Safety outcomes in advanced non-small-cell lung cancer patients treated with first-line platinum-based regimens in the United States

Lei Chen[1], Jong Seok Kim[1], Belen San Antonio[2], Yajun Emily Zhu[1], Lucy Mitchell[3], William John[1]*

[1]Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN, USA; [2]Eli Lilly and Company, Madrid, 28108, Spain; [3]Eli Lilly and Company, Erl Wood, Windlesham, Surrey, UK

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Correspondence to: Jong Seok Kim, MD. Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46285, USA. Email: kim_jong_seok@lilly.com.

Background: We analyzed the treatment patterns and safety outcomes of the most common first-line platinum-based regimens initiated on or after non-small cell lung cancer (NSCLC) diagnosis in a real-world setting.

Methods: Based on a United States oncology electronic medical record (EMR) database, patients treated with first-line platinum-based regimens after advanced NSCLC diagnosis from September 2008 to November 2014 were analyzed. Baseline characteristics and selected adverse events during treatment [incidence proportions and incidence rates (IRs)] were described by regimen. Propensity score stratification was used to adjust for baseline characteristics differences. Hazard ratios (HRs) were estimated using Cox proportional hazards model, with paclitaxel (Pac)/carboplatin (Carbo) as reference. Subgroup analysis was conducted for elderly patients (≥70 years old).

Results: The most common five regimens for the eligible patients were as follows: Pac/Carbo (n=3,009), pemetrexed (Pem)/Carbo (n=1,625), Pem/Carbo/bevacizumab (Bev) (n=735), Pac/Carbo/Bev (n=531), Pem/cisplatin (Cis) (n=357), and docetaxel (Doc)/Carbo (n=355). Highest IRs were reported for anemia, neutropenia, nausea, and vomiting across these regimens in patients of all ages. After propensity score stratification, compared with Pac/Carbo, risk of anemia was significantly lower with Pac/Carbo/Bev (HR =0.67), Pem/Cis (HR =0.68), and Pem/Carbo/Bev (HR =0.82); risk of neutropenia was comparable among all regimens except Doc/Carbo (significantly lower risk; HR =0.72); and risk of nausea (HR =1.45) and vomiting (HR =1.50) was significantly higher with Pem/Cis. Safety outcomes in elderly patients were consistent with the overall population.

Conclusions: While EMR data have limitations, the real-world safety outcome with individual chemotherapy regimen could be considered for the better selection of platinum-based therapies in NSCLC.

Keywords: Chemotherapy; elderly patients; non-small cell lung cancer (NSCLC); real-world setting; safety profile

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* Current Affiliation: Abbvie Inc., 1 North Waukegan Rd., North Chicago, IL 60064, USA

Introduction

Non-small cell lung cancer (NSCLC) accounts for 80% to 85% of all lung cancer (222,500 new cases per year in the United States) (1), and the predominant proportion of the patients (80%) are ultimately diagnosed as stage IV disease (1-3). Until the recent emergence of immune checkpoint inhibitors (ICIs), platinum-based chemotherapy has been the gold standard for the first-line treatment of patients with advanced NSCLC without *EGFR* mutation or *ALK/ROS-1* rearrangement (4,5). Still, as a current standard of care in NSCLC patients without a targetable gene aberration, platinum doublet chemotherapy is actively studied in combination with various ICIs (6-8). ECOG 1594 study proved four platinum doublet chemotherapy (cisplatin and paclitaxel, cisplatin and gemcitabine, cisplatin and docetaxel, carboplatin and paclitaxel) were not significantly different in clinical benefit (9). Several anti-cancer targeted agents were tested in combination with these chemotherapy regimens for the initial treatment of NSCLC. Adding bevacizumab, an angiogenesis inhibitor, to carboplatin plus paclitaxel improved overall survival in the first-line treatment of patients with non-squamous NSCLC if there are no contraindications (10). Docetaxel plus platinum combination therapy is an effective treatment option with a favorable therapeutic index for first-line treatment of advanced or metastatic NSCLC (11). Pemetrexed-based combination chemotherapy represents a therapeutic option in patients with advanced non-squamous NSCLC (12-15).

Although there are a number of available platinum based treatment options, toxicity is a major concern when clinicians select their regimen (16-18). The accumulated data support the treatment guidelines to consider tumor histology, performance status, age, and comorbidities in association with the expected safety profile of a particular regimen at the time of regimen selection for individual patients (4).

The pattern of commonly used platinum-based regimens in routine clinical practice and their safety profiles have not been sufficiently investigated in the United States population. In this retrospective observational study, data from Integrated Medical Services (IMS) Oncology electronic medical records (EMR), a United States oncology clinic-based EMR database, were analyzed to determine the safety outcomes of first-line platinum-based therapy in patients with locally advanced or metastatic NSCLC.

Methods

Study design and data source

Data for this retrospective, observational, cohort study were extracted from IMS's private-practice Oncology databases of longitudinal, patient-level EMR, hospital charge data, and medical and pharmacy claims collected from physicians and other healthcare providers across the 50 states in the United States. Patient-level EMR were collected from about 550 treating providers representing 344 locations from 37 states in the United States. Data in the databases were de-identified, and the databases were certified as being compliant with the Health Insurance Portability and Accountability Act. This study was exempt from institutional review board approval because it was retrospective, did not involve any intervention, and used anonymized data. Given the nature of structured administrative data in the database, medical conditions captured were considered to be severe conditions requiring medical attention; less severe conditions might not have been recorded. Grade or severity of disease, performance status, frailty, and laboratory abnormalities were not available. The analysis included demographic and clinical characteristics of the eligible patients and incidence proportions and incidence rates (IRs) of the safety outcomes among the eligible patients, by chemotherapy regimens. The IRs, rate differences, and hazard ratios (HRs) of safety outcomes between the chemotherapy regimens were also estimated by adjusting patients' demographic and clinical characteristics for groups with adequate sample sizes. We also conducted subgroup analysis for patients ≥70 years old to further examine the safety profiles of the eligible patients treated with each chemotherapy regimen in elderly patients (70 years or older) with adequate data. Additional analysis at 3, 6, and 9 months after the last dose was also conducted to determine the exposure risk during the follow-up period.

The key patient eligibility criteria included the following: (I) diagnosis of lung cancer, excluding small cell lung cancer; (II) locally advanced or metastatic disease (Stage IIIB/IV); (III) platinum-based first-line treatments initiated after advanced lung cancer diagnosis, with at least 100 eligible patients for each regimen in the database, the first date of administration of the treatments being the index date, and receiving the indexed treatment between September 26, 2008 and November 30, 2014; (IV) ≥18 years on index date; and (V) stable oncology practice for patient's

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study physician between the index date and the end of the observation. The observation period was defined as between the index date until the occurrence of the adverse event of interest; 30 days after the last dose of the study drugs; an administration/prescription record indicating a switch from the study medicines to another systemic treatment; end of patient record in the database; or December 31, 2014, whichever occurred first.

Data assessment

Data were assessed by patients' baseline characteristics and clinical characteristics during treatment, including demographics, cancer diagnoses, comorbidity conditions (any cardiovascular disease, cerebrovascular disease, chronic pulmonary disease, congestive heart failure, dementia, hemiplegia or paraplegia, liver disease, myocardial infarction, peptic ulcer disease, peripheral vascular disease, renal disease, rheumatologic disease, type 2 diabetes, and type 2 diabetes with chronic issues), diagnoses recorded up to 6 months prior to the index date, medications recorded up to 3 months prior to the index, and selected adverse events diagnosed during the on-treatment period. The adverse events were selected based on literature and clinical interest of targeted treatments and disease. Adverse events with an IR ≥1 per 100 person-years in each treatment group of the overall population were further analyzed by the adjusted analysis. Comorbidities and adverse events were identified from the structured EMR data using ICD-9-CM diagnosis codes.

Statistical analysis

The results were reported as descriptive analysis in counts and proportions for categorical variables, and means, standard deviations, and median for continuous variables. Propensity score stratification was used to adjust for baseline differences in potential confounding factors, which included patients' gender, race, age, cancer stage and histology, underlying comorbidities, and medical history with previous anti-cancer treatment or supportive care. Time to first occurrence of AE was conducted utilizing survival analysis. HRs with 95% confidence intervals were estimated using Cox proportional hazards regression model with paclitaxel/carboplatin as reference and stratified by propensity score quintiles. Propensity score matching was applied as a sensitivity analysis. Subgroup analyses were performed for elderly patients (≥70 years old).

Results

Patient characteristics

The 6 eligible first-line platinum-based regimens (each with at least 100 eligible advanced NSCLC-treated patients) in the database during the study period were paclitaxel/carboplatin (Pac/Carbo), docetaxel/carboplatin (Doc/Carbo), pemetrexed/carboplatin (Pem/Carbo), pemetrexed/cisplatin (Pem/Cis), paclitaxel/carboplatin/bevacizumab (Pac/Carbo/Bev), and pemetrexed/carboplatin/bevacizumab (Pem/Carbo/Bev). A total of 6,612 eligible NSCLC patients were identified.

Baseline characteristics of each regimen group, including comorbidities and a summary of prior treatments for each cohort are presented in *Table 1*. Patient distribution among the 6 regimens were Pac/Carbo (n=3,009; 43% elderly), Pem/Carbo (n=1,625; 40% elderly), Pem/Carbo/Bev (n=735; 35% elderly), Pac/Carbo/Bev (n=531; 34% elderly), Pem/Cis (n=357; 19% elderly), and Doc/Carbo (n=355; 44% elderly). The median age (62.0–68.3 years) and the gender (50.3–58.2% male) were similar across the groups. The majority of patients (95.5–99.1%) had Stage IV disease across all groups. Diagnoses of any comorbidities were found in a small percentage of patients, and the proportion was similar (7.3–8.7%) across all groups. Chronic pulmonary disease (2.8–4.5%), type 2 diabetes (0.8–3.1%), and renal diseases (0.8–2.3%) were the most common comorbidities across the group in patients of all ages. The other comorbidities were found in <1% of each treatment group. Less than 10% of patients in each group had received prior chemotherapy, biologics, or supportive care drugs prior to index. Elderly patients were less likely to receive prior chemotherapy or biologic treatments as cancer treatment prior to index compared to the patients of all ages (data not shown).

Adverse events

Crude incidence proportions and IRs of selected adverse events in patients of all ages and elderly (≥70 years) patients are shown in *Table 2* and *Table 3*, respectively. The most frequently diagnosed adverse events in all groups were anemia (17.7–30.6%), neutropenia (15.2–21.0%), nausea (9.3–20.7%), and vomiting (8.5–18.2%). Among all adverse events analyzed, IRs per 100 person-years during treatments were highest for anemia (36.6–73.4), neutropenia (24.5–49.2), nausea (13.2–30.4), and vomiting (12.0–25.8) across the groups. Similarly, the IRs for anemia and neutropenia

Table 1 Baseline characteristics among the NSCLC patients in 6 groups representing commonly used platinum-based regimens in the United States

Categories	First-line platinum chemotherapy combination regimen (%)					
	Pac/Carbo (N=3,009)	Pac/Carbo/Bev (N=531)	Doc/Carbo (N=355)	Pem/Carbo (N=1,625)	Pem/Cis (N=357)	Pem/Carbo/Bev (N=735)
Age (years)						
Mean [SD]	67.2 [9.7]	65.3 [9.4]	68.0 [9.3]	66.7 [9.9]	61.4 [9.6]	65.5 [9.7]
Median [IQR]	68.2 [60.5–74.8]	66.3 [59.3–72.1]	68.3 [61.5–75.9]	67.4 [60.1–74.2]	62.0 [55.1–68.6]	66.2 [58.7–72.5]
Gender						
Male	1,751 (58.2)	295 (55.6)	205 (57.8)	818 (50.3)	190 (53.2)	397 (54.0)
Female	1,258 (41.8)	236 (44.4)	150 (42.3)	807 (49.7)	167 (46.8)	338 (46.0)
Staging						
IIIB	134 (4.5)	11 (2.1)	16 (4.5)	15 (0.9)	8 (2.2)	9 (1.2)
IV	2,875 (95.6)	520 (97.9)	339 (95.5)	1,610 (99.1)	349 (97.8)	726 (98.8)
Comorbidities diagnosed during 6 months prior to the index[a]						
Any comorbidities	237 (7.9)	40 (7.5)	31 (8.7)	119 (7.3)	28 (7.8)	58 (7.9)
Cerebrovascular disease	11 (0.4)	1 (0.2)	2 (0.6)	4 (0.3)	1 (0.3)	5 (0.7)
Chronic pulmonary disease	126 (4.2)	20 (3.8)	14 (3.9)	58 (3.6)	10 (2.8)	33 (4.5)
Peripheral vascular disease	7 (0.2)	1 (0.2)	2 (0.6)	6 (0.4)	2 (0.6)	3 (0.4)
Renal disease	50 (1.7)	12 (2.3)	6 (1.7)	21 (1.3)	5 (1.4)	6 (0.8)
Rheumatologic disease	7 (0.2)	3 (0.6)	1 (0.3)	2 (0.1)	2 (0.6)	5 (0.7)
Type 2 diabetes	62 (2.1)	4 (0.8)	7 (2.0)	38 (2.3)	9 (2.5)	23 (3.1)

Bev, bevacizumab; Carbo, carboplatin; Cis, cisplatin; Doc, docetaxel; IQR, interquartile range; N, total number of patients identified in each regimen; n, number of patients in each category; Pac, paclitaxel; Pem, pemetrexed; SD, standard deviation. [a], comorbidities examined were any cardiovascular disease, cerebrovascular disease, chronic pulmonary disease, congestive heart failure, dementia, hemiplegia or paraplegia, liver disease, myocardial infarction, peptic ulcer disease, peripheral vascular disease, renal disease, rheumatologic disease, type 2 diabetes, and type 2 diabetes with chronic issues. Only the diseases with at least 1 patient diagnosed in each treatment group were shown

were high across the treatment groups in elderly patients. The IRs for nausea (18.7–28.7) and vomiting (16.0–27.7) were high (≥10%) for all treatment groups in the elderly except the Doc/Carbo group (≤7.2). The crude incidence proportions of selected adverse events at 3 months, 6 months, and 9 months after the last dose in patients of all ages and elderly patients were consistent with the results presented in *Table 2* and *Table 3*, respectively (results not shown, available upon request). We also examined the use of supportive care medications including erythropoiesis stimulating agent (ESA) and granulocyte-colony stimulating factor (G-CSF), however without knowing the administration timing of those agents, we could not interpret any relationship between the supportive care and adverse events (*Tables S1,S2*).

Adjusted HRs and P values (Pac/Carbo as reference) among patients of all ages and elderly patients (≥70 years) after propensity score stratification are presented in *Table 4* and *Table 5*, respectively. In patients of all ages, the risk of anemia was significantly lower (P<0.05) in Pac/Carbo/Bev (HR =0.67), Pem/Cis (HR =0.68), and Pem/Carbo/Bev (HR =0.82) groups as compared to the reference (Pac/Carbo) group. The risk of neutropenia was comparable among all groups except the Doc/Carbo group (significantly

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Table 2 Crude incidence proportions (%) and incidence rates of selected adverse events among the NSCLC patients of all ages in 6 groups representing commonly used platinum-based regimens in the United States

Adverse events	Pac/Carbo		Pac/Carbo/Bev		Doc/Carbo		Pem/Carbo		Pem/Cis		Pem/Carbo/Bev	
	n (%)	IR per 100 PY	n (%)	IR per 100 PY	n (%)	IR per 100 PY	n (%)	IR per 100 PY	n (%)	IR per 100 PY	n (%)	IR per 100 PY
All age	N=3,009		N=531		N=355		N=1,625		N=357		N=735	
Hematologic events												
Anemia	922 (30.6)	60.47	94 (17.7)	45.07	105 (29.6)	51.93	478 (29.4)	73.38	87 (24.4)	36.61	175 (23.8)	65.80
Neutropenia	572 (19.0)	34.83	82 (15.4)	38.70	54 (15.2)	24.45	280 (17.2)	36.12	75 (21.0)	32.84	132 (18.0)	49.16
Thrombocytopenia	82 (2.7)	4.09	7 (1.3)	2.84	9 (2.5)	3.52	52 (3.2)	5.76	12 (3.4)	4.11	12 (1.6)	3.72
Non-hematologic events												
Infection	114 (3.8)	5.71	26 (4.9)	10.77	8 (2.3)	3.08	56 (3.4)	6.20	24 (6.7)	8.41	15 (2.0)	4.64
Thromboembolic events	124 (4.1)	6.18	14 (2.6)	5.78	18 (5.1)	7.27	75 (4.6)	8.38	28 (7.8)	9.75	16 (2.2)	5.00
Fatigue	79 (2.6)	3.92	13 (2.4)	5.27	11 (3.1)	4.35	41 (2.5)	4.50	17 (4.8)	5.91	15 (2.0)	4.68
Diarrhea	44 (1.5)	2.18	10 (1.9)	4.05	3 (0.8)	1.16	19 (1.2)	2.06	10 (2.8)	3.43	5 (0.7)	1.54
Nausea	418 (13.9)	22.38	59 (11.1)	25.64	33 (9.3)	13.19	208 (12.8)	24.55	74 (20.7)	30.36	84 (11.4)	27.85
Vomiting	353 (11.7)	18.58	52 (9.8)	22.30	30 (8.5)	11.96	185 (11.4)	21.58	65 (18.2)	25.83	75 (10.2)	24.68

Bev, bevacizumab; Carbo, carboplatin; Cis, cisplatin; Doc, docetaxel; IR, incidence rate; N, total number of patients identified in each regimen; n, number of patients in each category; NSCLC, non-small cell lung cancer; Pac, paclitaxel; Pem, pemetrexed; PY, person-years. Only adverse events with an incidence rate ≥1 per 100 PY in every treatment group of all ages shown.

Table 3 Crude incidence proportions (%) and incidence rates of selected adverse events among the elderly NSCLC patients in 6 groups representing commonly used platinum-based regimens in the United States

Adverse events	Pac/Carbo		Pac/Carbo/Bev		Doc/Carbo		Pem/Carbo		Pem/Cis		Pem/Carbo/Bev	
	n (%)	IR per 100 PY	n (%)	IR per 100 PY	n (%)	IR per 100 PY	n (%)	IR per 100 PY	n (%)	IR per 100 PY	n (%)	IR per 100 PY
Elderly (≥70 years)	N=1,296		N=178		N=155		N=650		N=67		N=256	
Hematologic events												
Anemia	432 (33.3)	69.66	26 (14.6)	60.88	52 (33.5)	66.05	189 (29.1)	69.53	20 (29.9)	41.12	60 (23.4)	70.06
Neutropenia	277 (21.4)	40.78	25 (14.0)	61.30	23 (14.8)	23.42	126 (19.4)	39.24	18 (26.9)	42.28	49 (19.1)	60.79
Thrombocytopenia	32 (2.5)	3.77	0	0	6 (3.9)	5.42	21 (3.2)	5.58	1 (1.5)	1.55	3 (1.2)	2.87
Non-hematologic events												
Infection	45 (3.5)	5.29	2 (1.1)	3.92	0	0	18 (2.8)	4.68	4 (6.0)	6.60	6 (2.3)	5.72
Thromboembolic events	51 (3.9)	5.95	2 (1.1)	3.88	9 (5.8)	8.39	29 (4.5)	7.63	3 (4.5)	4.66	4 (1.6)	3.85
Fatigue	40 (3.1)	4.69	3 (1.7)	5.83	5 (3.2)	4.58	19 (2.9)	4.96	7 (10.4)	11.55	2 (0.8)	1.92
Diarrhea	18 (1.4)	2.09	3 (1.7)	5.83	0	0	6 (0.9)	1.55	5 (7.5)	8.23	0	0
Nausea	150 (11.6)	18.72	14 (7.9)	28.70	8 (5.2)	7.22	82 (12.6)	22.85	14 (20.9)	27.74	21 (8.2)	21.64
Vomiting	130 (10.0)	15.95	12 (6.7)	23.98	7 (4.5)	6.30	72 (11.1)	19.80	14 (20.9)	27.71	20 (7.8)	20.56

Bev, bevacizumab; Carbo, carboplatin; Cis, cisplatin; Doc, docetaxel; IR, incidence rate; N, total number of patients identified in each regimen; n, number of patients in each category; NSCLC, non-small cell lung cancer; Pac, paclitaxel; Pem, pemetrexed; PY, person-years.

Table 4 Adjusted hazard ratios (Pac/Carbo as reference) among the NSCLC patients of all ages after propensity score stratification in 6 groups representing commonly used platinum-based regimens in the United States

Adverse events	Pac/Carbo	Pac/Carbo/Bev		Doc/Carbo		Pem/Carbo		Pem/Cis		Pem/Carbo/Bev	
		n	HR[a,b]	n	HR[a,b]	N	HR[a,b]	n	HR[a,b]	n	HR[a,b]
All ages	N=3,009	N=531		N=355		N=1,625		N=357		N=735	
Hematologic events											
Anemia	920	94	0.67[c]	105	0.89	477	1.07	87	0.68[c]	175	0.82[c]
Neutropenia	572	82	1.00	54	0.72[c]	278	0.97	75	1.05	132	1.05
Thrombocytopenia	82	7	0.62	9	0.88	52	1.32	12	1.08	12	0.74
Non-hematologic events											
Infection	114	25	1.54[c]	8	0.55	56	1.01	24	1.51	15	0.66
Thromboembolic events	124	14	0.82	18	1.20	75	1.27	28	1.69[c]	16	0.64
Fatigue	79	12	1.11	11	1.12	41	1.09	17	1.61	15	0.98
Diarrhea	44	9	1.35	3	0.55	19	0.89	10	1.68	5	0.53
Nausea	418	57	0.99	33	0.63[c]	208	1.08	74	1.45[c]	84	1.07
Vomiting	353	50	1.06	30	0.69	185	1.17	65	1.50[c]	75	1.18

Bev, bevacizumab; Carbo, carboplatin; Cis, cisplatin; Doc, docetaxel; HR, hazard ratio; N, total number of patients identified in each regimen; n, number of patients in each category; NSCLC, non-small cell lung cancer; Pac, paclitaxel; Pem, pemetrexed. [a], only HRs of adverse events with an incidence rate ≥1 per 100 person-years (see *Table 1*) in every treatment group of all ages shown. [b], HRs were calculated using Pac/Carbo (N=3,009 for all ages) as reference. [c]P value≤0.05.

lower risk; P<0.05, HR =0.72). The risk of nausea (HR =1.45), vomiting (HR =1.50), and thromboembolic events (HR =1.69) was significantly higher (P<0.05) in the Pem/Cis group. The risk of hematological and gastrointestinal adverse events was similar (P>0.05) between Pac/Carbo and Pem/Carbo, the 2 most common regimens.

The trends for adverse events in elderly patients with sufficient numbers were generally consistent with patients of all ages (*Tables 4,5*). The risk of anemia was significantly lower (P<0.05) with Pac/Carbo/Bev (HR =0.60), and numerically lower with Pem/Carbo/Bev (HR =0.77, P=0.06). The risk of hematological and gastrointestinal adverse events was similar between elderly populations in the Pac/Carbo and Pem/Carbo groups. The adjusted HRs were not shown for elderly patients in the Pem/Cis group due to the small number of patients in this subgroup (n=67) and the associated insufficient statistical power. The hazard ratios at 3 months, 6 months, and 9 months after the last dose for patients of all ages and the elderly were consistent with the results presented in *Table 3* and *Table 4*, respectively (results not shown). The incidence rates of hypertension and haemorrhage were numerically higher in the bevacizumab-containing treatment groups;

Pac/Carbo/Bev had a numerically higher incidence of those two adverse events compared to Pem/Carbo/Bev group (3.27, 4.95 *vs.* 0.93, 3.14, respectively; *Tables S1,S2*).

Discussion

The results of this retrospective cohort analysis from United States EMR data collected from the routine clinical practice setting confirmed that carboplatin has been the preferred platinum prescribed overall in NSCLC patients and in elderly patients. Our analysis showed that only 19% of patients receiving cisplatin-based chemotherapy (Pem/Cis) were elderly compared with 34% to 44% of patients receiving carboplatin-based regimens, which could indicate that cisplatin is not the preferred component for the elderly. Though the benefits of survival and tumor response of cisplatin over carboplatin have been reported previously (15,19), the results were either derived from unspecified subgroup analysis of a small subgroup of patients (15) or from retrospective analysis (19). Given the low level of clinical evidence, the efficacy of cisplatin versus carboplatin for the chemotherapy combination is still debatable, and as our study indicates, most US physicians prefer

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Table 5 Adjusted hazard ratios (Pac/Carbo as reference) among the elderly NSCLC patients after propensity score stratification in 6 groups representing commonly used platinum-based regimens in the United States

Adverse events	Pac/Carbo	Pac/Carbo/Bev		Doc/Carbo		Pem/Carbo		Pem/Cis		Pem/Carbo/Bev	
		n	HR[a,b]	n	HR[a,b]	N	HR[a,b]	n	HR[a,b]	n	HR[a,b]
Elderly (≥70 years)	N=1,296	N=178		N=155		N=650		N=67		N=256	
Hematologic events											
Anemia	430	26	0.60[d]	52	0.97	189	0.93	–	–	60	0.77
Neutropenia	277	25	0.96	23	0.63[d]	125	0.94	–	–	49	1.05
Thrombocytopenia	32	0	–	6	1.50	21	1.41	–	–	3	0.60
Non-hematologic events											
Infection	45	2	0.58	0	–	18	0.86	–	–	6	0.92
Thromboembolic events	51	2	0.52	9	1.42	29	1.23	–	–	4	0.52
Fatigue	40	2	0.66	5	1.03	19	1.08	–	–	2	0.32
Diarrhea	18	2	1.07	0	–	6	0.70	–	–	0	–
Nausea	150	13	1.07	8	0.42[d]	82	1.24	–	–	21	0.99
Vomiting	130	11	1.08	7	0.43[d]	72	1.27	–	–	20	1.14

Bev, bevacizumab; Carbo, carboplatin; Cis, cisplatin; Doc, docetaxel; HR, hazard ratio; N, total number of patients identified in each regimen; n, number of patients in each category; NSCLC, non-small cell lung cancer; Pac, paclitaxel; Pem, pemetrexed. [a], for elderly patients, only hazard ratios of adverse events with n≥5 (see *Table 1*) in individual treatment group shown. [b], HRs were calculated using Pac/Carbo (N=1,296 for elderly) as reference. [c], adjusted HR estimates are not shown because the total number of elderly patients treated with first-line Pem/Cis in the database (n=67) is small and thus lacks statistical power. [d], P value≤0.05.

to use carboplatin rather than cisplatin for the doublet chemotherapy in NSCLC treatment. In our study, patients receiving Pem/Cis, including the elderly population, had a lower IR of anemia than patients receiving a carboplatin doublet. However, given the small number of elderly patients receiving Pem/Cis, it was not feasible to further assess the anemia risk for this subgroup in the adjusted analysis.

Anemia, neutropenia, nausea, and vomiting were observed to be the most common adverse events in the patient groups receiving these treatments. However, the IR for thromboembolic events was similar to nausea and vomiting in the elderly patients treated with Doc/Carbo. The observed IR was higher for anemia and neutropenia in elderly patients than in patients of all ages for most treatment groups; it was, however, comparable for anemia in the Pem/Carbo group and neutropenia in the Doc/Carbo and Pem/Carbo groups. The IRs of other adverse events were comparable between elderly patients and patients of all ages. The consistent safety outcomes between elderly patients and the population of all ages aligns with recent publications in the sense that treatment in the elderly

should not solely be based on age (20-22).

The Pem/Cis regimen group, the only cisplatin-based regimen, had a numerically higher proportion of patients diagnosed with thromboembolic events (7.8%) compared to the other regimens consisting of carboplatin (2.2–5.1%). These results are consistent with the findings from a retrospective study that used hospital records of all patients with NSCLC from 2000 through 2012, which reported that 7.9% of the cisplatin-treated patients and 4.2% of carboplatin-treated patients in a first-line setting were diagnosed with thromboembolic events (23). The observed higher frequency of thromboembolic events in the Pem/Cis group than in all the carboplatin-based regimen groups in this study may reflect the differences between the risks associated with the 2 platinum backbones.

The adjusted analysis among patients of all ages after propensity score stratification provided additional information on the risk of adverse events for patients treated with different regimens compared with patients treated with Pac/Carbo: anemia was significantly lower in Pac/Carbo/Bev, Pem/Cis, and Pem/Carbo/Bev groups; neutropenia was comparable among all groups except the

Doc/Carbo group; nausea, vomiting, and thromboembolic events were significantly higher in the Pem/Cis group. Overall, the adjusted analysis indicated that hematological and gastrointestinal adverse events were similar between the 2 most commonly used regimens (Pac/Carbo and Pem/Carbo). Additional analysis with the varying duration of follow-up after the last dose showed consistency with the overall results.

Our results indicate that Pem/Carbo/Bev has a lower incidence of adverse events overall than Pem/Carbo alone. However, we aimed to focus on common toxicities related to chemotherapeutic agents and did not include some bevacizumab-associated adverse events such as haemorrhage, hypertension, and pain, as part of our main safety analysis. Thus, it does not lead to our interpretation that bevacizumab-containing chemotherapy (triplet) regimens have better tolerability than platinum doublet chemotherapy overall. Multiple clinical trials have previously proven that bevacizumab in combination with platinum-based chemotherapy provide improved efficacy benefit in patients with advanced nonsquamous NSCLC (12,24-26). However, with no available predictive biomarkers for bevacizumab, the choice of treatment should be based on clinical factors of individual patients. Given the nature of structured administrative data in the database, medical conditions captured were considered severe, requiring medical attention, and less severe conditions might not have been recorded. Although, we did not collect performance status (ECOG PS), lab abnormality, frailty, and severity of disease at the baseline, it is possible that patients in the Pem/Carbo group were more fragile in organ function and performance status which might have affected the development of toxicity.

A few limitations of our study warrant careful consideration. The severity of adverse events and patient performance status were not recorded in the database. Given that the captured medical conditions in the EMR were considered severe enough to require medical attention, less severe conditions may not have been recorded. The small number of elderly patients with adverse events other than anemia, neutropenia, nausea, and vomiting further limited the study power for the adjusted analyses in our elderly population. Carboplatin was the most commonly prescribed platinum in the overall NSCLC patients and in elderly patients in the US during the indexed treatment period. Prospective studies on the survival benefits of cisplatin *vs.* carboplatin with focus on performance status and outcome are still lacking.

The safety versus tumor histology was not analyzed since the histology was not captured in these populations. Finally, the EMR data for this study did not contain accurate death dates, which prevented accurate evaluation of treatment-related deaths and assessment of survival benefit associated with the 6 regimens.

Despite the limitations associated with EMR data and the retrospective design of the study, these results provided additional information about safety profiles for common platinum-based doublet therapies that may help clinicians make informed treatment decisions. The results from this analysis are helpful to understand the impact of combination therapy in patients of all ages and in elderly patients since platinum doublets in combination with targeted therapies have the potential to increase toxicity in elderly patients (20,22). Given that lung cancer mainly occurs in older people, further analysis in a large number of elderly patients treated with these regimens will be needed to determine the optimal combination therapy for patients with NSCLC.

Acknowledgments

Footnote

Conflicts of Interest: L Chen, JS Kim, B San Antonio, YE Zhu, L Mitchell, W John are current/former employees and own stock in Eli Lilly and Company.

Ethical Statement: The authors are accountable for all aspects of the work and for ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was exempt from institutional review board approval because it was retrospective, did not involve any intervention, and used anonymized data.

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Table S1 The incidence of the use of supportive care drugs in the treatment population

Types of supportive care	Carb/Pacl (N=3,009)			Carb/Pacl/Bev (N=531)			Carb/Peme (N=1,625)			Carb/Peme/Bev (N=735)			Cisp/Peme (N=357)			Doc/Carb (N=355)		
	n	IP (95% CI)	IR (95% CI) per 100 person-years	n	IP (95% CI)	IR (95% CI) per 100 person-years	n	IP (95% CI)	IR (95% CI) per 100 person-years	n	IP (95% CI)	IR (95% CI) per 100 person-years	n	IP (95% CI)	IR (95% CI) per 100 person-years	n	IP (95% CI)	IR (95% CI) per 100 person-years
Any Supportive Care Drugs	2,820	93.70% (0.929, 0.945)	1,788.55 (1,722.54, 1,854.56)	512	96.40% (0.948, 0.98)	4,471.62 (4,084.28, 4,858.96)	1,519	93.50% (0.923, 0.947)	2,107.09 (2,001.13, 2,213.05)	703	95.60% (0.94, 0.972)	5,046.66 (4,673.6, 5,419.7)	342	95.80% (0.936, 0.98)	2,172.81 (1,942.53, 2,403.09)	349	98.30% (0.969, 0.997)	6,155.2 (5,509.42, 6,800.98)
G-CSF	1,177	39.10% (0.373, 0.409)	95.99 (90.5, 101.48)	237	44.60% (0.403, 0.489)	200.92 (175.34, 226.5)	1,016	62.50% (0.601, 0.649)	276.13 (259.16, 293.1)	478	65.0% (0.615, 0.685)	392.87 (357.65, 428.09)	193	54.10% (0.49, 0.592)	134.07 (115.16, 152.98)	173	48.70% (0.434, 0.54)	149.33 (127.08, 171.58)
ESA	791	26.30% (0.247, 0.279)	49.67 (46.2, 53.14)	77	14.50% (0.116, 0.174)	35.1 (27.26, 42.94)	429	26.40% (0.242, 0.286)	63.67 (57.65, 69.69)	164	22.30% (0.194, 0.252)	60.83 (51.52, 70.14)	68	19.00% (0.149, 0.231)	26.6 (20.27, 32.93)	112	31.50% (0.266, 0.364)	57.82 (47.12, 68.52)

Bev, bevacizumab; Carb, carboplatin; Cisp, cisplatin; CI, Confidence interval; Doc, docetaxel; ESA, Erythropoiesis-stimulating agents; G-CSF, Granulocyte colony stimulating factor; IP, Incidence Proportion; IR, incidence rate; N, total number of patients identified in each regimen; n, number of patients in each category; Pacl, paclitaxel; Peme, pemetrexed.

Table S2 The incidence of adverse events in the treatment population

Adverse Events	Carb/Pacl (N=3,009)			Carb/Pacl/Bev (N=531)			Carb/Peme (N=1,625)			Carb/Peme/Bev (N=735)			Cisp/Peme (N=357)			Doc/Carb (N=355)		
	n	IP (95% CI)	IR (95% CI) per 100 person-years	n	IP (95% CI)	IR (95% CI) per 100 person-years	n	IP (95% CI)	IR (95% CI) per 100 person-years	n	IP (95% CI)	IR (95% CI) per 100 person-years	n	IP (95% CI)	IR (95% CI) per 100 person-years	n	IP (95% CI)	IR (95% CI) per 100 person-years
Constipation	46	1.50% (0.011, 0.019)	2.29 (1.62, 2.96)	16	3.00% (0.016, 0.044)	6.54 (3.33, 9.75)	24	1.50% (0.009, 0.021)	2.61 (1.57, 3.65)	11	1.50% (0.007, 0.023)	3.42 (1.4, 5.44)	10	2.80% (0.01, 0.046)	3.43 (1.31, 5.55)	1	0.30% (0, 0.009)	0.39 (0, 1.15)
Hemorrhage	39	1.30% (0.009, 0.017)	1.93 (1.32, 2.54)	8	1.50% (0.005, 0.025)	3.27 (1, 5.54)	18	1.10% (0.005, 0.017)	1.95 (1.05, 2.85)	3	0.40% (0, 0.008)	0.93 (0, 1.99)	5	1.40% (0.002, 0.026)	1.7 (0.21, 3.19)	4	1.10% (0, 0.023)	1.54 (0.03, 3.05)
Hypertension	36	1.20% (0.008, 0.016)	1.78 (1.19, 2.37)	12	2.30% (0.009, 0.037)	4.95 (2.15, 7.75)	13	0.80% (0.004, 0.012)	1.41 (0.65, 2.17)	10	1.40% (0.006, 0.022)	3.14 (1.2, 5.08)	5	1.40% (0.002, 0.026)	1.7 (0.21, 3.19)	7	2.00% (0.006, 0.034)	2.71 (0.71, 4.71)
Anorexia	35	1.20% (0.008, 0.016)	1.72 (1.15, 2.29)	9	1.70% (0.005, 0.029)	3.65 (1.26, 6.04)	17	1.00% (0.006, 0.014)	1.85 (0.97, 2.73)	3	0.40% (0, 0.008)	0.92 (0, 1.96)	5	1.40% (0.002, 0.026)	1.68 (0.21, 3.15)	2	0.60% (0, 0.014)	0.77 (0, 1.83)
Edema	29	1.00% (0.006, 0.014)	1.42 (0.91, 1.93)	7	1.30% (0.003, 0.023)	2.84 (0.74, 4.94)	20	1.20% (0.006, 0.018)	2.18 (1.22, 3.14)	2	0.30% (0, 0.007)	0.61 (0, 1.45)	8	2.20% (0.006, 0.038)	2.75 (0.85, 4.65)	0	0.00%	0
Pain	16	0.50% (0.003, 0.007)	0.78 (0.39, 1.17)	7	1.30% (0.003, 0.023)	2.84 (0.74, 4.94)	1	0.10% (0, 0.003)	0.11 (0, 0.33)	1	0.10% (0, 0.003)	0.31 (0, 0.92)	3	0.80% (0, 0.018)	1.01 (0, 2.15)	3	0.80% (0, 0.018)	1.16 (0, 2.47)

Bev, bevacizumab; Carb, carboplatin; Cisp, cisplatin; CI, Confidence interval; Doc, docetaxel; ESA, Erythropoiesis-stimulating agents; G-CSF, Granulocyte colony stimulating factor; IP, Incidence Proportion; IR, incidence rate; N, total number of patients identified in each regimen; n, number of patients in each category; Pacl, paclitaxel; Peme, pemetrexed.