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Hospitalizations, outcomes, and management costs of febrile neutropenia in patients from a managed care population

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Abstract

Purpose—The study objective was to evaluate chemotherapy treatment patterns and incidence, cost, and resource utilization of febrile neutropenia-related hospitalization (FNH) in patients with breast cancer, lung cancer, and non-Hodgkin's lymphoma (NHL) from Kaiser Permanente Southern California (KPSC), a large integrated delivery system.

Methods—Adults ≥18 years with any stage breast cancer, lung cancer, or NHL who initiated myelosuppressive chemotherapy from 01/01/2006 to 12/31/2009 were included. Chemotherapy dose delays ≥7 days, relative dose intensity (RDI), regimen switching, FNH and all-cause mortality, granulocyte colony-stimulating factor (G-CSF) and antibiotic use, and healthcare utilization/cost were evaluated by cancer type, regimen, and/or cycle.

Results—Among 3314 breast cancer patients, 25.3% received an RDI ≤85%, 13.9% experienced FNH with an all-cause mortality rate of 2.0%, and 20.2% received primary prophylaxis with G-CSF. Among those with FNH, mean hospital length of stay (LOS) was 4.1 days, and mean total costs were $20,462. Among 1443 lung cancer patients, 17.9% had an RDI ≤85%, 8.0% experienced FNH with an all-cause mortality rate of 25.2%, and 4.5% received primary prophylaxis with G-CSF. Among those with FNH, mean LOS was 6.8 days, and mean total costs were $32,964. Among 581 NHL patients, 27.9% had an RDI ≤85% and 22.4% experienced FNH with an all-cause mortality rate of 13%. Among those with FNH, mean LOS was 7.9 days, and mean total costs were $37,555.

Conclusions—Marked variability was observed among different cancer types and chemotherapy regimens. Given the variability, detailed insight into incidence, management, and burden of FN can help inform clinical decision making.

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Compliance with ethical standards

Conflicts of interest RB, FV, and DC are employees of and stockholders in Amgen Inc. AK, AF, CC, and WC are employees of KPSC, which received research funding for this study.

Keywords

Febrile neutropenia; Healthcare utilization; Relative dose intensity; Outcomes

Introduction

Chemotherapy-induced febrile neutropenia (FN) is a potentially life-threatening and dose-limiting side effect of myelosuppressive chemotherapy that often requires immediate hospitalization and treatment with intravenous (IV) antibiotics [1–3]. On average, the FN-related mortality rate is ~5–11%; however, FN-related mortality can approach or exceed 50% for certain high-risk populations [4]. FN may also require chemotherapy dose reductions, dose delays, or even discontinuation of chemotherapy, thereby reducing relative dose intensity (RDI) and potentially compromising long-term patient outcomes [5].

FN-related hospitalization (FNH) can be resource intensive. In studies conducted in the USA, mean length of stay (LOS) for FNH was 8–11 days for patients with solid tumors and as much as 10 to 11 days for those with lymphoma [1, 4, 6]. The mean costs for FNH were estimated to range between $13,181 and $24,218 (USD) per episode and varied by cancer type [7–9].

Primary prophylaxis with granulocyte colony-stimulating factors (G-CSFs) has been shown to reduce the frequency, duration, and severity of chemotherapy-induced FN [10–12] and is recommended when a patient has a high risk of FN (>20%) [13, 12, 14]. Individual patient risk for FN is determined based on a combination of patient-related risk factors, chemotherapy regimen, and treatment intent.

The risk of FN varies markedly among different chemotherapy regimens, and NCCN categorizes many chemotherapy regimens as high, intermediate, or low risk of FN based primarily on clinical trial data [14, 13]. For example, dose-dense chemotherapy regimens are considered high-risk regimens, and primary prophylaxis with G-CSF is routinely recommended. However, data on the risk of FNH within individual chemotherapy regimens are not well understood. Risk of FN in the absence of G-CSF is often lacking in clinical trials, risk of FN in real-world clinical practice is often much higher than that reported in clinical studies [15], and some regimens lack real-world data to support FN risk assessment.

The objectives of this study were to evaluate chemotherapy regimens used, RDI, and dose modification; FNH and mortality; and FN management for patients within the managed care population of Kaiser Permanente Southern California (KPSC) diagnosed with breast cancer, lung cancer, and non-Hodgkin’s lymphoma (NHL). Among patients with FNH, we also evaluated resource utilization and costs. Together, this information can help inform clinical decision making by providing a detailed description of FNH and its consequences within cancer types and chemotherapy regimens.

Methods

Study design

This was a retrospective cohort study of patients with any stage breast cancer, lung cancer, and NHL identified from the health plan enrollees of KPSC, an integrated healthcare system that provides comprehensive health services for approximately 4.2 million residents of Southern California. The population served by KPSC is socioeconomically diverse and is broadly representative of the racial/ethnic groups living in Southern California [16]. The study was approved by the institutional review board of KPSC. The primary data sources used for this study were KPSC electronic medical records (EMRs), including KPSC's SEER-affiliated cancer registry.

Patients

This study included adults aged ≥18 years with a new primary diagnosis of breast cancer, lung cancer, or NHL between January 1, 2006 and December 31, 2009, who initiated myelosuppressive chemotherapy within 1 year from diagnosis and who were continuously enrolled in the health plan for at least 1 year before diagnosis and 1 month after first cycle of chemotherapy. Patients were excluded if they had undergone a bone marrow/stem cell or solid organ transplant within 1 year before diagnosis, received chemotherapy within 1 year before diagnosis, had any white blood cell diseases (ICD-9-CM diagnosis code 288.1, 288.2, 288.3, 288.4, 288.5x, or 288.6x) within 6 months before diagnosis, or had multiple types of cancer.

Study variables

Clinical characteristics—Cancer stage was based on the TNM classification of malignant tumors for breast and lung cancer and on Ann Arbor staging for NHL [17, 18], which was recategorized into stages 0–4 and other for this analysis (see Supplemental Methods). Chronic comorbidities, history of blood disorders, and infections were assessed for the 12-month period prior to cancer diagnosis.

Chemotherapy regimens—Chemotherapy regimens were determined based on the agents received in the first cycle. The first chemotherapy cycle began at the date of chemotherapy initiation (i.e., the index date) and ended 1 day before administration of the next chemotherapy cycle. The second and all subsequent cycles of chemotherapy, up to a maximum of eight for breast cancer and NHL and a maximum of six for lung cancer, were similarly defined. Initiation of a new line of chemotherapy was designated based on a record of administration of myelosuppressive chemotherapy that was preceded by a 365-day period without evidence of receipt of chemotherapy ("pretreatment"). The chemotherapy course was considered to have ended if there was no evidence of receipt of a subsequent cycle of chemotherapy within 60 days. In this case, the end date for the cycle and course was defined using NCCN standards for cycle duration. If there was evidence of switching chemotherapy agents before the end of the standard NCCN-recommended treatment regimen, the cycle and the course of chemotherapy were considered to have been completed on the day before initiation of new chemotherapy agents.

The analysis only included regimens that were administered to >100 patients in the first cycle to obtain meaningful estimates of FNH incidence and mortality; the CHOP regimen (without rituximab) administered to patients with NHL (n = 60) was the only exception.

FNH incidence and all-cause mortality—FNH incidence was determined using a validated algorithm that included hospitalization with diagnosis of neutropenia (ICD-9-CM 288.0X) or laboratory documentation of neutropenia (ANC < 1000/μL) and a diagnosis of infection, fever, or use of antibiotics during a hospital stay within a cycle of chemotherapy. Because FN is not always listed as the underlying cause of death, the all-cause mortality rate among patients with FNH was determined instead of FN-related mortality. A patient was considered at risk of death from the day of FNH until 30 days after discharge.

Chemotherapy delivery, dose delays, and RDI—Chemotherapy dose delays were defined as a delay ≥7 days from NCCN standards in at least one myelosuppressive agent. Only drugs that were part of the initial, cycle 1 chemotherapy regimen were considered for this calculation.

RDI was calculated as the ratio of delivered dose intensity to planned dose intensity over a given time interval. Delivered dose intensity was calculated as the ratio of actual dose received to the actual time to complete chemotherapy. Planned dose intensity was defined as a ratio of the planned total dose (based on the dose in the first cycle) and the NCCN-standard time to complete the regimen. Only agents considered to be myelosuppressive were included in the calculation of RDI, and RDI was based on the mean value across all myelosuppressive agents for regimens containing multiple myelosuppressive agents.

G-CSF and antibiotic use—Prophylaxis with G-CSF (e.g., filgrastim or pegfilgrastim) was defined as administration within 5 days following completion of administration of chemotherapy. Prophylaxis with antibiotics was defined as administration within 5 days for IV antibiotics and within 7 days for oral antibiotics following completion of administration of chemotherapy. Primary prophylaxis was defined as prophylaxis in the first chemotherapy cycle, and secondary prophylaxis was defined as prophylaxis that began in any subsequent cycle, regardless of prior FN.

FNH and costs—Economic outcomes included number of FNH and hospital LOS, office-based and emergency department visits, and costs (in 2013 USD) associated with these visits for the first course of chemotherapy. Economic outcomes were evaluated by cycle among patients who experienced FNH in a given cycle. Office-based visits were further categorized as all-cause visits which included oncology and non-oncology department visits, oncology visits which included visits with or without chemotherapy administration, and oncology without chemotherapy visits.

Resource utilization was determined up to the average expected cycle days based on each chemotherapy regimen or the beginning of the next cycle of chemotherapy, whichever was earlier. Costs were calculated based on the average cost obtained from nationally representative samples of the 2012 Medical Expenditure Panel Survey (MEPS) [19]. Inpatient costs were obtained by multiplying the hospital LOS by per diem costs. Emergency

department visit costs were calculated specific to each discharge diagnosis. For office-based oncology visits, averages were calculated separately for oncology visits associated with chemotherapy administration and oncology visits not associated with chemotherapy.

Statistical analysis

Descriptive statistics were used to characterize patient demographics, disease characteristics, chemotherapy RDI and dose delays, and FNH incidence, management, and mortality. Confidence intervals (CIs) for FNH incidence and mortality were calculated using Clopper-Pearson confidence limits for the binomial proportion. For economic analyses, means and 95% CIs were evaluated on a cycle-specific basis and were calculated via a bias-corrected bootstrap procedure with 10,000 replications.

Results

Patients

In total, 5338 patients were included in the study (breast cancer, $n = 3314$; lung cancer, $n = 1443$; NHL, $n = 581$). Patient demographics and disease characteristics are shown in Table 1.

Chemotherapy treatments

For patients with breast cancer, the most prevalent chemotherapy regimens were TC (24.6%), AC-T (19.1%), and TCH (14.0%). For patients with lung cancer, the most prevalent chemotherapy regimen was carboplatin with paclitaxel (60.8%), and similar numbers of patients received EP (13.7%), EC (13.0%), and G/C (12.5%). For patients with NHL, the most prevalent chemotherapy regimen was R-CHOP (89.7%); the remaining patients received CHOP alone (10.3%). The number of treatment cycles and treatment duration are shown in Table 2 and Supplemental Table 1.

Chemotherapy delivery, dose delays, and RDI

Considerable variability was seen among cancer types and among chemotherapy regimens (Table 2). Among patients with breast cancer, 9.3% of patients had a dose delay ≥7 days, 25.3% had an RDI ≤85%, and 5.6% switched regimens. The regimens that had the highest percentage of patients with RDI ≤85% were AC-T (71.2%), trastuzumab + AC-T (59.9%), and ddAC-T (33.8%).

Among patients with lung cancer, 11.2% had a dose delay ≥7 days, 17.9% had an RDI ≤85%, and 15.7% switched regimens. Dose delays and RDI ≤85% were most common with EC (23.0 and 29.9%, respectively), and regimen switching was most common with G/C (21.7%).

Among patients with NHL, 16.5% had a dose delay ≥7 days, 27.9% had an RDI ≤85%, and 6.5% switched regimens. More patients had an RDI ≤85% with CHOP than with R-CHOP (40.0 versus 26.5%), and dose delays and regimen switching were similar among these two regimens.

FNH incidence and all-cause mortality

The incidences of FNH and mortality varied by cancer type. Among the 3314 patients with breast cancer, 459 (13.9%) experienced FNH (95% CI 12.7%–15.1%), and the all-cause mortality rate among this latter patient group was 2.0% (0.9–3.7%). Among the 1443 patients with lung cancer, 115 (8.0% [6.6–9.5%]) experienced FNH, and the all-cause mortality rate among this patient group was 25.2% (17.6–34.2%). Among the 581 patients with NHL, 130 (22.4% [19.1–26.0%]) experienced FNH, and the all-cause mortality rate among this patient group was 13% (7.8–20.1%).

Rates of FNH were higher in cycle 1 for most, but not all, regimens (Supplemental Table 2). For patients with breast cancer, a higher cycle 1 incidence of FNH was seen with AC-T, TC, TAC, CAF, and TCH. For lung cancer, a higher cycle 1 incidence of FNH was seen with carboplatin + paclitaxel. For NHL, a higher cycle 1 incidence of FNH was seen for both CHOP and R-CHOP. However, the incidences of FNH were often low, especially in later cycles, making it difficult to determine trends in incidences of FNH across chemotherapy cycles.

G-CSF and antibiotic use

Though variance was seen among different cancer types and different chemotherapy regimens, G-CSF was predominantly administered prophylactically and antibiotics were predominantly administered as treatment for FN (Table 3).

For patients with breast cancer, 20.2% received prophylactic G-CSF in the first chemotherapy cycle, 41.0% received prophylactic G-CSF in the second and/or subsequent cycles, and 24.6% received G-CSF as treatment. The use of G-CSF as primary prophylaxis seemed to have been primarily driven by high FN risk regimens like ddAC-Tand TAC. In total, 2.3% of patients received prophylactic antibiotics in the first cycle, 11.8% received prophylactic antibiotics in the second and/or subsequent cycles, and 30.6% received antibiotics as treatment.

For patients with lung cancer, 4.5% received prophylactic G-CSF in the first chemotherapy cycle, 11.3% received prophylactic G-CSF in the second and/or subsequent cycles, and 10.8% received G-CSF as treatment. In total, 3.9% of patients received prophylactic antibiotics in the first cycle, 7.4% received prophylactic antibiotics in the second and/or subsequent cycles, and 18.8% received antibiotics as treatment.

For patients with NHL, 21.2% received prophylactic G-CSF in the first chemotherapy cycle, 45.3% received prophylactic G-CSF in the second and/or subsequent cycles, and 31.8% received G-CSF as treatment. In total, 5.3% of patients received prophylactic antibiotics in the first cycle, 10.0% received prophylactic antibiotics in the second and/or subsequent cycles, and 41.1% received antibiotics as treatment.

Healthcare utilization and costs

Healthcare utilization and costs were calculated for patients who experienced FNH (N = 704). Patient demographics and disease characteristics for this patient subset (Supplemental Table 3) were similar to the overall population. FNH was associated with considerable costs

across cancer types and chemotherapy cycle (Supplemental Tables 4–6). The overall hospital LOS ranged from 4.1 to 7.9 days, and most costs were incurred during the hospital stay (Table 4).

For breast cancer (Supplemental Table 4), mean (95% CI) total costs per episode of FNH were $20,462 (19,072–22,181). Mean LOS was 4.1 (3.7–4.5) days, and mean costs associated with the hospital stay were $16,940 (15,689–18,590). Patients had 1.2 (1.2–1.3) emergency department visits for a cost of $1215 (1131–1295) and 3.9 (3.7–4.2) all-cause office-based visits for a cost of $2317 (2199–2451).

For lung cancer (Supplemental Table 5), mean (95% CI) total costs cost per episode of FNH were $32,964 (28,166–39,278). Mean LOS was 6.8 (5.7–8.3) days, and mean costs associated with the hospital stay were $28,413 (23,686–34,536). Patients had 1.2 (1.1–1.3) emergency department visits for a cost of $1422 (1264–1611) and 5.3 (4.3–6.7) all-cause office-based visits for a cost of $3126 (2617–3787).

For NHL (Supplemental Table 6), mean (95% CI) total costs cost per episode of FNH were $37,555 (32,060–44,174). Mean LOS was 7.9 (6.7–9.5) days, and mean costs associated with the hospital stay were $33,006 (27,628–39,382). Patients had 1.5 (1.3–1.7) emergency department visits for a cost of $1729 (1520–1970) and 5.3 (4.6–6.0) all-cause office-based visits for a cost of $2813 (2522–3153).

Discussion

Through the use of comprehensive medical records in a large managed care cancer population, we identified the clinical and economic burden of FN associated with specific cancer types, chemotherapy regimens, and chemotherapy cycles. FN management practices, resource utilization, and costs differed markedly among different tumor types and among different chemotherapy regimens. Thus, detailed information on the risks and consequences of FN is needed to help support informed clinical decision making.

RDI ≤85% is considered to be a clinically meaningful reduction in the efficacy of a chemotherapy regimen and is associated with worse long-term patient outcomes in several cancer types, including breast cancer, lung cancer, and NHL [5, 20]. Overall, 25% of patients with breast cancer, 18% of patients with lung cancer, and 28% of patients with NHL had an RDI ≤85%. These values were slightly lower than those reported in the literature (29–39% among patients with solid tumors) [21]. However, RDI may not be directly comparable across publications due to methodological differences and differences in the study populations. Detailed methods regarding analysis of RDI are needed to allow comparisons between studies and over time.

The proportion of patients who experienced FNH in our study is similar to previous estimates that indicate that approximately 7–22% of cancer patients who are treated with chemotherapy require hospitalization for FN [22]. However, the all-cause mortality rate was higher than previously published for some cancer types. Previous studies estimated the mortality rate associated with FNH as 5–11% in patients with solid tumors or hematologic malignancies [4]. In this study, the all-cause mortality rate was 2% for patients with breast

cancer, 25% for patients with lung cancer, and 13% for patients with NHL. The higher mortality rates in lung cancer and NHL seen here may be partially explained by advanced cancer stage, advanced age, and multiple chronic conditions in these cohorts, since we did not control for such factors.

Prophylactic administration of G-CSF has been associated with a lower incidence of FN and with reductions of inpatient healthcare utilization [4, 23]. Current clinical guidelines recommend primary prophylaxis with chemotherapy regimens that have a high risk of FN (>20%). Additionally, patients receiving intermediate- or even low-risk chemotherapy regimens might be at high risk of FN due to patient risk factors. Primary prophylaxis with G-CSF was highly variable across different chemotherapy regimens. For example, 73% of patients receiving ddAC-T received primary prophylaxis with G-CSF and 9.0% of patients receiving TC received primary prophylaxis with G-CSF.

Mean LOS in this study was longer for patients with lung cancer (7 days) and NHL (8 days) compared to patients with breast cancer (4 days); older age, more comorbidities, and advanced disease stage at diagnosis in patients with lung cancer and NHL likely contributed to these differences. LOS in this study was slightly lower than the LOS reported in a recent study (6 days for breast cancer, 8 days for lung cancer, and 10 days for NHL) [9]. Availability of EMRs across all KPSC facilities may help improve communication and speed of decision making, thereby reducing LOS in this cohort. Differences in LOS seen among studies may reflect differences in patient populations or differences in FN patient management in fee-for-service versus managed care settings.

The primary driver of costs was management and stabilization of patients during the hospitalization with FN. Within each cancer type, cost estimates were remarkably stable across chemotherapy cycle. In contrast with LOS, the average inpatient costs associated with hospitalization for FN were higher in this study compared with previous studies; previous studies estimated mean FNH costs between $7100–$12,400 (versus $16,940 in this study) for patients with breast cancer, $8500–$17,700 (versus $28,413) for patients with lung cancer, and $11,000–$24,218 (versus $33,006) for patients with NHL [1, 9, 24]. Differences in patient populations among the studies, changes over time in the cost of care and management of FN, and monetization of resource counts may have contributed to these differences.

This study had several limitations. The means and CIs presented need to be interpreted with caution, as estimates may be influenced by both observable and unobservable confounding, making the true patient-level estimates significantly different from the unadjusted estimates reported. Moreover, the generalizability of these estimates is limited to the sample studied and may not generalize to non-KPSC population. Additionally, at higher-numbered cycles, the relatively low sample size could bias the estimate of the true mean and variance around the mean. Furthermore, the true incidence and burden of FN may be underreported. FN is difficult to characterize in large datasets because a single ICD-9-CM code for febrile neutropenia does not exist. The validated FN algorithm used here is similar to other studies and includes hospitalization with neutropenia (ICD-9-CM 288.0X) or ANC <1000 μ/L and a diagnosis of infection, or fever, or use of antibiotics during hospital stay [25, 26]. However,

some cases of FN may have been missed. Additionally, FN events treated in the outpatient setting only and the subsequent costs of FN beyond the index cycle were not captured.

Our study describes the heterogeneity in FN incidence and associated clinical and economic burden within specific tumor types, chemotherapy regimens, and chemotherapy cycles. Overall, our study identifies a need to understand the causes of variation in FNH management and costs. Better understanding of the factors that contribute to a high incidence of FNH may ultimately support better patient outcomes. Finally, a more comprehensive understanding of the risks associated with myelosuppressive chemotherapy regimens can help in choosing treatment options that are well suited to the individual patient.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1

Baseline patient demographics and disease characteristics

	Total (*N* = 5338)	Breast cancer (*n* = 3314)	Lung cancer (*n* = 1443)	NHL (*n* = 581)
Mean (SD) age at diagnosis, years	58.5 (11.7)	54.6 (10.5)	66.0 (9.5)	62.1 (13.4)
Women, *n* (%)	4233 (79.3)	3300 (99.6)	658 (45.6)	275 (47.3)
Race, *n* (%)				
White	3578 (67.0)	2134 (64.4)	1027 (71.2)	417 (71.8)
Black	780 (14.6)	523 (15.8)	209 (14.5)	48 (8.3)
Asian	543 (10.2)	377 (11.4)	121 (8.4)	45 (7.7)
Other/unknown/multiple	437 (8.2)	280 (8.4)	86 (6.0)	71 (12.2)
Hispanic ethnicity, *n* (%)	1169 (21.9)	832 (25.1)	172 (11.9)	165 (28.4)
Stage at diagnosis, *n* (%)				
0	10 (0.2)	10 (0.3)	0	0
1	1091 (20.4)	863 (26.0)	78 (5.4)	150 (25.8)
2	1881 (35.2)	1703 (51.4)	58 (4.0)	120 (20.7)
3	1200 (22.5)	623 (18.8)	461 (31.9)	116 (20.0)
4	1059 (19.8)	82 (2.5)	792 (54.9)	185 (31.8)
Other	97 (1.8)	33 (1.0)	54 (3.7)	10 (1.7)
Mean (SD) cumulative length of health plan enrollment, years	14.8 (11.4)	13.9 (11.0)	16.1 (11.7)	16.5 (12.4)
Mean (SD) total number of comorbid conditions	2.2 (2.3)	1.5 (1.8)	3.4 (2.5)	3.2 (2.6)
Mean (SD) Charlson Comorbidity Index	1.1 (2.0)	0.5 (1.1)	2.3 (2.8)	1.7 (2.3)
Chronic comorbid conditions, *n* (%)				
Anemia	450 (8.4)	148 (4.5)	175 (12.1)	127 (21.9)
AIDS/HIV	15 (0.3)	1 (0.0)	6 (0.4)	8 (1.4)
Cerebrovascular disease	148 (2.8)	26 (0.8)	96 (6.7)	26 (4.5)
Congestive heart failure	115 (2.2)	25 (0.8)	77 (5.3)	13 (2.2)
Connective tissue disease	134 (2.5)	69 (2.1)	37 (2.6)	28 (4.8)
COPD/emphysema	1010 (18.9)	365 (11.0)	561 (38.9)	84 (14.5)
Dementia	4 (0.1)	1 (0.0)	2 (0.1)	1 (0.2)
Diabetes with complications	321 (6.0)	142 (4.3)	129 (8.9)	50 (8.6)
Diabetes without complications	770 (14.4)	392 (11.8)	272 (18.8)	106 (18.2)
Dyslipidemia	1901 (35.6)	967 (29.2)	671 (46.5)	263 (45.3)
History of blood disorders	534 (10.0)	174 (5.3)	207 (14.3)	153 (26.3)
Hypertension	2404 (45.0)	1179 (35.6)	916 (63.5)	309 (53.2)
Hypotension	46 (0.9)	7 (0.2)	29 (2.0)	10 (1.7)
Hypovolemia	4 (0.1)	0	4 (0.3)	0
Infections	1088 (20.4)	467 (14.1)	476 (33.0)	145 (25.0)
Liver disease	80 (1.5)	34 (1.0)	20 (1.4)	26 (4.5)
Myocardial infarction	165 (3.1)	23 (0.7)	120 (8.3)	22 (3.8)
Osteoarthritis	687 (12.9)	339 (10.2)	242 (16.8)	106 (18.2)
Other autoimmune conditions	295 (5.5)	150 (4.5)	89 (6.2)	56 (9.6)
Peptic ulcer disease	38 (0.7)	10 (0.3)	17 (1.2)	11 (1.9)

	Total (*N* = 5338)	Breast cancer (*n* = 3314)	Lung cancer (*n* = 1443)	NHL (*n* = 581)
Peripheral vascular disease	198 (3.7)	29 (0.9)	138 (9.6)	31 (5.3)
Renal disease	324 (6.1)	119 (3.6)	150 (10.4)	55 (9.5)
Rheumatoid disease	20 (0.4)	6 (0.2)	10 (0.7)	4 (0.7)
Thrombocytopenia	29 (0.5)	6 (0.2)	7 (0.5)	16 (2.8)
Thrombosis	26 (0.5)	6 (0.2)	13 (0.9)	7 (1.2)
Thyroid disorder, including autoimmune thyroiditis	539 (10.1)	315 (9.5)	151 (10.5)	73 (12.6)

BUN blood urea nitrogen, *COPD* chronic obstructive pulmonary disease

Table 2

Chemotherapy treatment patterns

Chemotherapy regimen	Abbreviation	Number	Dose delays ≥7 days n (%)	RDI ≤85% n (%)	Switched regimen n (%)
Breast cancer		3314	307 (9.3)	840 (25.3)	186 (5.6)
Doxorubicin + cyclophosphamide	AC	352	14 (4.0)	37 (10.5)	12 (3.4)
AC followed by paclitaxel or docetaxel	AC-T	633	85 (13.4)	451 (71.2)	6 (0.9)
Dose-dense AC-T	ddAC-T	293	61 (20.8)	99 (33.8)	4 (1.4)
Cyclophosphamide + docetaxel	TC	814	38 (4.7)	74 (9.1)	50 (6.1)
Docetaxel + doxorubicin + cyclophosphamide	TAC	423	40 (9.5)	42 (9.9)	22 (5.2)
Cyclophosphamide + doxorubicin + fluorouracil	CAF	148	9 (6.1)	10 (6.8)	7 (4.7)
Trastuzumab + AC-T	--	187	25 (13.4)	112 (59.9)	19 (10.2)
Docetaxel + carboplatin + trastuzumab	TCH	464	35 (7.5)	15 (3.2)	66 (14.2)
Lung cancer		1443	161 (11.2)	259 (17.9)	227 (15.7)
Etoposide + carboplatin	EC	187	43 (23.0)	56 (29.9)	26 (13.9)
Gemcitabine + carboplatin	G/C	180	31 (17.2)	42 (23.3)	39 (21.7)
Carboplatin + paclitaxel	NA	878	79 (9.0)	134 (15.3)	158 (18.0)
Etoposide + cisplatin	EP	198	8 (4.0)	27 (13.6)	4 (2.0)
NHL		581	96 (16.5)	162 (27.9)	38 (6.5)
Cyclophosphamide + doxorubicin + vincristine + prednisone	CHOP	60	8 (13.3)	24 (40.0)	5 (8.3)
Rituximab + CHOP	R-CHOP	521	88 (16.9)	138 (26.5)	33 (6.3)

Table 3

G-CSF and antibiotic use

Chemotherapy regimen, *n* (%)	G-CSF[a] use			Antibiotic use		
	Primary Prophylaxis	Secondary Prophylaxis	Treatment	Primary Prophylaxis	Secondary Prophylaxis	Treatment
Breast cancer (*n* = 3314)	669 (20.2)	1358 (41.0)	815 (24.6)	75 (2.3)	392 (11.8)	1015 (30.6)
AC (*n* = 352)	6 (1.7)	68 (19.3)	59 (16.8)	5 (1.4)	26 (7.4)	76 (21.6)
AC-T (*n* = 633)	25 (3.9)	179 (28.3)	137 (21.6)	9 (1.4)	94 (14.8)	194 (30.6)
ddAC-T (*n* = 293)	213 (72.7)	261 (89.1)	92 (31.4)	9 (3.1)	36 (12.3)	54 (18.4)
TC (*n* = 814)	73 (9.0)	225 (27.6)	201 (24.7)	18 (2.2)	67 (8.2)	270 (33.2)
TAC (*n* = 423)	292 (69.0)	346 (81.8)	133 (31.4)	22 (5.2)	78 (18.4)	169 (40.0)
CAF (*n* = 148)	1 (0.7)	31 (20.9)	29 (19.6)	0 (0)	5 (3.4)	22 (14.9)
Trastuzumab + AC-T (*n* = 187)	3 (1.6)	54 (28.9)	28 (15.0)	1 (0.5)	34 (18.2)	43 (23.0)
TCH (*n* = 464)	56 (12.1)	194 (41.8)	136 (29.3)	11 (2.4)	52 (11.2)	187 (40.3)
Lung cancer (*n* = 1443)	65 (4.5)	163 (11.3)	156 (10.8)	56 (3.9)	107 (7.4)	271 (18.8)
EC (*n* = 187)	16 (8.6)	38 (20.3)	34 (18.2)	7 (3.7)	17 (9.1)	55 (29.4)
G/C (*n* = 180)	9 (5.0)	20 (11.1)	13 (7.2)	17 (9.4)	17 (9.4)	15 (8.3)
Carboplatin + paclitaxel (*n* = 878)	28 (3.2)	72 (8.2)	67 (7.6)	23 (2.6)	56 (6.4)	146 (16.6)
EP (*n* = 198)	12 (6.1)	33 (16.7)	42 (21.2)	9 (4.5)	17 (8.6)	55 (27.8)
NHL (*n* = 581)	123 (21.2)	263 (45.3)	185 (31.8)	31 (5.3)	58 (10.0)	239 (41.1)
CHOP (*n* = 60)	15 (25.0)	25 (41.7)	19 (31.7)	8 (13.3)	8 (13.3)	28 (46.7)
R-CHOP (*n* = 521)	108 (20.7)	238 (45.7)	166 (31.9)	23 (4.4)	50 (9.6)	211 (40.5)

[a]G-CSF includes filgrastim and/or pegfilgrastim

Table 4

Overall average costs (2013 USD) and utilization by cancer type for patients with FNH

Costs and utilization, mean (95% CI)	Emergency department visit	Hospitalization stay	Office-based visit			Total[b]
			All-cause	Oncology	Oncology without chemotherapy	
Breast cancer (n = 459)						
Costs, $	1215 (1131–1295)	16,940 (15,689–18,590)	2317 (2199–2451)	1831 (1737–1938)	504 (331–611)	20,462 (19,072–22,181)
Visit[a] n	1.2 (1.2–1.3)	4.1 (3.7–4.5)	3.9 (3.7–4.2)	2.2 (2.0–2.4)	1.1 (0.9–1.2)	6.3 (6.0–6.7)
Lung cancer (n = 115)						
Costs, $	1422 (1264–1611)	28,413 (23,686–34,536)	3126 (2617–3787)	2505 (2080–3063)	450 (331–611)	32,964 (28,166–39,278)
Visit[a] n	1.2 (1.1–1.3)	6.8 (5.7–8.3)	5.3 (4.3–6.7)	2.7 (2.2–3.3)	0.9 (0.7–1.3)	7.7 (6.6–9.2)
NHL (n = 130)						
Costs, $	1729 (1520–1970)	33,006 (27,628–39,382)	2813 (2522–3153)	2209 (1965–2497)	834 (658–1049)	37,555 (32,060–44,174)
Visit[a] n	1.5 (1.3–1.7)	7.9 (6.7–9.5)	5.3 (4.6–6.0)	2.9 (2.5–3.4)	1.8 (1.4–2.2)	8.2 (7.4–9)

[a] Hospitalization stays are indicated as bootstrapped mean (95% CI) LOS in days; all other visits are indicated as bootstrapped mean (95% CI) number of visits

[b] Total visits is the sum of emergency department visits + hospitalization stays + outpatient visits divided by the cycle-specific sample (n); total costs is the sum of emergency department costs + hospitalization costs + outpatient costs divided by the cycle-specific sample (n)