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ORIGINAL RESEARCH

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

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ABSTRACT

Aims: Chemotherapy-induced myelosuppression, which commonly exhibits as neutropenia, anemia, or thrombocytopenia, represents a substantial burden for patients with cancer that affects health-related quality of life and increases healthcare resource utilization (HCRU). We evaluated the burden of myelosuppression among chemotherapy-treated patients with small cell lung cancer (SCLC) using real-world data from community cancer care providers in the Western United States.

Materials and methods: This was a retrospective, observational analysis of electronic medical records (EMRs) from Providence St. Joseph Health hospital-associated oncology clinics between January 2016 and December 2019. Patient demographics were assessed from the date of first SCLC diagnosis in adult patients with chemotherapy-induced grade ≥3 myelosuppression in first-line (1L) or second-line-and-beyond (2L+) treatment settings. Myelosuppressive adverse events (AEs), treatment patterns, and HCRU were assessed from the date of chemotherapy initiation (index date) until 12 months, date of the last visit, date of death, or study end, whichever occurred earliest.

Results: Of 347 eligible patients with SCLC who had received chemotherapy (mean age 66; 49% female), all had received at least 1L treatment, and 103 (29.7%) had a 2L + treatment recorded within the EMR during the study period. Of 338 evaluable patients with longitudinal laboratory data, 206 (60.9%) experienced grade ≥3 myelosuppressive AEs, most commonly neutropenia, anemia, and thrombocytopenia (44.9, 41.1, and 25.4 per 100 patients, respectively). Rates of granulocyte colony-stimulating factor use and red blood cell transfusions were 47.0 and 41.7 per 100 patients, respectively. There was a trend toward increasing the use of supportive care interventions and visits to inpatient and outpatient facilities in patients with myelosuppressive AEs in more than one cell lineage.

Conclusions: Chemotherapy-induced myelosuppression places a substantial real-world burden on patients with SCLC in the community cancer care setting. Innovations to protect bone marrow from chemotherapy-induced damage have the potential to reduce this burden.

PLAIN LANGUAGE SUMMARY

This study looked at the medical records of people with a particular type of lung cancer known as small cell lung cancer. When treated with chemotherapy, people with this cancer may develop a condition called myelosuppression. This causes people to have fewer blood cells, which can lead to tiredness, or increase the risk of infection or bleeding. The study looked at what types of chemotherapy people with small cell lung cancer were given, what the side effects of myelosuppression were, how often the side effects were reported, and what treatments were given to manage these side effects. The study also looked at whether people with side effects from myelosuppression needed more visits to the doctor or hospital. Around 3 out of 5 people in the study experienced serious side effects resulting in reduced numbers of white blood cells (which fight infection), red blood cells (which carry oxygen), or platelets (which help the blood to clot), and many needed drugs or blood transfusions to treat these side effects. On average, people with side effects from myelosuppression had more visits to healthcare facilities than those people without these side effects. The findings suggest that myelosuppression places a large burden on people with small cell lung cancer who are treated with chemotherapy.

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Introduction

Small cell lung cancer (SCLC) accounts for ~13% of all lung cancer cases in the United States, with most patients diagnosed at an advanced stage[1,2]. Prognosis is poor, with a 5-year survival rate of 6%, decreasing to 3% among patients with distant metastasis[1].

Unlike other solid tumor types, for which various hormonal and molecular targeted therapies have been developed, very few advances have been made in the treatment of SCLC, and chemotherapy remains a major component of treatment for both limited-stage (LS-) and extensive-stage (ES-) disease[3]. In the United States, systemic chemotherapy agents commonly used for the treatment of patients with SCLC include cisplatin and carboplatin (platinum agents), etoposide, irinotecan, paclitaxel, and topotecan[3,4]. Until recently, the first-line (1L) standard treatment for SCLC (including LS- and ES-SCLC) in the United States has been etoposide plus platinum, with a preference for carboplatin over cisplatin owing to its comparable efficacy and favorable toxicity profile[3,4]. In March 2019, combination therapy with the immune checkpoint inhibitor atezolizumab plus etoposide and carboplatin was approved by the United States Food and Drug Administration (FDA) for 1L treatment of ES-SCLC[5,6]. In March 2020, the combination of durvalumab plus etoposide and cisplatin or carboplatin was additionally approved for this indication[7]. These recently approved immunotherapies in combination with platinum plus etoposide chemotherapy regimens are recommended (category 1) for 1L systemic treatment of ES-SCLC in the National Comprehensive Cancer Network® Clinical Practice Guidelines in Oncology (NCCN Guidelines®)[3]. For the past 20 years, topotecan has been the only preferred regimen for subsequent systemic therapy[3]; however, in June 2020, lurbinectedin was approved by the FDA for second-line (2L) systemic treatment of SCLC after the failure of platinum-based therapy[8].

Although effective in prolonging survival, chemotherapy (and chemotherapy plus immunotherapy combination) regimens for SCLC present a treatment challenge due to the resulting damage to hematopoietic stem and progenitor cells in the bone marrow. In turn, this causes clinically significant, multilineage myelosuppression that manifests as a range of cytopenias (including anemia, neutropenia, and thrombocytopenia)[9]. The burden associated with chemotherapy-induced myelosuppression for patients with cancer is substantial, contributing to increased fatigue, time spent receiving additional treatment for myelosuppressive adverse events (AEs), and reduced health-related quality of life[10,11]. Additionally, hematologic toxicities may potentially lead to poor treatment outcomes related to dose reductions (e.g. shorter duration of response, earlier disease recurrence), treatment delays, and treatment discontinuation[12–14]. Serious and life-threatening complications, such as infections and bleeding complications from neutropenia and thrombocytopenia, respectively, can also occur[9,12,13]. Patients with SCLC are often older and have comorbid conditions, which may further impact their prognosis and tolerance of cancer treatments[15,16].

In addition to dose modifications, current supportive interventions recommended in clinical practice guidelines to manage myelosuppression include granulocyte colony-stimulating factor (G-CSF) agents and red blood cell (RBC) transfusions; erythropoiesis-stimulating agents (ESAs) are used less frequently[3,12,17]. Management strategies include primary prophylaxis, such as administration of G-CSF to patients at risk of developing neutropenia, or secondary prophylaxis to treat occurrences of myelosuppression[12,17–20].

Myelosuppression has been associated with higher healthcare resource utilization (HCRU), particularly hospitalizations, and higher healthcare-related costs[13,21–23]. However, most previous studies have included patients with cancers across multiple tumor sites (e.g. breast, lung, or colon) and there are limited data specific to SCLC, despite treatments for this diagnosis being particularly notable for their degree of myelotoxicity. In addition, previous studies used data from insurance claims or national inpatient databases. Although it is estimated that up to 65% of patients with cancer are treated at community cancer centers[24–26], there are very few data on the real-world burden of myelosuppression among chemotherapy-treated patients with SCLC in this setting. For these reasons, we conducted a study to describe the burden of myelosuppression in patients with SCLC using data from electronic medical records (EMRs) from a community cancer care provider network in the Western United States.

The study objectives were to describe the incidence of myelosuppressive AEs and associated treatment patterns among patients diagnosed with SCLC and to characterize HCRU associated with myelosuppression among patients receiving chemotherapy. A better understanding of the incidence of myelosuppression and associated treatment patterns and HCRU may help clinicians to better design and use treatment regimens that maximize patient benefit and minimize potential damage to healthy cells.

Methods

Data source

This retrospective observational study utilized EMR data from the Providence St. Joseph Health (PSJH primary EMR [Epic Systems, Inc.]) and the Providence Cancer Reporting Registry. PSJH is the third-largest non-profit health system in the United States, formed by the merger of St Joseph Health of Irvine, California, and Providence Health and Services of Renton, Washington in 2016[27]. The dataset was obtained from 40 oncology clinics associated with community hospitals across seven states in the United States. Data curation and analysis were performed by members of the PSJH Health Insights analytics group in Renton, Washington.

This study was approved by the PSJH institutional review board (IRB 2019000565). Only minimally required protected health information was accessed for this retrospective study, and study databases and analyses utilized anonymized data. As such, the IRB waived the requirement for informed consent. All investigators and research staff were trained in compliance and data-handling practices, and no protected health information is included in this publication.

Patient selection and study design

Adult patients with SCLC considered for the analysis were identified by ≥1 clinical encounter with a code for SCLC (International Classification of Diseases, Tenth Revision, Clinical Modification C34*, and International Classification of Diseases for Oncology histology between 8041 and 8045) between January 2016 and December 2019 in the PSJH primary EMR. Patients were required to have received chemotherapy in 1L or both 1L and 2L-and-beyond (2L+) treatment settings between January 2016 and December 2018. Patients with prior stem cell transplants or preexisting disorders of the bone marrow were excluded. The date of the first chemotherapy dose was considered the index date. Myelosuppressive AEs, treatment patterns, and HCRU were assessed for the follow-up period of 12 months from the index date, or until the date of the last visit, date of death, or the end of the study period (December 2019), whichever occurred earliest (Figure 1).

Study measures

The date of the first diagnosis of SCLC was used to assess patient demographics and other clinical characteristics. Patients' baseline characteristics and Charlson-defined[28] comorbidities were evaluated during a pre-index period of 24 months before the index date, or between study start (January 2016) and index, whichever was shorter. Patient baseline characteristics included age, sex, race, smoking history, Eastern Cooperative Oncology Group performance status, radiation treatment, and payer type. For the analysis of treatment patterns, percentages of patients receiving 1L and/or 2L + treatment were reported.

Myelosuppressive AEs were identified based on laboratory values from EMR data according to the Common Toxicity Criteria definition of grade 3 or above AEs[29]. Myelosuppressive AEs were defined as follows: anemia, hemoglobin <8.0 g/dL; neutropenia, absolute neutrophil count <1,000 mm^3; and thrombocytopenia, platelet count <50,000 mm^3. Patients could have experienced multiple AEs depending on whether their laboratory values fell within the defined parameters. Time to myelosuppressive AE was reported. Treatment of myelosuppressive AEs were evaluated in terms of transfusions (RBC or platelet), G-CSF administration, and ESA use. Both prophylactic (received before documented low absolute neutrophil count) and therapeutic (received after documented low absolute neutrophil count) administration of G-CSF were reported.

For the analysis of myelosuppressive AE–related HCRU, patients were stratified into four separate groups according to the number of grades ≥3 myelosuppressive AEs by lineage (i.e. neutropenia, anemia, and/or thrombocytopenia) that they experienced (i.e. no grade ≥3 AEs, grade ≥3 AE in one lineage, grade ≥3 AEs in two lineages, or grade ≥3 AEs across all three lineages). Patients who had more than one episode of the same lineage event were counted only once when reporting the percentage of patients with that type of AE. Healthcare resources assessed were outpatient visits (as recorded within the EMR), emergency department (ED) visits, inpatient visits (including inpatient service, and patients who were treated in the ED and then admitted for inpatient services), and admissions to an intensive care unit. Chemotherapy and supportive care regimens administered at PSJH were also reported.

Statistical analyses

Descriptive statistics were used to describe patient characteristics and outcomes. Continuous variables were summarized with means and standard deviations, and median and range values. Frequency counts and the percentage of patients within each category were reported for categorical variables. For the rates of myelosuppressive AEs, time to AE, and treatment of myelosuppressive AEs (transfusions, G-CSF administration, and ESA use), stratified analyses were conducted by the line of therapy (1L: AEs that occurred after initiation of 1L therapy and before 2L therapy start date; 2L: AEs that occurred after initiation of 2L therapy).

Results

Patient characteristics

A total of 347 patients diagnosed with SCLC who had received chemotherapy were eligible for the analysis. Patients' baseline demographic and clinical characteristics are shown in Table 1. The median (range) age of patients was 65 (35–93) years, 48.7% were female, and 88.8% were White. Almost two-thirds of patients (61.1%) presented with stage IV (ES) disease at diagnosis. Overall, 36.9% were reported as current smokers and 26.5% as past smokers; 6.1% were reported as having never smoked, and 30.5% as not

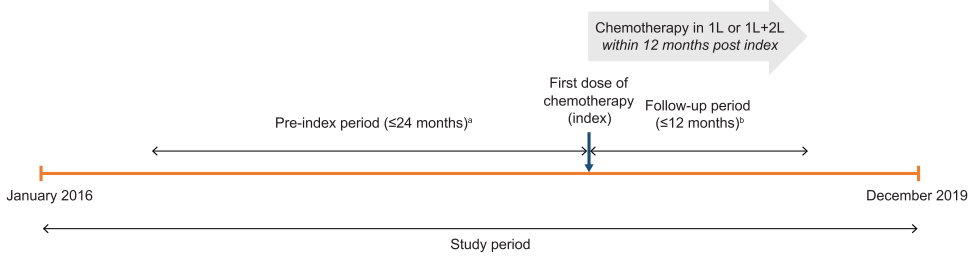

Figure 1. Study design. [a]The pre-index period was the period from study start (January 2016) to index, or the 24-month period prior to index, whichever was shorter. [b]Patients were followed for 12 months post-index date, or until death, loss to follow-up, or end of the study period (December 2019), whichever occurred sooner. 1L: first line; 2L: second line; SCLC: small cell lung cancer.

Table 1. Patient baseline demographic and clinical characteristics.

Characteristic	Patients ($N = 347$)
Age, years	
Mean (*SD*)	66 (9.0)
Median	65
Range	35–93
Sex, *n* (%)	
Female	169 (48.7)
Male	178 (51.3)
SCLC stage at diagnosis, *n* (%)	
Stage I	12 (3.5)
Stage II	19 (5.5)
Stage III	80 (23.1)
Stage IV	212 (61.1)
Stage not documented	64 (18.4)
ECOG performance status, *n* (%)[a]	
0	16 (4.6)
1	86 (24.8)
2	64 (18.4)
3	6 (1.7)
Not documented	175 (50.4)
Radiation, *n* (%)	
Radiation received	146 (42.1)
No radiation received	176 (50.7)
Unknown if radiation received	25 (7.2)
Race, *n* (%)	
White	308 (88.8)
Asian	8 (2.3)
African American	4 (1.2)
American Indian/Native Alaskan	3 (0.9)
Other	12 (3.5)
Unknown	12 (3.5)
Smoking status, *n* (%)	
Current smoker	128 (36.9)
Past smoker	92 (26.5)
Never smoked	21 (6.1)
Not asked	19 (5.5)
Not documented	87 (25.1)
Payer type, *n* (%)	
Medicare/Medicare HMO	201 (57.9)
Medicaid/Medicaid HMO	31 (8.9)
Commercial	42 (12.1)
Other government	14 (4.0)
Self-pay	14 (4.0)
Other	10 (2.9)
Not documented (historical data)	35 (10.1)

ECOG: Eastern Cooperative Oncology Group; HMO: health maintenance organization; SD: standard deviation.
[a]Performance status documented as Karnofsky was converted to ECOG.

documented or not asked. Among patients with documented Charlson comorbid conditions[28] ($n = 338$), the most prevalent conditions (present in >10% of patients) included chronic obstructive pulmonary disease (51.8%), diabetes (23.4%), and peripheral vascular disease (19.5%). At baseline, 42.1% of patients had received radiation therapy. During follow-up, 226 patients out of 338 patients with longitudinal laboratory data (66.9%) died.

Treatment patterns

Among study patients ($N = 347$), all had received at least 1L treatment, and 29.7% ($n = 103$) had a documented 2L + treatment recorded within the EMR during the study period. Over 70% of patients received platinum plus etoposide as 1L treatment (carboplatin plus etoposide: $n = 192$, 55.3%; cisplatin plus etoposide: $n = 67$, 19.3%). Overall, 7.5% ($n = 26$) of patients received an immune checkpoint inhibitor (atezolizumab [$n = 19$], nivolumab [$n = 4$], pembrolizumab [$n = 2$], or durvalumab [$n = 1$]) as part of their 1L treatment regimen (including treatments received as part of a clinical trial). The most common 2L + treatment regimens were topotecan ($n = 21$ of 103, 20.4%), combination therapy with ipilimumab plus nivolumab or pembrolizumab ($n = 20$ of 103, 19.4%), carboplatin (alone or in combination with irinotecan or etoposide; $n = 15$ of 103, 14.6%), and paclitaxel ($n = 11$ of 103, 10.7%). Immune checkpoint inhibitors were prescribed sparingly by PSJH clinicians in this study since the study cut-off date was December 2019 and FDA approvals for the use of these treatments in 1L were only granted in 2019 and 2020.

Myelosuppressive AEs and treatments

Among evaluable patients with longitudinal laboratory data ($n = 338$), 206 (60.9%) had at least one grade ≥3 myelosuppressive AE during the follow-up. Grade ≥3 neutropenia (44.9 events per 100 patients) and anemia (41.1 events per 100 patients) were the two most frequently observed AEs, followed by grade ≥3 thrombocytopenia (25.4 events per 100 patients; Table 2). Similar results were observed in the analysis by the line of therapy. Rates of grade ≥3 myelosuppressive AEs (events per 100 patients) were 33.4 during 1L treatment (24.5 during 2L treatment) for neutropenia, 29.9 (21.6) for anemia, and 18.3 (15.7) for thrombocytopenia. Baseline demography and clinical presentation did not appear to predispose patients to have one or more types of grade ≥3 myelosuppressive AE (neutropenia, anemia, and/or thrombocytopenia; Table 3).

The median number of days from 1L therapy to myelosuppressive AE was shortest for thrombocytopenia (15 days) and neutropenia (19 days), and longest for anemia (41 days) (Figure 2). A similar pattern was observed for the median number of days from 2L + therapy to myelosuppressive AEs, with time to thrombocytopenia being the shortest (9 days) and time to anemia the longest (75 days).

The most frequently used treatment for myelosuppressive AEs across all patients was G-CSF, with an incidence of 47.0 per 100 patients (1.7 prophylactic and 45.6 therapeutic; Table 2). The rate of G-CSF use during 1L (40.5 per 100 patients; 1.7 prophylactic and 40.2 therapeutic) was higher than during 2L (17.6 per 100 patients; 0 prophylactic and 17.6 therapeutic). RBC transfusion was the second-most frequently used treatment, with an incidence of 41.7 per 100 patients (1L: 31.4; 2L: 41.2). The incidence of platelet transfusion was 13.3 per 100 patients (1L: 9.2; 2L: 11.8). The use of ESAs was low, at 2.0 per 100 patients (1L: 2.0; 2L: 1.9). There was a trend toward increased use of supportive care interventions among patients with AEs in more than one lineage (Table 4). For example, 25% of patients with no myelosuppressive AEs received G-CSF, *vs.* 54, 66, and 67% of patients with AEs across one, two, and three lineages, respectively.

HCRU

Percentages of patients with inpatient, outpatient, ED, and intensive-care-unit visits and numbers of each type of visit in the 12 months following chemotherapy initiation in patients

Table 2. Grade ≥3 myelosuppressive AEs and treatments.

	Events by LOT[a,b]		
	All LOT ($n = 338$ patients)	1L[c] ($n = 338$ patients)	2L[d] ($n = 102$ patients)
Grade ≥3 myelosuppressive AEs, *n* (rate per 100 patients)			
Neutropenia[e]	152 (44.9)	113 (33.4)	25 (24.5)
Anemia[f]	139 (41.1)	101 (29.9)	22 (21.6)
Thrombocytopenia[g]	86 (25.4)	62 (18.3)	16 (15.7)
Transfusions, *n* (rate per 100 patients)			
RBC transfusion	141 (41.7)	106 (31.4)	42 (41.2)
Platelet transfusion	45 (13.3)	31 (9.2)	12 (11.8)
Hematopoietic treatments, *n* (rate per 100 patients)			
G-CSF	159 (47.0)	137 (40.5)	18 (17.6)
Prophylactic	6 (1.7)	6 (1.7)	0 (0)
Therapeutic	154 (45.6)	136 (40.2)	18 (17.6)
ESA	7 (2.0)	7 (2.0)	2 (1.9)

1L: first line; 2L: second line; AE: adverse event; ESA: erythropoiesis-stimulating agent; G-CSF: granulocyte colony-stimulating factor; LOT: line of therapy; RBC: red blood cell.
[a]Evaluable patients with longitudinal laboratory data.
[b]Patients are included in multiple event categories if each laboratory value falls within the defined parameters.
[c]Myelosuppressive AEs that occurred after 1L therapy start date and before 2L therapy start date.
[d]Myelosuppressive AEs that occurred after the 2L therapy start date.
[e]Neutropenia: $<1{,}000\ mm^3$.
[f]Anemia: hemoglobin <8.0 g/dL.
[g]Thrombocytopenia: $<50{,}000\ mm^3$.

Table 3. Baseline characteristics among patients with no grade ≥3 myelosuppressive AEs and in patients with grade ≥3 myelosuppressive AEs in one, two, or three lineages.

Characteristic	Patients with no AEs[a] ($n = 132$)	AE in one lineage[a] ($n = 90$)	AEs in two lineages[a] ($n = 61$)	AEs in all three lineages[a] ($n = 55$)
Mean age, years	68.7	66.1	66.6	68.0
Female, *n* (%)	61 (46.2)	44 (48.9)	36 (59.0)	25 (45.5)
SCLC stage at diagnosis, *n* (%)				
Stage I	7 (5.3)	4 (4.4)	0	1 (1.8)
Stage II	5 (3.8)	5 (5.6)	6 (9.8)	3 (5.5)
Stage III	28 (21.2)	20 (22.2)	17 (27.9)	15 (27.3)
Stage IV	83 (62.9)	57 (63.3)	38 (62.3)	34 (61.8)
Not documented	9 (6.8)	4 (4.4)	0	2 (3.6)
ECOG performance status, *n* (%)[b]				
0	7 (5.3)	2 (2.2)	0	6 (10.9)
1	20 (15.2)	31 (34.4)	17 (27.9)	18 (32.7)
2	24 (18.2)	20 (22.2)	10 (16.4)	10 (18.2)
3	3 (2.3)	1 (1.1)	2 (3.3)	0
Not documented	78 (59.1)	36 (40.0)	32 (52.5)	21 (38.2)
Radiation received, *n* (%)	50 (37.9)	39 (43.3)	30 (49.2)	26 (47.3)
Race, *n* (%)				
White	119 (90.2)	82 (91.1)	56 (91.8)	46 (83.6)
Asian	2 (1.5)	3 (3.3)	1 (1.6)	2 (3.6)
African American	2 (1.5)	0	1 (1.6)	1 (1.8)
American Indian/Native Alaskan	3 (2.3)	0	0	0
Other	5 (3.8)	3 (3.3)	1 (1.6)	3 (5.5)
Unknown	1 (0.8)	2 (2.2)	2 (3.3)	3 (5.5)
Smoking status, *n* (%)				
Current smoker	46 (34.8)	33 (36.7)	22 (36.1)	26 (47.3)
Past smoker	33 (25.0)	26 (28.9)	19 (31.1)	13 (23.6)
Never smoked	8 (6.1)	6 (6.7)	2 (3.3)	4 (7.3)
Not asked	5 (3.8)	8 (8.9)	4 (6.6)	2 (3.6)
Not documented	40 (30.3)	17 (18.9)	14 (23.0)	10 (18.2)
Payer type, *n* (%)				
Medicare/Medicare HMO	82 (62.1)	50 (55.6)	34 (55.7)	32 (58.2)
Medicaid/Medicaid HMO	10 (7.6)	9 (10.0)	6 (9.8)	5 (9.1)
Commercial	0	3 (3.3)	1 (1.6)	1 (1.8)
Other government	2 (1.5)	4 (4.4)	5 (8.2)	3 (5.5)
Self-pay	4 (3.0)	6 (6.7)	2 (3.3)	1 (1.8)
Other	22 (16.7)	11 (12.2)	7 (11.5)	7 (12.7)
Not documented (historical data)	12 (9.1)	7 (7.8)	6 (9.8)	6 (10.9)

ECOG: Eastern Cooperative Oncology Group; HMO: health maintenance organization; SD: standard deviation.
[a]Grade 1/2 myelosuppressive AEs were not included in the analysis. Patients reported as having no grade ≥3 AEs or grade ≥3 AEs in a particular lineage (e.g. neutropenia only) may also have had lower-grade AEs affecting other blood cell lineages.
[b]Performance status documented as Karnofsky was converted to ECOG.

with grade ≥3 myelosuppressive AEs in none, one, two, or three lineages are shown in Table 5. Among patients with SCLC who had received chemotherapy and were included in the analysis ($n = 338$), there was a trend toward increasing resource use with multilineage myelosuppression. The hospitalization rate among patients with no myelosuppressive AEs,

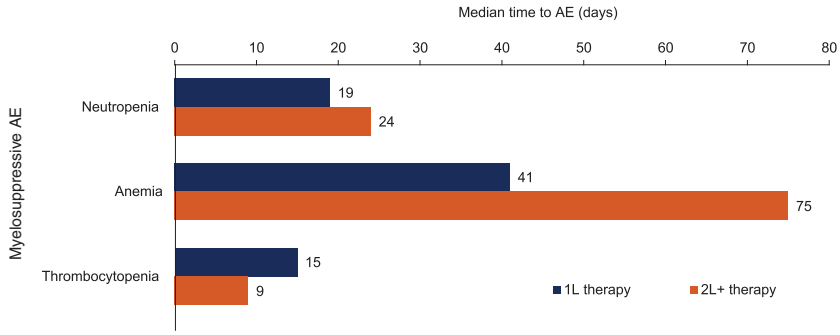

Figure 2. Median time from chemotherapy/immunotherapy to myelosuppressive AEs ($N = 338$). 1L: first-line; 2L+: second-line and beyond; AE: adverse event.

Table 4. Supportive care treatments among patients with no grade ≥3 myelosuppressive AEs and in patients with grade ≥3 myelosuppressive AEs in one, two, or three lineages.

Myelosuppressive AE category[a]	Patients, *n*	Patients with each type of supportive treatment, %			
		G-CSF	ESA	RBC transfusion	Platelet transfusion
No myelosuppressive AEs	132	25	1	11	0
Grade ≥3 AE in one lineage	90	54	1	37	7
Neutropenia only	46	59	0	11	2
Anemia only	33	45	3	76	12
Thrombocytopenia only	11	64	0	27	9
Grade ≥3 AEs in two lineages	61	66	3	77	20
Neutropenia and anemia	41	68	2	80	15
Neutropenia and thrombocytopenia	10	70	0	40	20
Anemia and thrombocytopenia	10	50	10	100	40
Grade ≥3 AEs in all three lineages (neutropenia, anemia, and thrombocytopenia)	55	67	5	85	49
Total population	338	47	2	42	13

AE: adverse event; ESA: erythropoiesis-stimulating agent; G-CSF: granulocyte colony-stimulating factor; RBC: red blood cell.
[a]Grade 1/2 myelosuppressive AEs were not included in the analysis. Patients reported as having no grade ≥3 AEs or grade ≥3 AEs in a particular lineage (e.g. neutropenia only) may also have had lower-grade AEs affecting other blood cell lineages.

Table 5. Healthcare resource utilization among SCLC patients within 12 months of chemotherapy initiation.

Myelosuppressive AE category[a]	Patients, *n*	Patients with each type of visit, %				Mean visits per patient			
		IP visits[b]	OP visits[c]	ED visits	ICU admissions	IP visits[b]	OP visits[c]	ED visits	ICU admissions
No myelosuppressive AEs	132	60.6	69.7	26.5	3.8	1.1	14.3	0.53	0.08
Grade ≥3 AE in one lineage	90	63.3	81.1	45.6	20.0	1.5	23.4	0.81	0.23
Neutropenia only	46	54.3	89.1	45.7	8.7	1.1	31.5	0.87	0.15
Anemia only	33	72.7	69.7	42.4	24.2	1.9	14.7	0.71	0.32
Thrombocytopenia only	11	72.7	81.8	54.5	27.3	2.2	14.1	0.82	0.27
Grade ≥3 AEs in two lineages	61	85.2	85.2	49.2	34.4	2.1	35.5	1.1	0.42
Neutropenia and anemia	41	85.4	87.8	46.3	34.1	2.0	27.8	1.5	0.45
Neutropenia and thrombocytopenia	10	80.0	90.0	50.0	30.0	2.1	28.0	0.70	0.30
Anemia and thrombocytopenia	10	90.0	70.0	60.0	40.0	2.4	8.6	1.2	0.40
Grade ≥3 AEs in all three lineages (neutropenia, anemia, and thrombocytopenia)	55	85.5	80.0	56.4	25.5	2.3	35.5	1.2	0.26
Total population	338	69.8	77.2	41.7	18.6	1.6	22.1	0.81	0.21

AE: adverse event; ED: emergency department; ICU: intensive care unit; IP: inpatient; OP: outpatient; SCLC: small cell lung cancer.
[a]Grade 1/2 myelosuppressive AEs were not included in the analysis. Patients reported as having no grade ≥3 AEs or grade ≥3 AEs in a particular lineage (e.g. neutropenia only) may also have had lower-grade AEs affecting other blood cell lineages.
[b]Includes IP and ED to IP visits. ED to IP includes patients who were treated in the ED and then admitted to the same or a different hospital for IP services.
[c]OP refers to a hospital-based outpatient department setting. Multiple OP visits on the same day are counted as a single visit; OP visits also include imaging encounters.

for example, was 60.6%, *vs.* 63.3, 85.2, and 85.5% for patients with myelosuppressive AEs in one, two, and three lineages, respectively (Table 5).

Subgroup analysis of myelosuppressive AEs

The number of patients with grade ≥3 myelosuppressive AEs was stratified by G-CSF use (prophylactic and therapeutic), disease stage, prior radiation, and index chemotherapy (Table 6). Among patients receiving G-CSF, 59.6% had neutropenia, 52.5% had anemia, and 36.9% had thrombocytopenia. Among the most common index chemotherapy regimens, etoposide plus cisplatin was associated with the highest rates of neutropenia and anemia.

Discussion

This real-world retrospective EMR study evaluated the burden of myelosuppression among patients diagnosed with SCLC in US clinical practice. To our knowledge, this was the first study to evaluate multilineage myelosuppression in

Table 6. Incidence of grade ≥3 myelosuppressive AEs, stratified by G-CSF use, disease stage, prior radiation, and index chemotherapy.

	Grade ≥3 neutropenia, *n* (%)[a]	Grade ≥3 anemia, *n* (%)[a]	Grade ≥3 thrombocytopenia, *n* (%)[a]
Overall (*n* = 338)	152 (44.9)	139 (41.1)	86 (25.4)
By G-CSF use			
With G-CSF (*n* = 141)	84 (59.6)	74 (52.5)	52 (36.9)
Without G-CSF (*n* = 197)	68 (34.5)	65 (33.0)	34 (17.3)
By prophylactic G-CSF use			
With prophylactic G-CSF (*n* = 19)	11 (57.9)	12 (63.2)	6 (31.6)
Without prophylactic G-CSF (*n* = 319)	141 (44.2)	127 (39.8)	80 (25.1)
By therapeutic G-CSF use			
With therapeutic G-CSF (*n* = 122)	73 (59.8)	62 (50.8)	46 (37.7)
Without therapeutic G-CSF (*n* = 216)	79 (36.6)	77 (35.6)	40 (18.5)
By stage			
Stage I (*n* = 12)	2 (16.7)	3 (25.0)	2 (16.7)
Stage II (*n* = 19)	11 (57.9)	9 (47.4)	6 (31.6)
Stage III (*n* = 80)	43 (53.8)	36 (45.0)	20 (25.0)
Stage IV (*n* = 212)	92 (43.4)	87 (41.0)	56 (26.4)
By radiation			
With radiation (*n* = 145)	74 (51.0)	64 (44.1)	39 (26.9)
Without radiation/unknown radiation (*n* = 193)	78 (40.4)	75 (38.9)	47 (24.4)
By index regimen			
Carboplatin plus etoposide (*n* = 192)	86 (44.8)	77 (40.1)	54 (28.1)
Cisplatin plus etoposide (*n* = 67)	39 (58.2)	32 (47.8)	14 (20.9)
Atezolizumab plus platinum and etoposide, or atezolizumab alone (*n* = 15)	6 (40.0)	6 (40.0)	4 (26.7)

AE: adverse event; G-CSF: granulocyte colony-stimulating factor.
[a]Percentages calculated based on denominators indicated in the first column.

SCLC in the real-world community cancer care setting using EMR data, with prior studies focusing on patients with cancers across different tumor sites (e.g. breast, lung, or colon) and using other data sources (e.g. insurance claims or national inpatient databases). Our findings revealed that almost two-thirds of patients experienced grade ≥3 myelosuppressive AEs, most commonly neutropenia and anemia, during the study period. Rates of events were similar between patients receiving 2L + therapy and those receiving 1L, with the most common event being neutropenia in both patient groups. Baseline characteristics were consistent across patient subgroups with no grade ≥3 myelosuppressive AEs and grade ≥3 myelosuppressive AEs in one, two, or three lineages, and there was no clear pattern in AE rates according to disease stage, suggesting that multilineage myelosuppression should be of equal concern for patients with LS- and ES-SCLC being treated with chemotherapy.

Although published incidence rates of myelosuppression in patients with SCLC vary owing to factors, such as patient population characteristics, study design, treatment regimens, AE definitions, and methods of reporting (e.g. event rate *vs.* percentage of patients), the findings in this study are generally in line with those of the refereed literature. Neutropenia was the most common grade ≥3 chemotherapy-induced cytopenia observed in this study, experienced at a rate of 44.9 events per 100 patients across all lines of therapy. In clinical trials of treatments for ES-SCLC, the percentage of patients with grade 3/4 neutropenia has ranged from 22.7% for atezolizumab plus etoposide and carboplatin[5], and 24.5%[5], and 33.0%[30] for etoposide plus carboplatin, to higher rates of 44.0–86.5%[31–34] for etoposide plus cisplatin. An observational study by Igawa et al. reported a rate of chemotherapy-induced neutropenia of 40.0% with etoposide plus carboplatin in their patient population[35], which is broadly comparable with the current study.

As the second-most common grade ≥3 myelosuppressive AE, chemotherapy-induced anemia was observed at a rate of 41.1 events per 100 patients in this study. Several clinical trials of therapies for ES-SCLC (e.g. atezolizumab plus etoposide and carboplatin, etoposide plus carboplatin, and etoposide plus cisplatin) have reported rates of grade ≥3 anemia of <20%[5,31,32,34,36]. This apparent disparity may be due to differences in study methodologies and differences in patient populations between clinical trials and real-world practice; for example, the inclusion of patients who would typically be excluded from Phase 3 drug trials, methodological differences due to heterogeneity in AE definitions and severity grading[10], or the utilization of laboratory data to evaluate grade ≥3 myelosuppressive AEs rather than investigator assessment. Observational studies have generally observed higher prevalence rates of anemia than in clinical trials. For example, in the 2001 European Cancer Anemia Survey[37]—a large, prospective, observational, epidemiologic survey that assessed the prevalence, incidence, and treatment of anemia in 24 countries—the prevalence of anemia (defined as hemoglobin <12 g/dL) was reported as 83% among patients with lung cancer who were receiving chemotherapy; however, that study included anemia that is less severe than grade ≥3, and the prevalence of severe anemia is likely to be lower.

It is notable that 42.1% of patients in the current study had received radiation therapy since previous studies have shown that radiotherapy is associated with bone marrow suppression and contributes to severe myelosuppression in patients with SCLC receiving chemotherapy[38,39]. Subgroup analysis indicated that patients who received radiation had higher rates of grade ≥3 myelosuppressive AEs (particularly neutropenia and anemia) compared with those without/with unknown radiation, suggesting that prior receipt of radiation therapy may have contributed to some of the myelosuppressive AEs reported in this study.

High usage of supportive therapies to manage myelosuppression was reported in this study, including 41.7 RBC transfusions and 47.0 G-CSF regimens per 100 patients. Notably, patients who received G-CSF also had high rates of grade ≥3 anemia and thrombocytopenia, highlighting the large multilineage burden of myelosuppression among these patients. The trend toward increasing use of supportive care interventions, as well as increasing numbers and frequencies of visits to healthcare facilities as the number of myelosuppressive AEs in each lineage increased underscores the substantial real-world burden that multilineage myelosuppression places on the healthcare system.

Although not directly comparable due to differences in methodology and reporting, the rate of RBC transfusion appears high in relation to the proportion of patients with RBC transfusions reported in some other studies. For example, in a recent clinical trial among patients with ES-SCLC, 24% received RBC transfusions[40]. Similarly, in the European Cancer Anemia Survey observational study[37], only 18% of anemic patients with lung cancer undergoing chemotherapy received RBC transfusions, and 53% received no treatment for anemia. Importantly, the high rate of transfusions observed in the current real-world study would have a significant impact on the patient burden, given the time and multiple visits required to complete blood testing and the RBC transfusion procedure[11].

United States guidelines recommend primary G-CSF prophylaxis for chemotherapy regimens that carry a >20% risk of FN, while patient-specific risk factors (e.g. age >65 years, comorbidities) should be considered for those receiving intermediate (10–20%) risk regimens[41]. Prophylactic use of G-CSF was observed in 1.7% of patients in this study, which is lower than what might be expected based on the guidelines for primary G-CSF prophylaxis, given the patient population. In this study, most patients received either carboplatin or cisplatin in combination with etoposide as first-line treatment. Almost a third (29.7%) of patients received second-line treatment, with topotecan being the most common (given to ∼20% of patients who received a second-line treatment). Among these treatments, only topotecan is considered to present a high (>20%) risk for FN[41]. The median age in this study was 65 years, indicating that only half of the patients might be considered to have a supervening risk factor for the development of FN with intermediate-risk chemotherapies based on age. It is also possible that what would be considered as secondary prophylaxis according to guidelines (administration of G-CSF before second and subsequent chemotherapy cycles in patients with a history of febrile or dose-limiting neutropenia)[41] was classed as therapeutic G-SCF in this analysis, contributing to the lower-than-expected use of prophylactic G-CSF. Of note, some cost-effectiveness models do not support G-CSF use for primary or secondary prophylaxis for patients with SCLC, which may be prohibitive to prescribing G-CSF in some settings[42–44]. Indeed, G-CSF utilization has been shown to vary in clinical practice, with trends suggesting potential underutilization in high-risk patients and overutilization in lower-risk patients[45]. This divergence in the use of G-CSF could be problematic, with underutilization resulting in adverse outcomes, and overuse of ineffective/unnecessary treatment having a substantial impact on costs and resource use[46]. On the other hand, the MONITOR-GCSF study in patients receiving biosimilar filgrastim identified patterns of G-CSF prophylaxis above guideline recommendations and noted that this "over-prophylaxis" was associated with better outcomes among patients with chemotherapy-induced neutropenia and FN[18,47,48].

The risk of myelosuppression in patients receiving chemotherapy must be considered alongside the potential benefits of cytotoxic treatment for SCLC. If left untreated, ES-SCLC is usually fatal within 2–5 months[49]. By comparison, median overall survival with 1L platinum plus etoposide is ∼8–10 months, and this further increases to ∼12–13 months with the addition of an immune checkpoint inhibitor (atezolizumab or durvalumab)[5,30–34,50,51]. Survival times with 2L topotecan treatment in patients with relapsed SCLC range from ∼6 to 8 months, with one study reporting a survival improvement of ∼3 months with the addition of oral topotecan to best supportive care[52–54]. In addition to prolonging survival, chemotherapy treatment may also provide symptom control, thereby improving quality of life[52,55]. As such, the clinical benefit of cytotoxic chemotherapy may outweigh the risk of toxicity for many patients with SCLC. Nonetheless, the potential impact of myelosuppression on treatment outcomes must also be deliberated, since hematologic AEs commonly lead to dose delays, dose reductions, and reductions in relative dose intensity, the latter of which is significantly associated with decreased survival outcomes and quality of life in certain cancer types[12–14,56]. Furthermore, data suggest that patients with lung cancer and febrile neutropenia have higher mortality than those without febrile neutropenia (incidence per 100 person-months: 44.3 *vs.* 29.6, respectively)[57].

Results from this study highlight that myelosuppression places a significant real-world burden on patients with SCLC and the healthcare system. The burden of myelosuppression shown in this study supports the need for innovation in a discipline where current mitigation approaches (G-CSF and ESA) were first approved over 30 years ago. Fortuitously, several newer agents are under clinical investigation for the treatment of single- or multilineage myelosuppression in various cancer types, including plinabulin (Phase 3), ALRN-6924 (Phase 1/2), roxadustat (Phase 2), romiplostim (Phase 3), and avatrombopag (Phase 3)[58]. Of course, further assessment of the benefit: risk ratio of these investigational agents in controlled clinical evaluations is needed before any conclusions can be drawn regarding their value in the prevention/mitigation of chemotherapy-induced myelosuppression. In March 2021, trilaciclib, an intravenous cyclin-dependent kinase 4/6 inhibitor, was approved by the US FDA to decrease the incidence of chemotherapy-induced myelosuppression in patients with ES-SCLC when administered before a platinum/etoposide- or topotecan-containing regimen[59]. In three randomized, double-blind, placebo-controlled Phase 2 trials, the addition of trilaciclib before chemotherapy resulted in clinically meaningful reductions in multilineage myelosuppression, a reduced need for supportive care interventions, and dose reductions, and an improved safety profile[40,60,61].

Ultimately, it is hoped that these newer approaches may help to overcome some of the limitations of G-CSF and ESAs.

A key strength of this study is that grade ≥3 myelosuppressive AEs were reported based on laboratory values rather than relying on physician reports in medical charts or claims data, therefore increasing the reliability of the dataset compared with other commonly utilized real-world data sources. The dataset also reflects a broad oncology setting from multiple hospital-based oncology clinics across seven states and thus is likely to provide a good representation of the US SCLC patient population. Although the current analysis was of a static dataset from a defined period (January 2016 to December 2019), the dynamic nature of real-world data sources, such as EMRs, which can be used to collect data almost continuously, is advantageous given that disease populations, clinical practice patterns, and healthcare systems are continually evolving. The use of EMRs for dynamic evaluation of a large variety and volume of clinical data may also facilitate the prediction of future healthcare trends, including in the burden of myelosuppression and its management.

This study possesses some limitations, yet it also spotlights important areas of future research. Our analysis focused on grade ≥3 myelosuppressive AEs only; however, patients reported as having no (grade ≥3) myelosuppressive AEs or myelosuppressive AEs in a particular lineage (e.g. neutropenia only) may have also experienced grade 1 or 2 AEs in other blood cell lineages. This is notable as lower-grade AEs may also require supportive care interventions, such as transfusions in some cases. Some outpatient infusions and transfusions may not have been captured if they were conducted in clinics not included in this analysis or not recorded in the EMR. Therefore, possibly, HCRU associated with myelosuppression may have been underestimated slightly in this study. Of interest for further study would be the rates of myelosuppressive events associated with the constellation of chemotherapy regimens that are preferred or acknowledged in published clinical guidelines. Lastly, a follow-on study that examines myelosuppressive AEs in ES-SCLC specifically would be especially useful. The NCCN Guidelines® now recommend that the preferred regimen for primary treatment of ES-SCLC includes a checkpoint inhibitor (atezolizumab or durvalumab) in combination with etoposide and platinum chemotherapy for 4–6 treatment cycles[3]. Considering nearly two-thirds of patients with SCLC have the extensive-stage disease at diagnosis[2], the findings of the present study in SCLC should provide clinicians with important insights regarding preventing and managing myelosuppressive AEs in patients with ES-SCLC.

Conclusions

In this real-world study, a large and meaningful proportion of patients with SCLC experienced grade ≥3 hematologic toxicity, which was associated with a substantial increase in HCRU. Multilineage myelosuppression places an ever greater real-world burden on patients and the healthcare system in a community cancer care setting. Innovative or improved management strategies, which may include trilaciclib and other novel agents for the treatment of one or more cytopenias, have the potential to address this burden.

Transparency

Declaration of funding

This study was funded by G1 Therapeutics, Inc. The study sponsor provided support in the form of salary for TS at the time of study and consultancy fees to RSE, RKW, ASP, and JK, and was involved in the study design, collection, analysis, and interpretation of data, writing of the report, and the decision to submit the report for publication. Epstein Health LLC. and Providence Health & Services provided support in the form of salaries for RSE and JK, and RKW and ASP, respectively, but did not have any additional role in the study design, data collection, and analysis, decision to publish, or preparation of the manuscript.

Declaration of financial/other relationships

RE is an employee of Epstein Health, LLC and has received research funding and consultancy fees from G1 Therapeutics, Inc. Outside of the submitted work, RE is a board member for Fate Therapeutics, Illumina, and Veracyte, and has received consultancy fees from Halozyme, Intracellular Therapies, Merck, Otsuka, Radius Health, and Taiho Oncology. RKW is an employee of Providence Health & Services, and has received consultancy fees from G1 Therapeutics, Inc. ASP is an employee of Providence Health & Services, and has received consultancy fees from G1 Therapeutics, Inc. Outside of the submitted work, ASP owns stock in IQVIA. JK is an employee of Epstein Health, LLC and has received consultancy fees from G1 Therapeutics, Inc. Outside of the submitted work, JK owns stock in Cigna, Express Scripts, and Medco Health Solutions. Outside of the submitted work, RS has received honoraria from Amgen and AstraZeneca, consultancy fees from Amgen, AstraZeneca, AbbVie, Ariad, Celldex, EMD Serono, Genentech-Roche, Peregrine Pharmaceuticals, Seattle Genetics, and Takeda, expenses from Five Prime Therapeutics and Janssen Oncology, and institutional research grants from Bristol-Myers Squibb, MedImmune, and Merck. TS was an employee of G1 Therapeutics, Inc., at the time of study completion, and is currently a paid employee of Taiho Oncology, Inc.

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Authors contributions

All authors were involved in the study conception and design and/or analysis and interpretation of the data, drafting the paper and/or revising it critically for intellectual content, approved the final version to be published, and agree to be accountable for all aspects of the work.

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Data availability statement

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

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