee on Cancer; ER = estrogen receptor; PR = progesterone receptor.

† All hypothesis tests are two-sided chi-square and *t* tests.

‡ AJCC staging (25).

(AJCC) stage 0 or stage IV disease (25) because our evaluation was focused on adjuvant treatment; women who had end-stage renal disease; women who died or were censored within 18 months of their diagnosis of breast cancer; women who had prior leukemia, MDS, or other cancer before their breast cancer diagnosis; and women who had lymphoid leukemia after their breast cancer diagnosis. For each patient, information was collected from 12 months before her breast cancer diagnosis to her death or censoring at December 31, 2003. Informed consent was not required for this study.

Measurement of Treatments and Outcomes

Chemotherapy and radiation therapy exposure were ascertained from the Medicare files using codes of the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) Diagnosis, ICD-9-CM Procedural, Current Procedural Terminology, Healthcare Common Procedure Coding System (HCPCS), and revenue centers (26). We distinguished patients who received any cyclophosphamide or any doxorubicin from those who received other chemotherapy.

In addition, we used chemotherapy claims dates in Medicare data to determine which patients experienced a breast cancer relapse after their first series of chemotherapy treatments. Patients who had an interval between chemotherapy claims that was greater than 100 days were categorized as having a recurrence and were censored in the analysis at the time of recurrence to differentiate the effects of initial treatment from those of treatment for recurrent disease. Duration of chemotherapy exposure was calculated as months from first to last chemotherapy claim before recurrence. We calculated the follow-up interval as months from breast cancer diagnosis to the date of relapse, AML or MDS diagnosis, death, or end-of-study date, whichever came first.

We searched the linked Medicare file for HCPCS codes indicating treatment with G-CSF or GM-CSF. The HCPCS codes for G-CSF treatment are J1440 and J1441; the code for GM-CSF treatment is J2820. Both G-CSF and GM-CSF were included together as G-CSF in the analysis and will be referred to together as G-CSF. We used diagnosis codes in the Medicare files to identify leukemia and MDS outcomes. We searched for ICD-9 codes corresponding to the following diagnoses: myeloid leukemia (205.XX, v1062), monocytic leukemia (206.XX, v1063), and MDS (238.7). Patients who developed AML or MDS 18 months or longer after their diagnosis of breast cancer were counted as case subjects. To validate the MDS and AML claims data, we performed a sensitivity analysis in which we included as case patients only those with two or more claims for MDS and/or AML.

Comorbid Conditions

We searched the inpatient and outpatient Medicare data for diagnosis and procedure claims relevant to conditions identified by Charlson et al. (27) and included in the comorbidity index developed by Klabunde et al. (28). The Charlson scale is considered to be a reliable measure of comorbidity in cancer trials of older patients (29) and has been found to be predictive of hospitalization among breast cancer patients in the SEER–Medicare linked database (30). We used the comorbidity score and other demographic and clinical factors to control for baseline differences between groups in the multivariable analysis.

Statistical Analysis

We used the chi-square test to compare subjects who did and did not receive G-CSF with respect to year of diagnosis; age (5-year groups) at diagnosis; race/ethnicity (white, black, other); location of residence (urban, nonurban); type of hospital (teaching, other); marital status (married, other); AJCC breast cancer stage; hormone receptor status (estrogen receptor [ER]–positive or progesterone receptor [PR]–positive, ER- and PR-negative, unknown); Charlson–Klabunde comorbidity score (0, 1, >1); receipt or nonreceipt of radiation therapy, of doxorubicin, and of cyclophosphamide; tumor size (<2, 2–5, >5 cm); number of positive lymph nodes (0, 1–3, >3); duration of chemotherapy (<90, 90–180, >180 days); and AML and/or MDS claims. All hypothesis tests were two-sided. We used stratified analyses to test the main effect in treatment subgroups, to control for confounding, and to describe effect modification.

We used Cox proportional hazards modeling to analyze the association between diagnosis of AML or MDS and G-CSF treatment, controlling for all covariates and stratifying by year of diagnosis. Follow-up time was defined as months from breast cancer diagnosis to AML or MDS diagnosis for AML or MDS patients and as the date of relapse, death, or end-of-study date, whichever came first, for patients who were not diagnosed with AML or MDS. Separate models were created stratifying on year of breast cancer diagnosis only, controlling for clinical variables (age, hormone receptor status, comorbidity, radiation, chemotherapy, stage, and duration of chemotherapy), and controlling for clinical variables as well as demographic variables (race, geographic location, diagnosis in a teaching hospital, and marital status).

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Table 2. Baseline characteristics of breast cancer patients undergoing chemotherapy and risk of subsequent AML and MDS*

	AML or MDS (N = 64; 1.16%)		No AML or MDS (N = 5446; 98.84%)			All chemotherapy (N = 5510)	
Variable	**N**	**%**	**N**	**%**	***P* value†**	**N**	**%**
Year of breast cancer diagnosis‡							
1991	8	12.5	457	8.4	.05	465	8.4
1992	4	6.2	562	10.3		566	10.3
1993	12	18.7	489	9.0		501	9.1
1994	8	12.5	525	9.6		533	9.7
1995	8	12.5	542	9.9		550	10.0
1996	8	12.5	534	9.8		542	9.8
1997	6	9.4	670	12.3		676	12.3
1998	6	9.4	822	15.1		828	15.0
1999	4	6.2	845	15.5		849	15.4
Age at breast cancer diagnosis (y)							
Mean	71.2	32.8	72.0	37.7	.65	72.1	37.6
65–69	21	32.8	2051	37.7	.89	2072	37.6
70–74	26	40.6	1883	34.6		1909	34.6
75–79	12	18.7	1062	19.5		1074	19.5
80–85	4	6.2	346	6.3		350	6.3
>85	1	1.6	104	1.9		105	1.9
Race/ethnicity							
White	58	90.6	4831	88.7	.28	4889	88.7
Black	1	1.6	311	5.7		312	5.7
Other	5	7.8	304	5.6		309	5.6
Urban residence							
No	4	6.2	572	10.5		576	10.4
Yes	60	93.7	4874	89.5	.27	4934	89.5
Teaching hospital							
No	50	78.1	4584	84.2	.19	4634	84.1
Yes	14	21.9	862	15.8		876	15.9
Married							
No	28	43.7	2556	46.9	.86	2584	46.9
Yes	35	54.7	2793	51.3		2828	51.3
Unknown	1	1.6	97	1.8		98	1.8
AJCC stage							
Stage I	13	20.3	1170	21.5	.60	1183	21.5
Stage II	43	67.2	3365	61.8		3408	61.8
Stage III	8	12.5	911	16.7		919	16.7
Hormone receptor status							
ER+ or PR+	32	50.0	2408	44.2	.25	2440	44.3
ER–/PR–	20	31.2	2247	41.3		2267	41.1
Unknown	12	18.7	791	14.5		803	14.6
Comorbidity score							
0	49	76.6	4272	78.4	.64	4321	78.4
1	10	15.6	892	16.4		902	16.4
≥2	5	7.8	282	5.2		287	5.2
Radiation treatment							
No	26	40.6	2619	48.1	.23	2645	48.0
Yes	38	59.4	2827	51.9		2865	52.0
Doxorubicin treatment							
No	46	71.9	3877	71.2	.90	3923	71.2
Yes	18	28.1	1569	28.8		1587	28.8
Cyclophosphamide treatment							
No	24	37.5	2116	38.8	.82	2140	38.8
Yes	40	62.5	3330	61.1		3370	61.2
G-CSF/GM-CSF treatment							
No	48	75.0	4556	83.7	.06	4604	83.6
Yes	16	25.0	890	16.3		906	16.4
Tumor size (cm)							
<2	22	34.4	1994	36.6	.78	2016	36.6
2–5	34	53.1	2659	48.8		2693	48.9
>5	5	7.8	596	10.9		601	10.9
Unknown	3	4.7	197	3.6		200	3.6

(Table continues)

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Table 2 (continued).

Variable	AML or MDS (N = 64; 1.16%) N	AML or MDS (N = 64; 1.16%) %	No AML or MDS (N = 5446; 98.84%) N	No AML or MDS (N = 5446; 98.84%) %	*P* value†	All chemotherapy (N = 5510) N	All chemotherapy (N = 5510) %
Positive lymph nodes							
0	14	21.9	1713	31.4	.21	1727	31.3
1–3	17	26.6	1593	29.2		1610	29.2
≥4	33	51.6	2136	39.2		2169	39.4
Unknown	0	0	4	0.07		4	0.07
Duration of chemotherapy (days)							
<90	22	34.4	1798	33.0	.97	1820	33.0
90–180	29	45.3	2528	46.4		2557	46.4
>180	3	20.3	1120	20.6		1133	20.6

* AML = acute myelogenous leukemia; MDS = myelodysplastic syndrome; AJCC = American Joint Committee on Cancer; ER = estrogen receptor; PR = progesterone receptor; G-CSF = granulocyte colony-stimulating factor; GM-CSF = granulocyte–macrophage colony-stimulating factor.

† All hypothesis tests are two-sided chi-square tests.

‡ Log-rank statistic, $P = .16$.

Using Cox proportional hazards models, we developed hazard rate ratios of AML or MDS events among patients who received G-CSF compared with other patients. Maximum partial likelihood estimates of hazard ratios (HRs) with 95% confidence intervals were obtained. The assumption of proportionality was confirmed visually. We generated Kaplan–Meier curves and applied the log-rank test to compare rates of AML and MDS across groups. Similarly, Cox proportional hazards models were developed to evaluate all-cause mortality. All statistical analyses were conducted using the SAS system for Windows Version 9.1.

Results

The SEER–Medicare database included 5510 women aged 65 years and older who were diagnosed with histologically confirmed AJCC stages I–III breast cancer between January 1, 1991, and December 31, 1999, and who received chemotherapy within 12 months of diagnosis and met the other eligibility requirements. Among these women, 906 (16%) were treated with at least one course of G-CSF (N = 832), GM-CSF (N = 29), or both (N = 49) within 18 months of their breast cancer diagnosis. Use of these growth factors increased over time, from 0% to 26% of patients. Compared with patients who did not receive G-CSF or GM-CSF, those who received it were younger (mean age = 71 versus 72 years; $P = .002$), more likely to have been diagnosed with advanced-stage breast cancer, more likely to live in an urban area, more likely to have had comorbid conditions, more likely to have undergone radiation therapy, more likely to have been treated with doxorubicin, more likely to have been treated with cyclophosphamide, and more likely to have received chemotherapy for more than 180 days (Table 1).

Among the 5510 patients, 64 (1.16%) developed AML or MDS at least 18 months after diagnosis. Year of diagnosis was the only variable that was associated in multivariable analysis with risk of AML or MDS, possibly because patients with longer follow-up had more opportunity to develop the outcome (Table 2). Of the 906 patients who were treated with G-CSF, 16 (1.77%) developed AML or MDS; of the 4604 patients not treated with G-CSF, 48 (1.04%) developed AML or MDS. Only one patient treated with GM-CSF developed leukemia. No other demographic, clinical, or treatment-related factor was related to risk of AML or MDS (Table 2).

Cox proportional hazards models evaluating the association between G-CSF and AML or MDS are shown in Table 3. Because year of diagnosis was the only variable that was associated with subsequent diagnosis of AML or MDS (Table 2), we stratified by it in all the models. The hazard ratio for AML or MDS in patients stratified by year of diagnosis showed that the risk was twice as high among patients treated with G-CSF as among those not treated with G-CSF (HR = 2.24, 95% CI = 1.22 to 4.10). The risk of AML or MDS did not change substantially when clinical and treatment variables were added to the model (HR = 2.22, 95% CI = 1.17 to 4.22) or when clinical, treatment, and demographic variables were added (HR = 2.14, 95% CI = 1.12 to 4.08). The results were similar when the criterion for AML or MDS was more than one AML- or MDS-related claim. The hazard ratio for MDS associated with G-CSF treatment was 2.19 (95% CI = 1.1 to 4.5) and for AML associated with G-CSF treatment was 3.78 (95% CI = 1.4 to 10.5).

Figure 1 presents Kaplan–Meier incidence curves for the development of AML or MDS among patients treated with chemotherapy. The incidence curves for patients receiving and not receiving G-CSFs differed statistically significantly by the log-rank test ($P = .02$).

We evaluated the association between G-CSF and survival using a Cox proportional hazards model. The hazard ratios for all-cause mortality were 0.94 (95% CI = 0.83 to 1.09) for those given G-CSF compared with those who were not and 1.94 (95% CI = 1.4 to 2.6) for those who developed AML or MDS as compared with those who did not, after adjusting for other confounding variables.

Discussion

Our findings support the hypothesis that elderly women with breast cancer who receive G-CSF or GM-CSF as an adjunct to adjuvant chemotherapy are at increased risk of developing acute leukemia or MDS.

Two patterns of second primary leukemia incidence have been described following chemotherapy. Patients treated with alkylating

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Table 3. Cox proportional hazards model results (as HRs with 95% CIs) for the association between baseline variables and occurrence of AML or MDS after breast cancer diagnosis*

Variable	Base model†	Clinical variable–adjusted model‡	Fully adjusted model§
G-CSF/GM-CSF treatment			
No	Referent	Referent	Referent
Yes	2.24 (1.22 to 4.10)	2.22 (1.17 to 4.22)	2.14 (1.12 to 4.08)
Age category (y)			
65–69		Referent	Referent
70–74		1.45 (0.81 to 2.60)	1.45 (0.81 to 2.60)
75–79		1.32 (0.64 to 2.734)	1.32 (0.63 to 2.75)
≥80		1.66 (0.60 to 4.60)	1.75 (0.62 to 4.90)
ER/PR status			
ER–/PR–		Referent	Referent
ER+ or PR+		1.32 (0.74 to 2.36)	1.30 (0.73 to 2.32)
Unknown		1.46 (0.71 to 3.01)	1.41 (0.68 to 2.91)
Comorbidity score			
None		Referent	Referent
1		1.06 (0.53 to 2.11)	1.08 (0.54 to 2.15)
≥2		1.97 (0.77 to 5.05)	2.09 (0.81 to 5.39)
Radiation treatment			
No		Referent	Referent
Yes		1.55 (0.91 to 2.64)	1.50 (0.88 to 2.56)
Cyclophosphamide treatment			
No		Referent	Referent
Yes		1.20 (0.67 to 2.15)	1.24 (0.69 to 2.24)
Doxorubicin treatment			
No		Referent	Referent
Yes		0.86 (0.45 to 1.66)	0.87 (0.45 to 1.67)
Tumor size (cm)			
<2		Referent	Referent
2–5		1.26 (0.73 to 2.18)	1.26 (0.73 to 2.182)
>5		0.81 (0.30 to 2.20)	0.83 (0.31 to 2.27)
Unknown		1.28 (0.38 to 4.38)	1.36 (0.397 to 4.659)
Positive lymph nodes			
0		Referent	Referent
1–3		1.20 (0.58 to 2.48)	1.15 (0.557 to 2.393)
≥4		1.89 (0.96 to 3.7)	1.83 (0.920 to 3.631)
Duration of chemotherapy (days)			
<90		Referent	Referent
90–180		0.77 (0.42 to 1.39)	0.76 (0.42 to 1.38)
>180		0.78 (0.38 to 1.60)	0.78 (0.38 to 1.61)
Race			
White			Referent
Black			0.30 (0.04 to 2.16)
Other			1.65 (0.65 to 4.16)
Geography			
Urban			Referent
Nonurban			0.68 (0.24 to 1.90)
Teaching hospital			
No			Referent
Yes			1.24 (0.67 to 2.28)
Married			
Yes			Referent
No			0.96 (0.58 to 1.60)
Unknown			0.89 (0.12 to 6.64)

* HR = hazard ratio; CI = confidence interval; AML = acute myelogenous leukemia; MDS = myelodysplastic syndrome; G-CSF = granulocyte colony-stimulating factor; GM-CSF = granulocyte–macrophage colony-stimulating factor; ER = estrogen receptor; PR = progesterone receptor.

† Stratified by year of diagnosis.

‡ Stratified by year of diagnosis and adjusted for clinical variables. All variables adjusted for others in the model.

§ Stratified by year of diagnosis and adjusted for clinical and demographic variables. All variables adjusted for others in the model.

agents have been found to have an increased risk of developing an MDS preleukemic condition characterized by unbalanced chromosomal alterations that is related to cumulative dose, after a latency of 4 years (31). Patients treated with drugs that interact with topoisomerase, such as anthracyclines, are more likely to develop leukemia within 1–3 years; the leukemia lacks a preleukemic phase,

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involves a balanced chromosomal aberration, and is not dose dependent (31). Both alkylating agents and anthracyclines are used frequently in the adjuvant treatment of breast cancer, and exposure to those agents may account for some of the increased risks of AML or MDS that we observed. (22,32–36).

In our study population, patients who received G-CSF were more likely than other patients to have been treated with radiation, doxorubicin, or cyclophosphamide, but in the Cox models, those treatments were not associated with an increased risk of AML or MDS. Patients in our sample who received radiation therapy had a 50% higher incidence of MDS and AML combined than other patients, but the association was not statistically significant. In the NSABP analysis of leukemia in patients who had received adjuvant doxorubicin and cyclophosphamide, patients who received radiation therapy were twice as likely to develop leukemia as those who had not (14). This difference in observed risks may have been due to differences in patient characteristics, such as age.

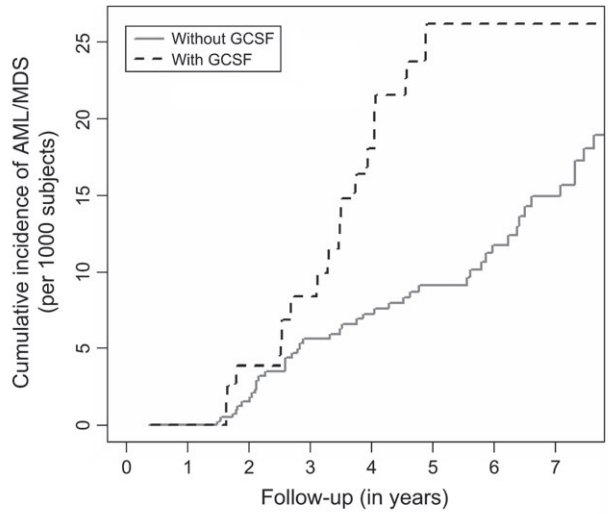
Others have found (7), as we observed in this study, that treatment with G-CSF is increasingly common among women with breast cancer. It is used to prevent complications from neutropenia (7), to improve quality of life, and to maintain dose and schedule (37–41). In 2003, among 2005 breast cancer patients in a randomized Cancer and Leukemia Group B (CALGB) trial, those who received dose-dense (every 2 weeks) chemotherapy with G-CSF support were reported to have better disease-free survival than patients who received therapy every 3 weeks without routine G-CSF support. (8). Since then, dose-dense therapy with G-CSF support has become the standard of care for node-positive breast cancer.

Among the 2005 relatively young (mean age = 50 years) participants in the CALGB trial (8), only 11 (0.5%) developed AML or MDS in 3 years of follow-up (for an incidence of 182.9/100 000 person-years). The risk of MDS/AML was not higher in patients treated with dose-dense therapy with G-CSF than in patients treated on the 3-week arm, perhaps because patients in the 3-week arm were treated with G-CSF when indicated. Among the 5510 patients in our sample, with a mean age of 72 years, 64 (1.2%) developed MDS or AML with up to 12 years of follow-up (for an incidence of 193.3/100 000 person-years).

Like all studies of the association between G-CSFs and leukemia, this study was limited by our inability to control for confounding by indication. The purpose of G-CSF is to support the marrow in patients treated with more intensive chemotherapy regimens. The more dose intensive the adjuvant therapy regimen, the higher the risk of secondary leukemia (14,42). Failure to recover marrow after exposure to chemotherapy is an indication for G-CSF, but such failure may also be a marker of marrow deficiency that may increase susceptibility to malignant transformation.

Even individuals without any history of malignancy may incur an increased risk of leukemia if treated with G-CSF (14–16,18, 19,42). Two peripheral blood stem cell donors were recently reported to have developed AML after G-CSF–primed harvests (19,20,43).

Patients with congenital neutropenia are prescribed G-CSF to prevent life-threatening infections (44). Among patients in two large registries, the Severe Chronic Neutropenia International



No. of Pts at risk								
With GCSF	906	857	726	646	587	378	243	156
Without GCSF	4604	4339	3668	3213	2930	2302	1751	1359

		GCSF			Without GCSF	
Years	N	Incidence (per 1000)	95% CI	N	Incidence (per 1000)	95%CI
4	587	18.0	(7.8-28.1)	2930	7.2	(4.4-10.0)
7	156	26.2	(13.2-39.0)	1359	14.9	(10.0-19.8)

Fig. 1. Kaplan–Meier incidence curves for secondary acute myelogenous leukemia (AML) and myelodysplastic syndrome (MDS) among women treated with and without granulocyte colony-stimulating factor (G-CSF). **Dashed line** indicates G-CSF–treated patients; **solid line** indicates patients who did not receive G-CSF. At 4 years, the incidence of AML or MDS in patients treated with G-CSF was 18 per 1000 (95% confidence interval [CI] = 7.8 to 28.1); at 7 years, the incidence was 26.2 per 1000 (95% CI = 13.2 to 39.0). At 4 years, the incidence of leukemia or MDS in patients not treated with G-CSF was 7.2 per 1000 (95% CI = 4.4 to 10.0); at 7 years, the incidence was 14.9 per 1000 (95% CI = 10.0 to 19.8).

Registry and the French Severe Chronic Neutropenia Registry, those treated with G-CSF have been found to have higher risk of AML or MDS than those not treated (15,45,46). Risk of AML or MDS was associated with more severe neutropenia, younger age at diagnosis, and increased exposure to G-CSF (15). The risk was higher in patients who, because of poorer neutrophil responses to G-CSF, received G-CSF at higher doses or for a longer time (46). However, leukemia may also be part of the natural history of severe chronic neutropenia, such that it is not directly caused but rather uncovered by G-CSF because it reduces mortality from infections.

A strength of this study is its use of the SEER–Medicare database, an invaluable tool for studying unanticipated treatment effects and long-term outcomes in a population-based sample of patients who, for various reasons, have been underrepresented in clinical trials. Given the constraints on eligibility for such trials and other barriers to trial participation, the use of such databases is the only way to determine how treatments work in the real world. Our study extends the findings of clinical trial research conducted among younger women to elderly breast cancer patients, who may be at higher risk for treatment-related adverse outcomes. However, a limitation of the use of the database is that findings among such patients may not be generalizable to younger patients.

Despite the value of the SEER–Medicare database, it has some additional limitations. The SEER database consists of data

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provided by hospital cancer registries based on patient charts. The Medicare database consists of reimbursement claims for medical care. Medicare claims data have not been validated, nor has SEER's sensitivity for second primary cancers diagnosed through ICD-9 claims. Our sensitivity analysis was motivated by concern that patients with only one AML or MDS claim might have been miscoded. Defining AML or MDS cases as those with at least two claims reduced the likelihood of misclassification and did not change the hazard ratio for the association between G-CSF and second primary AML or MDS.

Another major limitation of our study is that we could not measure dose and dose intensity for individual patients. However, adjusting for type of chemotherapy, duration of chemotherapy, radiation exposure, and stage of disease had a minimal effect on the overall hazard ratio; these results are reassuring because these variables are reasonable surrogates for dose and dose intensity.

In the past few years, the discovery of late toxic effects of a number of commonly used medications has raised serious concerns about the drug evaluation process (47–52). Unfortunately, many questions cannot be addressed in premarketing studies. A recent proposal calls for postmarketing studies of new drugs tailored to address the long-term issues associated with each new medication, including adequately powered safety studies, long-term studies of drugs for chronic diseases, epidemiologic investigations of rare adverse effects and special populations, and randomized trials that assess relative efficacy and clinical endpoints (52).

Our study demonstrates that the elevated risk of AML or MDS associated with adjuvant chemotherapy may be further increased by the concurrent use of growth factors. It is unclear if the growth factors cause an increased risk or if the requirements for their use cause an increased risk; however, the absolute overall risk appeared to be small, even among the elderly patients we studied. Nevertheless, if further research confirms this finding, this risk should be factored into clinical decisions with regard to the use of growth factors.

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Notes

D. Hershman is the recipient of an American Society of Clinical Oncology Career Development Award and a K07 Award from the National Cancer Institute (NCI) (CA95597). A. I. Neugut is the recipient of a K05 Award from the NCI (CA89155) and a grant from the American Cancer Society (RSGT-01-024-04-CPHPS). V. R. Grann is the recipient of a grant from the American Cancer Society (RSGHP PBP-105710). C. L. Bennett is supported, in part, from grants from the NCI (1R01CA 102713-01 and P30 CA60553).

The funding agencies had no input in the design, collection, analysis, interpretation of the data, writing of the manuscript, or decision to submit the manuscript for publication. C. L. Bennett is a consultant for AMGEN, which did not fund this project and had no involvement in this study.

This study used the linked SEER–Medicare database. The interpretation and reporting of these data are the sole responsibility of the authors. The authors thank the Applied Research Branch, Division of Cancer Prevention, NCI; the Office of Information Services and the Office of Strategic Planning, CMS; Information Management Services, Inc; and the SEER program tumor registries for creating the SEER–Medicare database.

Manuscript received May 20, 2006; revised November 15, 2006; accepted December 5, 2006.

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