Chemotherapy-Associated Toxicity in a Large Cohort of Elderly Patients with Non-small Cell Lung Cancer

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Background: The objective of this study was to examine the risks for short-term (≤3 months) and long-term (>3 months) chemotherapy-associated toxicities in a large population-based cohort of patients with non-small cell lung cancer from 1991 to 2002.

Methods: The population consisted of 41,361 men and 30,804 women ≥65 years identified from the Surveillance, Epidemiology, and End Results—Medicare-linked database. The incidence of 50 toxicity-associated end points was calculated for 14 chemotherapy agents. Short- and long-term toxicities with a ≥2-fold increase in incidence compared with the no-chemotherapy group were defined as chemotherapy-associated toxicities. Hazard ratios and 95% confidence intervals for the risk of toxicity were calculated for the four most common chemotherapy agents for non-small cell lung cancer: cisplatin/carboplatin, paclitaxel, vinorelbine/vinblastine, and gemcitabine.

Results: The most common short-term toxicities (9.2–60%) included acute anemia, nausea, and neutropenia. The most common long-term toxicities (15–37%) included acute anemia, respiratory failure, pulmonary fibrosis, dehydration, neutropenia, nausea, and fever. Multivariate analysis for selected chemotherapies demonstrated that after adjusting for other risk factors and confounders, some short-term toxicities became nonsignificant; however, almost all long-term toxicities remained significant. Long-term toxicity increased over time and was more likely in women, minority populations, those with fewer baseline comorbidities, and across disease stages.

Conclusions: The administration of various chemotherapy agents for non-small cell lung was associated with a number of short- and long-term toxicities. The projected survival benefits of chemotherapy must be weighed against the risk of long-term toxicities.

Key Words: Non-small cell lung cancer, Chemotherapy, Toxicity, Years of diagnosis, Tumor stage, Comorbidities.

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Chemotherapy has been shown to improve survival and palliate disease-related symptoms in patients with stage IV non-small cell lung cancer (NSCLC).[1] The guidelines for the administration of specific chemotherapeutic agents endorsed by the American College of Chest Physicians derived from evidence from randomized trials and were based on evidence that demonstrated a substantial benefit for both survival and palliation in patients with stage IIIB and stage IV disease with good performance status.[2] To extrapolate these treatment recommendations to additional subsets of patients with poorer performance status or significant comorbidities, it is critical for clinicians to have accurate estimates of the risks that include short- and long-term toxicities of various chemotherapy regimens and to engage patients in discussion of preferences.

It has been suggested that the risk-benefit ratio of treatment rendered in the setting of randomized clinical trials may not be applicable to patients treated in the community. There are a number of plausible explanations: (1) randomized trials are designed to examine the efficacy of various regimens in eligible patients, which often include only those with the best performance status, and (2) randomized trials are often performed at trial sites, which are often supported by extensive clinical infrastructure. In such settings, acute toxicities associated with treatment are often identified and managed expeditiously and long-term toxicities are not often reported because of short-term trial follow-up, which precludes their identification. As a result, the efficacy or benefit of treatment is often maximized while the risks of treatment are minimized. For these reasons, it is critical to obtain estimates of the spectrum of chemotherapy-associated toxicities administered in the community using population-based data that include older patients, ethnic minorities, and those with comorbidities.

The first objective of this study was to determine the incidence of short-term toxicity (≤3 months) and long-term toxicity (>3 months) associated with various chemotherapy agents administered for NSCLC. An additional aim was to determine the risks for toxicities with a ≥2-fold incidence for the most common agents administered: cisplatin and carboplatin combined (CARCIS), paclitaxel (PAC), vinorelbine and vinblastine combined (VINVinb), and gemcitabine (GEM) compared with the group who received no-chemotherapy.

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METHODS

Data Sources

The Surveillance, Epidemiology, and End Results (SEER) Program—Medicare-linked database was used to provide information about incident cancer cases and cancer-directed therapy, as well as Medicare eligibility, enrollment, and claims for those ≥65 years.[3] Patients who did not have full coverage of both Medicare Parts A and B or who were members of a Health Maintenance Organization after diagnosis through the date of last follow-up or death were excluded from the study. The University of Texas School of Public Health at Houston Committee for Protection of Human Subjects approved the study protocol.

Study Variables

The outcome variable was time to development (in days) of chemotherapy toxicity-related conditions calculated from the date of diagnosis of NSCLC to the date of toxicity, censoring, or the last date of follow-up. The exposure variable, chemotherapy, was designated as whether or not patients received one or more chemotherapy claim within 12 months of diagnosis. Patients who developed toxicities after chemotherapy was administered were included in the analysis. Patients with existing toxicity conditions before cancer diagnosis were excluded from the study.

The following patient and tumor characteristics were considered for covariate adjustment in multivariate analyses: race/ethnicity was designated as whites (non-Hispanic white), blacks (African Americans and non-Hispanic blacks from other countries), Asians, Hispanics, other and unknown ethnicity; years of diagnosis (1991–2002); age (65–69, 70–74, 75–79, or 80+ years); marital status (married, unmarried, or unknown); sex (male or female); socioeconomic status (quartiles of poverty), disease stage (American Joint Committee on Cancer stages I–IV, unstaged); tumor grade (well differentiated, moderately differentiated, poorly differentiated, and unknown); positive number of nodes (1, 2–3, 4–5, 6–9, and 10–51); SEER areas (16 US regions); and surgery and radiation therapy within 12 months of diagnosis. A weighted comorbidity score (explained elsewhere)[4] coded as 0, 1, 2, 3, or ≥4 was calculated from comorbidities ascertained from Medicare claims by identifying 18 diagnoses or related procedures recorded between 1 year before and 1 month after the diagnosis of NSCLC. Comorbidities before the year of cancer diagnosis could not be ascertained.

Chemotherapy

Chemotherapy is recommended as part of standard therapy for patients with NSCLC according to the National Comprehensive Cancer Network guidelines.[5] For stages I–IIIA disease, as an adjunct treatment to surgical resection, chemotherapy with or without chemoradiation is given. For stages IIIB and IV disease, chemotherapy and radiation therapy are recommended.

In brief, patients who were treated with chemotherapy were identified using the ICD-9 procedure code 9925 for injection or infusion of cancer chemotherapeutic substance, current procedural terminology (CPT) codes (96400-96549, J8510, J8520, J8521, J8530-J8999, J9000-J9999, and Q0083-Q0085) for chemotherapy administration, revenue center codes 0331 (chemotherapy injected), 0332 (chemotherapy oral), 0335 (chemotherapy intravenous), and ICD-9-CM V codes (V58.1, V66.2, or V67.2) for follow-up examination or care after chemotherapy. Surgery and radiation therapy within 12 months of diagnosis were identified from SEER codes,[6] ICD-9 procedure codes,[7,8] and CPT codes[8,9] as referenced.

Statistical Analysis

Analyses were performed using STATA, version 10.1 (STATACORP, College Station, TX) and SAS, version 9.1 (SAS Institute Inc., Cary, NC). Descriptive statistics for patients who received and did not receive chemotherapy for all covariates were performed using Pearson's χ^2 tests of hypothesis for independence with p value of 0.05 as the cut-off point (Table 1). The observed incidence rates for developing short-term (≤3 months) and long-term (>3 months) chemotherapy toxicities were calculated as a percentage of 14 different chemotherapy agents for 50 toxicity-related end points (Tables 2 and 3). The toxicities were then categorized as ≥2-fold increase, >1.5- to <2-fold increase, and 1- to 1.5-fold increase by comparing the incidence of a specific toxicity with the incidence observed in the cohort of patients who did not receive chemotherapy. Chemotherapy-associated toxicity was subsequently arbitrarily defined as a ≥2-fold increase in percent above the level of that seen in the no-chemotherapy group.

An ordinal logistic regression analysis using a proportional odds model with composite toxicity scores was used to compute the odds ratios (ORs) and 95% confidence intervals (CIs) of developing long-term toxicities across toxicity levels for age, gender, racial/ethnic groups, stage, comorbidity scores, and year of diagnosis (Table 4). Long-term toxicities levels were categorized as: 0, no toxicity; 1, only 1 toxicity; and 2, having 2 to 9 toxicities. Additionally, Cox proportional regression analyses were then performed for short- and long-term toxicities associated with the more commonly administered four groups of chemotherapy agents: CARCIS, PAC, VINVinb, and GEM (Table 5). Bonferonni-Sidak correction was used to control for the false discovery rate from multiple comparisons testing.[10] Effect modifiers were identified for chemotherapy (the exposure variable) and the covariates using the likelihood ratio test with a p value cut-off point of 0.05. When the proportional hazards assumption was violated, time varying covariates were constructed to address variables that interacted with time. Both effect modifiers and time dependent covariates were added to the multivariate model.

RESULTS

The study population consisted of 41,361 (57.3%) men and 30,804 (42.7%) women, ≥65 years, diagnosed with NSCLC between January 1, 1991, and December 31, 2002. The median survival time for the short- and long-term chemotherapy toxicity composite groups that were more than or equal to two times that of the no-chemotherapy group was 29 and 241 days, respectively. Patients who received chemotherapy had a lower median age (72 years) compared with those who did not received chemotherapy (75 years) (Table 1). As

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TABLE 1. Characteristics of Patients with Non-small Cell Lung Cancer by Chemotherapy Status within 12 mo of Diagnosis

	Number and Column % of Cases			
	No-Chemotherapy (n = 50,632)		Chemotherapy (n = 21,533)	
Characteristics	***n***	**%**	***n***	**%**
Median age (range)	75 (65–89)		72 (65–89)	
Age (yr)				
65–69	11,273	22.3	17,259	33.7
70–74	13,615	26.9	7267	33.8
75–79	13,248	26.2	4740	22.0
80–84	8754	17.3	1826	8.5
85–89	3742	7.4	441	2.1
Race/ethnicity				
Caucasian	41,788	82.5	18,184	84.5
African American	4782	9.4	1761	8.2
Asian	1490	2.9	636	3.0
Hispanic	570	1.1	232	1.1
Other race	1625	3.2	626	2.9
Unknown	377	0.7	94	0.4
Gender				
Male	28,588	56.5	12,773	59.3
Female	22,044	43.5	8760	40.7
Unknown	1920	3.8	744	3.5
Tumor stage				
I	11,190	22.1	1786	8.3
II	4104	8.1	1143	5.3
IIIA	4492	8.9	3010	14.0
IIIB	9352	18.5	5129	23.8
IV	16,497	32.6	8863	41.2
Unstaged	4997	9.9	1602	7.4
Tumor size (cm)				
<1	538	1.1	154	0.7
1–1.9	3085	6.1	711	3.3
2–2.9	6084	12.0	1977	9.2
3–3.9	6001	11.9	2373	11.0
≥4	15,863	31.3	7569	35.2
Missing	19,061	37.7	8749	40.6
Tumor grade				
Well differentiated	2246	4.4	611	2.8
Moderately differentiated	8347	16.5	2823	13.1
Poorly differentiated	16,832	33.2	7614	35.4
Undifferentiated	2874	5.7	1308	6.1
Unknown/missing	20,333	40.2	9177	42.6
Histology				
Carcinoma, nonspecific	10,289	20.3	4653	21.6
Large cell	3961	7.8	1795	8.3
Squamous cell	15,861	31.3	5737	26.6
Adenocarcinoma	17,676	34.9	8490	39.4
Bronchus	2101	4.2	574	2.7
Adenosquamous cell	744	1.5	284	1.3
Comorbidity scores				
0	17,486	34.5	9722	45.2
1	17,660	34.9	7573	35.2
2	8074	16.0	2627	12.2
3	3480	6.9	1008	4.7
≥4	3932	7.8	603	2.8
Surgery				
No	37,579	74.2	18,521	86.0
Yes	13,053	25.8	3012	14.0
Radiotherapy				
No	27,323	54.0	6486	30.1
Yes	23,309	46.0	15,047	69.9

All p values were <0.0001 and calculated using Pearson's χ^2 tests of hypothesis for independence to assess statistical significance between chemotherapy groups.

anticipated, only a small fraction of patients receiving chemotherapy had stage I and stage II disease (8.3% and 5.3%, respectively). More than one-third of patients who received chemotherapy had a tumor size ≥4 cm, poorly-differentiated tumors, and adenocarcinoma. The chemotherapy cohort has a lower percentage of patients with comorbidity scores ≥2 at baseline compared with the no-chemotherapy cohort.

Tables 2 and 3 display the short-term (≤3 months) and long-term (>3 months) incidence rates for developing various chemotherapy-associated toxicities stratified by chemotherapy agent. The overall incidence categories were classified according to the results for CARCIS, and as such, there may be variation for other agents. Most importantly, in chemotherapy claims, the incidence of "adverse effects of antineoplastics" was reported as only 1.9 to 4.4% for short-term toxicities (Table 2) and 2 to 10% for long-term toxicities (Table 3), which vastly underestimates the overall chemotherapy-associated toxicities when compared with the incidence identified in claims when individual toxicity end points were assessed.

The most common short-term (≤3 months) toxicities included acute anemia (20–35.9%), nausea (20.1–60%), and neutropenia (9.2–22.5%) (Table 2). Other less common short-term toxicities were thrombocytopenia (2.6–6.2%), diarrhea (2.6–10%), stomatitis (0.6–1.4%), hemolytic anemia (0.4–1.6%), and leukemia (0.2–0.8%). In general, unlike long-term toxicities, there was little variability in the incidence of short-term toxicities for the various agents. The most common long-term toxicities included acute anemia (30.7–37.6%), dehydration (24.9–33.6%), respiratory failure (26.3–40.8%), pulmonary fibrosis (25–33.3%), neutropenia (17.0–33.3%), nausea (16.0–25.6%), and fever (13.3–20%). Less common toxicities that occurred with an incidence of ≥2-fold increase in the incidence compared with the no-chemotherapy group included deep vein thrombosis, thrombocytopenia, hypotension, peripheral neuropathy, myocarditis, syndrome of inappropriate antidiuretic hormone secretion, stomatitis, dermatitis, and leukemia.

When individual toxicity end points were examined for nonplatinum based agents, the incidence of long-term chemotherapy-associated toxicities was much higher (Table 3). This was most evident for the long-term toxicity associated with docetaxel (DOC) and ifosfamide (IFO). DOC was associated with the highest incidence of pancytopenia (anemia, neutropenia, and thrombocytopenia) as well as pulmonary, cardiac, hepatocellular, gastrointestinal, mental status, infectious, and renal complications. Similarly, IFO was also associated with long-term pancytopenia, nausea, and pulmonary fibrosis and had the highest incidence of cardiomyopathy (7.0%), renal failure (17.1%), drug psychoses (6.2%), and encephalopathy (3.1%). There were some rare long-term toxicity end points, which were noted in this study that have not been identified in clinical trials. These are bolded and highlighted in gray (Table 3). These toxicities include pulmonary embolism (1.6–3%) associated with fluorouracil (FLU), mitomycin (MIT), leucovorin (LEU), and doxorubicin (DOX) which is 4- to 5-fold greater than in the no-

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TABLE 2. Incidence (%) of Short-Term Toxicities (≤3 mo) During Treatment of Various Chemotherapy Agents Compared with the No-Chemotherapy Group

	CARCIS	PAC	VINVinb	GEM	ETO	DOC	FLU	MIT	CYC	LEU	DOX	IFO	BEV	Other Chemotherapy	No-Chemotherapy
Median no. of doses	4	5	5	6	7	5	4	2	1	5	3	8	1.5	1	None
Toxicity ≥2-fold increase															
Adverse effect antineoplastics	**2.5**	**2.1**	**2.4**	**1.9**	**4.4**	**2.2**	**3.2**	**3.0**	**3.0**	**2.6**	**3.5**	**3.9**	0.0	**2.6**	0.1
Acute anemia	**30.1**	**29.8**	**30.2**	**36.2**	**24.5**	**35.9**	22.4	20.3	27.8	25.0	22.8	**29.5**	20.0	25.1	14.9
Diarrhea	**2.6**	**2.7**	2.0	**3.2**	1.2	**4.0**	1.4	0.9	0.9	1.2	0.3	0.8	**10.0**	1.4	1.3
Hemolytic anemia	**0.4**	0.3	**0.5**	**0.5**	**0.4**	0.2	**0.4**	**0.4**	**0.5**	**0.5**	**1.0**	**1.6**	0.0	0.3	0.2
Leukemia	**0.2**	0.1	**0.2**	**0.2**	**0.2**	0.1	**0.3**	**0.4**	**0.5**	**0.2**	**0.7**	**0.8**	0.0	**0.4**	0.1
Nausea	**29.4**	**29.3**	**25.9**	**31.6**	**25.3**	**30.1**	**25.7**	**20.3**	**27.4**	**32.0**	**20.1**	**29.5**	**60.0**	9.4	4.9
Neutropenia	**18.4**	**17.1**	**19.3**	**17.9**	**21.9**	**19.1**	**14.8**	**15.1**	**16.3**	**16.6**	**16.6**	**22.5**	0.0	**9.2**	0.6
Stomatitis	**0.6**	**0.6**	**0.7**	**0.6**	**0.6**	**0.9**	**1.0**	**0.7**	**0.5**	**1.4**	0.3	**0.8**	0.0	**0.7**	0.2
Thrombocytopenia	**3.4**	**2.6**	2.2	**4.6**	**3.6**	**3.2**	**2.7**	1.2	**6.2**	2.2	2.5	**3.1**	0.0	**3.7**	1.3
Toxicity ≥1.5- to <2-fold increase															
Bladder cancer	0.3	0.2	0.2	0.2	0.3	0.2	0.4	**0.5**	0.7	0.5	0.7	0.0	0.0	0.3	0.2
Dehydration	17.6	16.9	15.9	15.5	16.5	17.0	16.2	14.7	12.2	18.3	13.2	9.3	10.0	19.3	11.4
Dermatitis	0.6	0.6	0.5	0.6	0.6	0.5	0.3	0.5	0.7	0.0	0.5	**0.8**	10.0	0.5	0.4
Deep vein thrombosis	5.1	5.3	5.0	5.8	3.5	5.5	4.4	3.3	3.9	4.6	5.5	2.3	0.0	5.3	2.9
Fever	8.0	8.1	8.3	8.6	7.7	9.1	6.4	6.8	6.2	5.5	6.5	7.0	10.0	8.3	4.8
Hepatocellular dysfunction	2.4	2.3	2.0	2.7	2.5	2.5	2.5	1.3	**4.6**	**3.6**	**3.2**	0.8	0.0	2.5	1.5
Hypotension	1.3	1.3	1.3	1.1	1.1	1.4	1.0	0.9	0.7	0.7	0.0	0.0	0.0	1.6	0.8
Toxicity ≥1- to <1.5-fold increase															
Anorexia	4.0	4.1	3.5	5.4	2.2	5.4	1.5	1.6	1.8	2.2	1.2	1.6	10.0	3.1	3.0
Cardiac	3.1	2.8	3.0	3.3	3.5	3.5	3.6	2.8	1.8	4.6	3.5	**6.2**	0.0	4.1	2.9
Chest pain	36.4	35.5	35.2	34.5	37.1	34.0	34.0	34.1	34.0	34.1	39.0	34.1	34.1	33.7	37.6
Cognitive disorder	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.0	0.1	0.1	0.1	0.1
Conduction abnormalities	3.1	3.0	2.5	3.1	2.5	3.1	3.1	3.1	3.1	3.1	2.5	3.1	3.1	3.1	3.2
Gastroenteritis and colitis	2.1	1.9	1.9	2.0	2.7	1.5	2.5	2.2	2.1	**4.1**	3.5	3.1	0.0	2.7	1.8
Hematuria	2.4	2.6	2.2	3.0	2.0	2.6	2.2	2.8	1.4	2.2	2.5	1.6	0.0	3.1	2.2
Hypertension	41.4	42.7	41.5	44.7	34.5	46.4	33.8	31.4	34.5	35.3	30.5	33.3	50.0	38.4	34.7
Myocarditis	1.0	1.0	0.9	1.1	1.0	0.6	0.5	0.4	0.5	0.7	1.2	0.8	0.0	1.4	0.8
Ototoxicity	1.0	1.0	1.0	1.0	1.2	1.1	1.2	0.7	0.9	1.4	1.5	**2.3**	0.0	0.9	0.8
Peripheral neuropathy	0.7	0.9	0.7	0.9	0.4	0.8	0.3	0.2	0.0	0.5	0.3	0.0	0.0	0.5	0.6
Proteinuria	0.2	0.3	0.2	0.2	0.2	0.3	0.4	0.2	0.5	0.2	**0.5**	**0.8**	0.0	0.1	0.2
Pulmonary fibrosis	47.5	48.5	47.2	48.5	44.5	48.7	42.1	44.4	40.9	40.6	42.7	45.0	70.0	51.3	46.2
Raynauds syndrome	0.1	0.1	0.1	0.1	0.0	**0.2**	0.1	0.1	0.1	0.1	0.0	0.1	0.1	0.1	0.1
Repiratory failure	17.6	19.8	15.1	22.1	6.3	24.0	6.8	4.7	5.8	7.5	6.2	4.7	10.0	13.2	13.9
SIADH	0.8	0.9	0.8	0.7	0.7	0.6	0.5	0.6	0.9	0.2	0.5	0.8	0.0	1.4	0.8

Number of patients for each chemotherapy agent ranged from 9 to 13,168 and 45,266 for the no-chemotherapy group. Bolded toxicities are ≥2 times that of the no-chemotherapy group. Rare toxicities are bolded and highlighted in grey.

CARCIS, carboplatin and cisplatin combined; PAC, paclitaxel; VINVinb, vinorelbine and vinblastine combined; GEM, gemcitabine; ETO, etoposid; DOC, docetaxel; FLU, fluorouracil; MIT, mitomycin; CYC, cyclophosphamide; LEU, leucovorin; DOX, doxorubicin (adriomycin); IFO, ifosfamide; BEV, bevacizumab; SIADH, syndrome of inappropriate antidiuretic hormone secretion.

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TABLE 3. Incidence (%) of Long-Term Toxicities (>3 mo) During Treatment of Various Chemotherapy Agents Compared with the No-Chemotherapy Group

	CARCIS	PAC	VINVinb	GEM	ETO	DOC	FLU	MIT	CYC	LEU	DOX	IFO	BEV	Other Chemotherapy	No-Chemotherapy
Median no. of doses	5	5	5	6	7	5	4	2	1	5	3	8	1.5	1	None
Toxicity ≥2-fold increase															
Adverse effect antineoplastics	**3.6**	**3.3**	**3.9**	**4.5**	**5.0**	**4.7**	**4.9**	**5.4**	**6.7**	**3.6**	**8.7**	**8.5**	**10.0**	**2.0**	0.0
Acute anemia	**31.2**	**32.1**	**33.8**	**37.4**	30.7	**37.6**	**31.4**	**31.9**	**34.9**	**31.3**	**36.0**	**37.2**	**70.0**	16.5	13.5
Bladder cancer	**0.5**	**0.5**	**0.5**	**0.4**	**0.5**	**0.6**	**0.5**	**0.6**	**0.5**	**0.7**	0.0	**0.8**	0.0	0.1	0.2
Dehydration	**26.5**	**27.5**	**29.1**	**31.2**	**26.5**	**33.6**	**27.0**	**24.9**	**29.2**	**26.9**	**30.8**	**34.1**	**20.0**	17.7	12.1
Dermatitis	**1.1**	**1.1**	**1.7**	**1.9**	0.9	**2.4**	**1.3**	**1.5**	0.2	0.7	**1.0**	0.8	0.0	0.6	0.5
Deep vein thrombosis	**9.9**	**11.1**	**11.0**	**13.8**	**8.2**	**14.3**	**9.8**	**9.8**	**9.7**	**11.5**	**10.4**	**14.0**	0.0	4.1	2.9
Fever	**15.3**	**16.3**	**17.0**	**19.5**	**14.9**	**20.0**	**13.5**	**14.9**	**13.3**	12.0	**13.9**	**16.3**	**40.0**	8.0	6.6
Hemolytic anemia	**0.6**	**0.5**	**0.9**	**0.9**	**1.1**	**0.6**	**0.9**	**1.2**	**1.6**	**1.2**	**1.0**	**2.3**	0.0	**0.5**	0.2
Hypotension	**3.2**	**3.4**	**3.1**	**3.3**	2.7	**3.9**	2.8	2.2	**3.2**	2.4	**4.7**	1.6	**10.0**	1.6	1.5
Leukemia	**0.4**	**0.4**	**0.6**	**0.6**	**0.5**	**0.5**	**0.7**	**1.2**	**0.5**	**0.7**	**1.0**	**0.8**	0.0	**0.3**	0.1
Myocarditis	**2.2**	**2.2**	**2.3**	**2.8**	**2.5**	**2.5**	**2.4**	**1.7**	**2.5**	**1.9**	**2.5**	**3.1**	**10.0**	**1.4**	0.7
Nausea	**16.2**	**16.0**	**18.9**	**19.1**	**17.3**	**19.9**	**16.7**	**18.1**	**20.0**	**19.2**	**20.6**	**25.6**	**10.0**	9.3	7.4
Neutropenia	**17.7**	**18.3**	**21.5**	**22.5**	**20.1**	**26.1**	**18.1**	**17.0**	**21.2**	**21.9**	**23.6**	**33.3**	**50.0**	**6.1**	0.7
Peripheral neuropathy	**4.2**	**4.8**	**3.9**	**5.1**	**4.1**	**4.8**	**4.3**	3.3	**6.2**	**4.1**	**6.5**	3.1	**10.0**	1.8	1.8
Pulmonary fibrosis	**25.6**	**26.0**	**26.9**	**28.1**	**26.1**	**30.3**	**26.3**	**25.5**	**27.8**	**28.1**	**25.1**	**33.3**	**30.0**	15.5	12.5
Repiratory failure	**26.3**	**30.1**	**26.0**	**36.8**	15.4	**40.8**	15.4	13.4	13.1	16.4	11.4	12.4	**60.0**	11.0	13.3
SIADH	**1.3**	**1.3**	**1.2**	**1.4**	1.1	**1.5**	1.1	0.6	**1.8**	**1.2**	**2.5**	0.0	0.0	1.1	0.6
Stomatitis	**1.3**	**1.2**	**1.4**	**1.7**	**1.4**	**1.9**	**2.0**	**1.9**	**2.1**	**1.9**	**3.2**	**1.6**	**10.0**	0.4	0.4
Thrombocytopenia	**8.8**	**8.4**	**8.1**	**13.1**	**10.1**	**11.2**	**9.2**	**9.3**	**9.4**	**8.7**	**10.7**	**13.2**	**30.0**	**3.2**	1.3
Toxicity ≥1.5- to <2-fold increase															
Anorexia	8.2	8.9	8.2	**10.2**	6.3	**12.5**	4.4	5.0	7.1	4.3	5.7	6.2	**30.0**	3.9	4.6
Atrial/ventricular arrhythmias	25.6	26.2	25.2	27.6	25.5	**29.8**	23.4	25.5	28.3	26.0	29.5	27.1	**50.0**	16.3	14.9
Cardiogenic shock	1.2	1.0	1.0	1.1	1.1	1.0	0.4	0.9	0.9	0.2	1.2	0.0	0.0	1.0	0.8
Cardiomyopathy	4.4	4.8	4.4	4.5	3.7	5.4	3.8	3.4	4.1	2.6	3.2	**7.0**	**10.0**	2.2	2.8
Chest pain	27.3	28.0	28.5	31.2	26.9	**31.9**	23.5	24.0	28.7	23.3	26.3	29.5	30.0	17.2	15.7
Delirium	16.9	18.3	17.3	19.1	14.5	21.2	12.9	12.6	14.9	13.2	14.4	14.7	10.0	11.0	11.1
Diarrhea	6.8	7.9	6.7	**9.3**	3.9	**11.5**	4.2	3.5	3.5	7.0	3.5	3.9	**40.0**	2.0	3.8
Drug psychoses	4.6	4.7	4.7	4.9	4.3	4.9	4.7	3.9	4.1	**5.5**	4.5	**6.2**	0.0	2.5	2.5
Encephalopathy	2.5	2.4	2.5	2.7	2.8	2.8	2.3	2.5	1.6	2.6	1.7	**3.1**	0.0	1.9	1.5
Heart failure	19.7	20.0	21.2	23.0	18.6	24.4	18.6	20.1	20.9	22.8	20.4	22.5	20.0	14.4	13.3
Hepatocellular dysfunction	3.6	3.6	3.9	**4.4**	4.1	**4.8**	3.9	3.0	3.9	**5.3**	4.0	3.9	0.0	1.8	2.2
Infection	32.9	34.1	33.8	35.8	32.0	**39.8**	32.5	30.9	32.2	31.5	31.5	**37.2**	**60.0**	21.3	18.3
Paroxysmal tachycardia	26.0	26.7	25.7	28.3	25.8	**30.6**	23.7	26.0	27.6	26.2	28.8	27.9	**50.0**	16.6	15.3
Pulmonary embolism	1.1	0.9	**1.2**	0.7	**2.1**	0.6	**2.4**	**3.0**	**2.1**	**2.6**	**3.0**	**1.6**	0.0	**1.7**	0.6
Pulmonary toxicity	12.5	12.7	12.9	**14.2**	12.0	**15.2**	11.5	12.4	13.3	10.1	9.4	11.6	10.0	7.8	7.3
Acute renal failure	4.7	4.7	5.1	5.7	4.6	**6.5**	3.7	4.5	3.5	4.6	3.5	**7.8**	0.0	2.5	3.2

(*Continued*)

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TABLE 3. (*Continued*)

	CARCIS	PAC	VINVinb	GEM	ETO	DOC	FLU	MIT	CYC	LEU	DOX	IFO	BEV	Other Chemotherapy	No-Chemotherapy
Toxicity ≥1- to <1.5-fold increase															
Cardiac	4.4	4.4	4.4	4.8	4.4	5.3	4.2	3.7	4.6	3.9	3.2	3.1	**10.0**	2.9	4.0
Conduction abnormalities	4.6	4.6	5.2	5.3	4.2	5.3	4.4	3.1	3.7	3.1	3.5	3.1	0.0	3.0	3.9
Chronic renal failure	9.3	9.4	9.6	11.0	9.2	11.6	9.6	10.5	8.7	9.6	10.7	**17.1**	0.0	5.3	6.5
Fatigue	9.5	8.1	12.0	6.9	14.7	5.8	15.2	**16.4**	12.2	**16.4**	**15.9**	13.2	0.0	10.7	7.9
Gastroenteritis and colitis	5.0	4.8	5.1	5.1	6.3	6.3	6.9	6.6	6.0	**8.2**	6.0	7.8	10.0	4.0	4.1
Hematuria	6.1	6.1	6.1	6.8	6.2	7.7	5.5	6.9	4.8	6.5	5.5	**10.9**	10.0	3.5	5.2
Hypertension	18.4	19.3	18.1	20.8	17.8	21.1	15.7	15.5	17.0	13.7	20.6	21.7	30.0	12.0	13.1
Myocardial infarction	5.6	5.7	5.3	6.2	5.7	6.4	5.5	4.4	4.6	4.6	4.0	8.5	**10.0**	4.5	4.7
Other dementia	5.3	5.5	5.3	5.8	4.9	6.2	5.2	4.2	4.4	5.1	2.5	3.1	10.0	3.9	5.5
Ototoxicity	4.2	4.4	4.2	4.5	3.7	4.9	3.0	2.8	3.0	3.1	3.5	2.3	**10.0**	2.3	3.7
Pulmonary edema	8.3	8.4	8.7	9.7	7.1	10.9	8.0	7.3	6.4	7.9	5.2	7.8	**20.0**	5.9	5.8
Raynauds syndrome	0.2	0.2	0.2	0.3	0.2	0.2	0.2	0.2	0.2	**0.5**	0.3	0.0	0.0	0.1	0.2
Seizures	1.7	1.1	1.8	0.7	**3.7**	0.5	**4.1**	**5.0**	**3.5**	**3.6**	**4.5**	**4.7**	0.0	2.6	1.6
Stupor	10.9	12.1	10.8	12.4	8.6	13.7	7.9	7.0	10.3	7.7	8.2	7.0	0.0	7.0	7.2
Sudden death	0.1	0.2	0.0	0.1	0.1	0.2	0.2	0.1	0.2	0.2	0.3	0.0	0.0	0.0	0.1

Number of patients for each chemotherapy agent ranged from 10 to 12,595 and 30,938 for the no-chemotherapy group. Bold toxicities are ≥2 times of the no-chemotherapy group. Rare toxicities are bolded and highlighted in gray.
CARCIS, carboplatin and cisplatin combined; PAC, paclitaxel; VINVinb, vinorelbine and vinblastine combined; GEM, gemcitabine; ETO, etoposid; DOC, docetaxel; FLU, fluorouracil; MIT, mitomycin; CYC, cyclophosphamide; LEU, leucovorin; DOX, doxorubicin (adriomycin); IFO, ifosfamide; BEV, bevacizumab; SIADH, syndrome of inappropriate antidiuretic hormone secretion.

TABLE 4. Multivariable Analysis of Risk Factors for Long-Term Chemotherapy-Associated Toxicity

	Proportional Odds Ratio (95% Confidence Interval)Long Term Toxicity >3 mo
Chemotherapy	
No	1.00
Yes	4.44 (3.85–5.12)
Age (yr)	
65–69	1.00
70–74	0.99 (0.95–1.04)
75–79	1.04 (0.99–1.10)
80–84	1.03 (0.97–1.10)
85–89	1.06 (0.97–1.15)
Gender	
Men	1.00
Women	1.29 (1.24–1.34)
Race/ethnicity	
Caucasian	1.00
African American	1.37 (1.29–1.45)
Asian	1.73 (1.58–1.89)
Hispanic	1.42 (1.22–1.64)
Other race	1.12 (1.03–1.23)
Unknown	0.72 (0.58–0.89)
Disease stage	
IV	1.00
IIIB	1.74 (1.66–1.82)
IIIA	2.46 (2.32–2.61)
II	3.04 (2.84–3.25)
I	3.83 (3.63–4.04)
Unstaged	3.06 (2.88–3.25)
Comorbidity scores	
⩾4	1.00
3	1.27 (1.16–1.39)
2	1.24 (1.15–1.35)
1	1.27 (1.18–1.37)
0	1.37 (1.26–1.48)
Year of diagnosis	
1991–1995	1.00
1996–1999	1.13 (1.09–1.18)
2000–2002	1.15 (1.10–1.20)

Odds ratios calculated using a proportional odds model (toxicity outcome level: no toxicity = 0, one toxicity = 1, and 2–9 toxicities = 2). Multivariate analysis adjusted for age, race, gender, socioeconomic status, tumor stage, number of positive lymph nodes, tumor grade, histology, comorbidity scores, surgery, radiation therapy, SEER areas, years of diagnosis, and interaction terms for chemotherapy with gender, surgery, age, and years of diagnosis.
SEER, Surveillance, Epidemiology, and End Results.

chemotherapy group. Likewise, seizures (3.5–5%) were associated with FLU, MIT, cyclophosphamide, LEU, and DOX.

Table 4 shows the results of the ordinal logistic regression analysis (ORs and 95% CI) for the effect across toxicity response levels for long-term toxicities adjusted for various clinical and pathologic covariates. Patients who received chemotherapy had an adjusted OR = 4.44 (95% CI: 3.85–5.12) for long-term toxicity, which was an augmented effect when compared with the unadjusted crude model (OR = 3.27, 95% CI: 3.17–3.37). Women (OR = 1.29, 95% CI:

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TABLE 5. Multivariate Analyses of Common Short-Term and Long-Term Toxicities for Single Chemotherapy Agents

	Hazard Ratio (95% Confidence Interval)			
Toxicity Condition	**≥CARCIS**	**≥PAC**	**≥VINVinb**	**≥GEM**
Short-term toxicity ≤3 mo				
Acute anemia	1.09 (0.96–1.25)	0.86 (0.69–1.06)	1.04 (0.86–1.27)	0.93 (0.64–1.36)
Diarrhea	1.00 (0.73–1.38	1.00 (0.86–1.15)	0.88 (0.72–1.08)	1.11 (0.93–1.33)
Hemolytic anemia	**1.79 (1.26–2.53)**	**1.60 (1.07–2.39)**	**2.10 (1.34–3.29)**	**1.84 (1.14–2.95)**
Leukemia	1.13 (0.70–1.82)	0.89 (0.47–1.66)	1.33 (0.67–2.66)	1.67 (0.86–3.22)
Nausea	**4.80 (4.16–5.55)**[a]	**3.38 (2.65–4.31)**[a]	**2.92 (2.28–3.75)**[a]	**5.63 (3.93–8.06)**[a]
Neutropenia	**9.41 (7.71–11.48)**[a]	**3.08 (2.86–3.31)**[a]	**1.49 (1.18–1.87)**[a]	**2.42 (2.25–2.63)**[a]
Stomatitis	**1.69 (1.28–2.23)**[a]	1.34 (0.97–1.86)	**1.78 (1.24–2.59)**	1.12 (0.72–1.72)
Thrombocytopenia	1.19 (0.91–1.55)	0.90 (0.78–1.05)	0.89 (0.73–1.09)	**1.83 (1.56–2.14)**[a]
Long-term toxicity >3 mo				
Acute anemia	**2.14 (2.05–2.23)**[b]	**1.82 (1.51–2.21)**[b]	**2.31 (2.00–2.67)**[b]	**1.60 (1.19–2.16)**[b]
Dehydration	**1.55 (1.13–2.12)**[b]	**1.43 (1.15–1.79)**[b]	**1.78 (1.51–2.09)**[b]	1.27 (0.86–1.90)
Deep vein thrombosis	**2.06 (1.58–2.67)**[b]	**2.43 (1.98–2.97)**[b]	**1.75 (1.47–2.10)**[b]	**1.73 (1.16–2.59)**[b]
Fever	**1.54 (1.08–2.19)**	**1.83 (1.63–2.06)**[b]	**1.82 (1.60–2.09)**[b]	**1.89 (1.67–2.15)**[b]
Nausea	**3.46 (2.91–4.11)**[b]	**3.08 (2.26–4.22)**[b]	**2.34 (2.25–3.33)**[b]	**4.25 (2.72–6.65)**[b]
Neutropenia	**14.56 (12.69–16.71)**[b]	**8.17 (5.67–11.77)**[b]	**4.04 (2.93–5.58)**[b]	**7.79 (4.64–13.09)**[b]
Pulmonary fibrosis	**1.69 (1.56–1.83)**[b]	**1.92 (1.66–2.22)**[b]	**1.80 (1.59–2.04)**[b]	**1.67 (1.47–1.89)**[b]
Respiratory failure	1.13 (0.94–1.36)	**1.40 (1.29–1.53)**[b]	**1.35 (1.22–1.50)**[b]	**1.74 (1.59–1.90)**[b]
Thrombocytopenia	**3.62 (1.87–7.04)**[b]	**3.10 (1.75–5.49**[b]	**2.49 (173–3.58)**[b]	**3.50 (2.66–5.16)**[b]

Multivariate models adjusted for age, race, gender, socioeconomic status, tumor stage, number of positive lymph nodes, tumor grade, histology, comorbidity scores, surgery, radiation therapy, SEER areas, year of diagnosis, and various individual model interaction terms. Bold indicates hazard ratios <0.05.

[a] $p < 0.007$ using Bonferonni-Sidak adjustment for multiple comparisons testing.

[b] $p < 0.006$ using Bonferonni-Sidak adjustment for multiple comparisons testing.

CARCIS, carboplatin and cisplatin combined; PAC, paclitaxel; VINVinb, vinorelbine and vinblastine combined; GEM, gemcitabine; SEER, Surveillance, Epidemiology, and End Results.

1.24–1.34) were noted to be more likely to develop long-term toxicity than men. The risk of having long-term toxicity increased for other ethnic groups compared with Caucasians (OR: 1.12–1.37), those with localized disease stage (stage I: OR = 3.83, 95% CI: 3.63–4.04; stage II OR = 3.04, 95% CI: 2.84–3.25) compared with those with stage IV NSCLC, and those with no comorbidities (OR = 1.37, 95% CI: 1.26–1.48) compared with those with ≥4 comorbidities. Similarly, newer regimens administered from 1995 to 2002 were more likely to be associated with a small increase in long-term toxicity.

Table 5 shows hazard ratios (HR) and 95% CI associated with developing specific short- and long-term toxicities after adjusting for other risk factors and confounders. The individual toxicities included in the analysis were noted to have an incidence of ≥2-fold greater than the no-chemotherapy group for the specific agents: CARCIS, PAC, VINVinb, and GEM. There was a similar trend for the risk of hemolytic anemia and nausea for the various agents for the short-term toxicities. The platinum-based agents (CARCIS) were most strongly associated with developing neutropenia (HR = 9.41, 95% CI: 7.71–11.48). Stomatitis was significant only for CARCIS and VINVinb, and thrombocytopenia for GEM. However, when Bonferonni-Sidak adjustment for multiple comparisons was applied, only neutropenia and nausea for the four chemotherapies, stomatitis for CARCIS, and thrombocytopenia for GEM remained significant. Most of the long-term toxicities remained significantly associated with each of the chemotherapy agents examined after adjusting for other factors with the exception of dehydration for GEM and respiratory failure for CARCIS. The HR associated with nausea was similar for short- and long-term toxicities. Thrombocytopenia was noted to be a significant long-term toxicity for all four chemotherapy agents. The risk of associated neutropenia increased over time. For example for CARCIS, the risk for neutropenia increased from 9.41 (95% CI: 7.71–11.48) to 14.56 (95% CI: 12.69–16.71), and for PAC, the risk increased from 3.08 (95% CI: 2.86–3.31) to 8.17 (95% CI: 5.67–11.77). All long-term toxicities remained statistically significant except for fever for CARCIS, despite Bonferonni-Sidak adjustment for multiple comparisons.

DISCUSSION

In this study, chemotherapy administration was associated with significant short-term (≤3 months) and long-term (>3 months) toxicities. The majority of short-term toxicities noted were anemia, nausea, and neutropenia and are well described in clinical trials.[11–13] Female patients with localized disease stages (I and II) and with less comorbidities were more likely to have long-term toxicity. In multivariate analysis, platinum-based agents were associated with the greatest short-term toxicity and with the most significant risk for neutropenia, whereas GEM was associated with the highest

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risk of nausea. Pancytopenia was the most commonly noted long-term toxicity.

Toxicities for individual agents have been documented in a number of studies that included elderly patients with advanced NSCLC.[14–17] Moreover, the toxicity and efficacy of various chemotherapy agents as single or in combination regimens over the course of treatment have been compared.[17–21] Cisplatin in combination with vinorelbine was associated with bone marrow toxicity, leukopenia, and neutropenia.[19] GEM in combination with other chemotherapy agents has been reported to be associated with nausea, vomiting, anemia,[19] neutropenia, fatigue,[22] dyspnea, neutropenia infections, and thrombocytopenia.[23] In this study, the degree of long-term toxicity increased incrementally with less advanced disease stages. Some oncologists believe that toxicities may be an indication of the efficacy of treatment.[24]

Overall, the findings are in concordance with short-term toxicities seen in this current claims-based study and those commonly reported in clinical trials.[11–13] More importantly, our study reported on the long-term chemotherapy-associated toxicities with DOC and IFO, which are not commonly reported in clinical trials. There were also some rare long-term toxicities identified with FLU, MIT, LEU, DOX, and cyclophosphamide.

The strengths of this study include the large sample size, which provides sufficient power to examine individual chemotherapy agents and specific toxicities. In addition, a large no-chemotherapy cohort enabled us to stratify the incidence of toxicity into three levels. Furthermore, we were able to ascertain risks by creating a composite risk score for long-term toxicity and for the four most common chemotherapies. There are several limitations associated with this study. First, the study included only Medicare patients ≥65 years, so results may not be generalizable to younger age groups. Second, the actual doses of individual agents administered were not captured in the claims data. This study relied on CPT codes that specified standard dose for each chemotherapy agent, but in practice, physicians may have modified a standard chemotherapy dose for an individual patient according to preexisting medical conditions or tolerability. The findings that patients with localized disease stages (I and II) and with less comorbidities were also at greater risk is likely related to higher dosing administered to healthier patients, which was not accounted for in this analysis. Third, although Medicare claims on overall chemotherapy administration have been externally validated, the validity of claims on toxicities has not been well studied. Furthermore, although the incidences of the 50 toxicity-associated end points were analyzed for 14 chemotherapy agents, multimodal combination chemotherapy regimens administered varied widely and were not analyzed separately. The unavailability of data, which allows classification for "grade of toxicity," is a significant limitation to our study. We can make the assumption that the most significant toxicities (grades III and IV) were more likely to be included in Medicare claims, whereas grade I and II toxicities may less likely be included.

The ultimate goal of systemic chemotherapy is to extend survival. The decision to administer more aggressive chemotherapy regimens may be justified for patients with NSCLC who have the potential for prolonged survival. However, long-term chemotherapy-associated toxicities must be examined and carefully considered. Although regimens that contain DOC and IFO have been reported to have higher response rates in some populations, the increased long-term toxicity profile must be carefully studied. While some toxicities such as nausea and vomiting can be managed successfully pharmacologically,[25] other less common long-term toxicities may prove otherwise. The projected benefit to increase survival must be weighed against the discomfort of nonlife threatening toxic conditions resulting from chemotherapy.

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