Original Article

Use of White Blood Cell Growth Factors and Risk of Acute Myeloid Leukemia or Myelodysplastic Syndrome Among Elderly Patients With Non-Hodgkin Lymphoma

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BACKGROUND. The current study was conducted to evaluate the association between colony-stimulating factor (CSF) use and the risk of developing therapy-related myelodysplastic syndromes or acute myeloid leukemia (t-MDS/AML) among a large cohort of elderly patients with non-Hodgkin lymphoma (NHL) who were treated with chemotherapy. **METHODS.** A total of 13,203 NHL patients were identified from the Surveillance, Epidemiology, and End Results-Medicare database who were diagnosed from 1992 through 2002. Patients were followed from their initial chemotherapy date until the date they were diagnosed with t-MDS/AML, death, or last follow-up (October 31, 2006), whichever occurred first. **RESULTS.** Overall, 40% (n = 5266) of patients received CSF. During the follow-up period (median follow-up, 2.9 years [range, 1-14.7 years]), 272 (5.2%) patients who were treated with CSF developed t-MDS/AML, compared with 230 (2.9%) patients who did not ($P < .0001$, log-rank test). The 5-year incidence of t-MDS/AML for patients receiving CSF was 14.1 per 1000 person-years compared with 8.3 per 1000 person-years for patients not receiving CSF. In a multivariable Cox regression analysis adjusted for gender, histology, stage, comorbidities, radiotherapy, and chemotherapy agent, CSF use was found to be independently associated with a 53% increased risk of t-MDS/AML (hazard ratio [HR], 1.53; 95% confidence interval [95% CI], 1.26-1.84). The observed association between CSF use and t-MDS/AML persisted across histologic subgroups (ie, diffuse large B-cell lymphoma, follicular lymphoma, and others). Patients who received both CSF and antimetabolite chemotherapy were found to have a 2.5-fold increased risk of t-MDS/AML (HR, 2.49; 95% CI, 1.91-3.26) compared with patients who received neither agent. **CONCLUSIONS.** The current study, which to our knowledge is the first large population-based study published to date, demonstrated that the administration of CSF among elderly NHL patients receiving chemotherapy was associated with an increased risk of t-MDS/AML, although the absolute risk was low. ***Cancer* 2010;116:5279–89.** © *2010 American Cancer Society.*

KEYWORDS: non-Hodgkin lymphoma, colony-stimulating factor, chemotherapy, myelodysplastic syndromes, acute myeloid leukemia.

Therapy -related myelodysplastic syndromes and acute myeloid leukemia (t-MDS/AML), defined as MDS or AML occurring after chemotherapy and/or radiotherapy, are devastating long-term complications of cancer therapy. Initially recognized >30 years ago in patients with multiple myeloma who were treated with melphalan, these complications have been reported subsequent to the treatment of many cancers.[1,2] The general use of chemotherapy and/or radiotherapy has improved cancer survival; however, it has been reported that 1% to 15% of long-term cancer survivors treated with combination chemotherapy and radiotherapy develop t-MDS/AML.[3] Among non-Hodgkin lymphoma (NHL) patients treated with chemotherapy, most studies have reported a 10-year cumulative risk ranging from 4.6% to 10%.[4-10] Prognosis after a diagnosis of t-MDS/AML is bleak, with a median survival of <2 years.[11]

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Granulocyte-colony-stimulating factor (G-CSF) and granulocyte-macrophage-colony-stimulating factor (GM-CSF) are supportive care agents intended to minimize the risk of febrile neutropenia in patients receiving intensive chemotherapy. There has been speculation suggesting that G-CSF and GM-CSF (collectively referred to as CSFs) may be associated with an increased risk of t-MDS/AML. As early as 1996, Brodsky et al[12] suggested that the increased risk of AML noted in patients enrolled in clinical trials may be at least partially attributed to CSF administration among patients receiving intensive chemotherapy. Numerous clinical trials have monitored for t-MDS/AML as adverse events[13-20] after chemotherapy, and some studies have addressed the question specifically.[21-23] Recently, 2 studies using the Surveillance, Epidemiology, and End Results (SEER)-Medicare database have explored this relation in a population-based cohort of breast cancer patients[21,22]; 1 study found a positive association,[21] whereas the other study found no association.[22] In what to our knowledge is the only other population-based study published to date, also conducted among patients with breast cancer, a positive association was found.[23] In what to our knowledge is the only published study among patients with a hematologic malignancy, Relling et al[13] found that pediatric leukemia patients receiving G-CSF had an increased risk of developing t-MDS/AML.

Although NHL is known to be very responsive to intensive chemotherapy, elderly patients are particularly susceptible to the detrimental myelosuppressive effects of chemotherapy.[24] Therefore, the potential benefit of CSF therapy is likely to be significant among elderly patients with NHL because of the possibility of allowing for more dose-intense and dose-dense therapies while decreasing the likelihood of neutropenia. In fact, recently updated American Society of Clinical Oncology recommendations consider age as 1 condition for which the prophylactic use of growth factors may be indicated, regardless of the risk of neutropenia.[25]

The incidence of t-MDS/AML among NHL patients is among the highest of any cancer type,[10] possibly because of the underlying susceptibility of this patient population to hematologic malignancies. Therefore, we posit that although it is plausible that NHL patients, especially elderly patients, may benefit from the therapeutic effects of CSFs, they also may be particularly susceptible to the potential long-term leukemogenic effects of these agents. Therefore, the purpose of the current study was to explore the relation between CSF use and the incidence of t-MDS/AML among a large nationwide and population-based cohort of elderly patients with NHL receiving chemotherapy with up to 15 years of follow-up.

MATERIALS AND METHODS

Data Source

The current study used data from the merged SEER-Medicare database. The SEER database program is a population-based registry sponsored by the National Cancer Institute (NCI) that contains information regarding all newly diagnosed cancer cases. This study included the following geographic areas: Detroit, Atlanta, and Seattle; and the states of California, Connecticut, Iowa, New Mexico, Utah, Hawaii, Kentucky, Louisiana, and New Jersey. SEER data are highly valid and complete, with a completeness of case ascertainment of $>$98%.[26]

The SEER registry collects information concerning patient demographics, tumor characteristics, stage at diagnosis, treatment within 4 months of diagnosis, and date and cause of death. This registry data are linked to claims data from Medicare, which is the primary insurer for approximately 97% of the US population aged $\geq$65 years. All Medicare beneficiaries receive Part A coverage, which covers inpatient care, skilled nursing, home healthcare, and hospice care. Approximately 95% of beneficiaries also subscribe to Part B of Medicare to obtain benefits that cover physician services and outpatient care.[26] The Committee for the Protection of Human Subjects at the University of Texas Health Science Center at Houston approved the current study.

Study Population and Patient Characteristics

This retrospective cohort study included patients with incident cases of NHL diagnosed between January 1, 1992 and December 13, 2002 who received chemotherapy within 12 months of their diagnosis. Patients enrolled in a health maintenance organization during any period of the study time period were excluded because data were unavailable for these periods. Patients who did not participate in both Medicare Parts A and B during any month were also excluded because of potentially incomplete data.

Patients were characterized with respect to clinical and demographic variables available in the SEER-Medicare database as well as clinical and treatment characteristics that were abstracted from the Medicare claims data. Because of the reported reliability for differentiating certain histologic subtypes in the SEER data,[27] we specifically identified diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma, and grouped the remaining

histologic subtypes as "other" because of the relatively small number of cases. Chemotherapy and radiotherapy were characterized and quantified using International Statistical Classification of Diseases (ICD) diagnosis codes, ICD procedural codes, Current Procedural Terminology (CPT) codes, Healthcare Common Procedural Coding System codes, and revenue center codes.[26] The following codes were used for defining chemotherapy: ICD-9 Clinical Modification procedure code 9925 for chemotherapy infusion/injection; CPT codes 96,400 through 96,549, J9000 through J9999, and Q0083 through Q0085; revenue center codes 0331, 0332, and 0335; and ICD-9 V codes V58.1, V66.2, and V67.2. Chemotherapy use was stratified by type (eg, alkylating agents, topoisomerase II inhibitors, anthracyclines, and antimetabolites) using CPT codes. The use of CSF was identified by the procedure codes of J1440 and J1441 (for G-CSF) and J2820 (for GM-CSF). The incidence of secondary MDS/AML was identified by $\geq$2 claims with a primary or secondary diagnosis of AML/MDS (ICD-9 codes: myeloid leukemia [205.xx], monocytic leukemia [206.xx], and MDS [238.7]) occurring $\geq$30 days apart from each other, with the initial diagnosis occurring $\geq$1 year after the diagnosis of NHL. Claims before diagnosis were used to identify pre-existing comorbidities. Comorbidities were aggregated to formulate the NCI comorbidity index, a revised version of the Charlson comorbidity index.[28]

Data Analysis

Patients were described with respect to demographic, clinical, and treatment characteristics overall and were stratified according to CSF use to identify potential underlying differences across exposure strata of the population. We used chi-square tests and Student *t* tests to compare differences in patients by CSF status. Kaplan-Meier graphs and corresponding log-rank tests were used to compare the incidence of t-MDS/AML by CSF use. Follow-up time was defined as the time from the initial chemotherapy start date to the first diagnosis of t-MDS/AML. Patients who did not develop t-MDS/AML were censored at the date of death or the end-of-study date (October 31, 2006), whichever occurred first. Cox proportional hazards modeling was used to estimate the association between CSF use and the development of t-MDS/AML after controlling for potential confounders. The proportionality assumption was confirmed using the goodness-of-fit test developed by Harrell and Lee.[29] To further control for confounding, we calculated a propensity score and included this in a separate Cox regression model. Briefly, this score was calculated based on the probability of receiving CSF as calculated using logistic regression analysis in which CSF status (yes vs no) was the dependent variable and patient demographic/clinical/treatment characteristics were considered as possible independent variables. Finally, because of plausible interactive effects between CSF use and specific chemotherapy agents on the risk of t-MDS/AML, we evaluated these interactions by including the product term of CSF and the specific chemotherapy agent in separate Cox regression models.

RESULTS

We identified 13,203 NHL patients from the SEER-Medicare database who received chemotherapy within 12 months of their diagnosis and met the other eligibility criteria for this study. The overall median age of the patients at the time of diagnosis was 74 years (range, 65-102 years). Approximately 53% (n = 7051) of patients were female, and a large majority (n = 11,776; 89%) were non-Hispanic white and lived in an urban setting (n = 11,877; 90%). Approximately 44% (n = 5861) of patients had a diagnosis of DLBCL, 18% (n = 2428) had follicular lymphoma, 28% (n = 3665) had other histologies, and 9% (n = 1249) had an unknown histology. Patient distribution according to stage of disease at diagnosis was 29% (n = 3564) of patients with stage I disease, 18% (n = 2214) with stage II disease, 16% (n = 1971) with stage III disease, and 37% (n = 4519) with stage IV disease (grading determined according to the American Joint Committee on Cancer staging system). A large majority (n = 8216; 62%) of patients had a low comorbidity burden (comorbidity index, $\leq$1).

Tables 1 and 2 show patient demographic, clinical, and treatment characteristics according to CSF use. Overall, approximately 40% (n = 5266) of patients who were treated with chemotherapy received CSF during the follow-up period. The majority of patients treated with CSF received only G-CSF (n = 4581; 87%), whereas 316 (6%) received only GM-CSF and 369 (7%) received both G-CSF and GM-CSF. Patients treated with CSF were more likely to have been diagnosed recently. Although other statistically significant differences were observed according to CSF status (urban residence, age at diagnosis, race/ethnicity, marital status, socioeconomic status, stage of disease, and histology), the magnitude of these observed differences was relatively small (Table 1). With regard to patient treatment, those who received CSF were more likely to be treated with agents known to be associated with the development of t-MDS/AML. For example,

Table 1. Patient Demographic and Clinical Characteristics by CSF Use

Factor	Overall (N = 13,203) No. (%)	CSF Use: Yes (N = 5266) No. (%)	CSF Use: No (N = 7937) No. (%)	*P*
Y of diagnosis				
1992-1993	1759 (13.3)	318 (6.0)	1441 (18.2)	
1994-1995	1837 (13.9)	673 (12.8)	1164 (14.7)	
1996-1997	1912 (14.5)	827 (15.7)	1085 (13.7)	
1998-1999	1852 (14.0)	800 (15.2)	1052 (13.3)	
2000-2001	3778 (28.6)	1841 (35.0)	1937 (24.4)	
2002	2065 (15.6)	807 (15.3)	1258 (15.8)	<.001
No				
No	1326 (10.0)	407 (7.7)	919 (11.6)	
Yes	11,877 (90.0)	4859 (92.3)	7018 (88.4)	<.001
Age at diagnosis, y				
Mean (SD)	74.94 (6.35)	74.38 (5.92)	75.32 (6.59)	<.001
Median (range)	74 (65-102)	74 (65-98)	75 (65-102)	
65-69	3090 (23.4)	1276 (24.2)	1814 (22.9)	
70-74	3598 (27.3)	1548 (29.4)	2050 (25.8)	
75-79	3324 (25.2)	1389 (26.4)	1935 (24.4)	
80-84	2107 (16.0)	744 (14.1)	1363 (17.2)	<.001
≥85	1084 (8.2)	309 (5.9)	775 (9.8)	
Gender				
Male	6152 (46.6)	2469 (46.9)	3683 (46.4)	.57
Female	7051 (53.4)	2797 (53.1)	4254 (53.6)	
Race/ethnicity				
Non-Hispanic White	11,776 (89.2)	4716 (89.6)	7060 (89.0)	
Hispanic	236 (1.8)	100 (1.9)	136 (1.7)	
Black	441 (3.3)	155 (2.9)	286 (3.6)	
Asian	404 (3.1)	176 (3.3)	228 (2.9)	
Other	304 (2.3)	104 (2.0)	200 (2.5)	
Unknown	42 (0.3)	15 (0.3)	27 (0.3)	.04
Marital status				
Yes	7797 (59.1)	3291 (62.5)	4506 (56.8)	
No	4838 (36.6)	1778 (33.8)	3060 (38.6)	<.001
Unknown	568 (4.3)	197 (3.7)	371 (4.7)	
SES quartiles				
1 (high)	3376 (25.6)	1396 (26.5)	1980 (24.9)	
2	3251 (24.6)	1349 (25.6)	1902 (24.0)	
3	3305 (25.0)	1249 (23.7)	2056 (25.9)	.007
4 (low)	3065 (23.2)	1189 (22.6)	1876 (23.6)	
Missing	206 (1.6)	83 (1.6)	123 (1.5)	
Histology				
Diffuse large B-cell	5861 (44.4)	2538 (48.2)	3323 (41.9)	
Follicular	2428 (18.4)	922 (17.5)	1506 (19.0)	
Other	3665 (27.8)	1384 (26.3)	2281 (28.7)	<.001
Unknown	1249 (9.5)	422 (8.0)	827 (10.4)	
Stage at diagnosis				
I	3564 (27.0)	1336 (25.4)	2228 (28.1)	
II	2214 (16.8)	888 (16.9)	1326 (16.7)	
III	1971 (14.9)	888 (16.9)	1083 (13.6)	<.001
IV	4519 (34.2)	1835 (34.8)	2684 (33.8)	
Unknown	935 (7.1)	319 (6.1)	616 (7.8)	
Comorbidity score				
0	8216 (62.2)	3308 (62.8)	4908 (61.8)	
1	3148 (23.8)	1257 (23.8)	1891 (23.8)	.24
≥2	1839 (13.9)	701 (13.3)	1138 (14.3)	

CSF indicates colony-stimulating factor; SD, standard deviation; SES, socioeconomic status.

Table 2. Patient Treatment Characteristics by CSF Use

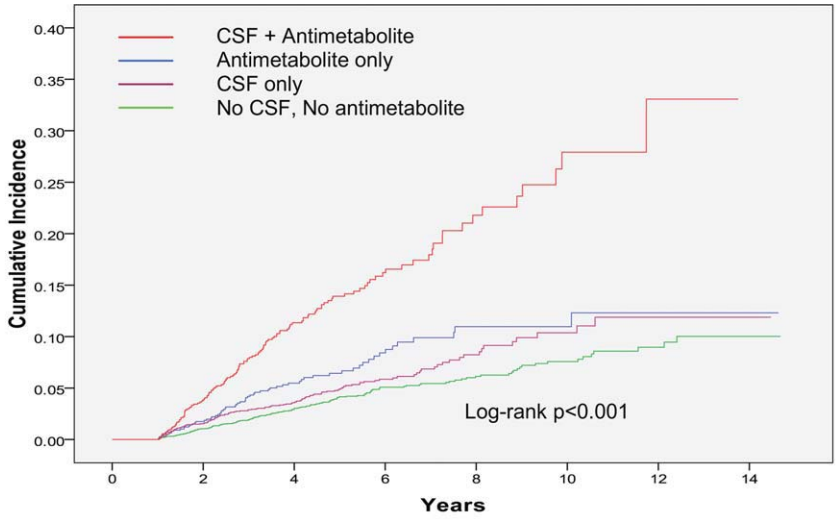
Factor	Overall (N=13,203) No. (%)	CSF Use Yes (N=5266) No. (%)	CSF Use No (N=7937) No. (%)	*P*
CSF use				
No	7937 (60.1)	—		
Yes	5266 (39.9)	5266 (100)		
G-CSF	*4581 (34.7)*	*4581 (87.0)*		
GM-CSF	*316 (2.4)*	*316 (6.0)*		
Both	*369 (2.8)*	*369 (7.0)*		
Chemotherapy agent				
Alkylating agents	10,951 (82.9)	4851 (92.1)	6100 (76.9)	<.0001
Topoisomerase II inhibitors	3328 (25.2)	1728 (32.8)	1600 (20.2)	<.0001
Anthracyclines	7068 (53.5)	3518 (66.8)	3550 (44.7)	<.0001
Antimetabolites	3148 (23.8)	1567 (29.8)	1581 (19.9)	<.0001
Platinums	520 (3.9)	358 (6.8)	162 (2.0)	<.0001
Taxanes	132 (1.0)	85 (1.6)	47 (0.6)	<.0001
Vinca alkaloids	10,718 (81.2)	4754 (90.3)	5964 (75.1)	<.0001
Targeted therapy	6937 (52.5)	3006 (57.1)	3931 (49.5)	<.0001
Other	1941 (14.7)	797 (15.1)	1144 (14.4)	.25
No. of chemotherapy claims				
Mean (SD)	18.9 (23.1)	27.7 (29.6)	13.1 (14.9)	
Median (range)	11 (1-394)	18 (1-394)	8 (1-212)	<.0001
Radiotherapy				
No	8194 (62.1)	3125 (59.3)	5069 (63.9)	
Yes	5009 (37.9)	2141 (40.7)	2868 (36.1)	<.0001

CSF indicates colony-stimulating factor; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; SD, standard deviation.

92% (n = 4851) of patients receiving CSF were treated with alkylating agents compared with 77% (n = 6100) of patients not receiving CSF, and 33% (n = 1728) of patients receiving CSF were treated with topoisomerase II inhibitors compared with 20% (n = 1600) of those not receiving CSF. Furthermore, patients receiving CSF were found to have a significantly higher number of chemotherapy administration services (mean, 27 days vs 13 days; $P < .0001$).

Figure 1 shows the cumulative incidence of t-MDS/AML according to the use of CSF and by the number of CSF claims (in quartiles). After a median follow-up of 2.9 years (range, 1-14.7 years), 502 (3.8%) patients developed t-MDS/AML. Of those patients who did not develop t-MDS/AML (n = 12,701), 68% (n = 8589) died whereas 32% (n = 4112) of patients were alive without evidence of t-MDS/AML at the end of the follow-up period. The median time to the development of t-MDS/AML was 3 years (range, 1-12 years). Over the follow-up period, a total of 272 (5.2%) patients receiving CSF developed t-MDS/AML compared with 230 (2.9%) patients who did not receive CSF ($P <.0001$, log-rank test). The 3-year incidence of t-MDS/AML for patients receiving CSF was 13.2 per 1000 person-years compared with 6.9 per 1000 person-years for patients not receiving CSF (95% confidence interval [95% CI] for rate difference, 3.7-8.8 cases/1000 person-years). The 5-year incidence of t-MDS/AML for patients receiving CSF was 14.1 per 1000 person-years compared with 8.3 per 1000 person-years for patients not receiving CSF (95% CI for rate difference, 3.6-8.1 cases/1000 person-years). When we evaluated the cumulative incidence of t-MDS/AML by number of CSF claims (categorized by quartile)(Fig. 2), we found a significant dose-response effect ($P < .0001$. log-rank test) with the incidence noted to be increasing by quartile. Those in the highest quartile ($\geq$23 claims) had a 10-year cumulative incidence of 21%, followed by those in the third quartile (10-22 claims; 15%), those in the second quartile (4-9 claims; 13%), and those in the first quartile (1-3 claims; 12%). The lowest incidence (8%) was noted among patients who received no CSF.

Cox proportional hazards modeling was used to estimate the association between CSF use and time to the development of t-MDS/AML after adjusting for potential confounders (Table 3). CSF use remained significantly



		Incidence Density (cases/1,000 person-years)			Multivariable* Cox Regression	
	N (%)	3-year	5-year	10-year	HR	95% CI
No CSF, No antimetabolite	6,356 (48.1)	5.6	7.3	7.6	1.00	reference
CSF Only	1,581 (12.0)	8.8	9.2	9.8	1.26	0.94 – 1.71
Antimetabolite only	3,699 (28.0)	12.1	12.2	12.7	**1.33**	**1.04 – 1.69**
CSF + Antimetabolite	1,567 (11.9)	23.2	26.0	26.9	**2.49**	**1.91 – 3.26**

*Adjusted for diagnosis year, gender, histology, stage, comorbidity index, radiation, and chemotherapy agents.

Figure 1. Joint effect of colony-stimulating factor (CSF) and antimetabolite therapy on the risk of developing myelodysplastic syndromes or acute myeloid leukemia is shown. HR indicates hazard ratio; 95% CI, 95% confidence interval.

associated with the risk of developing t-MDS/AML (hazard ratio [HR], 1.53; 95% CI, 1.26-1.84) after adjusting for gender, histology, stage, comorbidities, chemotherapy service claims, and chemotherapy agent. The dose-response effect remained significant, with an increasing risk noted by quartile of more CSF claims. To further control for confounding, we included a propensity score to adjust for the baseline probability of receiving CSF in a separate model and found that CSF use remained significantly associated, with a 42% increased risk of t-MDS/AML (HR, 1.42; 95% CI, 1.18-3.98). Again, patients receiving more doses of CSF were found to have the higher risk of developing t-MDS/AML (HR, 1.83; 95% CI, 1.40-2.40).

In analyses stratified by histologic subtype, we found that CSF use remained a significant predictor of developing t-MDS/AML for patients within each of the major histologic subgroups. For patients with DLBCL, CSF use was found to be associated with a 36% increased risk of developing t-MDS/AML (HR, 1.36; 95% CI, 1.04-1.89); for patients with follicular lymphoma, there was a 90% increased risk (HR, 1.90; 95% CI, 1.21-2.98); and for patients with other histologic types, there was an 80% increased risk (HR, 1.80; 95% CI, 1.30-2.49).

We tested for interactions between CSF use and chemotherapy agents on the risk of developing t-MDS/AML. No significant interactions were observed between CSF and alkylating agents, topoisomerase II inhibitors, anthracyclines, or vinca alkaloids. However, we did find a significant interaction between CSF and antimetabolite use (*P* for interaction, .04). Patients who were treated with both antimetabolites and CSFs were found to have a 2.5-fold increased risk of developing t-MDS/AML (HR, 2.49; 95% CI, 1.91-3.26) compared with patients who received neither agent (Fig. 1).

DISCUSSION

The results of the current study support our hypothesis that CSF use among elderly patients with NHL who are

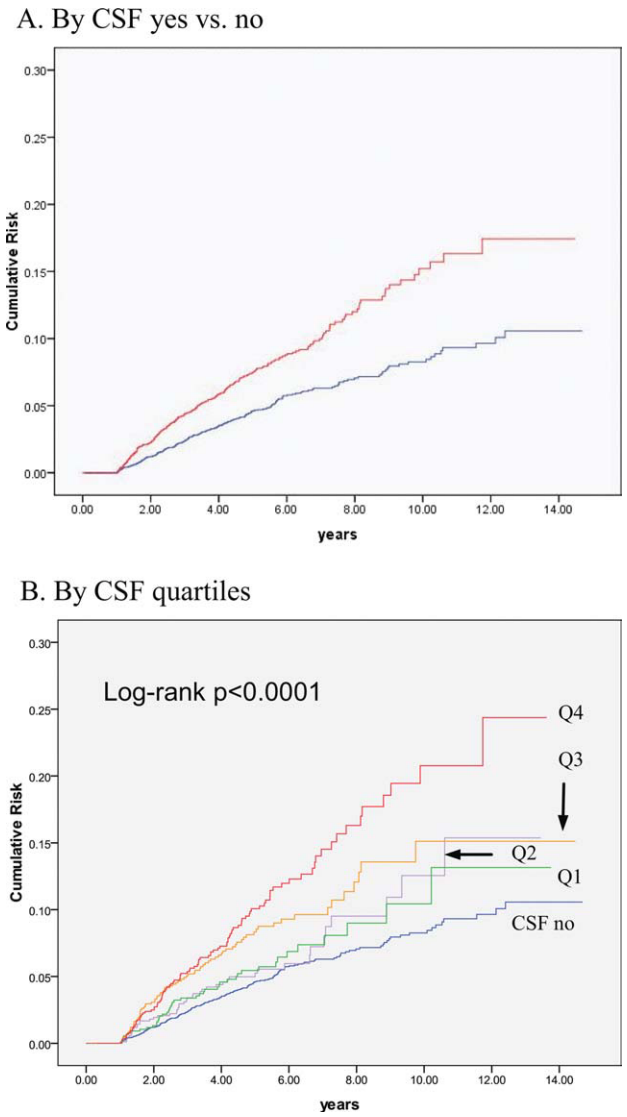


Figure 2. Cumulative incidence of developing myelodysplastic syndromes or acute myeloid leukemia is shown by colony-stimulating factor (CSF) use (yes vs no) and by quartiles (Q) of CSF claims.

receiving chemotherapy was significantly associated with an increased risk of developing t-MDS/AML. We found that CSF use overall was associated with a 1.5-fold increased risk of developing t-MDS/AML, which increased with increasing numbers/doses of CSFs. This association persisted within histologic subtypes. In addition, we found a significant interaction between CSF use and antimetabolite chemotherapy. Patients who received both CSFs and antimetabolites had a 2.5-fold increased risk of developing t-MDS/AML. This finding has clinical significance considering that approximately 10% of the overall population received this therapeutic combination.

These results are in keeping with previous studies of t-MDS/AML occurring among NHL patients.[4-9] We found that the 10-year cumulative risk of t-MDS/AML ranged from approximately 5% to 10% depending on CSF status, which is very similar to the range of 4.6% to 10% reported in previous studies.[4-9] The main outlier was the subset of the current study population who received both antimetabolites and a CSF, who were found to have a 10-year cumulative incidence of approximately 25% (Fig. 2).

The biological plausibility behind the hypothesis that CSFs may be leukemogenic is based on the observation that CSFs not only stimulate the proliferation and differentiation of hematopoietic stem cells, but also interfere with apoptosis.[12] This suppression of apoptotic cell regulation could contribute to a leukemogenic effect of growth factors either independently or by interacting with cytotoxic therapies. Lieschke et al[30] reported that CSF induced the growth of AML blast cells in vitro in approximately 50% of cases; however, they were not found to be leukemogenic.

An important finding of the current study was the interactive effect between CSF and antimetabolite therapy on the risk of t-MDS/AML. Several studies have demonstrated an increased risk of t-MDS/AML among patients receiving nucleoside analogue therapy, including antimetabolite therapy.[31] These agents incorporate themselves into the DNA, leading to DNA damage and interference with repair pathways.[31-36] Therefore, it is plausible that antimetabolites might interact synergistically with the proliferative and/or antiapoptotic activity of CSFs to initiate and then facilitate leukemogenesis.

To the best of our knowledge, this is the first large nationwide and population-based study to evaluate the association between CSF use and the risk of t-MDS/AML among patients with NHL. The strengths of this study include the use of SEER-Medicare data, which allows for the design of large population-based studies of long-term outcomes after cancer therapy. Although many clinical trials of CSF use that monitored for t-MDS/AML as an adverse event were hampered by insufficient follow-up time or smaller sample size, the current study had a large population with a long follow-up period. In addition, although clinical trial data typically have strong internal validity, the application of a sound study design to population-based data has the potential to yield results that are more generalizable to community-based care and may be more reflective of real-world outcomes. Furthermore, the focus on elderly patients with NHL also has clinical significance, because this is a population for whom treatment

Table 3. HR of Risk of Developing MDS/AML by CSF Use

	Univariable			Covariate-Adjusted			Propensity Score-Adjusted		
	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
CSF use									
No	1.00			1.00			1.00		
Yes	1.73	1.45-2.07	<.001	1.53	1.26-1.84	<.001	1.42	1.18-3.98	<.001
Q1 (1-3 administrations)	1.29	0.94-1.77	.12	1.22	0.89-1.68	.22	1.20	0.87-1.65	.28
Q2 (4-9 administrations)	1.28	0.93-1.77	.13	1.20	0.87-1.66	.26	1.14	0.82-1.57	.45
Q3 (10-22 administrations)	1.84	1.42-2.38	<.001	1.70	1.43-2.41	<.001	1.57	1.19-2.05	.001
Q4 (≥23 administrations)	2.35	1.86-2.97	<.001	1.75	1.75-2.82	<.001	1.83	1.40-2.40	<.001
P for trend			<.001			<.001			<.001
Y of diagnosis									
1992-1995	1.00	0.80-1.25	.98						
1996-1999	0.99	0.82-1.27	.87						
2000-2002	1.02								
Age at diagnosis	0.99	0.98-1.01	.50						
Gender									
Female	1.00			1.00					
Male	1.30	1.09-1.55	.003	1.22	1.02-1.46	.03			
Race									
Non-Hispanic white	1.00								
Hispanic	1.21	0.68-2.15	.51						
Black	1.03	0.62-1.72	.92						
Asian	0.95	0.58-1.57	.84						
Other	0.64	0.28-1.42	.27						
SES quartile									
1 (high)	1.00								
2	1.09	0.85-1.39	.50						
3	1.05	0.82-1.35	.69						
4 (low)	1.11	0.86-1.43	.44						
Histology									
Diffuse large B-cell	1.00			1.00					
Follicular	1.23	0.96-1.58	.10	0.94	0.73-1.22	.65			
Other	1.95	1.58-2.41	<.001	1.28	1.01-1.62	.04			
Stage at diagnosis									
I	1.00			1.00					
II	0.63	0.44-0.91	.02	1.19	0.89-1.60	.25			
III	0.76	0.51-1.12	.17	1.58	1.19-2.11	.002			
IV	1.18	0.81-1.73	.40	1.50	1.18-1.81	.001			
Comorbidity score									
0	1.00								
1	1.24	1.01-1.53	.004	1.24	1.00-1.53	.050			
≥2	1.45	1.10-1.91	.008	1.40	1.06-1.85	.018			
Chemotherapy									
Duration (DOS)	1.01	1.009-1.012	<.001	1.007	1.005-1.009	<.001			
Chemotherapy agent (yes vs no)									
Alkylating agents	0.68	0.55-0.85	.001	1.04	0.73-1.47	.83			
Topoisomerase II inhibitor	1.31	1.08-1.59	.007	0.89	0.71-1.11	.30			
Anthracyclines	0.69	0.58-0.82	<.001	0.79	0.63-0.98	.03			
Antimetabolite	2.43	2.03-2.90	<.001	1.58	1.28-1.95	<.001			
Platinums	1.71	1.19-2.48	.004	1.11	0.74-1.65	.62			
Taxanes	1.81	0.90-3.64	.10	0.76	0.55-1.07	.11			

(Continued)

Table 3. (Continued)

	Univariable			Covariate-Adjusted			Propensity Score-Adjusted		
	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
Vinca alkaloids	0.61	0.49-0.75	<.001	1.09	0.54-2.22	.81			
Targeted therapy	1.37	1.14-1.65	.001	1.11	0.92-1.34	.29			
Other	1.37	1.10-1.70	.005	1.17	0.93-1.46	.18			
Radiotherapy									
No	1.00								
Yes	1.06	0.89-1.26	.53						

HR indicates hazard ratio; MDS/AML, myelodysplastic syndromes or acute myeloid leukemia; CSF, colony-stimulating factor; 95% CI, 95% confidence interval; Q, quartile; SES, socioeconomic status; DOS, chemotherapy duration.

choice is not straightforward and therefore the identification of patient subpopulations that may be at an increased risk for adverse events (including t-MDS/AML) could provide valuable guidance in delineating treatment options.

The current study had its limitations. Although the results are more generalizable to the elderly Medicare population, they may have limited application to younger populations and to populations covered under managed care or other private insurance. However, as the aging population continues to grow in the United States, it will become increasingly important to focus attention on this demographic cohort. Other limitations are related to the nature of the data used to conduct this study. By using claims data, one cannot fully quantify and control for chemotherapy dose and intensity, which are likely significant confounders. We did attempt to control for this confounding by including the number of chemotherapy administrations as a covariate in the multivariable analyses. Although this might be considered a reasonable proxy for dose and intensity, the possibility for residual confounding remains. In addition, the "other" category of NHL included many types of NHL that may be heterogeneous with regard to receiving chemotherapy and CSF, and the risk of t-MDS/AML. Small sample sizes of patients with these subtypes of NHL limited the generation of meaningful results, thus requiring caution when interpreting the findings of the current study for these subtypes combined. Furthermore, because of the inability to determine exact dosing for CSF, it was not possible to categorize dosing according to clinically meaningful cutpoints; instead, we had to categorize the number of CSF claims by quartile to evaluate dose-response effect. Because of the observational nature of the data used for the current study, it is likely that a certain degree of selection bias was introduced. For example, many patients received CSF for the primary prevention of febrile neutropenia and infection, whereas some received it as treatment after neutropenia and infection. There was no accurate information available from these study data regarding bone marrow function at the time of CSF use, and therefore it was difficult to quantify the risk of t-MDS/AML that was associated with the disease itself or with the receipt of CSF. In addition, although we studied only those patients who received chemotherapy within 12 months of diagnosis, the sequence of various chemotherapy agents (such as first-line or second-line antimetabolite therapy) was not well ascertained, which might have confounded the study findings, although we adjusted for the number of chemotherapy claims and the number of CSF claims. We attempted to thoroughly describe our treatment cohorts to the greatest extent possible to identify potential confounding factors that might be unbalanced between the 2 comparison groups, and we tried to evaluate this using separate models and propensity scores to control for selection bias. However, we cannot entirely rule out the possibility that there may be factors associated with the use of CSF that may increase the risk of t-MDS/AML. Therefore, it will become increasingly important in the future to incorporate more clinically rich data (eg, emergency room visits and laboratory data) into studies to explore the causal mechanisms underlying observed associations. Future studies should also incorporate markers of genetic susceptibility to fully evaluate the etiology of t-MDS/AML.

In conclusion, this population-based study documented that CSF use among elderly patients with NHL who are treated with chemotherapy was associated with an increased risk of developing t-MDS/AML. These findings, suggesting an interactive effect between CSF and antimetabolites on the risk of developing t-MDS/AML, highlight the potential clinical importance of exploring

plausible interactions between therapeutic agents in the "real world." Further studies, both observational and clinical, are necessary to verify these results in younger population and to determine the potential clinical implications of this observed interaction. These studies should evaluate CSF use relative to other clinical outcomes as well as its cost-effectiveness to more fully explain the appropriate use of CSF in the care of elderly patients with NHL.

CONFLICT OF INTEREST DISCLOSURES

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