HHS Public Access

Author manuscript

J Am Geriatr Soc. Author manuscript; available in PMC 2019 January 18.

Published in final edited form as:

J Am Geriatr Soc. 2010 October ; 58(10): 1885–1895. doi:10.1111/j.1532-5415.2010.03081.x.

Comparative Effectiveness of White Blood Cell Growth Factors on Neutropenia, Infection and Survival Among Elderly Non-hodgkin's Lymphoma Patients Treated With Chemotherapy

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Abstract

Objectives: To determine the effect of colony-stimulating factor (CSF) on incidence of febrile neutropenia/infection and survival among elderly Non-Hodgkin's lymphoma (NHL) patients treated with chemotherapy.

Design: In this retrospective cohort study, we identified 13,203 patients diagnosed with NHL at age ≥65 from the Surveillance, Epidemiology, and End Results (SEER)-Medicare database in 1992–2002 who received chemotherapy within 12 months of diagnosis. Primary prophylaxis was defined as CSF administered at the start of chemotherapy prior to febrile neutropenia/infection, while secondary prophylaxis was defined as CSF use after febrile neutropenia/infection.

Results: Mean age was 74.9 years, ranging 65–102. Patients with 5–9 administrations of primary prophylactic CSF had 42% reduced risk of febrile neutropenia (odds ratio=0.58; 95% CI=0.41–0.83), and patients with 10+ administrations had 48% reduced risk of febrile neutropenia (0.52, 0.36–0.76) after adjusting for age, stage, histology, and comorbidity. Results did not differ significantly after adjusting for propensity score of receiving CSF. There was no significant association between primary prophylactic CSF and overall survival, but secondary prophylactic CSF was significantly associated with improved survival. The 4–10 administrations of secondary prophylactic CSF were associated with 9% reduction in mortality risk (hazard ratio=0.91; 95% CI=0.84–0.99), 11–23 administrations were associated with 23% reduction (0.77, 0.71–0.84) and

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Author contribution: SKG, DL and XLD made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; LKD and JR made substantial contributions to analysis and interpretation of data. All authors contributed to drafting the article or revising it critically for important intellectual content; and final approval of the version to be published.

Conflict of Interest: The editor in chief has reviewed the conflict of interest checklist provided by the authors and has determined that the authors have no financial or any other kind of personal conflicts with this paper.

>23 administrations were associated with 13% reduction (0.87, 0.79–0.95) compared to patients without receiving CSF following neutropenia/infection.

Conclusion: Primary prophylactic CSF was observed to be effective in reducing the incidence of neutropenia and infection. These findings substantiate the clinical guidelines for recommending prophylactic CSF among elderly NHL patients receiving chemotherapy.

Keywords

non-Hodgkin's lymphoma; colony-stimulating factor; neutropenia; infection; survival

INTRODUCTION

Non-Hodgkin's lymphoma (NHL) is the fifth most common noncutaneous cancer in the United States for both men and women, with approximately 66,120 people diagnosed in 2008.[1] Furthermore, NHL is the second-fastest rising cancer in terms of incidence and mortality. Since the 1970s, the incidence of NHL has nearly doubled.[2] Approximately half of all NHL cases are diagnosed in individuals over 65 years. Among the elderly population, the decision to treat with chemotherapy is not always straightforward because myelosuppression increases with age.[3–5] Consequently, risk of febrile neutropenia following myelosuppressive chemotherapy is also increased among the elderly.[6,7]

Granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF) are cytokines that stimulate the bone marrow to produce granulocytes and stem cells and also enhance the survival and function of existing neutrophils. G-CSF primarily stimulates the proliferation, maturation, and persistence of neutrophils,[8,9] while GM-CSF enhances the proliferation of macrophages as well.[9] Febrile neutropenia is a common complication of chemotherapy and is associated with life-threatening infections, chemotherapy dose reductions and delays, and hospitalization. By stimulating the production of white blood cells, prophylaxis using G-CSF and GM-CSF (hereon referred to collectively as CSF) has been shown to reduce the incidence and duration of febrile neutropenia, infections, hospitalization, and the use of antibiotics. However, the preponderance of evidence to date originated from randomized clinical trials. A meta-analysis by Clark et al [10] and a systematic review by Kuderer et al[11] both found that prophylactic use of G-CSF was associated with a decrease in short-term mortality. A recent compilation of data on CSF use summarized 13 trials comprising 2,607 patients.[12] Among these trials, it was found that CSF use did not improve overall survival or freedom from treatment failure. However, prophylaxis significantly reduced risk for febrile neutropenia and infection.[12]

Treatment recommendations have remained largely the same since the introduction of CSFs as supportive agents for chemotherapy in the early 1990s.[13] The prophylactic use of CSFs has typically been recommended to support the administration of planned doses of chemotherapy and to reduce the incidence of febrile neutropenia and possible infection. However, evidence to date has limited recommendations from being extended to suggest that CSFs have an impact on outcomes such as response rates, progression-free survival, or overall survival. Further, no research has been conducted to evaluate long term outcomes

(i.e. overall survival) of CSF use in the “real world” setting. Therefore, the overall objective of this study was to evaluate the population-based effectiveness of CSF use at reducing the incidence of febrile neutropenia and infection and at improving overall survival among a large nationwide and population-based cohort of elderly non-Hodgkin’s lymphoma (NHL) patients treated with chemotherapy.

PATIENTS AND METHODS

Data Source

This study used data from the Surveillance, Epidemiology, and End Results (SEER)-Medicare database. The SEER database program is a population-based registry sponsored by the National Cancer Institute that contains information on newly diagnosed cancer cases with the completeness of case ascertainment of >98%.[14] This study included 12 selected geographic areas: Detroit, Seattle, Atlanta and rural Georgia; and the states of California, Connecticut, Iowa, New Mexico, Utah, Hawaii, Kentucky, Louisiana, and New Jersey. The SEER registry collects information on patient demographics, tumor characteristics, stage at diagnosis, treatment within 4 months of diagnosis, and date and cause of death. Medicare is the primary insurer for 97% of the U.S. population 65 years and older. All Medicare beneficiaries receive Part A coverage which covers inpatient care, skilled nursing, home health, and hospice care. Ninety-five percent of beneficiaries also subscribe to part B of Medicare to obtain benefits that cover physician services and outpatient care.[14] The Committee for the Protection of Human Subjects at the University of Texas Health Science Center at Houston approved this study.

Study Population and patient characterization

This study included incident cases of NHL diagnosed from 1992 to 2002 who received chemotherapy within 12 months of diagnosis. Patients enrolled in a health maintenance organization during the study time period were excluded because their data were unavailable in Medicare claims. Patients who did not participate in both Medicare parts A and B during any month were also excluded to ensure the completeness of the data.

Patients were characterized with respect to clinical and demographic variables available in the SEER-Medicare data. The following codes were used for defining chemotherapy and detailed in a previous study:[15] International Classification of Diseases (ICD-9) procedure code 9925 for chemotherapy infusion/injection; Current Procedural Terminology (CPT) codes 96400–96549, J9000–J9999 codes, and Q0083 – 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 (e.g. alkylating agent, topoisomerase II inhibitors, anthracyclines, and antimetabolites) using Healthcare Common Procedural Coding System (HCPCS) codes. Claims before diagnosis were used to identify pre-existing comorbidities within our study population. Comorbidities were aggregated to formulate the NCI comorbidity index, a revised version of the Charlson comorbidity index.[16]

The use of CSF was identified by the CPT codes J1440 and J1441 (for G-CSF) and J2820 (for GM-CSF).[13] Primary prophylaxis was defined as CSF administered during

chemotherapy prior to the occurrence of fever, neutropenia or infection. Secondary prophylactic CSF use was defined as CSF administered following fever, neutropenia or infection. Numbers of CSF and chemotherapy claims were assumed to correspond to the number of administrations.

Identification of Outcomes

A strict definition of febrile neutropenia was defined as having both neutropenia (ICD-9 code 288.0) and fever (780.6) present. We also created a broader definition for neutropenia which required only a claim for neutropenia regardless of fever status. Infections were identified using the ICD-9 codes 001.0–139.8. Overall survival was measured from initial chemotherapy initiation date until death or the date of last follow-up (October 31, 2006).

Data Analysis

Primary CSF prophylaxis and incidence of febrile neutropenia and infection— The demographic and clinical characteristics were described according to CSF status (no CSF, primary prophylaxis and secondary prophylaxis) in patients receiving chemotherapy. Because neutropenia or infection is an acute event, the results generated from logistic regression models and Cox proportional regression models were identical. Here only results by logistic regression models were reported. A multivariable model was constructed to explain the association between primary CSF use and the incidence of febrile neutropenia and infection after adjusting for relevant demographic and clinical covariates. We used the strict definition of febrile neutropenia which included patients with claims of both neutropenia and fever. We also evaluated the sensitivity of our findings by using a broader definition of neutropenia in which patients only had to have a claim for neutropenia with or without a claim for fever. For infections, only infections with claims within 28 days of a chemotherapy claim were considered to minimize the inclusion of infections not likely to be related to the immunosuppressive effects of chemotherapy.

Impact of primary and secondary CSF prophylaxis on overall survival—We evaluated the impact of primary and secondary CSF prophylaxis on overall survival using Cox Proportional hazards analysis. For the evaluation of primary prophylaxis, all patients treated with chemotherapy were included to determine the survival times from the date of chemotherapy to the date of death or the date of last follow-up (October 31, 2006). For the evaluation of CSF use for secondary prophylaxis, we included only patients who experienced neutropenia, fever, and/or infection and followed them from the initial neutropenia, fever or infection date until the date of death or last follow-up. The proportionality assumption was confirmed using goodness-of-fit test developed by Harrell and Lee.[17]Finally, to explore possible heterogeneity of effect across patient groups, we conducted the analyses within specific histologic subgroups (diffuse large B-cell lymphoma, follicular lymphoma, and other),[18] by number of chemotherapy administrations (<5, 6–10, 11–25, >25), and by the most common chemotherapy agents administered (alkylating agents, topoisomerase II inhibitors, anthracyclines, antimetabolites, and vinca alkaloids).

To minimize the potential selection bias, we calculated propensity scores of receiving CFS and included the scores in separate regression models for both logistic regression and Cox

proportional hazard regression analyses. Briefly, two scores were calculated based on the probability of 1) having received primary prophylactic CSF among all patients; and 2) having received secondary prophylactic CSF among patients who experienced fever, neutropenia and/or infection. These scores were calculated from logistic regression model in which primary/secondary CSF status (yes/no) was the dependent variable and patient demographic/clinical/treatment characteristics were considered as independent variables.

RESULTS

We identified 13,203 NHL patients diagnosed with NHL at age 65 or older who were treated with chemotherapy and met the other inclusion criteria for this study. The median age at diagnosis was 74 years (mean=74.9; range 65–102). Fifty-three percent (n=7,051) of patients were female, and a large majority (n=11,776; 90%) were non-Hispanic white and lived in an urban setting (n=11,877; 90%). Forty-four percent (n=5,861) of patients had a diagnosis of diffuse large B-cell lymphoma; 18% (n=2,428) had follicular lymphoma; and 37% had other histologies (n=3,665) or unknown histology (n=1,249). Patient distribution by stage at diagnosis was 27% stage I, 17% stage II, 15% stage III, and 34% stage IV. A large majority of patients (62%) had a low comorbidity burden (comorbidity score of ≤1).

Table-1 shows patient demographic and clinical characteristics by CSF use. Overall, 60% (n=7,937) patients did not receive CSF, while 10% (n=1,339) received CSF as primary prophylaxis and an additional 3,927 (30%) received CSF as secondary prophylaxis after neutropenia, fever, and/or infection. Patients receiving CSF were more likely to be diagnosed recently (68% and 65% of patients receiving primary and secondary CSF, respectively, were diagnosed since 1998 compared to 53% of patients who did not receive CSF). Patients by CSF status were similar with respect to age at diagnosis, gender, race/ethnicity, socioeconomic status, and comorbidities. Patients receiving CSF (primary and secondary prophylaxis) were more likely to reside in an urban setting compared to patients not receiving CSF (92% vs. 88%) and were more likely to be married (62% vs. 57%). Patients with diffuse large cell lymphoma were more likely to receive CSF (44%) compared to patients with follicular lymphoma (38%) and patients with ‘Other’ histology (38%).

Treatment characteristics by CSF utilization are presented in Table-2. Among patients who received primary prophylactic CSF, 90% received G-CSF only, 4% received only GM-CSF, while 6% received both G-CSF and GM-CSF. This distribution was similar among patients receiving secondary prophylaxis: 86% received only G-CSF; 7% received only GM-CSF; and 7% received both G-CSF and GM-CSF. Not surprisingly, patients receiving CSF were more likely to have received multiple myelosuppressive chemotherapy agents and had more chemotherapy administrations. Patients receiving CSF also were more likely to have had radiation therapy (40% vs. 36%).

Table-3 presents the logistic regression analysis describing the association between primary prophylactic CSF use and incidence of febrile neutropenia (as defined as having both neutropenia and fever) and infection. Patients with 5–9 administrations had a 42% reduced risk of febrile neutropenia (OR=0.58; 95% CI: 0.41–0.83), and patients with 10+ administrations had a 48% reduced risk of febrile neutropenia (0.52, 0.36–0.76) compared to

those without CSF after adjusting for age, marital status, stage, histology, comorbidity score, chemotherapy agent, and number of chemotherapy administrations. Results were similar in the propensity-score adjusted analysis. For example, risk was reduced by 43% for patients with 5–9 administrations and by 53% for patients with 10+ administrations. The results were similar when applying a broader definition of febrile neutropenia (data not shown).

A similar protective association was observed between primary prophylactic CSF use and incidence of infection. After adjusting for year of diagnosis, urban residence, race/ethnicity, marital status, stage, histology, comorbidity score, chemotherapy agent, and number of chemotherapy administrations, patients with 5–9 CSF administrations had a 27% reduced incidence of infection (0.73, 0.55–0.96) while patient with 10+ administrations had a 52% reduced risk (0.48, 0.35–0.66). Results were similar in the propensity-score adjusted model: 5–9 administrations were associated with a statistically significant 29% reduced risk and 10+ administrations were associated with a 54% reduced risk of infection.

To determine whether CSF use was associated with long-term outcomes, we evaluated the effectiveness of primary prophylactic CSF on overall survival among all patients treated with chemotherapy (Table-4). After adjusting for relevant demographic, clinical, and treatment characteristics, primary prophylactic CSF was not associated with prolonged overall survival. A similar result was observed in the propensity-score adjusted model. However, in the evaluation of the effect of *secondary* prophylactic CSF on overall survival among the subset of patients who experienced neutropenia, fever, and/or infection (Table-5), secondary CSF use was significantly associated with improved overall survival with a strong dose-response relationship. After adjusting for relevant covariates, 4–10 administrations of secondary prophylactic CSF were associated with a 9% reduction in the risk of mortality (hazard ratio=0.91, 95% CI: 0.84–0.99), 11–23 administrations were associated with a 23% reduction (0.77, 0.71–0.84), and >23 administrations were associated with a 13% reduction in risk of mortality (0.87, 0.79–0.95) compared to patients who did not receive CSF following neutropenia, fever, and/or infection.

Finally, we evaluated whether the observed associations between CSF use and incidence of febrile neutropenia and overall survival differed across subsets of the patient population. The protective effect of primary prophylactic CSF was highest among patients who received the highest number of chemotherapy administrations. Among patients who received only a few doses of chemotherapy (≤5 administrations), the protective effect of primary prophylactic CSF use on incidence of febrile neutropenia was small (odd ratio=0.80, 95% CI: 0.52–1.18), whereas the protective effect was much stronger and statistically significant for patients with greater numbers of chemotherapy administrations (0.38, 0.28–0.50 for patients receiving 11–25 chemotherapy administrations; 0.43, 0.31–0.62 for those receiving >25 chemotherapy administrations). The associations between CSF and the incidence of febrile neutropenia and overall survival did not differ significantly by chemotherapy agent. It appeared that primary prophylactic CSF had the strongest protective effect against febrile neutropenia among patients with diffuse large B-cell lymphoma compared to patients with follicular lymphoma and patients with ‘Other’ histology (Table-5). Finally, the majority of patients (N=1,079; 81%) who we identified as receiving primary CSF received CSF within 7 days of onset of chemotherapy. These subjects did not differ significantly in clinical/demographic

characteristics or outcomes (febrile neutropenia and overall survival) than the remaining 260 patients who received an initial CSF administration >7 days post initiation of chemotherapy but before documentation of neutropenia/fever/infection. Furthermore, a total of 5,167 (39%) of the study population received rituximab (J9310). Rituxumab use was associated with a higher frequency of CSF use compared to patients who did not receive rituximab, but rituximab did not modify the relationship between CSF and the outcomes of interest.

DISCUSSION

With an aging population, it is important to evaluate population-based outcomes in order to maximize the effectiveness of therapy in this ever-growing segment of the population. While several studies[13,19,20] have evaluated the efficacy of CSF use within the setting of randomized clinical trials, this is the first large population-based cohort study to evaluate a range of short and long term clinical outcomes of CSF use among elderly NHL patients. Results suggested that primary prophylactic CSF among elderly NHL patients receiving chemotherapy was effective in preventing febrile neutropenia and infection. However, these data found that primary prophylactic CSF was not translated into significant improvements in overall survival, supporting what was found in clinical trials. We did find, however, that administering CSF for secondary prophylaxis among patients who experienced febrile neutropenia events was associated with increased overall survival.

Treatment decisions are not always straightforward and may carry the risk of complication, especially among the elderly. Because of the myelosuppressive effects of chemotherapy,[3–5] risk of febrile neutropenia is especially high in the elderly population.[6,7] These issues are important when making treatment decisions and may introduce added reluctance to administer chemotherapy in the elderly population. There is strong clinical evidence that CSF use for primary prophylaxis among cancer patients receiving myelosuppressive chemotherapy leads to a reduction of febrile neutropenia events and subsequent infection.[10–13,19,20] A meta-analysis conducted in 2003 found that febrile neutropenia incidence and infection was reduced by 26%.[20] Among elderly patients with NHL, a similar association between CSF use and reduced febrile neutropenia and infection has been reported in a recent systematic review.[17] This review included 24 studies of CSF in the elderly NHL patients. While the studies consistently demonstrated reduced febrile neutropenia /infection, associations with other outcomes such as improved delivery of planned dose,[21–23] treatment response,[21,24,25] progression-free survival[21,24,25] and overall survival[21,26] have been inconsistently observed. Futhermore, recent studies [27, 28] using SEER-Medicare data have evaluated the association between CSF use and the risk of therapy-associated leukemia with conflicting results, so further research is needed to fully evaluate the clinical risks and benefits of CSF. Results of this current study coincide with these previous findings that CSF use was effective at reducing short term complications but this effectiveness did not translate to improvements in long term survival.

Given the growing constraints on healthcare systems, it is important to evaluate the population-based outcomes of interventions with respect to both short-term benefits and long-term outcomes. The use of sound study design and population-based data may address questions regarding treatment effects in clinical practice that cannot be feasibly answered

with randomized trials. While clinical trials typically evaluate the efficacy of an intervention (i.e. 'Can it work?'), observational studies of population-based data are to evaluate the effectiveness of interventions (i.e. 'Does it work?'). Furthermore, patients in clinical trials tend to be younger and healthier and as such may not be generalizable to the general population. They are also more likely to be treated by providers who are affiliated with large cancer centers.[29–33]

The limitations of this study should be noted. Because of the timeframe of the study, we were unable to evaluate the effectiveness of longer-acting peg-filgrastim (FDA-approved in 2002) relative to filgrastim or GM-CSF. Given the convenience of the single dose CSF (with accompanying high cost) it will be important to evaluate the comparative effectiveness of peg-filgrastim as those data continue to mature. Due to the observational nature of the data used for this study, it is likely that a certain degree of selection bias was introduced. We attempted to control for this bias by thoroughly describing our treatment cohorts to the greatest extent possible in order to identify potential confounding factors. Additionally, we utilized propensity scores to attempt to further control for confounding. Another important limitation is that the Medicare claims data do not provide the clinical/demographic details such as patient functional status, relative dose intensity, cycles of chemotherapy regimens, socio-demographic characteristics, and laboratory assessments that are commonly available with clinical trial data. Because of incomplete control of these potential confounding factors, the results should be interpreted with caution. Furthermore, claims data are mainly used for billing purpose but are not designed for research purpose. However, extensive validations have been conducted in supporting the SEER-Medicare as a valid source of data for conducting Health Services and Outcomes Research.[34–37] With the increased use of electronic medical records within medical oncology practices, future observational studies should attempt to link claims data to electronic medical records data to more completely match the richness of data available in clinical trials.

It is important to evaluate real-world outcomes among elderly cancer patients given the wide variability of treatment responses and outcomes and the relative difficulty in making treatment decisions in this population. In this study, primary prophylactic CSF use was observed to be effective in reducing the incidence of febrile neutropenia and infection in the population-based setting. These findings substantiate the clinical guidelines for recommending the use of prophylactic CSF among elderly NHL patients receiving chemotherapy regardless of neutropenia risk threshold. This finding provides important information to geriatricians in caring for their patients because NHL occurs mostly in the elderly population. However, given the continued uncertainty regarding the impact of CSF use on long-term outcomes such as survival, future research should further evaluate the utility of CSF use by focusing on cost-effectiveness, adverse events, and the incorporation of quality-of-life components.

ACKNOWLEDGMENTS

We acknowledge the efforts of the National Cancer Institute, Center for Medicare and Medicaid Services, Information Management Services, Inc.; and the SEER tumor registries in the creation of this database. The analyses, interpretation, and reporting are the sole responsibilities of the authors. This study was supported by a

grant from the Agency for Healthcare Research and Quality (RO1-HS016743). There is no any conflict of interest from all authors.

Sponsor's Role: We acknowledge the efforts of the NCI; CMS; IMS, and the SEER Program tumor registries in the creation of this database. The interpretation and reporting of these data are the sole responsibilities of the authors.

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Table 1.

Patient Clinical and demographic characteristics by colony-stimulating factor (CSF) use

Characteristics	Total (N=13,203)	CSF Status		
		No CSF (N=7,937; 60%)	Primary CSF (N=1,339; 10%)	Secondary CSF (N=3,927; 30%)
	N (%)	N (%)	N (%)	N (%)
Year of Diagnosis				
1992 – 1993	1,759 (13.3%)	1,441 (18.2%)	33 (2.5%)	285 (7.3%)
1994 – 1995	1,837 (13.9)	1,164 (14.7)	183 (13.7)	490 (12.5)
1996 – 1997	1,912 (14.5)	1,085 (13.7)	214 (16.0)	613 (15.6)
1998 – 1999	1,852 (14.0)	1,052 (13.3)	203 (15.2)	597 (15.2)
2000 – 2001	3,778 (28.6)	1,937 (24.4)	482 (36.0)	1,359 (34.6)
2002	2,065 (15.6)	1,258 (15.8)	224 (16.7)	583 (14.8)
Age at Diagnosis				
Mean (SD)	74.94 (6.35)	75.32 (6.59)	74.77 (5.98)	74.24 (5.90)
Median (range)	74 (65 – 102)	75 (65 – 102)	74 (65 – 97)	74 (65 – 98)
65–69	3,090 (23.4)	1,814 (22.9)	291 (21.7)	985 (25.1)
70–74	3,598 (27.3)	2,050 (25.8)	398 (29.7)	1,150 (29.3)
75–79	3,324 (25.2)	1,935 (24.4)	365 (27.3)	1,024 (26.1)
80–84	2,107 (16.0)	1,363 (17.2)	197 (14.7)	547 (13.9)
85+	1,084 (8.2)	775 (9.8)	88 (6.6)	221 (5.6)
Gender				
Male	6,152 (46.6)	3,683 (46.4)	644 (48.1)	1,825 (46.5)
Female	7,051 (53.4)	4,254 (53.6)	695 (51.9)	2,102 (53.5)
Race/Ethnicity				
White	11,776 (89.2)	7,060 (89.0)	1,188 (88.7)	3,528 (89.8)
Hispanic	236 (1.8)	136 (1.7)	21 (1.6)	79 (2.0)
Black	441 (3.3)	286 (3.6)	41 (3.1)	114 (2.9)
Asian	404 (3.1)	228 (2.9)	54 (4.0)	122 (3.1)
Other/Unknown	346 (2.6)	227 (2.8)	35 (2.6)	84 (2.2)
Urban Residence				
No	1,326 (10.0)	919 (11.6)	128 (9.6)	279 (7.1)
Yes	11,877 (90.0)	7,018 (88.4)	1,211 (90.4)	3,648 (92.9)
Marital Status				
Yes	7,797 (59.1)	4,506 (56.8)	812 (60.6)	2,479 (63.1)
No	4,838 (36.6)	3,060 (38.6)	480 (35.8)	1,298 (33.1)
Unknown	568 (4.3)	371 (4.7)	47 (3.5)	150 (3.8)
SES Quartiles				
1 (High)	3,376 (25.6)	1,980 (24.9)	298 (22.2)	1,098 (28.0)
2	3,251 (24.6)	1,902 (24.0)	322 (24.0)	1,027 (26.2)
3	3,305 (25.0)	2,056 (25.9)	353 (26.4)	896 (22.8)
4 (Low)	3,065 (23.2)	1,876 (23.6)	340 (25.4)	849 (21.6)
Missing	206 (1.6)	123 (1.5)	26 (1.9)	57 (1.5)

Characteristics	Total (N=13,203)	CSF Status		
		No CSF (N=7,937; 60%)	Primary CSF (N=1,339; 10%)	Secondary CSF (N=3,927; 30%)
Stage				
I	3,564 (27.0)	2,228 (28.1)	318 (23.7)	1,018 (25.9)
II	2,214 (16.8)	1,326 (16.7)	222 (16.6)	666 (17.0)
III	1,971 (14.9)	1,083 (13.6)	245 (18.3)	643 (16.4)
IV	4,519 (34.2)	2,684 (33.8)	486 (36.3)	1,349 (34.4)
Unknown	935 (7.1)	616 (7.8)	68 (5.1)	251 (6.4)
Histology				
Diffuse Large B-cell	5,861 (44.4)	3,323 (41.9)	686 (51.2)	1,852 (47.2)
Follicular	2,428 (18.4)	1,506 (19.0)	205 (15.3)	717 (18.3)
Other	3,665 (27.8)	2,281 (28.7)	336 (25.1)	1,048 (26.7)
Unknown	1,249 (9.5)	827 (10.4)	112 (8.4)	310 (7.9)
Comorbidity Score				
0	8,216 (62.2)	4,908 (61.8)	815 (60.9)	2,493 (63.5)
1	3,148 (23.8)	1,891 (23.8)	331 (24.7)	926 (23.6)
≥ **2**	1,839 (13.9)	1,138 (14.3)	193 (14.4)	508 (12.9)

Table 2.

Patient Treatment Characteristics by colony-stimulating factor (CSF) use

Characteristics	Total (N=13,203)	CSF status		
		No CSF (N=7,937; 60%)	Primary CSF (N=1,339; 10%)	Secondary CSF (N=3,927; 30%)
CSF use				
None	7,937 (60.1%)		-	-
G-CSF	4,581 (34.7)		1,198 (89.5%)	3,383 (86.1%)
GM-CSF	316 (2.4)		57 (4.3)	259 (6.6)
Both	369 (2.8)		84 (6.3)	285 (7.3)
Number of Administrations				
None	7,937 (60.1)		-	-
<5	1,588 (12.0)		425 (31.7)	1,163 (29.6)
5–14	1,627 (12.3)		408 (30.5)	1,219 (31.0)
15–24	837 (6.3)		197 (14.7)	640 (16.3)
25+	1,214 (9.2)		309 (23.1)	905 (23.0)
Chemotherapy Agent				
Alkylating	10,951 (82.9)	6,100 (76.9%)	1,215 (90.7)	3,636 (92.6)
Topo-isomerase II inhibitors	3,328 (25.2)	1,600 (20.2)	397 (29.6)	1,331 (33.9)
Anthracyclines	7,068 (53.5)	3,550 (44.7)	928 (69.3)	2,590 (66.0)
Antimetabolites	3,148 (23.8)	1,581 (19.9)	335 (25.0)	1,232 (31.4)
Platinums	520 (3.9)	162 (2.0)	79 (5.9)	279 (7.1)
Taxanes	132 (1.0)	47 (0.6)	20 (1.5)	65 (1.7)
Vinca Alkaloids	10,718 (81.2)	5,964 (75.1)	1,196 (89.3)	3,558 (90.6)
Non-anthracycline antibiotics	711 (5.4)	419 (5.3)	72 (5.4)	220 (5.6)
Targeted (Biologics)	6,937 (52.5)	3,931 (49.5)	746 (55.7)	2,260 (57.6)
Other	1,941 (14.7)	1,144 (14.4)	191 (14.3)	606 (15.4)
Number of Chemotherapy DOS				
Mean (SD)	18.9 (23.1)	13.1 (14.9)	23.4 (26.3)	29.1 (30.5)
Median (Range)	11 (1 – 394)	8 (1 – 212)	14 (1 – 273)	19 (1 – 394)
Radiation Therapy				
No	8,194 (62.1)	5,069 (63.9)	789 (58.9)	2,336 (59.5)
Yes	5,009 (37.9)	2,868 (36.1)	550 (41.1)	1,591 (40.5)

Table 3.

Logistic Regression Analysis: Incidence of febrile neutropenia* and infection

Characteristics	Febrile Neutropenia*				Infection			
	Univariable		Multivariable		Univariable		Multivariable	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Prophylactic CSF adminstrations								
0–1	1.00		1.00		1.00		1.00	
2	1.16	0.84 – 1.61	0.93	0.67 – 1.31	1.13	0.85 – 1.49	0.98	0.73 – 1.30
3–4	1.14	0.83 – 1.57	0.90	0.65 – 1.25	0.91	0.69 – 1.21	0.78	0.58 – 1.04
5–9	0.73	0.52 – 1.03	0.58	0.41 – 0.83	0.84	0.64 – 1.10	0.73	0.55 – 0.96
10+	0.78	0.54 – 1.12	0.52	0.36 – 0.76	0.64	0.47 – 0.87	0.48	0.35 – 0.66
Year Of Diagnosis								
1992 – 1995	1.00				1.00		1.00	
1996 – 1999	0.97	0.87 – 1.07	-		0.94	0.85 – 1.03	0.96	0.86 – 1.06
2000 – 2002	1.05	0.94 – 1.16	-		0.86	0.78 – 0.93	0.91	0.82 – 1.01
Urban Residence								
No	1.00				1.00		1.00	
Yes	0.94	0.81 – 1.08	-		1.24	1.09 – 1.40	1.16	1.02 – 1.32
Age at Diagnosis	0.98	0.97 – 0.98	0.99	0.99 – 1.01	0.99	0.99 – 1.00	-	
Gender								
Male	1.00				1.00			
Female	0.99	0.91 – 1.08	-		0.97	0.91 – 1.05	-	
Race/Ethnicity								
White	1.00				1.00		1.00	
Hispanic	0.87	0.62 – 1.22	-		1.01	0.77 – 1.33	0.93	0.71 – 1.23
Black	0.90	0.70 – 1.16	-		1.24	1.02 – 1.51	1.18	0.96 – 1.44
Asian	1.04	0.81 – 1.33	-		0.84	0.68 – 1.04	0.84	0.67 – 1.05
Other	1.35	1.04 – 1.76	-		1.16	0.92 – 1.47	1.20	0.94 – 1.52
Marital Status								
Yes	1.00		1.00		1.00		1.00	
No	0.96	0.93 – 0.98	0.98	0.95 – 1.01	0.98	0.95 – 0.99	0.99	0.97 – 1.02
SES Quartiles								
1 (High)	1.00				1.00			
2	0.94	0.83 – 1.06	-		0.95	0.86 – 1.05	-	
3	0.96	0.85 – 1.08	-		0.90	0.81 – 0.99	-	
4 (Low)	0.88	0.79 – 1.01	-		0.94	0.85 – 1.05	-	
Stage								
I	1.00		1.00		1.00		1.00	
II	1.11	0.96 – 1.27	1.02	0.88 – 1.17	1.02	0.91 – 1.14	0.95	1.04 – 1.33
III	1.33	1.16 – 1.52	1.20	1.04 – 1.38	1.28	1.14 – 1.43	1.18	1.13 – 1.37
IV	1.36	1.21 – 1.52	1.28	1.14 – 1.44	1.36	1.24 – 1.49	1.25	0.87 – 1.20

Characteristics	Febrile Neutropenia*				Infection			
	Univariable		Multivariable		Univariable		Multivariable	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Histology								
Diffuse Large B-cell	1.00		1.00		1.00		1.00	
Follicular	0.77	0.68 – 0.87	0.79	0.69 – 0.90	0.80	0.72 – 0.89	0.80	0.72 – 0.90
Other	0.87	0.74 – 1.01	0.97	0.87 – 1.09	1.01	0.93 – 1.11	1.05	0.95 – 1.15
Comorbidity Score								
0	1.00		1.00		1.00		1.00	
1	1.15	1.04 – 1.27	1.23	1.11 – 1.37	1.19	1.10 – 1.30	1.27	1.16 – 1.39
≥ 2	0.99	0.87 – 1.13	1.15	1.01 – 1.31	1.48	1.33 – 1.64	1.67	1.50 – 1.86
Chemotherapy Agent								
Alkylating Agents	3.04	2.60 – 3.56	1.62	1.30 – 2.02	1.76	1.59 – 1.96	1.31	1.11 – 1.53
Topo-isomerase II inhibitors	1.81	1.65 – 1.99	1.57	1.40 – 1.76	1.47	1.35 – 1.59	1.19	1.08 – 1.31
Anthracyclines	1.92	1.76 – 2.10	1.64	1.47 – 1.83	1.42	1.32 – 1.53	1.33	1.21 – 1.46
Antimetabolites	1.70	1.55 – 1.87	1.48	1.21 – 1.80	1.61	1.48 – 1.75	1.37	1.24 – 1.51
Platimums	2.15	1.78 – 2.60	0.98	0.79 – 1.21	2.07	1.73 – 2.46	1.25	1.03 – 1.52
Taxanes	2.15	1.50 – 3.10	1.47	0.99 – 2.17	1.57	1.11 – 2.21	1.04	0.72 – 1.50
Vinca Alkaloids	2.61	2.27 – 3.00	1.47	0.99 – 2.17	1.63	1.47 – 1.79	1.23	1.06 – 1.43
Non-anthracycline antibiotics	1.53	1.29 – 1.82	0.89	0.74 – 1.07	1.70	1.46 – 1.98	1.17	0.99 – 1.38
Targeted (Biologics)	1.25	1.14 – 1.36	1.08	0.98 – 1.19	1.18	1.09 – 1.26	1.11	1.03 – 1.21
Other	1.42	1.27 – 1.59	1.06	0.94 – 1.20	1.46	1.32 – 1.61	1.18	1.06 – 1.32
Number of Chemotherapy DOS	1.00		1.00		1.00		1.00	
≤ 5	1.33	1.16 – 1.53	1.18	1.02 – 1.36	1.01	0.91 – 1.13	0.95	0.85 – 1.07
6 – 10	1.82	1.59 – 2.07	1.45	1.26 – 1.67	1.46	1.31 – 1.61	1.28	1.15 – 1.43
11 – 25	2.98	2.61 – 3.40	2.06	1.77 – 2.40	2.16	1.94 – 2.40	1.69	1.49 – 1.91
> 25								
XRT								
No	1.00				1.00			
Yes	1.03	0.94 – 1.12	-		0.96	0.89 – 1.03	-	

*strict definition= neutropenia + fever

Table 4.

Cox Proportional Hazard Analysis on Primary colony-stimulating factor (CSF) use and overall survival among patients receiving chemotherapy

Characteristics		Overall Survival among all patients			
		Univariable		Multivariable	
	N(%)	HR	95% CI	HR	95% CI
Prophylactic CSF adminstrations					
0–1	12,293 (93%)	1.00		1.00	
2	213 (1.6%)	1.18	1.01 – 1.39	1.04	0.89 – 1.22
3–4	226 (1.7%)	1.04	0.88 – 1.22	1.01	0.85 – 1.19
5–9	252 (1.9%)	1.06	0.91 – 1.23	1.10	0.95 – 1.29
10+	219 (1.7%)	0.93	0.78 – 1.10	1.03	0.87 – 1.22
Year of Diagnosis					
1992–1995	3,596 (27%)	1.00		1.00	
1996–1999	3,764 (29%)	0.90	0.86 – 0.95	**0.89**	**0.84 – 0.94**
2000–2002	5,843 (44%)	0.75	0.71 – 0.79	**0.87**	**0.82 – 0.92**
Urban Residence					
Yes	1,326 (10%)	1.00		-	
No	11,877 (90%)	0.99	0.92 – 1.06	-	
Age at diagnosis (continuous)	74.94 (6.35)	1.05	1.046 – 1.053	**1.05**	**1.046 – 1.054**
Gender					
Female	6,152 (47%)	1.00			
Male	7,051 (53%)	0.79	0.76 – 0.82	**0.79**	**0.77 – 0.83**
Race					
Non-Hispanic White	11,776	1.00			
Hispanic	236	0.89	0.76 – 1.05	**0.81**	**0.69 – 0.96**
Black	441	1.16	1.04 – 1.30	1.09	0.97 – 1.22
Asian	404	0.95	0.84 – 1.07	**0.87**	**0.77 – 0.99**
Other	304	1.36	1.19 – 1.54	**1.24**	**1.09 – 1.42**
Marital Status					
Yes	7,797	1.00			
No	4,838	1.00	0.99 – 1.02	-	
SES Quartile					
1 (High)	3,376	1.00		1.00	
2	3,251	0.99	0.94 – 1.06	1.01	0.96 – 1.08
3	3,305	1.04	0.98 – 1.10	1.04	0.98 – 1.11
4 (Low)	3,065	1.13	1.09 – 1.20	**1.12**	**1.05 – 1.19**
Histology					
Diffuse Large B-cell	5,861	1.00		1.00	
Follicular	2,428	0.65	0.61 – 0.69	**0.72**	**0.67 – 0.77**
Other	3,665	0.93	0.88 – 0.98	**0.90**	**0.86 – 0.96**
Stage at Diagnosis					

Characteristics		Overall Survival among all patients			
		Univariable		Multivariable	
	N(%)	HR	95% CI	HR	95% CI
I	3,564	1.00		1.00	
II	2,214	1.19	1.11 – 1.27	**1.23**	**1.15 – 1.31**
III	1,971	1.46	1.36 – 1.56	**1.60**	**1.49 – 1.71**
IV	4,519	1.57	1.49 – 1.66	**1.74**	**1.64 – 1.84**
Comorbidity Score					
0	8,216 (62%)	1.00			
1	3,148 (24%)	1.36	1.30 – 1.43	**1.28**	**1.21 – 1.34**
≥2	1,839 (14%)	1.90	1.80 – 2.02	**1.75**	**1.65 – 1.86**
Chemotherapy					
Duration (DOS)	18.9 (23.1)	0.994	0.992 – 0.995	**0.992**	**0.990 – 0.993**
Chemotherapy Agent (yes vs. no)					
Alkylating Agents	10,951 (83%)	1.11	1.05 – 1.18	**1.20**	**1.14 – 1.27**
Topo-isomerase II inhibitor	3,328 (25%)	1.37	1.31 – 1.43	0.96	0.92 – 1.02
Anthracyclines	7,068 (54%)	0.85	0.81 – 0.88	**1.36**	**1.29 – 1.44**
Antimetabolite	3,148 (24%)	1.15	1.10 – 1.20	**1.25**	**1.13 – 1.39**
Platinums	520 (4%)	1.23	1.11 – 1.36	1.12	0.92 – 1.37
Taxanes	132 (1%)	1.11	0.91 – 1.36	**1.10**	**1.01 – 1.19**
Vinca Alkaloids	10,718 (82%)	1.08	1.02 – 1.14	**1.20**	**1.10 – 1.31**
Non-anthracycline antibiotics	711 (5%)	1.41	1.30 – 1.54	**0.70**	**0.67 – 0.73**
Targeted therapy	6,937 (52%)	0.62	0.60 – 0.65	**1.13**	**1.07 – 1.20**
Other	1,941 (15%)	1.19	1.13 – 1.26	1.00	0.96 – 1.05
Radiation Therapy					
No	8,194 (62%)	1.00			
Yes	5,009 (38%)	0.92	0.88 – 0.96	1.00	0.96 – 1.05

Table 5.

Cox Proportional Hazard Analysis – Secondary CSF use among patients with febrile neutropenia event

	Overall Survival among patients experiencing febrile neutropenia event (n=8,546)			
	Univariable		Multivariable	
	HR	95% CI	HR	95% CI
Secondary CSF administrations				
0	1.00		1.00	
1–3	0.88	0.81 – 0.96	0.93	0.85 – 1.01
4–10	0.85	0.79 – 0.92	**0.91**	**0.84 – 0.99**
11–23	0.68	0.63 – 0.74	**0.77**	**0.71 – 0.84**
>23	0.69	0.64 – 0.75	**0.87**	**0.79 – 0.95**
Year of Diagnosis				
1992–1995	1.00		1.00	
1996–1999	0.88	0.82 – 0.94	**0.88**	**0.82 – 0.94**
2000–2002	0.65	0.61 – 0.69	**0.74**	**0.69 – 0.79**
Urban Residence				
No	1.00			
Yes	0.95	0.87 – 1.04	-	
Age at diagnosis	1.04	1.033 – 1.042	1.036	1.031 – 1.040
Gender				
Female	1.00		1.00	
Male	0.79	0.75 – 0.83	0.81	0.77 – 0.85
Race				
Non-Hispanic White	1.00		1.00	
Hispanic	0.96	0.82 – 1.12	0.88	0.75 – 1.03
Black	1.19	1.04 – 1.37	1.07	0.93 – 1.24
Asian	0.84	0.68 – 1.03	**0.75**	**0.61 – 0.93**
Other	1.39	1.19 – 1.63	**1.28**	**1.09 – 1.49**
Marital Status				
Yes	1.00			
No	1.01	0.99 – 1.02	-	
SES Quartile				
1 (High)	1.00		1.00	
2	1.00	0.93 – 1.08	1.04	0.97 – 1.12
3	1.05	0.98 – 1.12	1.06	0.98 – 1.14
4 (Low)	1.13	1.05 – 1.21	**1.15**	**1.06 – 1.24**
Histology				
Diffuse Large B-cell	1.00		1.00	
Follicular	0.80	0.75 – 0.87	**0.84**	**0.78 – 0.91**
Other	1.09	1.02 – 1.16	1.01	0.94 – 1.08
Stage at Diagnosis				
I	1.00		1.00	

	Overall Survival among patients experiencing febrile neutropenia event (n=8,546)			
	Univariable		Multivariable	
	HR	**95% CI**	**HR**	**95% CI**
II	1.18	1.08 – 1.28	**1.23**	**1.13 – 1.34**
III	1.41	1.29 – 1.53	**1.51**	**1.39 – 1.64**
IV	1.54	1.44 – 1.64	**1.63**	**1.52 – 1.75**
Comorbidity Score				
0	1.00		1.00	
1	1.30	1.23 – 1.39	**1.23**	**1.16 – 1.31**
≥2	1.72	1.60 – 1.85	**1.56**	**1.45 – 1.67**
Chemotherapy				
Duration (DOS)	0.993	0.992 – 0.995	**0.992**	**0.991 – 0.994**
Chemotherapy Agent (yes vs. no)				
Alkylating Agents	0.86	0.79 – 0.94	1.03	0.92 – 1.16
Topo-isomerase II inhibitor	1.31	1.24 – 1.38	**1.18**	**1.11 – 1.26**
Anthracyclines	0.75	0.71 – 0.79	0.96	0.90 – 1.02
Antimetabolite	1.24	1.17 – 1.31	**1.40**	**1.31 – 1.50**
Platinums	1.18	1.06 – 1.31	**1.21**	**1.08 – 1.36**
Taxanes	1.14	0.92 – 1.42	1.18	0.94 – 1.48
Vinca Alkaloids	0.83	0.77 – 0.89	0.99	0.89 – 1.10
Non-anthracycline antibiotics	1.32	1.20 – 1.45	1.06	0.95 – 1.17
Targeted therapy	0.63	0.60 – 0.66	**0.73**	**0.69 – 0.77**
Other	1.20	1.13 – 1.28	**1.08**	**1.003 – 1.15**
Radiation Therapy				
No	1.00			
Yes	0.96	0.91 – 1.01	-	