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Treatment patterns and burden of myelosuppression for patients with small cell lung cancer: A SEER-medicare study

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ABSTRACT

Purpose: To depict the treatment journey for patients with small cell lung cancer (SCLC) and evaluate health care resource utilization (HCRU) associated with myelosuppression, a complication induced by chemotherapy or chemotherapy plus radiation therapy.

Patients and methods: This was a descriptive, retrospective study of patients with SCLC aged ≥65 years, identified from linked Surveillance, Epidemiology, and End Results (SEER)-Medicare data curated between January 2012 and December 2015. Treatment types (chemotherapy, radiation therapy, surgery) were classified as first, second, or third line, depending on the temporal sequence in which regimens were prescribed. For each year, the proportions of patients completing 4- or 6-cycle chemotherapy regimens, with hospital admissions associated with myelosuppression, or who used granulocyte colony–stimulating factors (G-CSFs), blood/platelet transfusions, or erythropoiesis-stimulating agents (ESAs), were calculated.

Results: Chemotherapy was administered as initial treatment in 7,807/11,907 (65.6%) patients whose treatment journey was recorded. Approximately one-third (n = 3,985) subsequently received radiation therapy. In total, 5,791 (57.8%) patients completed the guideline-recommended 4–6 cycles of chemotherapy. Among all chemotherapy-treated patients, 10,370 (74.3%) experienced ≥1 inpatient admission associated with myelosuppression (anemia, 7,366 [52.8%]; neutropenia, 4,642 [33.3%]; thrombocytopenia, 2,375 [17.0%]; pancytopenia, 1,983 [14.2%]). Supportive care interventions included G-CSF (6,756 [48.4%] patients), ESAs (1,534 [11.0%]), and transfusions (3,674 [26.3%]).

Conclusion: Chemotherapy remains a cornerstone of care for patients with SCLC. Slightly over half of patients completed the recommended number of cycles, underscoring the frailty of patients and aggressiveness of SCLC. HCRU associated with myelosuppression was prominent, suggesting a substantial burden on older patients with SCLC.

Abbreviations

AE	adverse event
CMS	Centers for Medicare and Medicaid Services
ESA	erythropoiesis-stimulating agent
ES-SCLC	extensive-stage small cell lung cancer
G-CSF	granulocyte colony–stimulating factor
HCPCS	Healthcare Common Procedure Coding System
HCRU	health care resource utilization
ICD	International Classification of Diseases
LS-SCLC	limited-stage small cell lung cancer
NLCA	National Lung Cancer Audit
NSCLC	non–small cell lung cancer
RBC	red blood cell
SCLC	small cell lung cancer
SEER	Surveillance, Epidemiology, and End Results

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Introduction

Small cell lung cancer (SCLC), which comprises approximately 13–17% of all lung cancer cases [1,2], is characterized by rapid progression and early, widespread metastases [3]. Guidelines from the American College of Chest Physicians recommend that limited-stage SCLC (LS-SCLC) is treated with curative intent, on the basis of an expected 5-year survival rate of 20% to 25% [4]. Standard treatment options include chemotherapy and radiation therapy, whereas surgery is recommended for only a minority of patients with very limited disease [5,6]. For extensive-stage SCLC (ES-SCLC), platinum-based combination chemotherapy remains the backbone of first-line therapy, even with the recent trend toward its use in combination with the immune checkpoint inhibitors atezolizumab and durvalumab [5,6]. Radiation therapy may also be administered to palliate localized metastatic sites, and patients who respond to chemotherapy may be considered for consolidative thoracic radiation therapy and/or prophylactic cranial irradiation [5,6].

The side effects of systemic chemotherapy used to treat cancer are often severe. Myelosuppression is a frequent complication of cytotoxic chemotherapy that results from damage to hematopoietic stem and progenitor cells in the bone marrow, and most commonly manifests as anemia, neutropenia, and thrombocytopenia [7–12]. Likewise, radiation therapy can also lead to clinically significant myelosuppression, especially when administered in combination with chemotherapy [13,14]. Patients with ES-SCLC are often elderly and have multiple comorbidities [15], rendering them particularly susceptible to the consequences of myelosuppression [16,17], which include increased risk of infections, fatigue, bleeding, and sepsis. The consequences of myelosuppression can have a negative impact on patients' quality of life and place significant burden on health care systems owing to the need for supportive care and/or hospitalizations [18–23]. Myelosuppression may also necessitate dose delays, reductions, and discontinuations, which contribute to a reduction in chemotherapy dose intensity and may compromise therapeutic efficacy [24].

In addition to dose modification, supportive care interventions are often utilized to manage myelosuppression; these include prophylactic or post-treatment interventions in the form of granulocyte colony–-stimulating factors (G-CSFs; for severe neutropenia), erythropoiesis-stimulating agents (ESAs) and red blood cell (RBC) and platelet transfusions [21,25,26]. However, these measures are also not without side effects, including bone pain with G-CSFs, thromboembolic adverse events (AEs) with ESAs, and infections and transfusion-related reactions with RBC and platelet transfusions [21,27-29]. Furthermore, supportive care interventions are typically administered reactively once patients have already experienced large declines in their cell counts.

Several recent studies have examined trends in SCLC treatment patterns in the US using the Surveillance, Epidemiology, and End Results (SEER) and/or Medicare databases, or other patient registries [30–33]. These studies have confirmed previous findings that most patients, including those aged ≥65 years, receive first-line treatment with chemotherapy [30–33]. However, to our knowledge, no "real-world" study has been conducted to examine sequential patterns in chemotherapy, radiation therapy, and surgery in the older (SEER-Medicare) population with SCLC or to assess the burden of multilineage myelosuppression. Using a SEER-Medicare linked data set, the aims of the current descriptive study were to: i) depict the treatment pathway, including examination of first-, second-, and third-line treatment patterns; and ii) evaluate the burden of myelosuppression among patients with LS- and ES-SCLC, including via the quantification of health care resource utilization (HCRU) and hospital admissions associated with myelosuppression among treated patients.

Patients and methods

Data source and study population

This was a retrospective, descriptive study using linked data sets from the SEER-Medicare database, which combines cancer incidence and survival data from population-based cancer registries in selected US geographic areas (SEER [National Cancer Institute]) with insurance claims data from the Medicare program (Centers for Medicare and Medicaid Services [CMS]) [34,35]. The SEER-Medicare database is widely used for cancer studies owing to its large size, comprehensiveness, and accessibility [36].

At the time of this study, the most recent SEER-Medicare linked database (released in 2018) included full data available through 2015 for both incident cancer cases and Medicare claims [35]. A list of all 12 of the SEER-Medicare registries with their respective administrative units is provided in Supplementary Table 1. In the current study, treatment patterns, chemotherapy-induced myelosuppression, and HCRU were assessed using data from 2012 to 2015.

The linked data set used in this study included data from claims for all inpatient hospitalizations, outpatient hospital services, physician services, home health agencies, durable medical equipment, and hospice services for Medicare beneficiaries. Prescription drug information was available from Part D pharmacy claims. Cancer characteristics were determined using the SEER Patient Entitlement and Diagnosis Summary File, and information on patient demographics, treatment patterns, and HCRU were determined from Medicare claims data.

Study population

This study included patients aged ≥65 years with a new primary diagnosis (no diagnosis prior to 2012) of SCLC, identified from linked SEER-Medicare data curated between January 2012 and December 2015. As this was a retrospective study of a de-identified data set, individual informed consent and ethics committee approval was not required. SCLC was identified using SEER lung tumor site codes (C34.0–C34.9), with histology codes 8041/3, 8042/3, 8043/3, 8044/3, and 8045/3 designated as SCLC. The use of SEER histology codes is important as they are specific to SCLC. By contrast, administrative claims data that rely on International Classification of Diseases (ICD) diagnosis codes, without specific histology codes, do not effectively distinguish between SCLC and non–small cell lung cancer (NSCLC) [37].

Treatment patterns

Descriptive analysis was performed on the usage of various types of treatment administered for SCLC between 2012 and 2015 using the Healthcare Common Procedure Coding System (HCPCS), ICD-9 and ICD-10 procedure codes, and drug codes, across multiple health care settings (inpatient, outpatient, home health, and hospice). The Medicare Part D drug event file was used to examine the frequency of prescriptions, quantity prescribed, and temporal sequence associated with each drug type.

Chemotherapies were identified within a time window from 30 days prior to the diagnosis index date up to the end of the follow-up period, using National Drug Codes and/or HCPCS codes from a comprehensive list of chemotherapy drugs, and Current Procedural Terminology (CPT) codes for chemotherapy administration (96401–96549). Radiation to any site of the body was identified using ICD-9 diagnosis codes (V58.0, V66.1, V67.1), ICD-9 procedure codes (92.21–92.29), ICD-10 codes (Z51.0, Z08, and Z09), revenue center codes (0330, 0333), and HCPCS codes (77401–77499, 77520, 77523, 77750–77799, G0256, G0261) as identified within the SEER-Medicare online documentation. Surgeries identified as of interest were flagged according to their respective ICD-9, ICD-10, and CPT/HCPCS codes (Supplementary Table 2). Chemotherapy, radiation, and surgery were identified and classified as first,

second, or third line depending on the temporal sequence of the dates when each type of treatment was received; first-line therapy was considered the first type of therapy with a completed claim in a patient's chronology. The patient's treatment journey was also captured to detail the sequence of treatment types (e.g., "chemotherapy then radiation then surgery", "radiation then surgery", "chemotherapy only", "surgery only") [38].

Among patients who received chemotherapy, the frequency and proportion of claims for specific chemotherapies (cisplatin, carboplatin, etoposide, and irinotecan) were tabulated. Percentages were calculated as the number of claims for each drug divided by the total number of claims for all four drugs. Topotecan was not included in this analysis of specific chemotherapy drugs, as we have previously observed that its use is relatively low compared with platinum-etoposide regimens [39,40]. However, topotecan use was captured by the chemotherapy administration CPT codes in the analysis of treatment patterns (Fig. 1).

Among patients with data describing the treatment journey, the proportion completing 4- or 6-cycle chemotherapy regimens was determined by calculating the number of cycles that patients completed for treatments initiated in calendar years 2012–2015, using an algorithm that considered the length of treatment and any treatment gaps (Supplementary Fig. 1) [41,42]. Rates were defined as the number of individuals who completed a given number of chemotherapy cycles, divided by the total number of individuals who were prescribed and who initiated chemotherapy each year. Because some individuals' chemotherapy cycles may transcend a given year, the number of cycles of chemotherapy was calculated and attributed to the index year of initiation. Patients who initiated treatment prior to 2012 were not included in the data set.

Myelosuppression-related event claims

Among patients who initiated chemotherapy within a given year, the number and percentage of individuals with at least one claim for a myelosuppression-related event (specifically anemia, thrombocytopenia, neutropenia, or pancytopenia) following the initiation of chemotherapy in any medical setting were calculated across the years 2012–2015. Myelosuppression-related events were identified using ICD diagnosis codes (Supplementary Table 3).

Hospitalizations associated with myelosuppression-related event claims

Among patients who initiated chemotherapy within a given year, the number and percentage of patients who had at least one subsequent inpatient claim associated with any myelosuppression event, and with each type of myelosuppression event, were calculated by study year.

Supportive care interventions

The number and percentage of chemotherapy-treated individuals who consumed SCLC-related health care resources, specifically those who used G-CSF, RBC or platelet transfusions, and ESAs, were tabulated by study year. G-CSF use was defined as any occurrence of the HCPCS codes C9119, J1440, J1441, J2505, J2820, Q4053, and S0135, and ESAs were characterized by HCPCS codes J0881, J0885, J0886, and J0887; both transfusion types were defined by CPT code 36430.

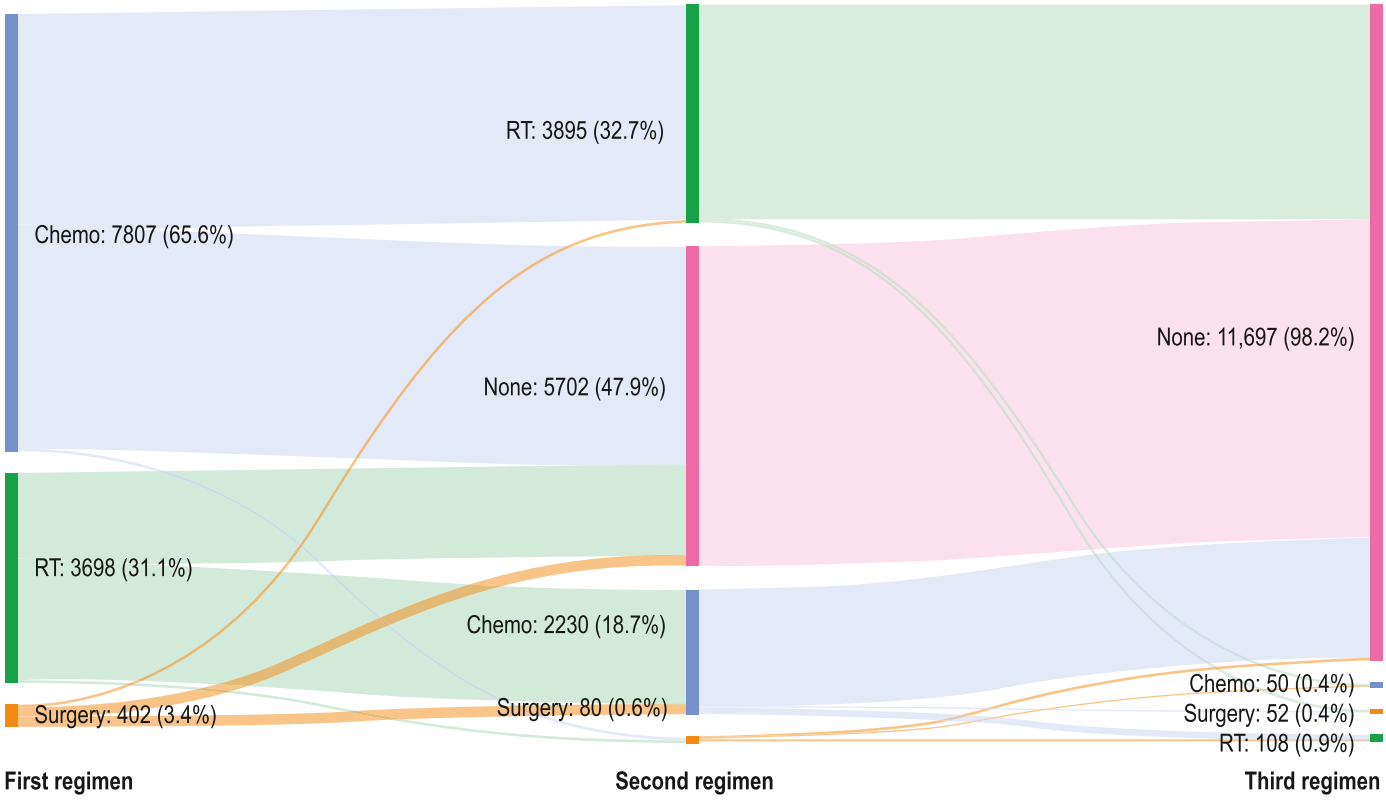

Fig. 1. Treatment patterns across lines of therapy: 2012–2015. Sankey diagram of treatments received [38].
The Sankey diagram should be read from left to right. Color codes are established on the left-hand side of the diagram for the treatment in question (for example, chemotherapy is blue). The number of patients receiving each treatment is given as a number and percentage of the total for that regimen. For each line of treatment, percentages were calculated using the total number of patients as the denominator. The reader may discern the treatment path by identifying a color and following it to the right-hand side of the diagram. As new endpoints are identified, new colors are used. Here, the vertical pink line in the middle of the diagram indicates that a new treatment pathway (in this case, no treatment or "None") was established. Abbreviations: Chemo = chemotherapy; RT = radiation therapy.

Results

Patient demographics

A total of 26,508 prevalent cases (14,411 incident cases) of patients aged ≥65 years with SCLC, were identified from the SEER-Medicare database. Approximately half of the SCLC population were female (range, 50.8–51.3%) and patients were consistently and predominantly White (range, 86.2–86.7%), with a mean (SD) age of between 74.2 (6.5) and 74.4 (6.5) years across the entire study period (Table 1).

Treatment patterns

The percentages of patients receiving chemotherapy (51.0–57.5%) and radiation therapy (34.1–37.9%) among the prevalent SCLC population were consistent from 2012 through 2015 (Table 2).

Among all patients for whom the treatment journey was recorded (n = 11,907), chemotherapy was prescribed as first-line treatment in 65.6% (Fig. 1), and radiation therapy as first-line treatment in 31.1%. Surgery was used far less commonly, administered to 3.4% of patients as first-line treatment and 4.4% in any line. Almost half of patients (47.9%) did not receive second-line treatment, and 98.2% of patients did not receive third-line treatment. Among patients who received first-line chemotherapy, approximately a third received radiation therapy as second-line or subsequent treatment (Fig. 1). Likewise, among patients who received first-line radiation therapy, most received subsequent chemotherapy (Fig. 1).

Overall, 57.8% of patients who received chemotherapy completed 4–6 cycles; this proportion was consistent across the study period (range, 56.9–58.4%), as was the percentage of patients completing 1, 2, or 3 cycles (Table 3). Of the 42.2% of patients who completed fewer than 4 cycles across all study years, 23.8% completed only 1 cycle, 9.3% completed 2 cycles, and 9.1% completed 3 cycles.

Specific chemotherapy products examined included cisplatin, carboplatin, etoposide, and irinotecan (Table 4). Etoposide was the most prescribed chemotherapy (44.1–57.3%), followed by carboplatin (27.3–34.3%), cisplatin (10.4–13.6%), and irinotecan (5.0–8.0%). The use of cisplatin, carboplatin, and irinotecan declined slightly from 2012 through 2015 (as a percentage of total prescriptions), whereas the use of etoposide increased.

Table 1
Patient demographics among the SCLC-prevalent population.

Stratifier	Year			
	2012	2013	2014	2015
Sex				
Male	3464 (49.2)	3366 (49.1)	3234 (48.7)	2927 (49.0)
Female	3572 (50.8)	3491 (50.9)	3406 (51.3)	3048 (51.0)
Age (5-year intervals)				
65–69 years	2030 (28.9)	1962 (28.6)	1867 (28.1)	1659 (27.8)
70–74 years	1925 (27.4)	1927 (28.1)	1883 (28.4)	1684 (28.2)
75–79 years	1511 (21.5)	1469 (21.4)	1440 (21.7)	1315 (22.0)
80–84 years	1012 (14.4)	948 (13.8)	889 (13.4)	804 (13.5)
≥85 years	558 (7.9)	551 (8.0)	561 (8.4)	513 (8.6)
Mean [SD] age, years	74.2 [6.5]	74.2 [6.5]	74.3 [6.5]	74.4 [6.5]
Race				
White	6099 (86.7)	5933 (86.5)	5761 (86.7)	5150 (86.2)
Black	546 (7.8)	510 (7.4)	507 (7.6)	466 (7.8)
Other	126 (1.8)	129 (1.9)	115 (1.7)	108 (1.8)
Asian/Pacific Islander	148 (2.1)	152 (2.2)	148 (2.2)	134 (2.2)
Hispanic/ Latino	65 (0.9)	74 (1.1)	55 (0.8)	58 (1.0)
American Indian	20 (0.3)	17 (0.2)	15 (0.2)	13 (0.2)
Unknown	32 (0.5)	42 (0.6)	39 (0.6)	46 (0.8)

Abbreviation: SCLC = small cell lung cancer.
Data are patients, n (%) unless otherwise indicated.

Table 2
Total number and percentage of patients with SCLC receiving chemotherapy and radiation by year.

Year	Prevalent SCLC cases, n	Chemotherapy		Radiation	
		n	%	n	%
2012	7036	3588	51.0	2398	34.1
2013	6857	3509	51.2	2385	34.8
2014	6640	3427	51.6	2376	35.8
2015	5975	3434	57.5	2265	37.9

Abbreviation: SCLC = small cell lung cancer.

Myelosuppression-related event claims

Overall, the percentage of patients receiving chemotherapy with a myelosuppression-related event claim after chemotherapy initiation was highest for anemia (71.7% overall; range, 62.1–76.8%; Table 5). The incidence of anemia was generally consistent across the years 2012–2014 but decreased slightly in 2015. Neutropenia was the second most common type of myelosuppression-related event claim, reported in 45.2% (range, 44.1–46.1%) of chemotherapy-treated patients overall. The percentage of chemotherapy-treated patients with neutropenia was generally consistent across the study period. Thrombocytopenia was consistently reported in 27.0% of patients overall (range, 25.1–28.5%). Pancytopenia occurred in 24.4% of patients overall, its incidence increasing very slightly over the study period (from 22.5% in 2012 to 25.7% in 2015).

Hospitalizations associated with myelosuppression-related event claims

During the study period, 74.3% (range, 68.3–77.5%) of patients treated with chemotherapy experienced at least one inpatient admission associated with any type of myelosuppression-related event claim (Table 5). The percentage of patients who had at least one inpatient claim for a myelosuppression event was highly consistent across 2012–2014 (73.5–77.6%), falling slightly in 2015 (68.3%).

Hospital admissions associated with myelosuppression-related event claims occurred most for anemia (overall [2012–2015], 52.8%; range, 45.7–56.9%), followed by neutropenia (overall, 33.3%; range, 31.9–34.0%), thrombocytopenia (overall, 17.0%; range, 16.1–18.8%), and pancytopenia (overall, 14.2%; range, 12.2–16.2%). The percentages of patients who had at least one inpatient claim for each type of myelosuppression event were generally consistent from 2012 through 2015, except for anemia, which was less frequent in 2015 (declining from 52.5% in 2014 to 45.7% in 2015), and pancytopenia, which increased slightly over the study period (from 12.2% in 2012 to 16.2% in 2015).

Supportive care interventions

Overall, G-CSF was received in 48.4% of chemotherapy-treated patients (range, 44.1–52.4%), ESAs in 11.0% of patients (range, 8.0–13.4%), and RBC/platelet transfusions in 26.3% of patients (range, 24.4–27.7%; Table 6). The use of G-CSF decreased in 2014 and 2015 (compared with 2012–2013), and ESA usage decreased slightly across the study period. The percentage of patients who received transfusions was highly consistent across 2012–2014, decreasing slightly in 2015.

Discussion

This study used real-world data from the SEER-Medicare claims database to investigate patterns of treatment for SCLC and evaluate myelosuppression-related event claims and their management among patients with SCLC who were treated with chemotherapy. The treatment patterns observed in this study were consistent with those reported previously [30,32,43], indicating that chemotherapy is the most common first-line treatment (administered to 65.6% of patients in

Table 3
Number of chemotherapy cycles patients completed by year[a].

	Year 2012		2013		2014		2015		Overall (2012–2015)	
Treatment cycles	n	%	n	%	n	%	n	%	n	%
1 cycle	836	23.4	531	23.9	524	24.6	496	23.6	2387	23.8
2 cycles	373	10.4	194	8.7	190	8.9	179	8.5	936	9.3
3 cycles	329	9.2	205	9.2	177	8.3	200	9.5	911	9.1
4–6 cycles	2034	56.9	1294	58.2	1235	58.1	1228	58.4	5791	57.8
4 cycles	414	11.6	301	13.5	283	13.3	306	14.6	1304	13.0
5 cycles	273	7.6	191	8.6	192	9.0	180	8.6	836	8.3
6 cycles	1347	37.7	802	36.1	760	35.7	742	35.3	3651	36.4

[a] Chemotherapy regimens are only counted for the year in which the regimen was started.

Table 4
Specific chemotherapy products used among patients with SCLC.

	Year							
	2012		2013		2014		2015	
	n	%[a]	n	%[a]	n	%[a]	n	%[a]
Cisplatin	2845	13.6	2737	13.0	2759	12.8	2464	10.4
Carboplatin	7167	34.3	6766	32.3	6451	29.9	6451	27.3
Etoposide	9216	44.1	10,110	48.2	11,138	51.6	13,555	57.3
Irinotecan	1681	8.0	1363	6.5	1229	5.7	1184	5.0
Total	20,909	–	20,976	–	21,577	–	23,654	–

Abbreviation: SCLC = small cell lung cancer.
[a] Percentages are calculated as the number of claims for each drug divided by the total number of claims for all four drugs.

Table 5
Occurrence of myelosuppression events and hospitalizations associated with myelosuppression among patients with SCLC receiving chemotherapy.

Condition	Year								Overall (2012–2015) (n = 13,958)	
	2012 (n = 3588)		2013 (n = 3509)		2014 (n = 3427)		2015 (n = 3434)			
	n	%	n	%	n	%	n	%	n	%
Occurrence of myelosuppression events										
Anemia	2757	76.8	2672	76.1	2444	71.3	2131	62.1	10,004	71.7
Thrombocytopenia	900	25.1	978	27.9	911	26.6	978	28.5	3767	27.0
Neutropenia	1592	44.4	1618	46.1	1513	44.1	1584	46.1	6307	45.2
Pancytopenia	809	22.5	848	24.2	867	25.3	881	25.7	3405	24.4
≥1 inpatient claim for any type of myelosuppression[a]	2782	77.5	2722	77.6	2519	73.5	2347	68.3	10,370	74.3
Anemia	2005	55.9	1995	56.9	1798	52.5	1568	45.7	7366	52.8
Thrombocytopenia	584	16.3	566	16.1	578	16.9	647	18.8	2375	17.0
Neutropenia	1206	33.6	1175	33.5	1092	31.9	1169	34.0	4642	33.3
Pancytopenia	437	12.2	479	13.7	510	14.9	557	16.2	1983	14.2

Abbreviation: SCLC = small cell lung cancer.
[a] Defined as the total number of patients with at least one claim for anemia, thrombocytopenia, neutropenia, and/or pancytopenia.

Table 6
Supportive care utilization among patients with SCLC receiving chemotherapy.

Resource/treatment Patients	Year								Overall (2012–2015) (n = 13,958)	
	2012 (n = 3588)		2013 (n = 3509)		2014 (n = 3427)		2015 (n = 3434)			
	n	%	n	%	n	%	n	%	n	%
G-CSF[a]	1875	52.3	1838	52.4	1512	44.1	1531	44.6	6756	48.4
ESA usage[b]	479	13.4	425	12.1	354	10.3	276	8.0	1534	11.0
RBC or platelet transfusion[c]	993	27.7	943	26.9	901	26.3	837	24.4	3674	26.3

Abbreviations: CPT = Current Procedural Terminology; ESA = erythropoiesis-stimulating agent; G-CSF = granulocyte colony–stimulating factor; HCPCS = Healthcare Common Procedure Coding System; RBC = red blood cell; SCLC = small cell lung cancer.
[a] G-CSF use is defined as any occurrence of the follow HCPCS codes: C9119, J1440, J1441, J2505, J2820, Q4053, S0135.
[b] ESA use is defined as any occurrence of the follow HCPCS codes: J0881, J0885, J0886, and J0887.
[c] Both transfusion types are defined by CPT code 36430.

2012–2015) and that its use may have increased over time. Radiation therapy was also common in the current study, whereas very few patients underwent surgery, as per previous findings in patients diagnosed with SCLC within the general SEER population [31]. Unlike previous studies, we also assessed sequential patterns in chemotherapy, radiation therapy, and surgery within the SEER-Medicare SCLC population and found that most patients who were administered more than one type of treatment received chemotherapy followed by radiation therapy, or vice

versa.

Across 2012–2015, 57.8% of patients completed the guideline-recommended [5] 4–6 cycles of chemotherapy, indicating that almost half of patients (42.2%) completed fewer than 4 cycles. This proportion is higher than the 26% of patients with ES-SCLC in a Dutch retrospective cohort analysis (2008–2014) who underwent early discontinuation (<4 cycles) of first-line treatment [44], but in line with findings from an English National Lung Cancer Audit (NLCA) database (2006–2011), in which 63% of patients with LS- or ES-SCLC who had Hospital Episodes Statistics chemotherapy data completed ≥4 cycles [45]. Discrepancies between studies may reflect variation in analysis methods, and/or differences in the patient populations (e.g., age, disease stage) or line of treatment, which may have contributed to variation in the rates of disease progression or toxicity. Treatment practices may also vary such that some patients may be prescribed an abbreviated treatment plan of chemotherapy (2 cycles) plus thoracic irradiation, an approach that has shown some efficacy in elderly or infirm patients with LS-SCLC [5,46]. In any case, it is notable that a considerable proportion of patients did not complete the full chemotherapy course in each of these real-world studies. If patients discontinued chemotherapy early for reasons of toxicity, this may correlate to suboptimal treatment outcomes [45]. Moreover, early discontinuation may also correlate to rapidly progressing, nonresponsive disease. Of note, a separate study that surveyed participants with breast, lung, or colorectal cancer found that, among the 301 chemotherapy-treated participants who had experienced at least one episode of myelosuppression in the past year, 64% recalled chemotherapy dose delays, reductions, discontinuations and/or changes due to myelosuppression, furthering highlighting its impact on completion of treatment as planned [23].

Our findings are consistent with previous reports describing widespread use of etoposide with either carboplatin or cisplatin. Shao et al. found that most first-line SCLC chemotherapies described in the SEER-Medicare database were carboplatin (71.0%) or cisplatin based (22.2%), primarily in combination with etoposide [30]. Other studies, focusing on patients with ES-SCLC, have also reported carboplatin-etoposide and cisplatin-etoposide as the most common first-line chemotherapies [32,33,44]. The use of topotecan was not assessed in the analysis of specific chemotherapy drugs; however, previous studies suggest that topotecan is typically used as a second-line treatment for SCLC in the US and Europe [30,32,33,39,40,44], in line with consensus-based treatment guidelines [5,47]. Given that most patients who received chemotherapy in the current study (77.4%) did so in first line, it is likely that platinum-etoposide treatment was the most prescribed chemotherapy regimen overall. Also of interest, would be to re-evaluate treatment patterns since the more recent (2019/2020) approvals of atezolizumab and durvalumab, both of which are now recommended as preferred treatment options for ES-SCLC in combination with platinum-etoposide chemotherapy regimens [5,6]. Our analysis did not include evaluation of myelosuppression associated with specific chemotherapy regimens. However, previous real-world studies and clinical trials have observed consistently high rates of myelosuppression across commonly used first-line chemotherapy/chemoimmunotherapy regimens for SCLC, despite some numeric differences [39,48-50]. Therefore, while we observed slight differences in the use of specific chemotherapy regimens across 2012 to 2015, it is likely that myelosuppression will continue to impose a substantial burden on patients with SCLC despite subtle changes in the use of different chemotherapy classes or the introduction of chemoimmunotherapy combinations.

Myelosuppression is a concern among oncology practitioners, especially those treating patients with chemotherapy. Our analysis confirmed this finding, with 71.7% of chemotherapy-treated patients experiencing anemia, 45.2% experiencing neutropenia, 27.0% experiencing thrombocytopenia, and 24.4% experiencing pancytopenia. Over the same period, almost three-quarters of patients receiving chemotherapy experienced at least one inpatient admission associated with myelosuppression. These findings highlight the substantial burden of myelosuppression on patients receiving chemotherapy, which can have a profound negative impact on patients' quality of life owing to symptoms such as fatigue and concerns over the risk of infection [22,23]. Moreover, myelosuppression and its management can incur considerable financial costs, particularly for episodes involving hospital admissions and readmissions [51,52].

Chemotherapy-induced myelosuppression is typically managed with supportive care interventions, namely G-CSF and ESA administration, and transfusions. Management strategies include primary prophylaxis with G-CSF to patients at risk of developing febrile neutropenia (FN), ESA administration and RBC transfusion to treat occurrences of anemia, and platelet transfusion to treat thrombocytopenia [21,25,53,54]. In this study, HCRU in the form of supportive care interventions associated with myelosuppression was prominent across all study years. Across 2012–2015, almost half of patients (48.4%) received G-CSF, whereas ESAs and transfusions (RBCs or platelets) were administered to 11.0% and 26.3% of patients, respectively. Specific G-CSF agents were not evaluated, and G-CSF use reflected administration of any G-CSF (which could be long-acting or short-acting G-CSF). However, a recent study reported that pegfilgrastim was the most commonly used G-CSF agent among patients with ES-SCLC (>65% of patients receiving chemotherapy) [40]. It was challenging to identify the reasons for G-CSF use in this study owing to data limitations. In addition, the purpose of the current study was to describe the burden of myelosuppression and the proportion of patients receiving single lineage supportive care interventions overall. Therefore, G-CSF administration reflected the use of G-CSF for any reason (which could be primary prophylaxis, secondary prophylaxis, or therapeutic use).

In line with the findings from this study, a recent real-world analysis including 338 patients with SCLC who had experienced grade 3/4 chemotherapy-induced myelosuppression found that rates of G-CSF use and RBC transfusions were 47.0 and 41.7 per 100 patients, respectively. The use of ESAs was low, at 2.0 per 100 patients, and there was a trend toward increased use of supportive care interventions among patients with AEs in more than one lineage; these findings underscore the real-world burden of chemotherapy-induced myelosuppression and its management on patients with SCLC in the community cancer care setting [39]. The ongoing need for measures to control costs associated with chemotherapy is reflected in the findings from the Oncology Care Model, a 6-year experimental payment model introduced by the CMS. The Oncology Care Model has placed a greater emphasis on total cost of care, especially around the use of supportive care drugs to prevent chemotherapy-related AEs, particularly for G-CSF use to prevent neutropenia. The use of home monitoring and telehealth systems may also be considered to enable earlier detection and intervention for myelosuppression [55].

The substantial economic burden of chemotherapy-induced myelosuppression described by others [51,52], together with the humanistic burden on patients and clinical implications for chemotherapy treatment outcomes, highlight the need for treatment that can proactively protect against myelosuppression and its consequences, thereby reducing the need for supportive care and hospitalizations. In February 2021, trilaciclib, an intravenous kinase inhibitor that is administered within 4 h prior to the start of chemotherapy, was approved to decrease the incidence of chemotherapy-induced myelosuppression in adult patients treated with a platinum/etoposide-containing or topotecan-containing chemotherapy regimen for ES-SCLC. Approval was based on results from three randomized phase 2 trials, in which trilaciclib reduced rates of myelosuppression compared with placebo across multiple hematopoietic lineages [48–50]. A recent pooled analysis of these trials showed that administering trilaciclib prior to chemotherapy significantly reduced the use of G-CSFs, ESAs, and RBC transfusions [56]. It is notable that the percentages of patients who received supportive care interventions in the placebo group (G-CSFs, 56.3%; ESAs, 11.8%; RBC transfusions on/after week 5, 26.1%), were comparable to those in the current study, as were the rates of

hematologic AEs (anemia, 60.2%; neutropenia, 66.1%; thrombocytopenia, 42.4%) [56]. Although clinical trial and real-world data are not directly comparable owing to differences in the study designs and patient populations, this finding further highlights the persistent burden of chemotherapy-induced myelosuppression in all treatment settings. It will be interesting to determine whether, in addition to its current indication, trilaciclib can decrease the incidence of hematologic AEs when administered prior to other myelosuppressive chemotherapies in patients with SCLC or other cancer types. Several ongoing clinical trials are evaluating the effects of trilaciclib in patients with other cancers (colorectal cancer [NCT04607668], triple-negative breast cancer [NCT04799249], and bladder cancer [NCT04887831]).

It is important to consider that radiation therapy was revealed to be a significant first-line and adjunctive intervention to chemotherapy in patients with SCLC. Like chemotherapy, radiation therapy has been widely associated with bone marrow suppression, with the level of bone marrow and peripheral cell depletion dependent on the radiation dose received by the biological tissue [57,58]. Indeed, in both SCLC and NSCLC, radiation to the thoracic vertebral body in patients receiving chemotherapy contributes to severe myelosuppression (anemia, neutropenia, leukopenia, and thrombocytopenia), with grade ≥3 hematologic toxicities being associated with greater doses of radiation [14,59]. Among patients with SCLC treated with concurrent once- versus twice-daily radiation therapy and cisplatin-etoposide in the phase 3 CONVERT study, grade ≥3 neutropenia was reported in 65.4% and 74.1% of patients, respectively [13]. Additionally, a recent study reported numerically higher rates of grade ≥3 myelosuppressive AEs in chemotherapy-treated patients with SCLC who had received prior radiation compared with those without or with unknown prior radiation therapy, although the burden of myelosuppression was prominent in both patient subgroups [39]. Chemotherapy-treated patients with SCLC receiving brain irradiation also experience more severe myelosuppression than non-irradiated patients and had a higher incidence of infectious complications [60]. Given this evidence, it must be acknowledged that receipt of radiation therapy before, concurrently with, or after chemotherapy may have contributed to the myelosuppression-related event claims reported in the current study. Accordingly, these episodes should be considered as treatment-induced myelosuppression occurring in patients receiving chemotherapy, rather than chemotherapy-induced myelosuppression per se.

Limitations of this study include those that are common in claims-based analyses. The SEER-Medicare database includes data from specific US regions and mostly includes individuals aged ≥65 years, and results may not be generalizable to the entire SCLC population, particularly in certain geographic regions. There is also an inherent lag between patients' diagnosis or receipt of services and inclusion of data in the SEER-Medicare database [35]. It was not possible to distinguish between patients with LS-SCLC and ES-SCLC owing to data limitations. However, several published studies have reported that approximately two-thirds of patients have ES disease at diagnosis [3,6,30,39]. Of note, there does not appear to be a clear pattern in the rates of myelosuppressive AEs according to disease stage, suggesting that myelosuppression should be of similar concern for patients with LS- and ES-SCLC [39]. Because data were not available on the specific timing between initiation of chemotherapy and radiation therapy, and the definition of concurrent versus sequential chemoradiotherapy varies across studies [5], it was not possible to define a fourth category of chemoradiotherapy in the analysis of treatment patterns. Accordingly, the 3895 patients denoted as having received chemotherapy followed by radiation therapy in Fig. 1 potentially includes patients who received concurrent or sequential chemoradiotherapy. In addition, radiation therapy in this study could have included prophylactic cranial irradiation or palliative radiation to metastatic sites, as well as thoracic radiation therapy. When evaluating chemotherapy treatment patterns, we used a combination of ICD diagnosis and procedures codes, as well as CPT codes for chemotherapy administration, the specific drugs administered, and follow-up encounters. The Part D event database detected certain chemotherapy agents, but the names of most drugs were missing. Therefore, National Drug Codes were used in conjunction with the diagnosis and procedure codes to capture whether a patient underwent chemotherapy. Our analysis of specific chemotherapy drugs included cisplatin, carboplatin, etoposide, and irinotecan, but not topotecan. Our results are like those of previous studies and commonly known trends, suggesting that the findings reflect treatment patterns in this study population. It is also possible that we did not detect every patient who had evidence of myelosuppression due to potential under-coding. Therefore, the results reported here represent conservative estimates. We cannot confirm that myelosuppression was the only reason for hospitalization among patients with inpatient claims associated with myelosuppression since one hospitalization claim could have multiple diagnosis codes. However, in all cases, myelosuppression was included as at least one of the reasons for hospitalization.

Notwithstanding these limitations, the SEER-Medicare database is a unique asset for enabling the conduct of cancer health service studies, and its large sample size and wide array of data on US patients with cancer and controls without cancer make it an invaluable resource. The linked database is an important and representative resource for examining real-world patterns across multiple care settings for patients with cancer aged ≥65 years [35], who are often particularly vulnerable to the complications of myelosuppression [16]. Indeed, the findings of the current study provide valuable insights into recent trends in SCLC treatment patterns and the burden of myelosuppression in older patients receiving chemotherapy.

In summary, evaluation of treatment patterns indicated that chemotherapy remains a cornerstone of treatment for patients with SCLC, with just over half of patients from the SEER-Medicare database completing the recommended number of cycles, underscoring the frailty of patients and the aggressive nature of this disease. HCRU associated with myelosuppression claims was prominent across all study years, suggesting that myelosuppression continues to impose substantial burden on elderly patients with SCLC while consuming resources available within the US health care system. Overall, the results suggest that agents to reduce the incidence of chemotherapy-induced myelosuppression and, in turn, reduce associated HCRU would be of value.

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Data availability

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

CRediT authorship contribution statement

Robert S. Epstein: Conceptualization; Formal analysis; Funding acquisition; Methodology; Validation; Writing - review & editing.

Jerrod Nelms: Data curation; Formal analysis; Methodology; Validation; Visualization; Writing - review & editing.

Donald Moran: Conceptualization; Formal analysis; Methodology; Validation; Writing - review & editing.

Cynthia Girman: Conceptualization; Formal analysis; Methodology; Validation; Writing - review & editing.

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Marc Chioda: Conceptualization; Formal analysis; Methodology; Validation; Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

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References

[1] N. Howlader, A.M. Noone, M. Krapcho, D. Miller, A. Brest, M. Yu, J. Ruhl, Z. Tatalovich, A. Mariotto, D.R. Lewis, H.S. Chen, E.J. Feuer, K.A. Cronin, SEER Cancer Statistics Rev. (2020) 1975–2017, https://seer.cancer.gov/archive/csr/1975_2017/ (Accessed June 2021).

[2] S. Wang, J. Tang, T. Sun, X. Zheng, J. Li, H. Sun, X. Zhou, C. Zhou, H. Zhang, Z. Cheng, H. Ma, H. Sun, Survival changes in patients with small cell lung cancer and disparities between different sexes, socioeconomic statuses and ages, Sci. Rep. 7 (2017) 1339, https://doi.org/10.1038/s41598-017-01571-0.

[3] L.A. Byers, C.M. Rudin, Small cell lung cancer: where do we go from here? Cancer 121 (2015) 664–672, https://doi.org/10.1002/cncr.29098.

[4] F.C. Detterbeck, S.Z. Lewis, R. Diekemper, D. Addrizzo-Harris, W.M. Alberts, Executive summary: diagnosis and management of lung cancer, 3rd ed, Am. College of Chest Physicians evidence-based Clin. Practice Guidelines, Chest 143 (2013) 7s–37s, https://doi.org/10.1378/chest.12-2377, 7s-37s.

[5] National Comprehensive Cancer Network, NCCN clinical practice guidelines in oncology (NCCN Guidelines®). Small Cell Lung Cancer. Version 3. 2021. https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1462, 2021 (Accessed March 24, 2021).

[6] PDQ Adult Treatment Editorial Board, Small cell lung cancer treatment (PDQ®): health professional version, in: PDQ Cancer Information Summaries, National Cancer Institute (US), Bethesda (MD), 2002-2021.

[7] K. Noda, Y. Nishiwaki, M. Kawahara, S. Negoro, T. Sugiura, A. Yokoyama, M. Fukuoka, K. Mori, K. Watanabe, T. Tamura, S. Yamamoto, N. Saijo, Irinotecan plus cisplatin compared with etoposide plus cisplatin for extensive small-cell lung cancer, N. Engl. J. Med. 346 (2002) 85–91, https://doi.org/10.1056/NEJMoa003034.

[8] N. Hanna, P.A. Bunn Jr., C. Langer, L. Einhorn, T. Guthrie Jr., T. Beck, R. Ansari, P. Ellis, M. Byrne, M. Morrison, S. Hariharan, B. Wang, A. Sandler, Randomized phase III trial comparing irinotecan/cisplatin with etoposide/cisplatin in patients with previously untreated extensive-stage disease small-cell lung cancer, J. Clin. Oncol. 24 (2006) 2038–2043, https://doi.org/10.1200/jco.2005.04.8595.

[9] A. Hermes, B. Bergman, R. Bremnes, L. Ek, S. Fluge, C. Sederholm, S. Sundstrøm, L. Thaning, J. Vilsvik, U. Aasebø, S. Sörenson, Irinotecan plus carboplatin versus oral etoposide plus carboplatin in extensive small-cell lung cancer: a randomized phase III trial, J. Clin. Oncol. 26 (2008) 4261–4267, https://doi.org/10.1200/jco.2007.15.7545.

[10] P.J. Loehrer Sr., R. Ansari, R. Gonin, F. Monaco, W. Fisher, A. Sandler, L. H. Einhorn, Cisplatin plus etoposide with and without ifosfamide in extensive small-cell lung cancer: a Hoosier Oncology Group study, J. Clin. Oncol. 13 (1995) 2594–2599, https://doi.org/10.1200/jco.1995.13.10.2594.

[11] H.B. Niell, J.E. Herndon 2nd, A.A. Miller, D.M. Watson, A.B. Sandler, K. Kelly, R. S. Marks, M.C. Perry, R.H. Ansari, G. Otterson, J. Ellerton, E.E. Vokes, M.R. Green, Randomized phase III intergroup trial of etoposide and cisplatin with or without paclitaxel and granulocyte colony-stimulating factor in patients with extensive-stage small-cell lung cancer: cancer and Leukemia Group B Trial 9732, J. Clin. Oncol. 23 (2005) 3752–3759, https://doi.org/10.1200/jco.2005.09.071.

[12] A. Schmittel, M. Sebastian, L. Fischer von Weikersthal, P. Martus, T.C. Gauler, C. Kaufmann, P. Hortig, J.R. Fischer, H. Link, D. Binder, B. Fischer, K. Caca, W. E. Eberhardt, U. Keilholz, Arbeitsgemeinschaft Internistische Onkologie Thoracic Oncology Study Group, A German multicenter, randomized phase III trial comparing irinotecan-carboplatin with etoposide-carboplatin as first-line therapy for extensive-disease small-cell lung cancer, Ann. Oncol. 22 (2011) 1798–1804, https://doi.org/10.1093/annonc/mdq652.

[13] C. Faivre-Finn, M. Snee, L. Ashcroft, W. Appel, F. Barlesi, A. Bhatnagar, A. Bezjak, F. Cardenal, P. Fournel, S. Harden, C. Le Pechoux, R. McMenemin, N. Mohammed, M. O'Brien, J. Pantarotto, V. Surmont, J.P. Van Meerbeeck, P.J. Woll, P. Lorigan, F. Blackhall, CONVERT Study Team, Concurrent once-daily versus twice-daily chemoradiotherapy in patients with limited-stage small-cell lung cancer (CONVERT): an open-label, phase 3, randomised, superiority trial, Lancet Oncol. 18 (2017) 1116–1125, https://doi.org/10.1016/s1470-2045(17)30318-2.

[14] C.L. Barney, N. Scoville, E. Allan, A. Ayan, D. DiCostanzo, K.E. Haglund, J. Grecula, T. Williams, M. Xu-Welliver, G.A. Otterson, J.G. Bazan, Radiation dose to the thoracic vertebral bodies is associated with acute hematologic toxicities in patients receiving concurrent chemoradiation for lung cancer: results of a single-center retrospective analysis, Int. J. Radiat. Oncol. Biol. Phys. 100 (2018) 748–755, https://doi.org/10.1016/j.ijrobp.2017.11.025.

[15] M.J. Aarts, J.G. Aerts, B.E. van den Borne, B. Biesma, V.E. Lemmens, J.S. Kloover, Comorbidity in patients with small-cell lung cancer: trends and prognostic impact, Clin. Lung Cancer 16 (2015) 282–291, https://doi.org/10.1016/j.cllc.2014.12.003.

[16] L. Balducci, Myelosuppression and its consequences in elderly patients with cancer, Oncology (Williston Park) 17 (2003) 27–32.

[17] G.H. Lyman, N.M. Kuderer, Epidemiology of febrile neutropenia, Support. Cancer Ther. 1 (2003) 23–35, https://doi.org/10.3816/SCT.2003.n.002.

[18] J.N. Barreto, K.B. McCullough, L.L. Ice, J.A. Smith, Antineoplastic agents and the associated myelosuppressive effects: a review, J. Pharm. Pract. 27 (2014) 440–446, https://doi.org/10.1177/0897190014546108.

[19] E. Bryer, D. Henry, Chemotherapy-induced anemia: etiology, pathophysiology, and implications for contemporary practice, Int. J. Clin. Transfus. Med. 6 (2018) 21–31, https://doi.org/10.2147/IJCTM.S187569.

[20] G.H. Lyman, Risks and consequences of chemotherapy-induced neutropenia, Clin. Cornerstone 8 (2006) S12–S18, https://doi.org/10.1016/s1098-3597(06)80054-2. Suppl 5S12-S18.

[21] D.J. Kuter, Managing thrombocytopenia associated with cancer chemotherapy, Oncology (Williston Park) 29 (2015) 282–294.

[22] R.S. Epstein, U.K. Basu Roy, M. Aapro, T. Salimi, D. Moran, J. Krenitsky, M. L. Leone-Perkins, C. Girman, C. Schlusser, J. Crawford, Cancer patients' perspectives and experiences of chemotherapy-induced myelosuppression and its impact on daily life, Patient Prefer. Adherence 15 (2021) 453–465, https://doi.org/10.2147/ppa.S292462.

[23] R.S. Epstein, M.S. Aapro, U.K. Basu Roy, T. Salimi, J. Krenitsky, M.L. Leone-Perkins, C. Girman, C. Schlusser, J. Crawford, Patient burden and real-world management of chemotherapy-induced myelosuppression: results from an online survey of patients with solid tumors, Adv. Ther. 37 (2020) 3606–3618, https://doi.org/10.1007/s12325-020-01419-6.

[24] L.J. Havrilesky, M. Reiner, P.K. Morrow, H. Watson, J. Crawford, A review of relative dose intensity and survival in patients with metastatic solid tumors, Crit. Rev. Oncol. Hematol. 93 (2015) 203–210, https://doi.org/10.1016/j.critrevonc.2014.10.006.

[25] M. Aapro, Y. Beguin, C. Bokemeyer, M. Dicato, P. Gascón, J. Glaspy, A. Hofmann, H. Link, T. Littlewood, H. Ludwig, A. Österborg, P. Pronzato, V. Santini, D. Schrijvers, R. Stauder, K. Jordan, J. Herrstedt, Management of anaemia and iron deficiency in patients with cancer: ESMO clinical practice guidelines, Ann. Oncol. 29 (2018) iv96–iv110, https://doi.org/10.1093/annonc/mdx758, iv96-iv110.

[26] P.S. Becker, E.A. Griffiths, L.M. Alwan, K. Bachiashvili, A. Brown, R. Cool, P. Curtin, S. Dinner, I. Gojo, A. Hicks, A. Kallam, W.Z. Kidwai, D.D. Kloth, E. H. Kraut, D. Landsburg, G.H. Lyman, R. Miller, S. Mukherjee, S. Patel, L.E. Perez, A. Poust, R. Rampal, R. Rosovsky, V. Roy, H.S. Rugo, S. Shayani, S. Vasu, M. Wadleigh, K. Westbrook, P. Westervelt, J. Burns, J. Keller, L.A. Pluchino, NCCN guidelines insights: hematopoietic growth factors, version 1.2020, J. Natl. Compr. Canc. Netw 18 (2020) 12–22, https://doi.org/10.6004/jnccn.2020.0002.

[27] N.M. Kuderer, D.C. Dale, J. Crawford, G.H. Lyman, Impact of primary prophylaxis with granulocyte colony-stimulating factor on febrile neutropenia and mortality in adult cancer patients receiving chemotherapy: a systematic review, J. Clin. Oncol. 25 (2007) 3158–3167, https://doi.org/10.1200/jco.2006.08.8823.

[28] G. Mountzios, G. Aravantinos, Z. Alexopoulou, E. Timotheadou, F. Matsiakou, C. Christodoulou, K. Laschos, E. Galani, A. Koutras, D. Bafaloukos, H. Linardou, D. Pectasides, I. Varthalitis, P. Papakostas, H.P. Kalofonos, G. Fountzilas, Lessons from the past: long-term safety and survival outcomes of a prematurely terminated randomized controlled trial on prophylactic vs. hemoglobin-based administration of erythropoiesis-stimulating agents in patients with chemotherapy-induced anemia, Mol. Clin. Oncol. 4 (2016) 211–220, https://doi.org/10.3892/mco.2015.693.

[29] S.K. Frazier, J. Higgins, A. Bugajski, A.R. Jones, M.R. Brown, Adverse reactions to transfusion of blood products and best practices for prevention, Crit. Care Nurs. Clin. North Am. 29 (2017) 271–290, https://doi.org/10.1016/j.cnc.2017.04.002.

[30] C. Shao, J. He, S. Kachroo, F. Jin, Chemotherapy treatments, costs of care, and survival for patients diagnosed with small cell lung cancer: a SEER-Medicare study, Cancer Med. 8 (2019) 7613–7622, https://doi.org/10.1002/cam4.2626.

[31] T. Lu, X. Yang, Y. Huang, M. Zhao, M. Li, K. Ma, J. Yin, C. Zhan, Q. Wang, Trends in the incidence, treatment, and survival of patients with lung cancer in the last four decades, Cancer Manag. Res. 11 (2019) 943–953, https://doi.org/10.2147/cmar.S187317.

[32] J. He, C. Shao, S.L. Hui, Z. Zhang, J. Baker, P.R. Dexter, S. Kachroo, F. Jin, Survival, chemotherapy treatments, and health care utilization among patients with advanced small cell lung cancer: an observational study, Adv. Ther. 37 (2020) 552–565, https://doi.org/10.1007/s12325-019-01161-8.

[33] M.D. DiBonaventura, B. Shah-Manek, K. Higginbottom, J.R. Penrod, Y. Yuan, Adherence to recommended clinical guidelines in extensive disease small-cell lung cancer across the US, Europe, and Japan, Ther. Clin. Risk Manag. 15 (2019) 355–366, https://doi.org/10.2147/tcrm.S183216.

[34] J.L. Warren, C.N. Klabunde, D. Schrag, P.B. Bach, G.F. Riley, Overview of the SEER-Medicare data: content, research applications, and generalizability to the

United States elderly population, Med. Care 40 (2002) Iv-3-18, https://doi.org/10.1097/01.Mlr.0000020942.47004.03. Iv-3-18.
[35] L. Enewold, H. Parsons, L. Zhao, D. Bott, D.R. Rivera, M.J. Barrett, B.A. Virnig, J. L. Warren, Updated overview of the SEER-Medicare data: enhanced content and applications, J. Natl. Cancer Inst. Monogr. 2020 (2020) 3–13, https://doi.org/10.1093/jncimonographs/lgz029.
[36] K. Lang, L.J. McGarry, H. Huang, D. Dorer, E. Kaufman, K. Knopf, Mortality and vascular events among elderly patients with chronic myeloid leukemia: a retrospective analysis of linked SEER-Medicare data, Clin. Lymphoma Myeloma Leuk. 16 (2016) 275–285, https://doi.org/10.1016/j.clml.2016.01.006, e271.
[37] P. Schwab, E. MacLean, M. Chioda, K. Moll, M.J. Pasquale, T. Futch, NSCLC observations combining medical charts and administrative claims data, Mol. Cancer Ther. 14 (2015), https://doi.org/10.1158/1535-7163.TARG-15-B102. Abstract B102.
[38] S. Thomas, C. Chirila, M.B. Ritchey, Visualization of Patient Electronic Records to Support Exploratory Analysis and Variable Derivation of Categorical Data, Presented at the 25th Annual SouthEast SAS Users Group (SESUG), Cary, NC, 2017. November.
[39] R.S. Epstein, R.K. Weerasinghe, A.S. Parrish, J. Krenitsky, R.E. Sanborn, T. Salimi, Real-world burden of chemotherapy-induced myelosuppression in patients with small cell lung cancer: a retrospective analysis of electronic medical data from community cancer care providers, J. Med. Econ. 25 (2022) 108–118, https://doi.org/10.1080/13696998.2021.2020570.
[40] J. Goldschmidt, A. Monnette, P. Shi, H. Huang, M. Chioda, Real-world burden of myelosuppression among patients with extensive-stage small cell lung cancer treated in the community oncology setting, J. Manag. Care Spec. Pharm 27 (2021) S1–S119, https://doi.org/10.18553/jmcp.2021.27.10-b.s1. S1-S119.
[41] W. Meng, W. Ou, S. Chandwani, X. Chen, W. Black, Z. Cai, Temporal phenotyping by mining healthcare data to derive lines of therapy for cancer, J. Biomed. Inform. 100 (2019), 103335, https://doi.org/10.1016/j.jbi.2019.103335.
[42] OPTUM, Determining lines of therapy (LOT) in oncology in claims databases. https://cdn-aem.optum.com/content/dam/optum3/optum/en/resources/white-papers/wf520768_guidelines-for-determining-lines-of-therapy.pdf, 2018 (Accessed June 2021).
[43] M. Behera, C. Ragin, S. Kim, R.N. Pillai, Z. Chen, C.E. Steuer, N.F. Saba, C.P. Belani, F.R. Khuri, S.S. Ramalingam, T.K. Owonikoko, Trends, predictors, and impact of systemic chemotherapy in small cell lung cancer patients between 1985 and 2005, Cancer 122 (2016) 50–60, https://doi.org/10.1002/cncr.29674.
[44] C.M. Cramer-van der Welle, F. Schramel, A.S. van Leeuwen, H.J.M. Groen, E.M. W. van de Garde, Real-world treatment patterns and outcomes of patients with extensive disease small cell lung cancer, Eur. J. Cancer Care (Engl.) 29 (2020) e13250, https://doi.org/10.1111/ecc.13250.
[45] H.A. Powell, L.J. Tata, D.R. Baldwin, V.A. Potter, R.A. Stanley, A. Khakwani, R. B. Hubbard, Treatment decisions and survival for people with small-cell lung cancer, Br. J. Cancer 110 (2014) 908–915, https://doi.org/10.1038/bjc.2013.812.
[46] N. Murray, C. Grafton, A. Shah, K. Gelmon, E. Kostashuk, E. Brown, C. Coppin, A. Coldman, R. Page, Abbreviated treatment for elderly, infirm, or noncompliant patients with limited-stage small-cell lung cancer, J. Clin. Oncol. 16 (1998) 3323–3328, https://doi.org/10.1200/jco.1998.16.10.3323.
[47] M. Früh, D. De Ruysscher, S. Popat, L. Crinò, S. Peters, E. Felip, Small-cell lung cancer (SCLC): ESMO clinical practice guidelines for diagnosis, treatment and follow-up, Ann. Oncol. 24 (2013) vi99–105, https://doi.org/10.1093/annonc/mdt178. Suppl 6vi99-105.
[48] J.M. Weiss, T. Csoszi, M. Maglakelidze, R.J. Hoyer, J.T. Beck, M. Domine Gomez, A. Lowczak, R. Aljumaily, C.M. Rocha Lima, R.V. Boccia, W. Hanna, P. Nikolinakos, V.K. Chiu, T.K. Owonikoko, S.R. Schuster, M.A. Hussein, D. A. Richards, P. Sawrycki, I. Bulat, J.T. Hamm, L.L. Hart, S. Adler, J.M. Antal, A. Y. Lai, J.A. Sorrentino, Z. Yang, R.K. Malik, S.R. Morris, P.J. Roberts, K.H. Dragnev; , G1T28-02 Study Group, Myelopreservation with the CDK4/6 inhibitor trilaciclib in patients with small-cell lung cancer receiving first-line chemotherapy: a phase Ib/randomized phase II trial, Ann. Oncol. 30 (2019) 1613–1621, https://doi.org/10.1093/annonc/mdz278.
[49] D. Daniel, V. Kuchava, I. Bondarenko, O. Ivashchuk, S. Reddy, J. Jaal, I. Kudaba, L. Hart, A. Matitashvili, Y. Pritchett, S.R. Morris, J.A. Sorrentino, J.M. Antal, J. Goldschmidt, Trilaciclib prior to chemotherapy and atezolizumab in patients with newly diagnosed extensive-stage small cell lung cancer: a multicentre, randomised, double-blind, placebo-controlled phase II trial, Int. J. Cancer. 148 (2020) 2557–2570, https://doi.org/10.1002/ijc.33453.
[50] L.L. Hart, R. Ferrarotto, Z.G. Andric, J.T. Beck, J. Subramanian, D.Z. Radosavljevic, B. Zaric, W.T. Hanna, R. Aljumaily, T.K. Owonikoko, D. Verhoeven, J. Xiao, S. R. Morris, J.M. Antal, M.A. Hussein, Myelopreservation with trilaciclib in patients receiving topotecan for small cell lung cancer: results from a randomized, double-blind, placebo-controlled phase II study, Adv. Ther. 38 (2021) 350–365, https://doi.org/10.1007/s12325-020-01538-0.
[51] S.Y. Liou, J.M. Stephens, K.T. Carpiuc, W. Feng, M.F. Botteman, J.W. Hay, Economic burden of haematological adverse effects in cancer patients: a systematic review, Clin. Drug Investig. 27 (2007) 381–396, https://doi.org/10.2165/00044011-200727060-00002.
[52] N. Rashid, H.A. Koh, H.C. Baca, K.J. Lin, S.E. Malecha, A. Masaquel, Economic burden related to chemotherapy-related adverse events in patients with metastatic breast cancer in an integrated health care system, Breast Cancer (Dove Med. Press) 8 (2016) 173–181, https://doi.org/10.2147/bctt.S105618.
[53] J. Klastersky, J. de Naurois, K. Rolston, B. Rapoport, G. Maschmeyer, M. Aapro, J. Herrstedt, ESMO guidelines committee, management of febrile neutropaenia: ESMO clinical practice guidelines, Ann. Oncol. 27 (2016) v111–v118, https://doi.org/10.1093/annonc/mdw325, v111-v118.
[54] J. Bohlius, K. Bohlke, R. Castelli, B. Djulbegovic, M.B. Lustberg, M. Martino, G. Mountzios, N. Peswani, L. Porter, T.N. Tanaka, G. Trifirò, H. Yang, A. Lazo-Langner, Management of cancer-associated anemia with erythropoiesis-stimulating agents: ASCO/ASH clinical practice guideline update, J. Clin. Oncol. 37 (2019) 1336–1351, https://doi.org/10.1200/jco.18.02142.
[55] B.A. McGregor, G.A. Vidal, S.A. Shah, J.D. Mitchell, A.E. Hendifar, Remote oncology care: review of current technology and future directions, Cureus 12 (2020) e10156, https://doi.org/10.7759/cureus.10156.
[56] J. Weiss, J. Goldschmidt, Z. Andric, K.H. Dragnev, C. Gwaltney, K. Skaltsa, Y. Pritchett, J.M. Antal, S.R. Morris, D. Daniel, Effects of trilaciclib on chemotherapy-induced myelosuppression and patient-reported outcomes in patients with extensive-stage small cell lung cancer: pooled results from three phase II randomized, double-blind, placebo-controlled studies, Clin. Lung Cancer 22 (2021) 449–460, https://doi.org/10.1016/j.cllc.2021.03.010.
[57] D.E. Green, C.T. Rubin, Consequences of irradiation on bone and marrow phenotypes, and its relation to disruption of hematopoietic precursors, Bone 63 (2014) 87–94, https://doi.org/10.1016/j.bone.2014.02.018.
[58] P. Mauch, L. Constine, J. Greenberger, W. Knospe, J. Sullivan, J.L. Liesveld, H. J. Deeg, Hematopoietic stem cell compartment: acute and late effects of radiation therapy and chemotherapy, Int. J. Radiat. Oncol. Biol. Phys. 31 (1995) 1319–1339, https://doi.org/10.1016/0360-3016(94)00430-s.
[59] M.P. Deek, B. Benenati, S. Kim, T. Chen, I. Ahmed, W. Zou, J. Aisner, S.K. Jabbour, Thoracic vertebral body irradiation contributes to acute hematologic toxicity during chemoradiation therapy for non-small cell lung cancer, Int. J. Radiat. Oncol. Biol. Phys. 94 (2016) 147–154, https://doi.org/10.1016/j.ijrobp.2015.09.022.
[60] J.S. Lee, T. Umsawasdi, H.M. Dhingra, H.T. Barkley Jr., W.K. Murphy, Effects of brain irradiation and chemotherapy on myelosuppression in small-cell lung cancer, J. Clin. Oncol. 4 (1986) 1615–1619, https://doi.org/10.1200/jco.1986.4.11.1615.