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Myelodysplastic Syndrome and Acute Myeloid Leukemia Following Use of Granulocyte Colony-Stimulating Factors in Older Non-Hodgkin Lymphoma Patients

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Abstract

Background—Granulocyte colony-stimulating factors(G-CSF), used for prevention of complications from chemotherapy-related neutropenia, are linked to risk of developing second primary myelodysplastic syndrome and acute myeloid leukemia(MDS/AML). Our purpose was to examine the relationship between use of a specific G-CSF agent and risk of MDS/AML among older patients with non-Hodgkin lymphoma(NHL).

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Conflict of interest disclosures:

Dr. Patel has consulted and received honoraria from Celgene for work unrelated to the current study. The other authors have no conflicts of interest to disclose.

Methods—We conducted a retrospective cohort study of adults aged >65 years with first primary NHL between 2001–2011, using the Surveillance Epidemiology and End Results-Medicare linked database. We estimated adjusted hazard ratios(HR) and 95% confidence intervals(CI) for MDS/AML risk associated with G-CSF(filgrastim and pegfilgrastim) use in Cox proportional hazards models stratified by treatment accounting for confounding by indication.

Results—Among 18,245 NHL patients with median follow up of 3.5 years, 56% received chemotherapy and/or immunotherapy, and G-CSF was most commonly used in those receiving rituximab plus multiple chemotherapy regimens(77%). Subsequent MDS/AML diagnoses were identified in 666(3.7%) patients. We observed modest increased risk of MDS/AML with use of G-CSF(HR=1.28, 95% CI 1.01–1.62) and a trend with increasing doses(P-trend <0.01). When analyzing specific agents, increased MDS/AML risk was consistently observed with filgrastim(10+ doses: HR=1.67, 95% CI 1.25–2.23), but not pegfilgrastim(10+ doses: HR=1.11, 95% CI 0.84–1.45).

Conclusions—We found higher MDS/AML risk among those receiving G-CSF that was specific to the use of filgrastim(≥10 doses), but not pegfilgrastim. Neutropenia prophylaxis is an essential component of highly effective NHL treatment regimens. Differential risk related to the type of G-CSF agents used warrants further study given their increasing use and newly available FDA-approved biosimilar products.

Precis:

We found higher MDS/AML risk among those receiving chemo-immunotherapy and G-CSF for neutropenia prophylaxis that was specific to the use of filgrastim, but not pegfilgrastim. Differential risk related to the type of G-CSF agents used warrants further study given their increasing use and newly available FDA-approved biosimilar products.

Keywords

Non-Hodgkin Lymphoma; Granulocyte Colony-Stimulating Factors; Myelodysplastic Syndrome; Acute Myeloid Leukemia; Epidemiology

INTRODUCTION

Myelodysplastic syndrome and acute myeloid leukemia (MDS/AML) are rare but lethal second primary cancers observed with treatment of non-Hodgkin lymphoma (NHL).[1, 2] The cytogenetic characteristics of treatment-related MDS/AML differ from their de novo counterparts, and the prognosis with these iatrogenic cancers is considerably worse.[3–7] Therapy-related MDS is more likely to transform to aggressive forms of AML[3], and the estimated four-year relapse-free survival and overall survival associated with treatment-related AML are 24.5% and 25.5% respectively.[8] The poor outcomes observed with these cancers warrants further investigation of second primary MDS/AML in patients with NHL in order to identify potentially modifiable treatment-related factors that may mitigate this risk. In particular, there is a need to investigate the risk in older NHL patients, as more than half of NHL cases occur in patients aged 65 years and older and there has been limited evaluation of the risks of second primary myeloid leukemia in this older population.

Several studies have investigated the incidence of therapy-related MDS/AML in patients diagnosed with NHL.[6, 9–17] The cumulative risk of MDS/AML following NHL diagnosis is estimated to be between 3% and 10.5% at five to six years post-primary treatment with either standard chemotherapy or high-dose chemotherapy and autologous stem cell transplantation.[6] The association between radiation therapy and second primary MDS/AML in NHL is inconsistent; although, total body irradiation in the context of stem cell transplantation was suggested as a possible risk factor for MDS/AML in patients with NHL.[2, 18–20] The risk of second primary MDS/AML is associated with both specific treatment agents and dose-intensity.[4, 6, 21] Specifically, alkylating agents and topoisomerase II inhibitors, common components of standard treatment regimens for multiple subtypes of NHL, have been associated with increased MDS/AML risk.[4, 21] The current standards of care for NHL have evolved with the introduction of rituximab-based treatment regimens. Rituximab[22], an anti-CD20 monoclonal antibody that induces apoptosis in human B-cell lymphoma cells, significantly increases survival in NHL patients when added to standard multiple chemotherapy treatments (e.g., CHOP).[23–25] MDS/AML risk in older patients with NHL has not been thoroughly investigated since the introduction of these rituximab-containing regimens.

Granulocyte colony-stimulating factors (G-CSF) are efficacious in reducing the severity and duration of neutropenia, the risk of febrile neutropenia and infection-related mortality, while enabling an increase in the dose-intensity of multiple chemotherapy regimens, including those commonly used in the treatment of NHL.[26, 27] However, concern for leukemogenesis exists with the use of G-CSF and there is a higher observed incidence of MDS/AML with its use in the treatment of many cancers, including NHL[28] and breast cancer.[29–31] It is suspected that G-CSF may help prevent mutant myeloid lineage-specific stem cells, resulting from cytotoxic therapy[32], from undergoing apoptosis, thus permitting survival of subsets of myeloid cells with genomic alterations, and ultimately leading to an increased risk of second primary myeloid malignancies.[33–36]

In a systematic review of clinical trials, Lyman et al[37] concluded that while the risk of MDS/AML is increased in patients receiving chemotherapy with G-CSF support, the apparent gains in dose-intensity and subsequent relative reductions in mortality likely outweigh the relative harms in inducing these rare second malignancies. Still, evidence from population-based studies is limited and the enhanced leukemogenic effect of G-CSF in addition to cytotoxic chemotherapy is not fully understood. Another consideration is the more recent introduction of the pegylated G-CSF formulation (i.e., pegfilgrastim) with its different dosing and pharmacokinetic properties.[38] Determining whether treatment-related myeloid cancer risk differs by the type of G-CSF agents used is critical as new biosimilar products for these drugs are now entering the market.

The purpose of this study was to examine the use of G-CSF and specific G-CSF agents on the incidence of MDS/AML in a population-based cohort of older patients diagnosed with NHL. This study uses data from the SEER-Medicare linked database between 2001 and 2011, a period during which MDS became a reportable malignancy to the SEER Program, rituximab-based therapies became standard, and use of G-CSF in conjunction with dose-intense treatment increased considerably.[39–41] Our study seeks to identify modifiable

changes to cytotoxic therapy that do not compromise immediate cancer treatment, but may mitigate the risk for potentially fatal long term side effects.

METHODS

Study population

This study utilized the SEER-Medicare linked database, developed by the National Cancer Institute and the Centers for Medicare and Medicaid Services, containing information on more than 94% of Medicare enrollees diagnosed with cancer in 18 population-based reporting regions.[42] These databases include demographic information, clinical and tumor characteristics, health care utilization and enrollment, inpatient and outpatient provider claims, vital status and the development of multiple primary cancers. An overview of the use of these data for research applications and generalizability to the U.S. elderly population are documented elsewhere.[43]

We conducted a retrospective cohort study of older patients aged 66 years and older diagnosed with first primary NHL between January 2001 and December 2011. Subjects were required to have continuous enrollment in Medicare Parts A and B for at least 12 months prior to and following NHL diagnosis (unless they died). For this analysis, we excluded patients with any of the following characteristics: (i) NHL not the first primary cancer; (ii) cancer diagnosis determined from death certificate or autopsy; (iii) non-age-related Medicare eligibility (i.e., end-stage renal disease or disability prior to age 65 years); and (iv) those for whom Medicare was not the primary payer (e.g., primary HMO enrollment) at the time of NHL diagnosis.

The study comprised a final analytic cohort of 18,245 men and women that were alive and at risk for the outcome of second primary MDS/AML, defined as not having any of the following by one year post-diagnosis: (i) synchronous MDS/AML and NHL; (ii) another second primary cancer diagnosis; or (iii), use of relapse or salvage chemotherapy (new chemotherapy initiation >120 days following previous cycle). The Institutional Review Board of the University of Illinois at Chicago approved this study in November 2017.

Data sources

Administrative data files used in this analysis of subjects from the SEER-Medicare linked database included the patient entitlement and diagnosis summary file (PEDSF); Medicare provider analysis and review (MEDPAR); carrier claims (NCH); outpatient (OUTSAF); and durable medical equipment (DME). Cancer registry information from SEER was the primary source of information for the incident primary NHL, Ann Arbor stage[44], and vital status. Diagnostic and procedure codes in the Medicare inpatient and outpatients files were used to determine baseline NCI Comorbidity Index scores.[45]

Exposures

We identified treatment-related claims by reviewing NCH, OUTSAF and DME administrative files. An algorithm for identifying chemotherapy and immunotherapy regimens characterized treatments into episodes of two or more administrations of a given

chemotherapeutic agent within 120 days of each other in the 12 months post-NHL diagnosis based on healthcare common procedure coding system (HCPCS) codes from provider claims and revenue centers.[46] We identified patients that received any chemotherapy and/or immunotherapy (yes/no); immunotherapy in our cohort refers specifically to the use of rituximab. We also collected information on the number of doses of specific agents which we further grouped as rituximab plus multiple chemotherapy regimens (e.g., R-CHOP), rituximab monotherapy, and other multiple chemotherapy regimens without rituximab (e.g., CHOP). Use of G-CSF in the 12 months post-NHL diagnosis was determined from the same claims data using diagnosis and procedural codes and described as any G-CSF use overall (yes/no), the total number of doses, and the specific G-CSF agent.

Outcomes

SEER records on the occurrence of second primary cancers were our criterion measure for defining the outcome of MDS and AML. During the study period, MDS became newly reportable as a malignancy to the SEER population-based registries. Therefore, we adapted an algorithm with high sensitivity and specificity for identifying cases of MDS (90% and 99%, respectively) and AML (89% and 99%, respectively) that uses two or more ICD-9-CM claims to identify second primary MDS/AML.[47] The date of incident MDS/AML was defined as the earlier of two or more ICD-9-CM inpatient or outpatient claims within 12 months of each other for MDS or AML, or the 15th of the month of a SEER-documented second primary MDS or AML.

Follow-up

Subjects were followed from first primary NHL diagnosis until the first day of MDS/AML diagnosis, development of a different second primary cancer, relapse treatment for NHL, death, or end of the study period on December 31, 2013. Patients entered the analysis when they became eligible for the outcome with a delayed entry of 365 days post-diagnosis (at risk time).[48]

Statistical analysis

Differences in demographic and clinical characteristics were compared between those who developed MDS/AML and those who did not using independent samples t-tests for means and chi-square tests for categorical variables. Multivariable Cox proportional hazards models were used to evaluate the association between G-CSF use and the risk of subsequent MDS/AML. In using cause-specific hazards models to account for competing risks, we estimated hazard ratios (HR) and 95% confidence intervals (CI) while adjusting for potential confounders determined *a priori*, including: age (66–69, 70–74, 75–79, 80–84, 85+ years); sex (female, male); race/ethnicity (non-Hispanic White, Black, Asian/Pacific Islander, Hispanic); NCI Comorbidity Index score at diagnosis (0, 1, 2+); year of NHL diagnosis (2001–2004, 2005–2008, 2009–2011); major NHL subtypes (diffuse large B-cell, follicular, chronic/small lymphocytic leukemia, mantle cell, marginal zone, other); Ann Arbor stage (I, II, III, IV); and type of primary NHL treatment (none, rituximab plus chemotherapy, rituximab monotherapy, other chemotherapy). We tested hypotheses comparing any G-CSF use (yes/no), and by tertiles of G-CSF doses (1–4, 5–9, 10+ doses) compared to none (reference). In models evaluating the use of filgrastim and pegfilgrastim separately in

relation to MDS/AML risk, we characterized use of each agent separately as any use (yes/no), and by tertiles of doses of the individual agents (1–4, 5–9, 10+ filgrastim doses; 1–3, 4–5, 6+ pegfilgrastim doses) with mutual adjustment for type of G-CSF in the same model; our results were robust to excluding patients that received both filgrastim and pegfilgrastim (n=1030, 15%) and stratification by G-CSF type.

The use of G-CSF is recommended for the prevention of complications from neutropenia when the risk of febrile neutropenia is approximately 20% or greater.[49–51] To account for confounding by indication with known therapy-related neutropenia risk, we modeled G-CSF risk with: (i) direct confounder adjustment for the type of chemo-immunotherapy regimen used; and (ii) in models restricted only to patients receiving any chemotherapy and/or immunotherapy and specifically rituximab plus chemotherapy regimens given the known association between alkylator and anthracycline chemotherapy with risk of myeloid leukemia.[4] In subgroup analyses, we also estimated risk of MDS/AML with G-CSF use in groups restricted to diffuse large B-cell lymphoma, follicular lymphomas separately, patients receiving alkylator-including and anthracycline regimens, and by time period of diagnosis.

We evaluated the proportional hazards assumption by testing for an interaction between G-CSF exposure covariates and the logarithm of follow up time and on the basis of post-estimation statistics from Schoenfeld residuals. All analyses were performed using Stata Statistical Software: Release 15 (College Station, TX: StataCorp LLC).

RESULTS

Our final analytic cohort included a total of 18,245 NHL patients with a median follow up of 3.5 years post-diagnosis (Table 1). A total of 666 (3.7%) patients developed second primary MDS/AML, including 81 patients with MDS that later transformed to AML. Compared to patients that did not develop MDS/AML during follow up, NHL patients with second primary MDS/AML were of similar age at NHL diagnosis (mean [SD]: 76.4 [6.7] and 76.2 [6.7] respectively), gender (female: 51% and 55%) and race/ethnicity (non-Hispanic White: 86% and 85%). A higher proportion of those that developed MDS/AML had NCI Comorbidity Index scores of 2 or higher (38% and 32%). More NHL patients that developed MDS/AML were diagnosed with “Other” subtypes (28% and 17%, respectively), not including DLBCL, follicular, chronic/small lymphocytic leukemia, mantle cell, and marginal zone lymphomas. More patients with second primary MDS/AML presented with NHL diagnoses at later tumor stages compared to patients without subsequent MDS/AML (Ann Arbor stages III-IV: 62% and 48%).

Patients that developed second primary MDS/AML were more likely to have received any chemotherapy and/or immunotherapy versus those that did not develop MDS/AML (62% and 56%) (Table 1). The most commonly received treatment in both groups was rituximab plus multiple chemotherapy regimens. Among those that received any chemotherapy and/or immunotherapy, the proportion of patients with alkylator-including regimens (75% and 67%) and anthracycline-including regimens (53% and 46%) was greater among patients that later developed MDS/AML versus those that did not. Subsequent MDS/AML cases were also slightly more likely to have received any G-CSF with treatment (40% and 37%).

Among those that received any G-CSF, a higher proportion of MDS/AML cases received filgrastim (47% and 36%) and a slightly lower proportion received pegfilgrastim (75% and 79%) with their treatment regimen compared to controls. The total number of G-CSF doses received was also higher among NHL patients that developed MDS/AML versus those that did not (10+ doses: 32% and 20%, respectively).

Among those NHL patients that received any chemotherapy and/or immunotherapy, 63% received G-CSF with their treatment regimen (Table 2). G-CSF use was most common among those that received rituximab plus multiple chemotherapy regimens (77%), and few patients treated with rituximab monotherapy received G-CSF (9%).

Cumulative hazards of MDS/AML among NHL patients by (a) treatment with chemotherapy and/or immunotherapy and (b) number of G-CSF doses among patients receiving chemotherapy and/or immunotherapy are shown in Figure 1. We found no evidence suggesting violation of the proportionality assumption. In cause-specific, multivariable Cox proportional hazards models, we found a modest overall increased risk of MDS/AML associated with receiving any G-CSF (HR=1.28, 95% CI 1.01–1.62) and observed a linear trend with increasing G-CSF doses (*P*-trend <0.01) (Table 3). In analyses restricted to those treated with any chemotherapy and/or immunotherapy, increased risk of MDS/AML was consistently observed in those that received 10 or more G-CSF doses (HR=1.51, 95% CI 1.14–2.01) and specifically among those receiving rituximab plus multiple chemotherapy regimens (10+ G-CSF doses: HR=1.64, 95% CI 1.14–2.37).

In models of G-CSF use in relation to MDS/AML risk by specific agent (Figure 2), filgrastim was associated with an overall increased risk of MDS/AML (HR=1.34, 95% CI 1.07–1.67) and the increased risk was greatest among those receiving 10 or more filgrastim doses (HR=1.67, 95% CI 1.25–2.23). No overall increased risk of MDS/AML was observed with pegfilgrastim (HR=1.00, 95% CI 0.81–1.24), nor was risk increased with increasing doses of pegfilgrastim.

In subgroup analyses, we modeled G-CSF risk among patients with the two most common NHL subtypes (diffuse large B-cell lymphoma and follicular lymphoma; Supplemental Tables S1 and S2). Results indicating increased risk were consistent for patients that received 10 or more G-CSF doses in analyses restricted to either subtype, diffuse large B-cell lymphoma (HR=1.72, 95% CI 1.06–2.81) and follicular lymphoma (HR=2.31, 95% CI 0.98–5.43). Similarly, in analyses stratified by diagnosis year (Supplemental Table S3) and by specific chemotherapy agents (Supplemental Table S4), trends in increased MDS/AML were consistent, though power was limited within subgroups.

DISCUSSION

In this large population-based cohort of older NHL patients, we found a positive association between G-CSF and increased risk of MDS/AML with evidence also suggesting a dose-response. The overall cumulative incidence of MDS/AML was 3.7%, and varied slightly by NHL subtype; notably however, the risk of MDS/AML associated with G-CSF use was elevated independently of histologic lymphoma subtype. In our analysis of G-CSF use in

terms of specific agents, we observed an increased MDS/AML risk that was specific to filgrastim, and not pegfilgrastim, a finding that to our knowledge has not been reported in epidemiologic studies of NHL patients since the introduction of pegylated G-CSF in 2002.

Our results are consistent with previously reported estimates of MDS/AML occurrence in patients diagnosed with NHL.[6, 14, 20, 28, 52, 53] A cohort study of 999 NHL patients treated (without GCSF) between 1970 and 1981 at the Duke University Medical Center[14] identified the 10-year cumulative risk of AML to be 4%, regardless of treatment received (i.e., chemotherapy only, radiation therapy only, or combined chemotherapy and radiation therapy). While these studies with estimates of second primary myeloid cancer post-NHL have long-term follow up and include clinical trial and real-world settings, most are based on data gathered prior to 2000, before the introduction of rituximab (and are therefore less representative of the current standard treatments) and focused on younger populations.

Few large epidemiological studies have investigated the association between receipt of G-CSF and the risk of MDS/AML among elderly patients with NHL, although leukemogenesis associated with G-CSF has been suggested in studies of other cancer sites such as breast cancer.[29–31] In a study using the SEER-Medicare linked database by Gruschkus et al.[28], NHL patients diagnosed between 1992 and 2002 that were treated with chemotherapy had a 5-year cumulative risk of MDS/AML of about 7% if they received G-CSF, compared to about 4% if they did not receive it. A significant dose-response effect was also observed, with a 10-year cumulative incidence of 21% for those patients receiving more than 23 doses of G-CSF, but only a 12% cumulative incidence for those with one to three doses of G-CSF. In the current report, we found a cumulative MDS/AML risk of 6% among patients receiving the highest tertile (10 or more) of total G-CSF doses, compared to those receiving fewer than 10 total G-CSF doses (3%). Our findings of a 51% increased risk of MDS/AML associated with 10 or more G-CSF doses in those treated with any chemotherapy and/or immunotherapy were similar to the overall finding by Gruschkus et al.[28] of increased risk with use of G-CSF in patients receiving chemotherapy (HR=1.53, 95% CI 1.26–1.84). Also like the previous study, our findings on MDS/AML risk were consistently elevated across NHL histologic subtypes. However, their analysis lacked information on the use of pegfilgrastim which was only FDA-approved in 2002, but is now widely used in current practice. Our analyses showed neither an association between pegfilgrastim and MDS/AML risk, nor a trend of increased risk with greater number of pegfilgrastim doses. Another study of older breast cancer patients identified in the SEER-Medicare linked database between 2001 and 2009 reported increased MDS/AML risk that was exclusive to filgrastim, and not observed with pegfilgrastim.[31] Risk associated with filgrastim was highest among women that were treated with an anthracycline-based chemotherapy regimen for breast cancer (HR=2.11, 95% CI 1.29–3.30). This was in agreement with our subgroup analysis that demonstrated a two-fold increased risk (95% CI 1.56–2.43) associated with filgrastim among NHL patients treated with anthracycline-including chemotherapy.

Although our study was focused on a population of Medicare-aged patients with NHL, the risk of treatment-related MDS/AML is greater among younger cancer patients. Radiation-related risk of leukemia is demonstrated to be age-dependent[54] with higher rates of secondary MDS or AML found in younger patients with Hodgkin lymphoma[55, 56] and breast

cancer[57] when combined with multiple chemotherapy. With more potential survival years beyond NHL diagnosis, aggressive and dose-intensive treatment strategies in younger patients are accompanied by a greater lifetime risk of myeloid leukemia. Future pharmacovigilance studies should investigate these differential effects of G-CSF on long-term outcomes of younger patients with NHL.

The concern for leukemogenesis with G-CSF is longstanding. Our study and others describing the incidence of MDS/AML following use of G-CSF for chemotherapy-induced neutropenia are not entirely consistent with a recent report by Dale, et al.[58] where 356 patients with cyclic neutropenia experienced no myeloid neoplasms over 3000 patient-years of treatment with G-CSF. In patients with severe congenital neutropenia receiving long-term G-CSF therapy, Rosenberg, et al.[59] described increasing incidence of MDS/AML over time owed to mutations in the gene for G-CSF receptors. It is hypothesized that such genomic instability may be responsible for higher rates of leukemic transformation.[60] Rather than an observed “bystander” effect of G-CSF with leukemogenesis, these findings may represent the potentiation of MDS/AML in hematopoietic cells with genetic alterations as a result of cytotoxic chemotherapy.[33] Our finding showing the greatest increase in risk of MDS/AML among NHL patients that received filgrastim in combination with anthracycline-including chemotherapy is consistent with this hypothesis and also aligns with the shorter latency of topoisomerase II inhibitor-related myeloid leukemias.[4]

To our knowledge, the current report is the first study of the difference in risk of MDS/AML among elderly patients with NHL by type of G-CSF received. Filgrastim and pegfilgrastim are the two major types of G-CSF available in the United States.[61, 62] Both drugs have the same mechanism of action, but the pegylated formulation of recombinant G-CSF is dosed less frequently (once per cycle) and the metabolism and clearance of filgrastim and pegfilgrastim differ.[38] Pharmacokinetic clearance of filgrastim involves both (i) renal elimination and (ii) binding to G-CSF receptors with subsequent endocytosis and degradation. Pegylation of G-CSF prevents renal elimination and results in a reliance on neutrophil-mediated clearance. Thus, following a single dose administration of pegfilgrastim, neutrophil recovery results in the prompt degradation of G-CSF. Dosing of daily administered filgrastim, relying on observed laboratory testing of the postnadir absolute neutrophil count recovery before discontinuation of G-CSF, may potentially result in an unnecessarily extended exposure to the growth factor, especially if renal function is inadequate.

The exact reason for the differential risk of MDS/AML induced by these agents is unknown; for example, it is still unclear whether it is the duration or the peak levels of G-CSF that are important for leukemogenesis. However, further studies are warranted given the 2015 FDA approval of a G-CSF biosimilar, filgrastim-sndz (Zarxio™)[63], and the 2018 FDA approval of pegfilgrastim-jmdb (Fulphila™)[64], which will likely expand use of this agent. These biosimilars are not approved as interchangeable products, and unlike small molecule generic drugs, the complexity of the protein structures and potential differences in the manufacturing processes could also have implications on safety or outcomes, even for the same biologic medication.[65]

Distinguishing between the leukemogenic effects of chemotherapeutic agents and G-CSF in epidemiological studies is complex, in part due to confounding by indication. Patients receiving dose-intense chemotherapy regimens are more likely to receive G-CSF to prevent complications associated with neutropenia. Further, the use of G-CSF allows for use of higher doses of chemotherapy and reduces delays between cycles, which can improve survival. Thus, a possible channeling bias in which patients receiving stronger chemotherapy regimens necessitate use of G-CSF (and vice versa) makes it difficult to separate the effects. We accounted for this by using both confounder adjustment and stratification. Our analyses suggest that if our findings were due entirely to the dose-intense chemotherapy indicating G-CSF use, we would be unlikely to observe findings similar to those of other clinical trials or risk that is differential by G-CSF type.

Strengths and Limitations

The strengths of this study include the use of a population-based cohort from the SEER-Medicare linked database during a more recent time period with widespread G-CSF use, and with MDS as a reportable malignancy to the SEER registries. Older NHL patients are less represented in clinical trials with long-term follow up; thus, information on treatment risks and surveillance for rare adverse events like MDS/AML in patients ages 65 and older are only answered by large population-based cohort studies such as this. Furthermore, our study captured a period of time (post-2002) when both filgrastim and pegfilgrastim products were available for use.

A limitation of our study is the identification of subsequent diagnoses of MDS and AML based on SEER and administrative Medicare claims data. Misclassification of MDS/AML outcomes solely from claims data (ICD-9 diagnosis codes) are based on the tendency for false-positive diagnosis of MDS/AML when based on a single claim. To minimize possible misclassification, we used a recommended case definition with high sensitivity and specificity.[47] To minimize confounding by disease severity and competing events that increase MDS/AML risk, we introduced a time lag with delayed cohort entry, and used cause-specific hazards models to censor at other second cancer events.[48] We also collected detailed information on treatment with chemotherapy and/or immunotherapy and stratified analyses to account for the potential confounding effect of dose-intense chemotherapy as the indication for G-CSF to prevent neutropenia. The presence of elevated risk in both the adjusted multivariable models and the stratum-specific analyses support our overall conclusions. Another limitation of our study was that we had limited information about the specific dosing schedules or dose intensity of G-CSF; therefore, we cannot know how specific G-CSF exposure patterns impact the risk of MDS/AML. Further, while we had information on specific NHL subtypes, we lacked other important information on factors that could drive treatment and G-CSF use.

Conclusions

The reasons for the differential risk of MDS/AML observed with filgrastim and pegfilgrastim remain unclear. Understanding possible differences in the long-term safety of G-CSF is extremely important with biosimilar products now entering the market. Further studies of MDS/AML risk following treatment of NHL should include all age groups and

biosimilar drugs to confirm and fully characterize the risk attributable to specific G-CSF agents.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments:

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REFERENCES

1. Travis LB, Curtis RE, Glimelius B, et al. Second cancers among long-term survivors of non-Hodgkin's lymphoma. J Natl Cancer Inst. 1993;85: 1932–1937. [PubMed: 8230284]
2. Bhatia S Therapy-related myelodysplasia and acute myeloid leukemia. Semin Oncol. 2013;40: 666–675. [PubMed: 24331189]
3. Larson RA. Etiology and management of therapy-related myeloid leukemia. Hematology / the Education Program of the American Society of Hematology. American Society of Hematology. Education Program. 2007: 453–459.
4. Godley LA, Larson RA. Therapy-related myeloid leukemia. Semin Oncol. 2008;35: 418–429. [PubMed: 18692692]
5. Granfeldt Ostgard LS, Medeiros BC, Sengelov H, et al. Epidemiology and Clinical Significance of Secondary and Therapy-Related Acute Myeloid Leukemia: A National Population-Based Cohort Study. J Clin Oncol. 2015;33: 3641–3649. [PubMed: 26304885]
6. Armitage JO, Carbone PP, Connors JM, Levine A, Bennett JM, Kroll S. Treatment-related myelodysplasia and acute leukemia in non-Hodgkin's lymphoma patients. J Clin Oncol. 2003;21: 897–906. [PubMed: 12610191]
7. Smith SM, Le Beau MM, Huo D, et al. Clinical-cytogenetic associations in 306 patients with therapy-related myelodysplasia and myeloid leukemia: the University of Chicago series. Blood. 2003;102: 43–52. [PubMed: 12623843]

8. Kayser S, Dohner K, Krauter J, et al. The impact of therapy-related acute myeloid leukemia (AML) on outcome in 2853 adult patients with newly diagnosed AML. Blood. 2011;117: 2137–2145. [PubMed: 21127174]
9. Sacchi S, Marcheselli L, Bari A, et al. Second malignancies after treatment of diffuse large B-cell non-Hodgkin's lymphoma: a GISL cohort study. Haematologica. 2008;93: 1335–1342. [PubMed: 18698083]
10. Mudie NY, Swerdlow AJ, Higgins CD, et al. Risk of second malignancy after non-Hodgkin's lymphoma: a British Cohort Study. J Clin Oncol. 2006;24: 1568–1574. [PubMed: 16520465]
11. Milligan DW, Ruiz De Elvira MC, Kolb HJ, et al. Secondary leukaemia and myelodysplasia after autografting for lymphoma: results from the EBMT. EBMT Lymphoma and Late Effects Working Parties. European Group for Blood and Marrow Transplantation. Br J Haematol. 1999;106: 1020–1026. [PubMed: 10520006]
12. Wheeler C, Khurshid A, Ibrahim J, et al. Incidence of post transplant myelodysplasia/acute leukemia in non-Hodgkin's lymphoma patients compared with Hodgkin's disease patients undergoing autologous transplantation following cyclophosphamide, carmustine, and etoposide (CBV). Leukemia & lymphoma. 2001;40: 499–509. [PubMed: 11426523]
13. McLaughlin P, Estey E, Glassman A, et al. Myelodysplasia and acute myeloid leukemia following therapy for indolent lymphoma with fludarabine, mitoxantrone, and dexamethasone (FND) plus rituximab and interferon alpha. Blood. 2005;105: 4573–4575. [PubMed: 15741224]
14. Lavey RS, Eby NL, Prosnitz LR. Impact on second malignancy risk of the combined use of radiation and chemotherapy for lymphomas. Cancer. 1990;66: 80–88. [PubMed: 2354413]
15. Krishnan A, Bhatia S, Slovak ML, et al. Predictors of therapy-related leukemia and myelodysplasia following autologous transplantation for lymphoma: an assessment of risk factors. Blood. 2000;95: 1588–1593. [PubMed: 10688812]
16. Howe R, Micallef IN, Inwards DJ, et al. Secondary myelodysplastic syndrome and acute myelogenous leukemia are significant complications following autologous stem cell transplantation for lymphoma. Bone marrow transplantation. 2003;32: 317–324. [PubMed: 12858205]
17. Carney DA, Westerman DA, Tam CS, et al. Therapy-related myelodysplastic syndrome and acute myeloid leukemia following fludarabine combination chemotherapy. Leukemia. 2010;24: 2056–2062. [PubMed: 20962860]
18. Travis LB, Weeks J, Curtis RE, et al. Leukemia following low-dose total body irradiation and chemotherapy for non-Hodgkin's lymphoma. J Clin Oncol. 1996;14: 565–571. [PubMed: 8636772]
19. Hosing C, Munsell M, Yazji S, et al. Risk of therapy-related myelodysplastic syndrome/acute leukemia following high-dose therapy and autologous bone marrow transplantation for non-Hodgkin's lymphoma. Annals of oncology : official journal of the European Society for Medical Oncology / ESMO. 2002;13: 450–459.
20. Leone G, Pagano L, Ben-Yehuda D, Voso MT. Therapy-related leukemia and myelodysplasia: susceptibility and incidence. Haematologica. 2007;92: 1389–1398. [PubMed: 17768113]
21. Morton LM, Dores GM, Tucker MA, et al. Evolving risk of therapy-related acute myeloid leukemia following cancer chemotherapy among adults in the United States, 1975–2008. Blood. 2013;121: 2996–3004. [PubMed: 23412096]
22. Porwancher R, Sheth A, Remphrey S, Taylor E, Hinkle C, Zervos M. Epidemiological study of hospital-acquired infection with vancomycin-resistant Enterococcus faecium: possible transmission by an electronic ear-probe thermometer. Infect Control Hosp Epidemiol. 1997;18: 771–773. [PubMed: 9397374]
23. Coiffier B, Lepage E, Briere J, et al. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. N Engl J Med. 2002;346: 235–242. [PubMed: 11807147]
24. Badin F, Hayslip J. Rituximab in the treatment of B-cell non-Hodgkin lymphoma, focus on outcomes and comparative effectiveness. Clinicoecon Outcomes Res. 2010;2: 37–45. [PubMed: 21935313]

25. Dotan E, Aggarwal C, Smith MR. Impact of Rituximab (Rituxan) on the Treatment of B-Cell Non-Hodgkin's Lymphoma. P T. 2010;35: 148–157. [PubMed: 20442809]
26. Trillet-Lenoir V, Green J, Manegold C, et al. Recombinant granulocyte colony stimulating factor reduces the infectious complications of cytotoxic chemotherapy. Eur J Cancer. 1993;29A: 319–324. [PubMed: 7691119]
27. Crawford J, Ozer H, Stoller R, et al. Reduction by granulocyte colony-stimulating factor of fever and neutropenia induced by chemotherapy in patients with small-cell lung cancer. N Engl J Med. 1991;325: 164–170. [PubMed: 1711156]
28. Gruschkus SK, Lairson D, Dunn JK, Risser J, Du XL. Use of white blood cell growth factors and risk of acute myeloid leukemia or myelodysplastic syndrome among elderly patients with non-Hodgkin lymphoma. Cancer. 2010;116: 5279–5289. [PubMed: 20665502]
29. Patt DA, Duan Z, Fang S, Hortobagyi GN, Giordano SH. Acute myeloid leukemia after adjuvant breast cancer therapy in older women: understanding risk. J Clin Oncol. 2007;25: 3871–3876. [PubMed: 17664457]
30. Hershman D, Neugut AI, Jacobson JS, et al. Acute myeloid leukemia or myelodysplastic syndrome following use of granulocyte colony-stimulating factors during breast cancer adjuvant chemotherapy. J Natl Cancer Inst. 2007;99: 196–205. [PubMed: 17284714]
31. Calip GS, Malmgren JA, Lee WJ, Schwartz SM, Kaplan HG. Myelodysplastic syndrome and acute myeloid leukemia following adjuvant chemotherapy with and without granulocyte colony-stimulating factors for breast cancer. Breast Cancer Res Treat. 2015;154: 133–143. [PubMed: 26450505]
32. Kaushansky K Lineage-specific hematopoietic growth factors. N Engl J Med. 2006;354: 2034–2045. [PubMed: 16687716]
33. Touw IP, Bontenbal M. Granulocyte colony-stimulating factor: key (f)actor or innocent bystander in the development of secondary myeloid malignancy? J Natl Cancer Inst. 2007;99: 183–186. [PubMed: 17284707]
34. Bennett CL, Evens AM, Andritsos LA, et al. Haematological malignancies developing in previously healthy individuals who received haematopoietic growth factors: report from the Research on Adverse Drug Events and Reports (RADAR) project. Br J Haematol. 2006;135: 642–650. [PubMed: 17054431]
35. Confer DL, Miller JP. Long-term safety of filgrastim (rhG-CSF) administration. Br J Haematol. 2007;137: 77–78; author reply 79–80. [PubMed: 17359373]
36. Shaw BE, Confer DL, Hwang W, Pulsipher MA. A review of the genetic and long-term effects of G-CSF injections in healthy donors: a reassuring lack of evidence for the development of haematological malignancies. Bone marrow transplantation. 2015;50: 334–340. [PubMed: 25599171]
37. Lyman GH, Dale DC, Wolff DA, et al. Acute myeloid leukemia or myelodysplastic syndrome in randomized controlled clinical trials of cancer chemotherapy with granulocyte colony-stimulating factor: a systematic review. J Clin Oncol. 2010;28: 2914–2924. [PubMed: 20385991]
38. Yang BB, Kido A. Pharmacokinetics and pharmacodynamics of pegfilgrastim. Clin Pharmacokinet. 2011;50: 295–306. [PubMed: 21456630]
39. Smith TJ, Khatcheressian J, Lyman GH, et al. 2006 update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline. J Clin Oncol. 2006;24: 3187–3205. [PubMed: 16682719]
40. Lyman GH. Guidelines of the National Comprehensive Cancer Network on the use of myeloid growth factors with cancer chemotherapy: a review of the evidence. J Natl Compr Canc Netw. 2005;3: 557–571. [PubMed: 16038646]
41. Aapro MS, Bohlius J, Cameron DA, et al. 2010 update of EORTC guidelines for the use of granulocyte-colony stimulating factor to reduce the incidence of chemotherapy-induced febrile neutropenia in adult patients with lymphoproliferative disorders and solid tumours. Eur J Cancer. 2011;47: 8–32. [PubMed: 21095116]
42. Epidemiology Surveillance and Results End (SEER) Program. Overview of the SEER Program http://seer.cancer.gov/about/overview.html.

43. Warren JL, Klabunde CN, Schrag D, Bach PB, Riley GF. Overview of the SEER-Medicare data: content, research applications, and generalizability to the United States elderly population. Med Care. 2002;40: IV-3–18.
44. Morton LM, Turner JJ, Cerhan JR, et al. Proposed classification of lymphoid neoplasms for epidemiologic research from the Pathology Working Group of the International Lymphoma Epidemiology Consortium (InterLymph). Blood. 2007;110: 695–708. [PubMed: 17389762]
45. Klabunde CN, Potosky AL, Legler JM, Warren JL. Development of a comorbidity index using physician claims data. J Clin Epidemiol. 2000;53: 1258–1267. [PubMed: 11146273]
46. Bikov KA, Mullins CD, Seal B, Onukwugha E, Hanna N. Algorithm for identifying chemotherapy/biological regimens for metastatic colon cancer in SEER-Medicare. Med Care. 2015;53: e58–64. [PubMed: 23552436]
47. Cogle CR, Craig BM, Rollison DE, List AF. Incidence of the myelodysplastic syndromes using a novel claims-based algorithm: high number of uncaptured cases by cancer registries. Blood. 2011;117: 7121–7125. [PubMed: 21531980]
48. Chubak J, Boudreau DM, Wirtz HS, McKnight B, Weiss NS. Threats to validity of nonrandomized studies of postdiagnosis exposures on cancer recurrence and survival. J Natl Cancer Inst. 2013;105: 1456–1462. [PubMed: 23940288]
49. Freifeld AG, Bow EJ, Sepkowitz KA, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the infectious diseases society of america. Clin Infect Dis. 2011;52: e56–93. [PubMed: 21258094]
50. Smith TJ, Bohlke K, Lyman GH, et al. Recommendations for the Use of WBC Growth Factors: American Society of Clinical Oncology Clinical Practice Guideline Update. J Clin Oncol. 2015;33: 3199–3212. [PubMed: 26169616]
51. Klastersky J, de Naurois J, Rolston K, et al. Management of febrile neutropaenia: ESMO Clinical Practice Guidelines. Ann Oncol. 2016;27: v111–v118. [PubMed: 27664247]
52. Greene MH, Young RC, Merrill JM, DeVita VT. Evidence of a treatment dose response in acute nonlymphocytic leukemias which occur after therapy of non-Hodgkin's lymphoma. Cancer Res. 1983;43: 1891–1898. [PubMed: 6572558]
53. Pedersen-Bjergaard J, Ersbøll J, Sørensen HM, et al. Risk of acute nonlymphocytic leukemia and preleukemia in patients treated with cyclophosphamide for non-Hodgkin's lymphomas. Comparison with results obtained in patients treated for Hodgkin's disease and ovarian carcinoma with other alkylating agents. Ann Intern Med. 1985;103: 195–200. [PubMed: 4014901]
54. Wakeford R The cancer epidemiology of radiation. Oncogene. 2004;23: 6404–6428. [PubMed: 15322514]
55. Swerdlow AJ, Barber JA, Hudson GV, et al. Risk of second malignancy after Hodgkin's disease in a collaborative British cohort: the relation to age at treatment. J Clin Oncol. 2000;18: 498–509. [PubMed: 10653865]
56. Mauch PM, Kalish LA, Marcus KC, et al. Second malignancies after treatment for laparotomy staged IA-IIIB Hodgkin's disease: long-term analysis of risk factors and outcome. Blood. 1996;87: 3625–3632. [PubMed: 8611686]
57. Kaplan HG, Malmgren JA, Li CI, Calip GS. Age related risk of myelodysplastic syndrome and acute myeloid leukemia among breast cancer survivors. Breast Cancer Res Treat. 2013;142: 629–636. [PubMed: 24265034]
58. Dale DC, Bolyard A, Marrero T, et al. Long-Term Effects of G-CSF Therapy in Cyclic Neutropenia. N Engl J Med. 2017;377: 2290–2292. [PubMed: 29211670]
59. Rosenberg PS, Alter BP, Bolyard AA, et al. The incidence of leukemia and mortality from sepsis in patients with severe congenital neutropenia receiving long-term G-CSF therapy. Blood. 2006;107: 4628–4635. [PubMed: 16497969]
60. Dong F, Brynes RK, Tidow N, Welte K, Lowenberg B, Touw IP. Mutations in the gene for the granulocyte colony-stimulating-factor receptor in patients with acute myeloid leukemia preceded by severe congenital neutropenia. N Engl J Med. 1995;333: 487–493. [PubMed: 7542747]
61. Product Information: NEUPOGEN® IV injection, filgrastim IV injection. Amgen Manufacturing,Limited, Thousand Oaks, CA, 2007.

62. Product Information: NEULASTA® subcutaneous injection, pegfilgrastim subcutaneous injection. Amgen Inc (per FDA), Thousand Oaks, CA, 2016.

63. Product Information: ZARXIO(TM) subcutaneous injection solution, intravenous injection solution, filgrastim-sndz subcutaneous injection solution, intravenous injection solution. Sandoz Inc. (per FDA), Princeton, NJ, 2015.

64. Product Information: FULPHILA(TM) subcutaneous injection solution, intravenous injection solution, pegfilgrastim-jmdb subcutaneous injection solution, intravenous injection solution. Mylan Institutional, LLC. (per FDA), Rockford, IL, 2015.

65. Rifkin RM, Peck SR. Biosimilars: Implications for Clinical Practice. Journal of oncology practice / American Society of Clinical Oncology. 2017;13: 24s–31s.

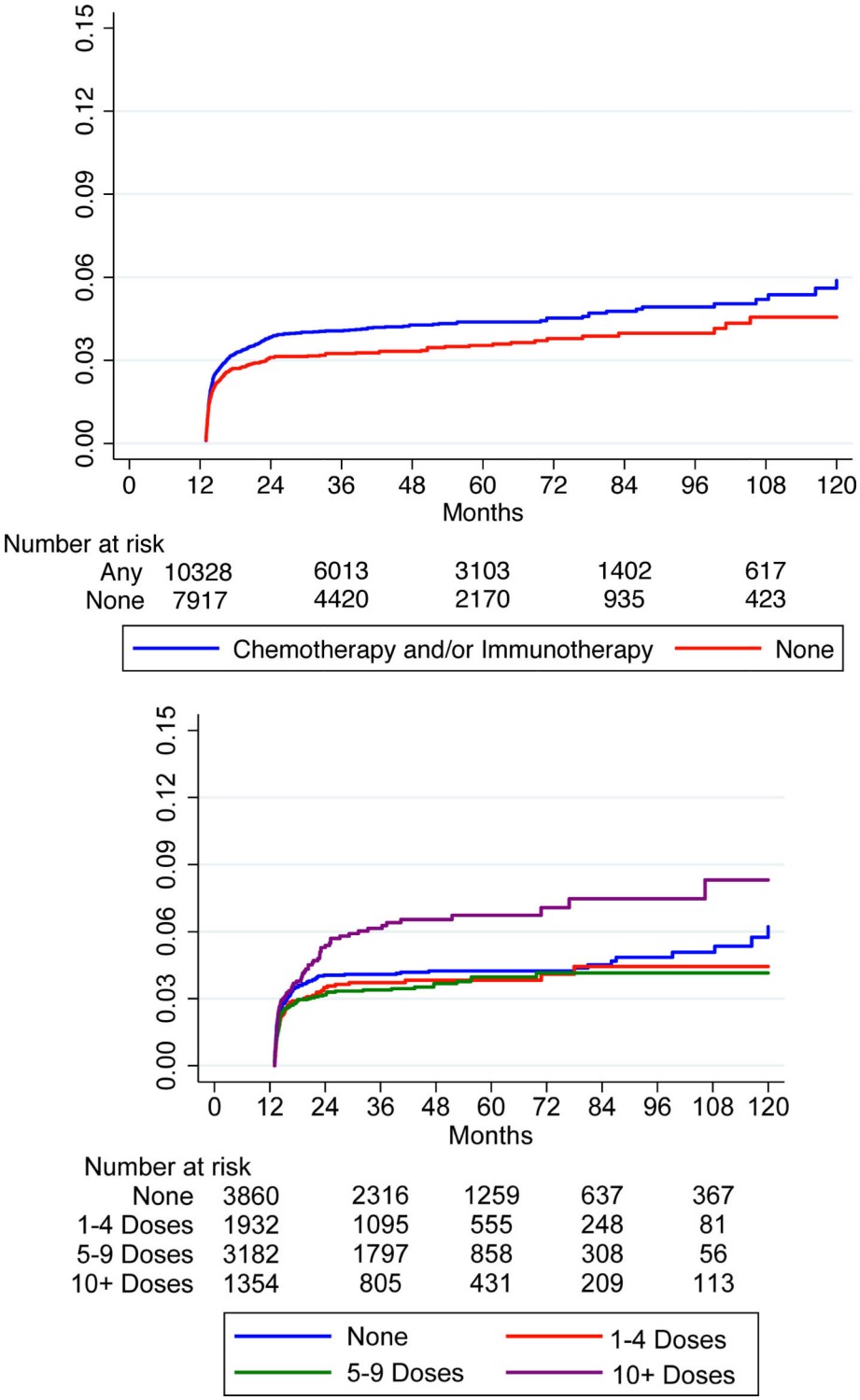

Figure 1.

Cumulative hazards of developing myelodysplastic syndrome and acute myeloid leukemia (MDS/AML) among Medicare beneficiaries diagnosed with non-Hodgkin lymphoma (NHL)

between 2001 and 2011 by (a) treatment with chemotherapy and/or immunotherapy and (b) doses of G-CSF

a.Treatment with any chemotherapy and/or immunotherapy

b.Number of G-CSF doses among patients receiving chemotherapy and/or immunotherapy

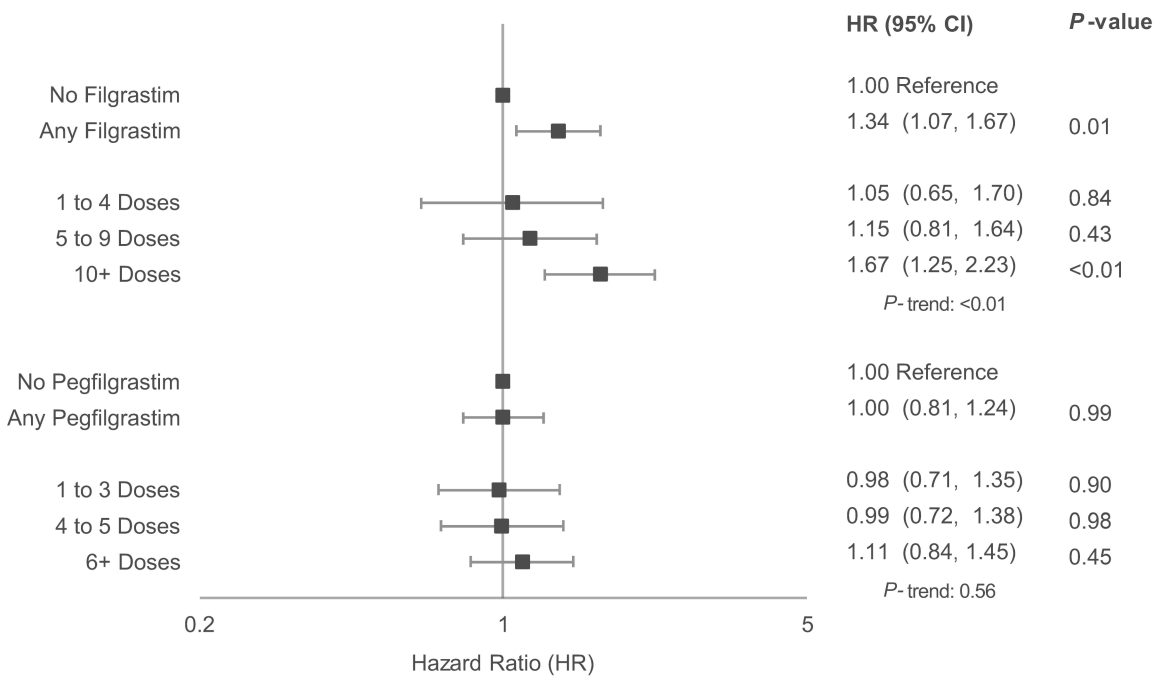

Figure 2.

Cox proportional hazards models relating total number of filgrastim and pegfilgrastim doses to risk of myelodysplastic syndrome and acute myeloid leukemia among Medicare beneficiaries diagnosed with non-Hodgkin lymphoma (NHL) from the SEER-Medicare linked database between 2001 and 2011 treated with any chemotherapy and/or immunotherapy

* Models are adjusted for age, gender, race/ethnicity, NCI Comorbidity Index score at diagnosis, year of diagnosis, non-Hodgkin lymphoma subtype, Ann Arbor stage, and type of chemotherapy and/or immunotherapy received.

Table 1.

Descriptive characteristics of Medicare beneficiaries diagnosed with first primary non-Hodgkin lymphoma (NHL) from the SEER-Medicare linked database between 2001 and 2011 by subsequent diagnosis of myelodysplastic syndrome or acute myeloid leukemia (MDS/AML)

	Overall(*N* = 18245)		MDS/AML (*n* = 666)		No MDS/AML(*n* = 17579)		*P* value
	n	(%)	n	(%)	n	(%)	
Age at NHL diagnosis, years							
Mean (SD)	76.2	(6.7)	76.4	(6.7)	76.2	(6.7)	0.40
66–69	3420	(18.7)	123	(18.5)	3297	(18.8)	0.43
70–74	4592	(25.2)	165	(24.8)	4427	(25.2)	
75–79	4591	(25.2)	152	(22.8)	4439	(25.3)	
80–84	3419	(18.7)	140	(21.0)	3279	(18.7)	
≥85	2223	(12.2)	86	(12.9)	2137	(12.2)	
Gender							
Male	8331	(45.7)	324	(48.6)	8007	(45.5)	0.12
Female	9914	(54.3)	342	(51.4)	9572	(54.5)	
Race/Ethnicity							
Non-Hispanic White	15548	(85.2)	573	(86.0)	14975	(85.2)	0.37
Black	755	(4.1)	31	(4.7)	724	(4.1)	
Asian/Pacific Islander	762	(4.2)	26	(3.9)	736	(4.2)	
Hispanic	1053	(5.8)	29	(4.4)	1024	(5.8)	
NCI Comorbidity Index							
0	6180	(33.9)	231	(34.7)	5949	(33.8)	<0.01
1	4542	(24.9)	168	(25.2)	4374	(24.9)	
≥2	5888	(32.3)	253	(38.0)	5635	(32.1)	
Year of NHL diagnosis							
2001–2004	3630	(19.9)	131	(19.7)	3499	(19.9)	0.24
2005–2008	7209	(39.5)	283	(42.5)	6926	(39.4)	
2009–2011	7406	(40.6)	252	(37.8)	7154	(40.7)	
Histology							
Diffuse large B-cell	6229	(34.1)	192	(28.8)	6037	(34.3)	<0.01
Follicular	4067	(22.3)	82	(12.3)	3985	(22.7)	
Chronic/small lymphocytic leukemia	1560	(8.6)	70	(10.5)	1490	(8.5)	
Mantle cell	799	(4.4)	30	(4.5)	769	(4.4)	
Marginal zone	2443	(13.4)	105	(15.8)	2338	(13.3)	
Other subtype	3147	(17.2)	187	(28.1)	2960	(16.8)	
Ann Arbor Stage							
I	5351	(29.3)	140	(21.0)	5211	(29.6)	<0.01
II	2742	(15.0)	66	(9.9)	2676	(15.2)	
III	2852	(15.6)	79	(11.9)	2773	(15.8)	
IV	5905	(32.4)	336	(50.5)	5569	(31.7)	
Primary NHL treatment							

	Overall(*N* = 18245)		MDS/AML (*n* = 666)		No MDS/AML(*n* = 17579)		*P* value
	n	(%)	n	(%)	n	(%)	
Chemotherapy and/or Immunotherapy							
No	7917	(43.4)	254	(38.1)	7663	(43.6)	0.01
Yes (any)	10328	(56.6)	412	(61.9)	9916	(56.4)	
Rituximab + Chemotherapy	7586	(73.5)	275	(66.7)	7311	(73.7)	0.01
Rituximab Monotherapy	1848	(17.9)	96	(23.3)	1752	(17.7)	
Chemotherapy without Rituximab	894	(8.7)	41	(10.0)	853	(8.6)	
Chemotherapy regimens							
Alkylator-including	7374	(71.4)	310	(75.2)	6643	(67.0)	<0.01
Anthracycline-including	5476	(53.0)	220	(53.3)	4525	(45.6)	<0.01
G-CSF use							
None	11556	(63.3)	398	(59.8)	11158	(63.5)	0.05
Any G-CSF**	6689	(36.7)	268	(40.2)	6421	(36.5)	
Filgrastim	2423	(36.2)	125	(46.6)	2298	(35.8)	<0.01
Pegfilgrastim	5296	(79.1)	200	(74.6)	5096	(79.4)	0.06
Number of G-CSF doses							
1-4	2064	(30.9)	73	(27.2)	1991	(31.0)	<0.01
5–9	3232	(48.3)	110	(41.0)	3122	(48.6)	
≥10	1393	(20.8)	85	(31.7)	1308	(20.4)	
Duration of follow up, years							
Median (interquartile range)	3.5	(2.1–5.3)	3.3	(2.0–5.3)	3.5	(2.1–5.3)	

** Type of G-CSF use not mutually exclusive

* To compare differences between groups we used independent samples *t*-tests for means and X^2 test for categorical variables

Table 2.

Cases of myelodysplastic syndrome and acute myeloid leukemia (MDS/AML) and use of granulocyte colony-stimulating factors (G-CSF) among Medicare beneficiaries diagnosed with Non-Hodgkin lymphoma (NHL) from the SEER-Medicare linked database between 2001 and 2011 treated with any chemotherapy and/or immunotherapy

	Any Chemotherapy and/or Immunotherapy (n = 10328)		Rituximab + Chemotherapy (n = 7586)		Rituximab Monotherapy (n = 1848)		Chemotherapy without Rituximab (n = 894)	
	n	(%)	n	(%)	n	(%)	n	(%)
MDS/AML	412	(4.0)	275	(3.6)	96	(5.2)	41	(4.6)
Any G-CSF use*	6468	(62.6)	5821	(76.7)	157	(8.5)	490	(54.8)
Filgrastim	2335	(22.6)	2019	(26.6)	67	(3.6)	249	(27.9)
Pegfilgrastim	5138	(49.7)	4721	(62.2)	105	(5.7)	312	(34.9)

*Type of G-CSF use not mutually exclusive

Table 3.

Cox proportional hazards models relating granulocyte colony-stimulating factors (G-CSF) to risk of myelodysplastic syndrome and acute myeloid leukemia among Medicare beneficiaries diagnosed with Non-Hodgkin lymphoma (NHL) from the SEER-Medicare linked database between 2001 and 2011 by primary treatment received

	All NHL Patients			Patients Receiving Any Chemotherapy and/or Immunotherapy			Patients Receiving Rituximab + Chemotherapy		
	HR	**(95% CI)**	***P***	**HR**	**(95% CI)**	***P***	**HR**	**(95% CI)**	***P***
None	1.00	Reference		1.00	Reference		1.00	Reference	
Any G-CSF	1.28	(1.01, 1.62)	0.04	1.07	(0.86, 1.32)	0.56	1.26	(0.93, 1.70)	0.13
1 to 4 Doses	1.07	(0.81, 1.43)	0.62	0.90	(0.69, 1.17)	0.44	1.12	(0.79, 1.57)	0.53
5 to 9 Doses	1.16	(0.86, 1.57)	0.32	0.99	(0.74, 1.33)	0.94	1.18	(0.81, 1.72)	0.39
10+ Doses	1.88	(1.39, 2.54)	<0.01	1.51	(1.14, 2.01)	0.01	1.64	(1.14, 2.37)	0.01
P-trend:		<0.01			<0.01			0.01	

*Models are adjusted for age, gender, race/ethnicity, NCI Comorbidity Index score at diagnosis, year of diagnosis, non-Hodgkin lymphoma subtype, Ann Arbor stage, and chemotherapy and/or immunotherapy received.