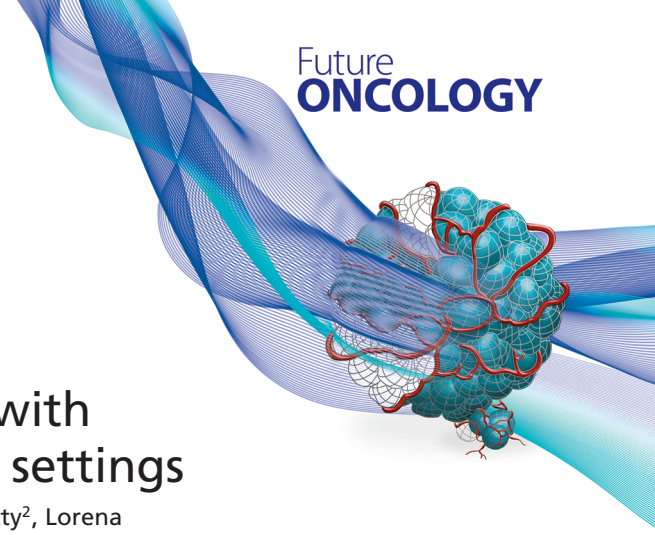
Research Article

For reprint orders, please contact: reprints@futuremedicine.com

Future ONCOLOGY



Burden of chemotherapy-induced myelosuppression among patients with ES-SCLC in US community oncology settings

Jerome Goldschmidt*[,1], Alisha Monnette[2], Ping Shi[2], Divea Venkatasetty[2], Lorena Lopez-Gonzalez[3] & Huan Huang[3]

[1]Blue Ridge Cancer Centers/The US Oncology Network, Blacksburg, VA, USA

[2]Ontada, Woodlands, TX, USA

[3]G1 Therapeutics®, Inc., Research Triangle Park, NC, USA

*Author for correspondence: Tel.: (540) 381-5291; jerome.goldschmidt@usoncology.com

Aim: To describe burden of chemotherapy-induced myelosuppression among chemotherapy-treated patients with extensive-stage small cell lung cancer (ES-SCLC). **Materials & methods:** Occurrence of grade ≥3 myelosuppressive hematological adverse events (HAEs), treatment patterns and healthcare resource utilization (HCRU) after chemotherapy initiation were evaluated using data from The US Oncology Network and Non-network clinics (1/1/2015–12/31/2020). **Results:** Among patients with laboratory values (Network: N = 1,374/1,574; Non-network: N = 661/959), over half-experienced grade ≥3 HAEs after chemotherapy initiation (Network = 56.6%; Non-network = 64.1%), and approximately one-third had grade ≥3 HAEs in at least two lineages (Network = 33.0%; Non-network = 31.3%). Patients with grade ≥3 HAEs had greater dose reductions, treatment delays and HCRU than those without. **Conclusion:** Myelosuppression is a burden to patients with ES-SCLC treated with chemotherapy and the healthcare system.

Plain language summary: Our objective was to describe the burden of myelosuppression, a side effect of chemotherapy that results from damage to blood-forming cells in the bone marrow, among patients with extensive-stage small cell lung cancer (ES-SCLC). We evaluated the prevalence of myelosuppression, chemotherapy treatment patterns and outpatient healthcare use and costs after chemotherapy initiation using data from The US Oncology Network and Non-network clinics between 1 January 2015 and 31 December 2020. Among patients with laboratory values, which were required to identify myelosuppression events, over half of patients experienced severe myelosuppression-related adverse events in one or more lineages after chemotherapy initiation, and approximately one-third experienced severe myelosuppression-related adverse events in at least two blood cell lineages. Patients with severe myelosuppression-related adverse events had greater dose reductions, treatment delays, and healthcare use and costs than those without. Myelosuppression is a burden to patients with ES-SCLC treated with chemotherapy and the healthcare system. Reduction of chemotherapy-induced myelosuppression has the potential to reduce burden on patients and healthcare organizations.

First draft submitted: 28 July 2022; Accepted for publication: 20 October 2022; Published online: 15 November 2022

Keywords: extensive-stage small cell lung cancer • health care costs • health care resource utilization • myelosuppression • supportive care interventions • treatment patterns

Small cell lung cancer (SCLC), the most aggressive form of lung cancer [1], accounts for approximately 13–17% of lung cancer diagnoses in USA [1–3]. SCLC is characterized by rapid tumor growth and early development of widespread metastases (e.g., in both lungs, lymph nodes and/or other parts of the body) [1,4], resulting in approximately two-thirds of patients presenting with extensive-stage disease (ES-SCLC) at diagnosis [4,5]. Over half (60.8%) of patients with ES-SCLC in USA are treated in the community setting [6]. Curative treatment options are restricted to patients with limited-stage SCLC; consequently, most patients with ES-SCLC are indicated to receive systemic treatment for the palliation of symptoms, and to prolong survival.

Future Medicine

Chemotherapy has provided the mainstay of treatment for ES-SCLC for several decades. Combination chemotherapy consisting of a platinum agent plus etoposide is the recommended first-line treatment [7,8]. Within the last 3 years, two immuno-oncology (IO) therapies, atezolizumab and durvalumab, have been approved for the treatment of ES-SCLC in combination with chemotherapy following phase III clinical trials showing improved overall- and progression-free survival compared with chemotherapy alone [7–10]. Although ES-SCLC is initially responsive to first-line treatment, most patients relapse within the first 6 to 12 months [7,8,11,12]. For relapsed ES-SCLC, the preferred second-line treatment has traditionally been topotecan, but second-line treatment options have recently expanded with the approval of lurbinectedin [8].

Chemotherapy-induced myelosuppression (CIM) is a major treatment-related complication, predominantly caused by cytotoxic damage to proliferating hematopoietic stem and progenitor cells in the bone marrow that give rise to individual blood cell lineages [13]. CIM commonly leads to the reduced production of red blood cells (RBCs; i.e., anemia), white blood cells (i.e., neutropenia and/or leukopenia) and/or platelets (i.e., thrombocytopenia) [13,14]. These hematologic adverse events (HAEs) are frequent complications in patients receiving systemic treatment for ES-SCLC [15–18].

CIM is associated with a substantial burden to both patients and healthcare systems. The administration of supportive care interventions, (e.g., erythropoiesis-stimulating agents [ESAs], granulocyte colony-stimulating factor [G-CSF], RBC/platelet transfusions) and/or hospitalizations, are commonly required to manage these hematologic adverse events [19–22]. In addition, patients with CIM may experience a reduced health-related quality of life (HRQoL) arising from an increased risk of fatigue, life-threatening infections, serious bleeding events and shortness of breath [23–25]. Other common and bothersome side effects associated with chemotherapy may include alopecia, nausea/vomiting and diarrhea [26]. Overall, CIM may be expected to increase healthcare resource utilization (HCRU) and associated costs in the management of patients with ES-SCLC.

There is very limited research on the real-world burden of CIM specific to patients with ES-SCLC. Two recent studies on the burden of myelosuppression in patients with SCLC were not limited to ES-SCLC [27,28]. To our knowledge, this would be the first study to examine CIM after immunotherapy was approved for the treatment of ES-SCLC in 2019. Thus, this study aimed to assess the occurrence of CIM, treatment patterns, healthcare resource utilization and costs among patients with ES-SCLC treated with chemotherapy in the US community oncology setting.

Materials & methods

Data source

Data from two separate networks of community oncology practices in the USA, The US Oncology Network ('Network') and Non-network clinics that have adopted the iKnowMed electronic health record (EHR; Ontada, TX, USA) system, were used for this study. The US Oncology Network covers approximately 1400 affiliated physicians in over 480 geographically dispersed sites and nearly 1 million patients annually who have been newly diagnosed with cancer. Non-network practices are independent community-based oncology clinics that have a partnership with Ontada. Approximately 80 Non-network clinics have adopted the iKnowMed EHR and participate in real-world research activities with Ontada. iKnowMed is an oncology specific EHR system that captures outpatient practice encounter history for patients receiving treatment in Network and Non-network clinics, including laboratory tests, diagnosis, therapy administration, line of therapy, staging, comorbidities, and performance status.

iKnowMed EHR data, from 1 January 2015 to 31 December 2020, were supplemented with vital status provided by the US Social Security Administration's Limited Access Death Master File (LADMF). Outpatient healthcare resource utilization (HCRU) and healthcare costs from the Financial Data Warehouse were available for the Network only (not available for Non-network clinics). The Financial Data Warehouse contains information from electronic healthcare claims submitted by Network practices to payers and the corresponding payments or remittance information submitted by payers back to the practices. All data were de-identified and handled in compliance with the Health Insurance Portability and Accountability Act and the Health Information Technology for Economic and Clinical Health Act of 1996. The US Oncology Inc. Institutional Review Board granted this study an exemption and waiver of consent.

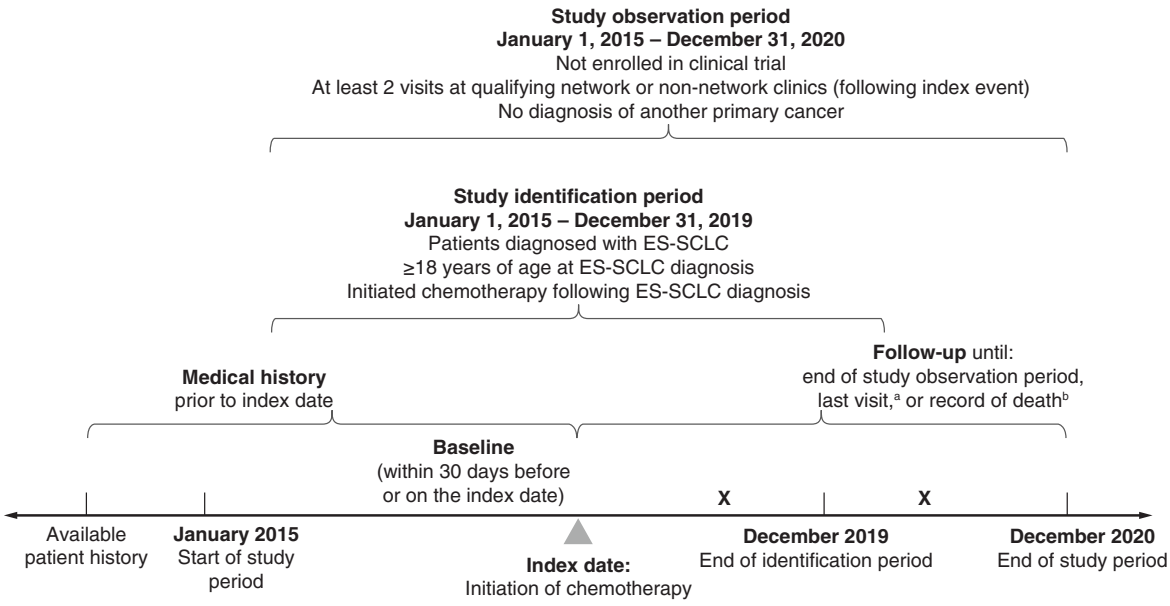


Figure 1. Study design.
[a]Last visit = Last physical encounter. [b]Whichever occurred first.
ES-SCLC: Extensive-stage small-cell lung cancer; HAE: Hematological adverse event; X: Additional visit at qualifying Network or Non-network clinic or record of death.

Study design & patient population

This was a retrospective observational study. For both Network and Non-network clinics, adult patients (≥18 years) diagnosed with ES-SCLC who initiated chemotherapy (with or without combination with immunotherapy), between 1 January 2015 and 31 December 2019, were eligible for inclusion in the analysis (Figure 1). Patients were excluded if they were clinical trial participants, under the age of 18, or diagnosed for other primary cancers. Diagnosis of ES-SCLC was determined based on a review of iKnowMed's discrete diagnosis and histology fields, which are populated during the routine course of care. Metastatic disease was identified by stage IV disease; tumor, node, metastasis (TNM) staging with metastasis stage 1 (M1); record of location of metastatic disease; or current or prior disease status containing reference to metastatic disease. The index date was defined as the date of chemotherapy initiation between 2015 and 2019 following diagnosis of ES-SCLC. Patients were followed longitudinally from 30 days prior to the index date ('baseline') until 31 December 2020, death, or last patient record, whichever came first ('follow-up').

Study measures

Patient demographics (age, sex and race), baseline clinical characteristics (Eastern Cooperative Oncology Group performance status [ECOG PS], count of metastatic sites at index, hemoglobin [Hgb], absolute neutrophil count [ANC], platelet, time from ES-SCLC diagnosis to index date, and line of therapy at index), length of follow-up, and reasons for end of follow-up were reported.

The outcomes of interest included the prevalence of grade ≥3 myelosuppression events (by type and grade), supportive care utilization, myelosuppression-related treatment management strategies, and treatment patterns during follow-up. Myelosuppression events were identified using laboratory values based on Common Terminology Criteria for Adverse Events v5.0 definitions for anemia (grade 3: Hgb <8.0 g/dl), neutropenia (grade 3: ANC of 500–1000/μl; grade 4: ANC <500/μl), thrombocytopenia (grade 3: platelets of 25,000–50,000/μl; grade 4: platelets <25,000/μl) [29]. Multilineage myelosuppression was defined as having myelosuppression events in at least two lineages (anemia, neutropenia and/or thrombocytopenia).

Supportive care utilization included eligibility for RBC or platelet transfusions, G-CSF use, ESA use, and intravenous [iv.] hydration use. Unique administrations for supportive care utilization outcomes were based on unique days of service. Eligibility for RBC transfusions was defined as hemoglobin <8.0 g/dl and for platelet transfusions as platelets <10,000/μl. G-CSF use was categorized as prophylactic (given within 3 days after

chemotherapy initiation) or therapeutic (given 4 or more days after chemotherapy initiation). Type of G-CSF and ESA were also reported during follow-up. Myelosuppression-related treatment management strategies included chemotherapy treatment hold, treatment delay, and dose reduction. Treatment hold was defined as a gap of ≥60 days without treatment. Treatment delay was defined as a gap of <60 days without treatment. Treatment holds and delays did not include patients who discontinued chemotherapy during the study. A dose reduction of at least one drug was counted as an event for dose reduction. Treatment patterns included the number of chemotherapy cycles received and sequence of treatment regimens.

Additional outcomes included HCRU and healthcare costs within 12 months after the index date for the Network only (not available for patients from Non-network clinics). HCRU included outpatient visits, G-CSF use, ESA use, and iv. hydration use. Healthcare costs included systemic therapy, outpatient visits, laboratory tests (within network), G-CSF, ESA, iv. hydration, and other treatment-related costs. Inpatient costs and costs for transfusions were not included because inpatient stays and transfusions were not captured in the iKnowMed EHR.

Statistical analysis

All analyses were conducted by network (Network or Non-network). Within each network, two sets of analysis were conducted: overall population with the intent to maximize the patients included in the analysis and subgroup analyses with patients stratified into two cohorts based on myelosuppression events after chemotherapy initiation (with grade ≥3 myelosuppression events vs without grade ≥3 myelosuppression events). Patients without laboratory information for all three labs (hemoglobin, platelets and ANC) were excluded from stratified analyses based on myelosuppressive events but were included in the analysis of other outcomes in the overall population. Where applicable, the percentage of patients with missing/not documented data was reported for the corresponding variables. No imputation was conducted for missing/not documented data.

Descriptive statistics were reported for patient characteristics, prevalence and frequency of myelosuppressive events, prevalence and frequency of supportive care utilization, prevalence of myelosuppression-related treatment management strategies, prevalence of treatment patterns, frequency of HCRU, and healthcare cost outcomes. Outcomes of interest were compared between the cohorts with and without grade ≥3 myelosuppression events using t-tests or Wilcoxon rank-sum tests for continuous variables and $\chi 2$ or Fisher's exact test for categorical variables. Costs were adjusted for inflation to 2021 USD using the medical care consumer price index from the Bureau of Labor Statistics [30]. In the case of missing observations, the number and percentage of missing values were reported. Statistical significance was defined as p-value < 0.05. All analyses were conducted using SAS 9.4 (SAS Institute Inc., NC, USA).

Results

Patient demographic & clinical characteristics at baseline

A total of 1574 adult patients with ES-SCLC receiving chemotherapy were identified in Network and 959 in Non-network clinics (Table 1). Mean age at chemotherapy initiation was 67–68 years (Network = 67.8; Non-network = 67.4). Most patients were Caucasian (Network = 82.2%; Non-network = 81.0%), approximately half were female (Network = 52.4%; Non-network = 51.0%), and most had an ECOG-PS score ≤1 (Network = 55.5%; Non-network = 45.5%). Almost all patients (Network = 99.5%; Non-network = 99.6%) received first-line chemotherapy at index. Mean follow-up was 9–10 months (Network = 8.9 months; Non-network = 9.5 months), and death was the most common reason for the end of follow-up (Network = 62.6%; Non-network = 61.5%).

Laboratory information was available for 87.3% (n = 1374/1574) of patients in Network and 68.9% (n = 661/959) in Non-network clinics. Except for average hemoglobin or platelet lab values, clinical characteristics at baseline were not clinically significantly different for patients with or without grade ≥3 myelosuppression events within each network.

Myelosuppression events during follow-up

Among patients with laboratory values, 56.6% of patients in Network had at least one grade ≥3 myelosuppression event after chemotherapy initiation (Figure 2A); 35.7% of patients had at least one grade ≥3 neutropenia event (27.3% [n = 358/1,312] grade 3 neutropenia, 16.7% [n = 218/1,312] grade 4 neutropenia), 28.5% had at least one grade ≥3 anemia event, 22.9% had at least one grade ≥3 thrombocytopenia event (19.3% [n = 263/1,365] grade 3 thrombocytopenia, 10.3% [n = 141/1,365] grade 4 thrombocytopenia), respectively. The mean numbers of events

Table 1. Patient demographic and clinical characteristics.

Characteristics	Network				Non-network			
	All Network (n = 1574)	Cohort with grade ≥3 HAEs (n = 778)	Cohort without grade ≥3 HAEs (n = 596)	p-value	All Non-network (n = 959)	Cohort with grade ≥3 HAEs (n = 424)	Cohort without grade ≥3 HAEs (n = 237)	p-value
Age at index, years, mean (SD)	67.8 (9.1)	67.3 (9.2)	68.0 (8.9)	0.19	67.4 (8.9)	67.4 (8.6)	66.9 (9.1)	0.43
Age group at index, n (%)				0.58				0.28
<65 years	611 (38.8)	313 (40.2)	231 (38.3)		378 (39.4)	159 (37.5)	99 (41.8)	
≥65 years	963 (61.2)	465 (59.8)	365 (61.2)		581 (60.6)	265 (62.5)	138 (58.2)	
Female sex, n (%)	824 (52.4)	400 (51.4)	320 (53.7)	0.40	489 (51.0)	231 (54.5)	112 (47.3)	0.07
Race, n (%)				0.13				0.61
Caucasian	1294 (82.2)	647 (83.2)	489 (82.1)		777 (81.0)	345 (81.4)	201 (84.8)	
African American	79 (5.0)	40 (5.1)	29 (4.9)		47 (4.9)	24 (5.7)	9 (3.8)	
Asian or other	31 (2.0)	18 (2.3)	5 (0.8)		20 (2.1)	6 (1.4)	2 (0.8)	
Not documented	170 (10.8)	73 (9.4)	73 (12.2)		115 (12.0)	49 (11.6)	25 (10.6)	
ECOG PS, n (%)				0.16				0.16
0	113 (7.2)	56 (7.2)	52 (8.7)		81 (8.5)	34 (8.0)	28 (11.8)	
1	761 (48.3)	382 (49.1)	306 (51.3)		355 (37.0)	152 (35.9)	92 (38.8)	
2	331 (21.0)	158 (20.3)	129 (21.6)		174 (18.1)	69 (16.3)	44 (18.6)	
≥3	36 (2.3)	17 (2.2)	14 (2.4)		12 (1.3)	5 (1.2)	2 (0.8)	
Not documented	333 (21.2)	165 (21.2)	95 (15.9)		337 (35.1)	164 (38.7)	71 (30.0)	
Count of metastatic site(s) at index, n (%)				<0.001				0.47
1	474 (30.1)	213 (27.4)	195 (32.7)		300 (31.3)	133 (31.4)	71 (30.0)	
2	253 (16.1)	110 (14.1)	119 (20.0)		150 (15.6)	69 (16.3)	37 (15.6)	
3	138 (8.8)	60 (7.7)	61 (10.2)		65 (6.8)	33 (7.8)	11 (4.6)	
≥4	83 (5.3)	49 (6.3)	26 (4.4)		35 (3.7)	13 (3.1)	10 (4.2)	
Not documented	626 (39.8)	346 (44.5)	195 (32.7)		409 (42.7)	176 (41.5)	108 (45.6)	
Hemoglobin at baseline, g/dl, mean (SD)[†]	12.4 (1.9)	12.2 (2.1)	12.6 (1.7)	<0.001	12.2 (1.9)	12.0 (2.0)	12.5 (1.8)	0.001
ANC at baseline, 1000/μl, mean (SD)[‡]	6.2 (3.5)	5.8 (3.5)	6.5 (3.5)	<0.001	5.9 (3.9)	5.8 (3.8)	6.0 (3.9)	0.74
Platelet count at baseline, 1000/μl, mean (SD)[§]	251.2 (115.1)	242.8 (118.0)	262.6 (111.2)	0.003	257.2 (115.6)	245.8 (117.7)	269.0 (102.5)	0.02
Time from ES-SCLC diagnosis at index, months, mean (SD)[¶]	1.0 (4.2)	0.9 (3.9)	1.0 (4.4)	0.83	0.7 (1.6)	0.7 (1.9)	0.7 (1.3)	0.97
Index LOT, n (%)[#]				0.66				0.46
LOT 1	1566 (99.5)	776 (99.7)	593 (99.5)		955 (99.6)	423 (99.8)	236 (99.6)	
LOT 2	8 (0.5)	2 (0.3)	3 (0.5)		4 (0.4)	1 (0.2)	1 (0.4)	
Follow-up duration from index date, months, mean (SD)	8.9 (8.5)	10.5 (8.8)	7.9 (7.9)	<0.001	9.5 (9.3)	11.3 (9.0)	8.6 (8.3)	<0.001
Reason for end of follow-up, n (%)				0.09				0.81
Death	986 (62.6)	506 (65.0)	366 (61.4)		590 (61.5)	274 (64.6)	151 (63.7)	
Last activity date on or before study end date	588 (37.4)	272 (35.0)	230 (38.6)		369 (38.5)	150 (35.4)	86 (36.3)	

[†]Patients counts for hemoglobin during baseline were 1299, 676, and 521 for overall, cohort with grade ≥3 HAEs, and cohort without grade ≥3 HAEs, respectively, in Network and 647, 330, 182 in Non-network clinics.
[‡]Patients counts for ANC during baseline were 1177, 629, and 505 for overall, cohort with grade ≥3 HAEs, and cohort without grade ≥3 HAEs, respectively, in Network and 443, 237, 175 in Non-network clinics.
[§]Patients counts for platelet count during baseline were 1308, 683, and 521 for overall, cohort with grade ≥3 HAEs, and cohort without grade ≥3 HAEs, respectively, in Network and 674, 344, 187 in Non-network clinics.
[¶]Patients counts for time from ES-SCLC diagnosis to index were 1532, 757, and 582 for overall, cohort with grade ≥3 HAEs, and cohort without grade ≥3 HAEs, respectively, in Network and 959, 424, 237 in Non-network clinics.
[#]This is the line of therapy for the index regimen received by the patient.
ANC: Absolute neutrophil count; ECOG PS: Eastern Cooperative Oncology Group performance status; ES-SCLC: Extensive-stage small cell lung cancer; HAE: Hematological adverse event; LOT: Line of therapy.

10.2217/fon-2022-0754

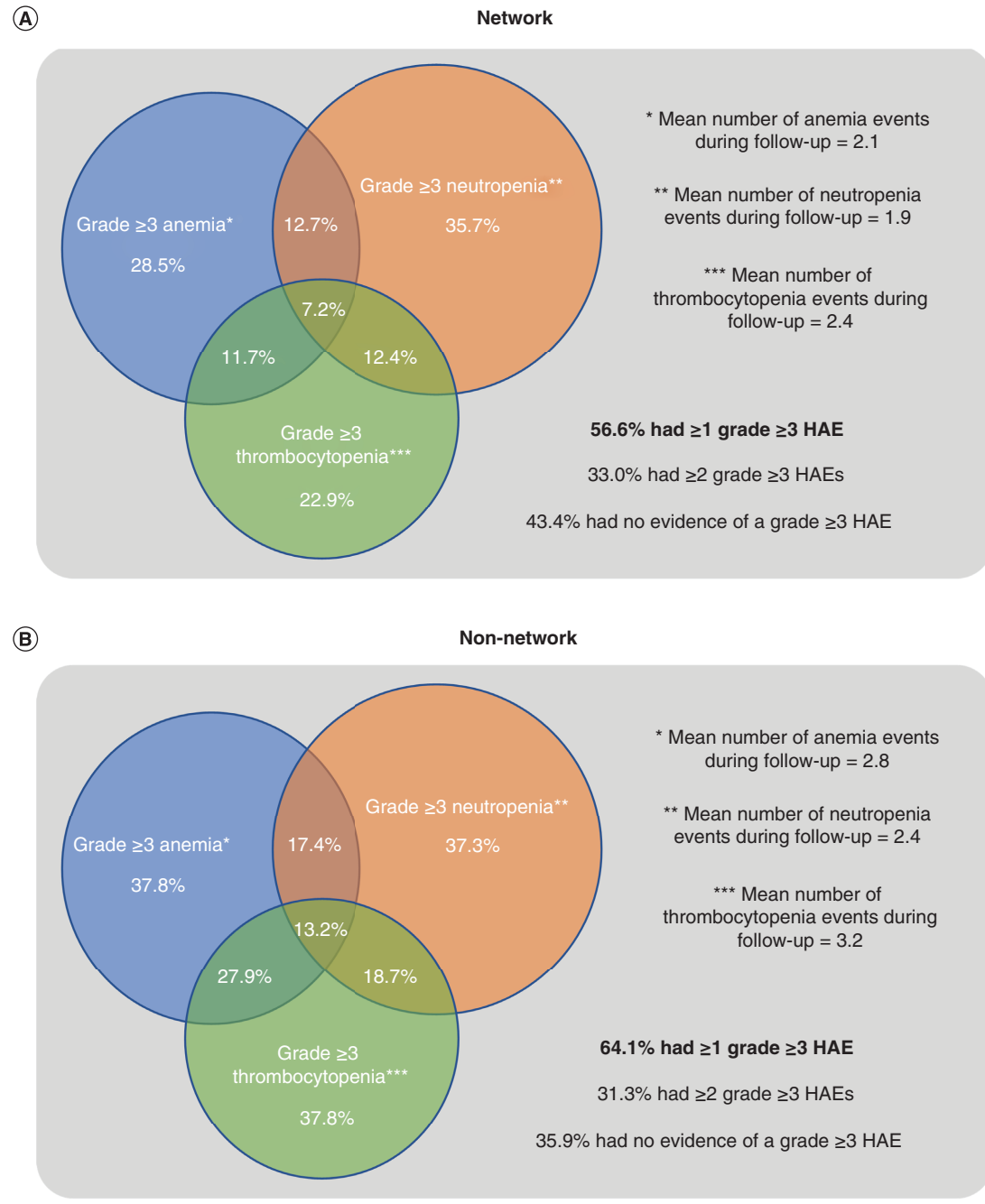


Figure 2. Multilineage myelosuppression events after chemotherapy among patients with at least one grade ≥3 myelosuppression event. (A) Network. **(B)** Non-network.
Categories are not mutually exclusive. Patients can be in multiple groups if they have multiple events in different linages.
HAE: Hematologic adverse event.

during follow-up were 2.1, 1.9 and 2.4 for patients who experienced grade ≥3 anemia, grade ≥3 neutropenia and grade ≥3 thrombocytopenia, respectively.

In Non-network clinics, 64.1% of patients had at least one grade ≥3 myelosuppression event after chemotherapy initiation (Figure 2B); 37.3% of patients had at least one grade ≥3 neutropenia event (28.4% [n = 157/552] grade 3 neutropenia, 20.3% [n = 112/552] grade 4 neutropenia), 37.8% had at least one grade ≥3 anemia event, 37.8% had at least one grade ≥3 thrombocytopenia event (32.8% [n = 216/658] grade 3 thrombocytopenia, 19.3%

Table 2. Supportive care interventions during follow-up.

Treatment outcomes	Network				Non-network			
	All Network (n = 1574)	Cohort with grade ≥3 HAEs (n = 778)	Cohort without grade ≥3 HAEs (n = 596)	p-value	All Non-network (n = 959)	Cohort with grade ≥3 HAEs (n = 424)	Cohort without grade ≥3 HAEs (n = 237)	p-value
Patients who met transfusion criteria, n (%)								
RBC transfusions (hemoglobin <8 g/dl)	335 (21.3)	335 (43.1)	0 (0.0)	<0.001	232 (24.2)	232 (54.7)	0 (0.0)	<0.001
Platelet transfusions (platelets <10,000/μl)	30 (1.9)	30 (3.9)	0 (0.0)	<0.001	31 (3.2)	31 (7.3)	0 (0.0)	<0.001
G-CSF use, n (%)								
Therapeutic	435 (27.6)	294 (37.8)	108 (18.1)	<0.001	271 (28.3)	157 (37.0)	38 (16.0)	0.01
≥6 days after chemo	375 (23.8)	263 (33.8)	85 (14.3)		232 (24.2)	139 (32.8)	30 (12.7)	
5 days after chemo	31 (2.0)	12 (1.5)	16 (2.7)		30 (3.1)	16 (3.8)	4 (1.7)	
4 days after chemo	29 (1.8)	19 (2.4)	7 (1.2)		9 (0.9)	2 (0.5)	4 (1.7)	
Prophylactic	691 (43.9)	301 (38.7)	297 (49.8)	0.40	396 (41.3)	167 (39.4)	118 (49.8)	0.23
3 days after chemo	238 (15.1)	107 (13.8)	104 (17.4)		182 (19.0)	80 (18.9)	48 (20.3)	
2 days after chemo	446 (28.3)	190 (24.4)	192 (32.2)		212 (22.1)	87 (20.5)	70 (29.5)	
1 day after chemo	7 (0.4)	4 (0.5)	1 (0.2)		2 (0.2)	0 (0.0)	0 (0.0)	
Type of G-CSF, n (%)				<0.001				<0.001
Pegfilgrastim	1029 (65.4)	531 (68.3)	384 (64.4)		525 (54.7)	242 (57.1)	137 (57.8)	
Filgrastim-sndz	158 (10.0)	117 (15.0)	25 (4.2)		97 (10.1)	63 (14.9)	9 (3.8)	
Filgrastim	63 (4.0)	50 (6.4)	10 (1.7)		44 (4.6)	34 (8.0)	1 (0.4)	
Pegfilgrastim-cbqv	19 (1.2)	9 (1.2)	8 (1.3)		30 (3.1)	13 (3.1)	8 (3.4)	
Type of ESA, n (%)				0.96				0.32
Darbepoetin alfa	198 (12.6)	159 (20.4)	34 (5.7)		23 (2.4)	15 (3.5)	5 (2.1)	
Epoetin alfa	8 (0.5)	6 (0.8)	1 (0.2)		88 (9.2)	61 (14.4)	9 (3.8)	
Epoetin alfa-epbx	5 (0.3)	4 (0.5)	1 (0.2)		13 (1.4)	11 (2.6)	1 (0.4)	
IV hydration, n (%)	928 (59.0)	510 (65.6)	295 (49.5)	<0.001	475 (49.5)	250 (59.0)	106 (44.7)	<0.001

ESA: Erythropoiesis-stimulating agent; G-CSF: Granulocyte colony-stimulating factor; HAE: Hematological adverse event; iv.: Intravenous; RBC: Red blood cell.

[n = 127/658] grade 4 thrombocytopenia, respectively. The mean numbers of events during follow-up were 2.8, 2.4 and 3.2 for patients who experienced grade ≥3 anemia, grade ≥3 neutropenia and grade ≥3 thrombocytopenia, respectively.

Multilineage myelosuppression was observed in 33.0% of patients in Network (12.7% for anemia and neutropenia, 12.4% for neutropenia and thrombocytopenia, 11.7% for anemia and thrombocytopenia, and 7.2% for all 3 lineages) and 31.3% of patients in Non-network clinics (17.4% for anemia and neutropenia, 18.7% for neutropenia and thrombocytopenia, 27.9% for anemia and thrombocytopenia and 13.2% for all 3 lineages) (Figure 2).

Supportive care utilization during follow-up

Supportive care utilization was common for Network (iv. hydration = 59.0%, prophylactic G-CSF = 43.9%, therapeutic G-CSF = 27.6%, RBC transfusion eligible = 21.3%) and Non-network (iv. hydration = 49.5%, prophylactic G-CSF = 41.2%, therapeutic G-CSF = 28.3%, RBC transfusion eligible = 24.2%) patients during follow-up (Table 2). For patients with grade ≥3 myelosuppression events, 43.1 and 3.9% in Network were eligible for RBC and platelet transfusions, respectively, as indicated by laboratory values. Likewise, for Non-network patients, 54.7 and 7.3% were eligible for RBC and platelet transfusions, respectively. Patients with grade ≥3 myelosuppression events were more likely to receive therapeutic G-CSF (Network = 37.8 vs 18.1%; $p < 0.001$; Non-network = 37.0 vs 16.0%; $p = 0.01$) compared with patients without grade ≥3 myelosuppression events, but prophylactic G-CSF use was not statistically significantly different (Network = 38.7 vs 49.8%; $p = 0.40$; Non-network = 39.4 vs 49.8%; $p = 0.23$). iv. hydration was statistically significantly greater among patients with versus without grade ≥3 myelosuppression events (Network = 65.6 vs 49.5%, $p < 0.001$; Non-network = 59.0 vs 44.7%; $p < 0.001$).

10.2217/fon-2022-0754

Table 3. Treatment patterns during follow-up.

Treatment outcomes	Network				Non-network			
	All Network (n = 1574)	Cohort with grade ≥3 HAEs (n = 778)	Cohort without grade ≥3 HAEs (n = 596)	p-value	All Non-network (n = 959)	Cohort with grade ≥3 HAEs (n = 424)	Cohort without grade ≥3 HAEs (n = 237)	p-value
Number of index chemotherapy cycles, n (%)				<0.001				<0.001
1	198 (12.6)	45 (5.8)	82 (13.8)		99 (10.3)	16 (3.8)	22 (9.3)	
2	161 (10.2)	68 (8.7)	66 (11.1)		75 (7.8)	16 (3.8)	24 (10.1)	
3	127 (8.1)	63 (8.1)	52 (8.7)		70 (7.3)	26 (6.1)	19 (8.0)	
4	467 (29.7)	242 (31.1)	183 (30.7)		228 (23.8)	104 (24.5)	64 (27.0)	
5	103 (6.5)	64 (8.2)	31 (5.2)		63 (6.6)	29 (6.8)	15 (6.3)	
6	376 (23.9)	204 (26.2)	142 (23.8)		289 (30.1)	165 (38.9)	59 (24.9)	
≥7	133 (8.5)	88 (11.3)	37 (6.2)		130 (13.6)	67 (15.8)	34 (14.4)	
Not documented	9 (0.6)	4 (0.5)	3 (0.5)		5 (0.5)	1 (0.24)	0 (0.0)	
Dose decrease of index treatment[†], n (%)	586 (38.1)	356 (46.7)	184 (32.2)	<0.001	472 (49.2)	258 (60.8)	94 (39.7)	<0.001
Index treatment hold[†,‡], n (%)	142 (9.2)	97 (12.7)	34 (5.9)	<0.001	89 (9.3)	49 (11.6)	14 (5.9)	0.02
Index treatment delay[†,§], n (%)								
14–60 days	1,298 (84.5)	703 (92.3)	482 (84.3)	<0.001	797 (83.1)	392 (92.5)	199 (84.0)	<0.001
14 30 days	1,276 (83.0)	693 (90.9)	474 (82.9)	<0.001	788 (82.2)	389 (91.7)	197 (83.1)	<0.001
31–60 days	283 (18.5)	175 (23.0)	84 (14.7)	<0.001	166 (17.3)	89 (21.0)	37 (15.6)	0.09

[†]Patients counts were 1537, 762 and 572 for overall, cohort with grade ≥3 HAEs, and cohort without grade ≥3 HAEs, respectively, in Network and 959, 424, 237 in Non-network clinics.
[‡]Treatment hold was defined as a gap of ≥60 days without treatment.
[§]Treatment delay was defined as a gap of <60 days without treatment.
HAE: Hematological adverse event.

Treatment patterns & management strategies during follow-up

Over one-quarter of patients received fewer than 4 cycles of index chemotherapy treatment (Network = 30.9%; Non-network = 25.4%) (Table 3). Patients with grade ≥3 myelosuppression events had a greater proportion of dose reductions (Network = 46.7 vs 32.2%; Non-network = 60.8 vs 39.7%; both $p < 0.001$), treatment holds (Network = 12.7 vs 5.9%; $p < 0.001$; Non-network = 11.6 vs 5.9%; $p = 0.02$), and treatment delays of 14–60 days (Network = 92.3 vs 84.3%; Non-network = 92.5 vs 84.0%; both $p < 0.001$) after chemotherapy initiation compared with patients without grade ≥3 myelosuppression events.

Approximately 80% of patients received a platinum-/etoposide-containing regimen (Network = 81.4%; Non-network = 78.5%) and 15% received platinum/etoposide in combination with immunotherapy at index (Network = 13.8%; Non-network = 17.1%) (Supplementary Figure 1). Index treatment regimens were similar between Network patients with and without grade ≥3 myelosuppression events (Supplementary Figures 2 & 3). For Non-network patients, use of a platinum-/etoposide-containing regimen in combination with immunotherapy appeared to be higher among patients without grade ≥3 myelosuppression events (24.9%) compared with those with grade ≥3 myelosuppression events (13.9%).

Following chemotherapy index treatment, more than half (Network = 58.8%; Non-network = 56.8%) of patients did not receive any further treatment (Supplementary Figure 1). Additionally, a higher percentage of patients without grade ≥3 myelosuppression events did not receive subsequent treatment when compared with patients with grade ≥3 myelosuppression events across Network (66.9 vs 47.5%) and Non-network (64.9 vs 47.4%) (Supplementary Figures 2 & 3). Among patients who received a subsequent regimen, a topotecan containing regimen was the most frequent regimen with the exception of Non-network patients without grade ≥3 myelosuppression events who most frequently went on to receive immunotherapy monotherapy (Supplementary Figures 2 & 3).

HCRU & healthcare costs within 12 months after index in Network

In Network, patients with grade ≥3 myelosuppression events had an average of 10.7 outpatient visits within 12 months post-index compared with 7.7 outpatient visits for patients without grade ≥3 myelosuppression events

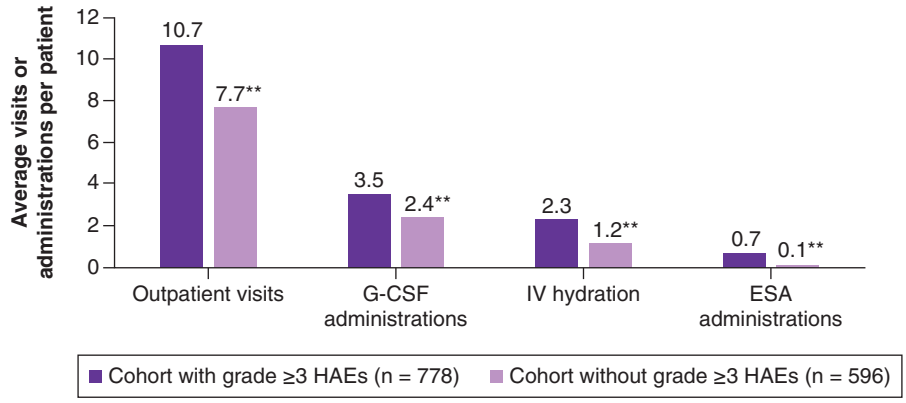


Figure 3. Outpatient healthcare resource use within 12 months after index in Network.
**Statistical significance at p-value < 0.001.
ESA: Erythropoiesis-stimulating agent; G-CSF: Granulocyte colony-stimulating factor; HAE: Hematological adverse event; IV: Intravenous.

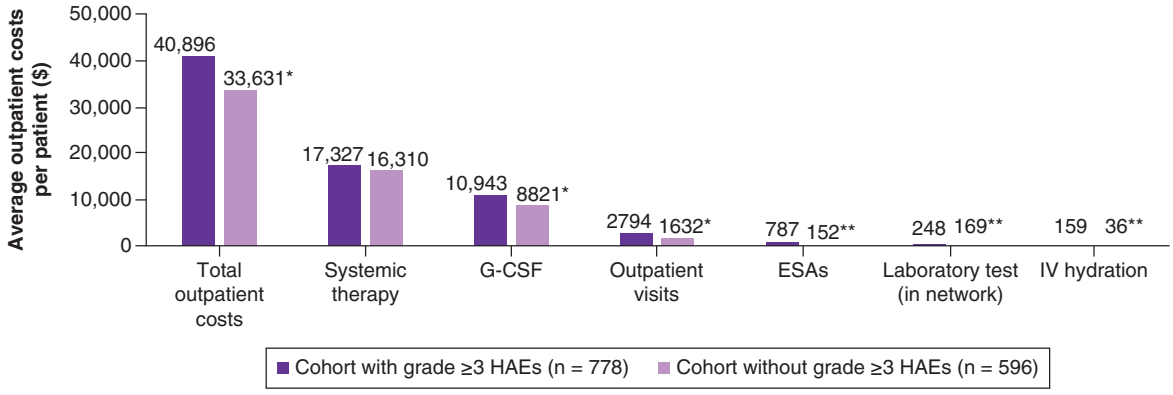


Figure 4. Outpatient healthcare costs within 12 months after index date in Network.
*Statistical significance at p-value < 0.01.
**Statistical significance at p-value < 0.001.
ESA: Erythropoiesis-stimulating agent; G-CSF: Granulocyte colony-stimulating factor; HAE: Hematological adverse event; IV: Intravenous.

($p < 0.001$) (Figure 3). Patients with grade ≥3 myelosuppression events also had greater average G-CSF use (3.5 vs 2.4), ESA use (0.7 vs 0.1), and IV hydration use (2.3 vs 1.2) compared with those without grade ≥3 myelosuppression events (all $p < 0.001$). Total outpatient costs within 12 months post-index were greater for patients with grade ≥3 myelosuppression events compared with those without grade ≥3 myelosuppression events (US$40,896 vs $33,361, $p < 0.01$) (Figure 4). Supportive care utilization costs were also greater per patient (G-CSF=$10,943 vs $8,821, $p < 0.01$; ESA = $787 vs $152, $p < 0.001$; IV hydration = $159 vs $36, $p < 0.001$).

Discussion

This retrospective analysis demonstrated that more than half of patients diagnosed with ES-SCLC in US community oncology sites of care experienced at least one grade ≥3 myelosuppression event after the initiation of chemotherapy. In addition, patients with grade ≥3 myelosuppression events had significantly greater outpatient costs and significantly more outpatient visits compared with those without a grade ≥3 myelosuppression event. Overall, these data suggest that the management of grade ≥3 myelosuppression among patients with ES-SCLC in routine clinical practice represents a burden for patients and healthcare systems.

Consistent with our analysis, other studies have reported that CIM may be experienced in a high proportion of patients receiving chemotherapy for the treatment of cancer. Anemia (61%), neutropenia (59%), lymphopenia (37%), and thrombocytopenia (34%) were the most common self-reported manifestations of CIM among a survey

of participants with breast, lung, and colorectal cancer [25]. Among patients with SCLC, a retrospective observational analysis of chemotherapy-treated patients treated at Providence St. Joseph Health hospital-associated oncology clinics (January 2016 – December 2019) reported that 61% of patients experienced grade ≥3 myelosuppression events, most commonly neutropenia (45%), anemia (41%) and thrombocytopenia (25%) [28]. In addition, an analysis of the Surveillance, Epidemiology, and End Results (SEER) Medicare-linked data (January 2012 – December 2015) reported that 72% of patients with SCLC had at least one claim for anemia, 45% for neutropenia, and 27% for thrombocytopenia after the initiation of chemotherapy [27]. This study expanded the time frame of community oncology clinic data (January 2015 – December 2020) to incorporate two immunotherapies approved by the US FDA to treat ES-SCLC and included atezolizumab (approved in March 2019) and durvalumab (approved in March 2020). To our knowledge, this would be the first study published to examine CIM after immunotherapy was approved for the treatment of ES-SCLC in 2019. This study examines single and multilineage myelosuppression among patients with ES-SCLC, which had not been previously reported. Within SCLC, it is important to examine CIM for limited-stage SCLC (LS-SCLC) versus ES-SCLC. ES-SCLC is approximately two-thirds of SCLC diagnoses [31]; is primarily treated with chemotherapy and immunotherapy compared with surgery, radiation, chemotherapy or prophylactic cranial irradiation for LS-SCLC; and has shorter median overall survival compared with LS-SCLC [32–34].

Notably, approximately a third of the patients in the current analysis had grade ≥3 myelosuppression events in two or more lineages, including 7–13% of patients with myelosuppression in all three lineages, indicating that multilineage myelosuppression occurred frequently. Additionally, a greater proportion of patients with grade ≥3 myelosuppression events experienced dose reductions and treatment holds/delays compared with those without a grade ≥3 myelosuppression event. Earlier studies on the burden of myelosuppression in patients with SCLC did not report on dose reductions and treatment holds/delays [27,28]. Evidence suggests that treatment interruption could subsequently impact tumor control and patient outcomes [35–37]; therefore, patients with grade ≥3 myelosuppression, who are managed with dose reductions and delays, may not optimally benefit from standard chemotherapy-based treatments.

Further, over one-quarter of patients in this analysis received fewer than 4 cycles of index chemotherapy treatment. This is in line with a Dutch retrospective cohort analysis of patients with ES-SCLC in which 26% of patients received fewer than 4 cycles of first line treatment [38]. In the SEER-Medicare analysis of patients with SCLC, 42% of patients failed to complete the guideline-recommended 4–6 cycles of chemotherapy [27]. Taken together, these data emphasize both the aggressive nature of ES-SCLC and the fragility of patients with this disease.

Current supportive care options for the management of CIM are specific to single hematopoietic lineages (G-CSF for the prevention or management of neutropenia; RBC transfusions, ESAs and/or iron supplementation for anemia; and platelet transfusion or antifibrinolytic agents for thrombocytopenia [19–22]). Consequently, patients with more than one grade ≥3 myelosuppressive event may require the administration of multiple myeloprotective therapies, which could be associated with greater HCRU and costs [28]. Protecting multiple blood cell lineages from the effects of CIM could decrease chemotherapy interruptions, increase completion of guideline-recommended chemotherapy cycles, and reduce HCRU.

Prevention of CIM may depend on chemotherapy regimen and other factors. For example, National Comprehensive Cancer Network (NCCN) Guidelines® Version 1.2022 for supportive care for Hematopoietic Growth Factors recommend primary G-CSF prophylaxis for chemotherapy regimens that carry a >20% risk of febrile neutropenia or consideration with intermediate (10–20%) risk regimens based on patient-specific risk factors (e.g., age >65 years receiving full chemotherapy dose intensity, comorbidities, prior chemotherapy treatment) [22,28]. Most patients in this study were treated with a platinum-/etoposide-containing regimen at index, which is considered intermediate risk regimens for febrile neutropenia. In this study, 39 and 50% of patients with and without grade ≥3 HAEs, respectively, received prophylactic G-CSF, which was defined as receiving G-CSF within 3 days of chemotherapy initiation.

Given the nature of this retrospective, real-world study, it is possible that underlying baseline demographic and clinical characteristics influenced providers' treatment selection or there are other confounding factors that lead to this observed difference. Of the demographic, clinical and treatment characteristics measured for this study, however, the two populations exhibited very similar patient profiles, except for baseline lab values. Myelosuppressive events during follow-up may be related to myelosuppressive events and corresponding lab values at baseline prior to the first chemotherapy regimen observed during the study period. When compared with Non-network patients without grade ≥3 myelosuppressive events, Non-network patients with grade ≥3 myelosuppressive events had statistically

significantly lower baseline hemoglobin and platelet values, higher rates of anemia and thrombocytopenia of any grade at baseline, higher rates of grade 3 anemia, and higher rates of grade 3 or 4 thrombocytopenia. Although similar differences were observed in Network patients with and without grade ≥3 myelosuppressive events, the cohort differences were larger among Non-network patients.

There is a need for innovation in the treatment of single- or multilineage myelosuppression, and newer agents under clinical investigations include plinabulin (Phase III), ALRN-6924 (Phase 1/2), roxadustat (Phase 2), romiplostim (Phase III), and avatrombopag (Phase III) [28,39]. Additionally, trilaciclib was approved by the US FDA in March 2021 to decrease the incidence of CIM in patients with ES-SCLC when administered before a platinum/etoposide- or topotecan-containing regimen [28,40]. Administration of trilaciclib prior to chemotherapy reduced multilineage myelosuppression, the need for supportive care interventions and dose reductions, and improved safety profiles as shown in three randomized, double-blind, placebo-controlled Phase 2 trials [28,41–43]. Trilaciclib has been added to NCCN Guidelines® Version 2.2022 for SCLC and Version 1.2022 for supportive care for Hematopoietic Growth Factors [8,22].

Strengths of this study include that data were obtained from two large separate oncology networks, capturing data from over 550 oncology sites of care across the US, and representing more than 1,500 physicians and more than 1 million patients; data were supplemented with vital status provided by the LADMF.

Limitations of this study include those inherently associated with retrospective observational studies or common to EHR and/or administrative databases [44,45]. Retrospective EHR database analyses are opportunistic in that they rely on databases that were developed for non-research purposes (e.g., practice management). As a result, there is potential misclassification of study measures such as transfusion, which was based on lab values rather than actual transfusion procedures. Second, the results may not be generalizable beyond the community oncology setting. Third, data on inpatient stays were not available, leading to an under-estimation of HCRU and healthcare costs. This study used EHR data because it contains laboratory results, which allowed for the comparison of patients with or without grade ≥3 myelosuppression for anemia, neutropenia, and thrombocytopenia based on laboratory values. While health insurance claims data would allow for examination of hospitalization costs associated with some adverse events, claims data lacks information on laboratory results. Therefore, myelosuppression would have needed to be defined using ICD-10-CM diagnosis codes, which may have led to under-reporting of myelosuppression. Finally, G-CSF prophylaxis was defined based on the time from chemotherapy initiation, which was a proxy for primary prophylaxis.

Conclusion

This retrospective study indicates that CIM is associated with human and economic burden among patients with ES-SCLC in the US community oncology setting. After the initiation of chemotherapy, more than 50% of patients experienced at least one grade ≥3 myelosuppression event, and those patients had significantly higher treatment-related costs and more healthcare visits versus those without a grade ≥3 myelosuppression event in the community oncology setting. This study highlighted that there is an unmet need to prevent or proactively manage chemotherapy-induced myelosuppression. Reduction of chemotherapy-induced myelosuppression has the potential to reduce burden on patients and healthcare organizations.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/suppl/10.2217/fon-2022-0754

Author contributions

All authors made substantial contributions to the conception or design of the work and/or the acquisition, analysis, or interpretation of data for the work; drafted or revised the work critically for important intellectual content; approved the final version to be published; and agreed to be accountable for all aspects of the work.

Acknowledgments

The authors thank B Blaylock from Blaylock Health Economics LLC for providing medical writing support.

Financial & competing interests disclosure

This study was funded by G1 Therapeutics, Inc. L Lopez-Gonzalez and H Huang are employees of G1 Therapeutics, Inc. J Goldschmidt is an employee of The US Oncology Network, which received funding from G1 Therapeutics, Inc., for this work. A Monnette, P Shi and D Venkatasetty are employees of Ontada, which received funding from G1 Therapeutics, Inc., for this work. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Medical writing assistance was provided by Barbara Blaylock from Blaylock Health Economics LLC funded by G1 Therapeutics, Inc.

Ethical conduct of research

All data were handled in compliance with the Health Insurance Portability and Accountability Act and the Health Information Technology for Economic and Clinical Health Act of 1996. The US Oncology Inc. Institutional Review Board granted this study an exception and waiver of consent.

Data sharing statement

This study used data from the Ontada iKnowMed electronic health records for The US Oncology Network and the Non-network clinics, which are not publicly available.

Previous presentations

Earlier versions of this work were presented as posters at the AMCP Nexus 2021 (Denver, CO, USA; October 18–21, 2021) and the 63rd ASH Annual Meeting (Atlanta, GA, USA; December 11–14, 2021).

Summary points

- This retrospective, observational study examined 1574 chemotherapy-treated patients with ES-SCLC from Network and 959 from Non-network clinics between 2015 and 2020.
- Patients were on average 67–68 years old. Half of patients were female (>51%), most patients were Caucasian (>81%), and almost all patients received first-line chemotherapy at index (>99%).
- Among patients with laboratory data, over half had at least one grade ≥3 myelosuppressive event after initiation of chemotherapy.
- Approximately a third of patients had grade ≥3 myelosuppressive event in at least 2 lineages.
- Over one-quarter of patients received fewer than the recommended 4–6 cycles of index chemotherapy treatment.
- Dose reductions, treatment holds, and treatment delays were statistically significantly more prevalent in patients with versus without grade ≥3 myelosuppressive events.
- Supportive care utilization including eligibility for RBC or platelet transfusion, G-CSF use, ESA use, and IV hydration use were statistically significantly more prevalent in patients with versus without grade ≥3 myelosuppressive events.
- HCRU and healthcare costs were significantly greater in Network patients with versus without grade ≥3 myelosuppressive events.
- This study highlighted that there is an unmet need to prevent or proactively manage chemotherapy-induced myelosuppression; reduction of chemotherapy-induced myelosuppression has the potential to reduce burden on patients and healthcare organizations.

References

Papers of special note have been highlighted as: • of interest; •• of considerable interest

1. Byers LA, Rudin CM. Small cell lung cancer: where do we go from here? *Cancer* 121(5), 664–672 (2015).
2. American Cancer Society. Cancer facts & figures 2021 (2021). Available at: www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2021/cancer-facts-and-figures-2021.pdf (Accessed 6 June 2022).
3. Wang S, Tang J, Sun T *et al.* Survival changes in patients with small cell lung cancer and disparities between different sexes, socioeconomic statuses and ages. *Sci. Rep.* 7(1), 1339 (2017).

4. American Cancer Society. Small cell lung cancer stages (2019). Available at: www.cancer.org/cancer/lung-cancer/detection-diagnosis-staging/staging-sclc.html (Accessed 31 January 2022).
5. Bernhardt EB, Jalal SI. Small cell lung cancer. In: *Lung Cancer.* Reckamp K (Ed.). Springer International Publishing Switzerland, Cham, CH, 301–322 (2016).
6. Tapan U, Furtado VF, Qureshi MM, Everett P, Suzuki K, Mak KS. Racial and other healthcare disparities in patients with extensive-xtage SCLC. *JTO Clin. Res. Rep.* 2(1), 100109 (2021).
7. Dingemans AC, Früh M, Ardizzoni A *et al.* Small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann. Oncol.* 32(7), 839–853 (2021).
8. National Comprehensive Cancer Network. Small cell lung cancer. *NCCN clinical practice guidelines in oncology.* Version 2.2022 (2021). Available at: www.nccn.org/professionals/physician_gls/pdf/sclc.pdf (Accessed 2 June 2022).
9. Horn L, Mansfield AS, Szczęsna A *et al.* First-line atezolizumab plus chemotherapy in extensive-stage small-cell lung cancer. *N. Engl. J. Med.* 379(23), 2220–2229 (2018).
10. Paz-Ares L, Dvorkin M, Chen Y *et al.* Durvalumab plus platinum-etoposide versus platinum-etoposide in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): a randomised, controlled, open-label, phase III trial. *Lancet* 394(10212), 1929–1939 (2019).
11. Ganti AKP, Loo BW, Bassetti M *et al.* Small cell lung cancer, version 2.2022, NCCN Clinical Practice Guidelines in oncology. *J. Natl Compr. Canc. Netw.* 19(12), 1441–1464 (2021).
12. Hiddinga BI, Raskin J, Janssens A, Pauwels P, Van Meerbeeck JP. Recent developments in the treatment of small cell lung cancer. *Eur. Respir. Rev.* 30, 210079 (2021).
13. Javarappa KK, Tsallos D, Heckman CA. A multiplexed screening assay to evaluate chemotherapy-induced myelosuppression using healthy peripheral blood and bone marrow. *SLAS Discov.* 23(7), 687–696 (2018).
14. Mauch P, Constine L, Greenberger J *et al.* Hematopoietic stem cell compartment: acute and late effects of radiation therapy and chemotherapy. *Int. J. Radiat. Oncol. Biol. Phys.* 31(5), 1319–1339 (1995).
15. Noda K, Nishiwaki Y, Kawahara M *et al.* Irinotecan plus cisplatin compared with etoposide plus cisplatin for extensive small-cell lung cancer. *N. Engl. J. Med.* 346(2), 85–91 (2002).
16. Lara PN Jr, Natale R, Crowley J *et al.* Phase III trial of irinotecan/cisplatin compared with etoposide/cisplatin in extensive-stage small-cell lung cancer: clinical and pharmacogenomic results from SWOG S0124. *J. Clin. Oncol.* 27(15), 2530–2535 (2009).
17. Hanna N, Bunn PA Jr, Langer C *et al.* 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(13), 2038–2043 (2006).
18. Han D, Wang G, Sun L *et al.* Comparison of irinotecan/platinum versus etoposide/platinum chemotherapy for extensive-stage small cell lung cancer: a meta-analysis. *Eur. J. Cancer Care (Engl.).* 26(6), (2017).
19. Kuter DJ. Managing thrombocytopenia associated with cancer chemotherapy. *Oncology (Williston Park).* 29(4), 282–294 (2015).

- **Review focused on the general approach to, and treatment of, thrombocytopenia in cancer patients, including thrombopoietin treatment in patients receiving non-myeloablative chemotherapy.**

20. Bryer E, Henry D. Chemotherapy-induced anemia: etiology, pathophysiology, and implications for contemporary practice. *Int. J. Clin. Transfus. Med.* 2018(6), 21–31 (2018).

- **Review focused on the development and evolution of chemotherapy-induced anemia with an emphasis on assorted therapeutic interventions.**

21. Gilreath JA, Rodgers GM. How I treat cancer-associated anemia. *Blood* 136(7), 801–813 (2020).
22. National Comprehensive Cancer Network. Hematopoietic growth factors. *NCCN clinical practice guidelines in oncology.* Version 1.2022 (2021). Available from: www.nccn.org/professionals/physician_gls/pdf/growthfactors.pdf (Accessed 2 June 2022).
23. Carey PJ. Drug-induced myelosuppression : diagnosis and management. *Drug Saf.* 26(10), 691–706 (2003).
24. Epstein RS, Basu Roy UK, Aapro M *et al.* Cancer patients' perspectives and experiences of chemotherapy-induced myelosuppression and its impact on daily life. *Patient Prefer. Adherence.* 2021(15), 453–465 (2021).

- **Analysis of an online survey of participants with breast, lung, or colorectal cancer recently treated with chemotherapy. The authors reported substantial real-world impact of chemotherapy-induced myelosuppresion on patient health-related quality of life.**

25. Epstein RS, Aapro MS, Basu Roy UK *et al.* Patient burden and real-world management of chemotherapy-induced myelosuppression: results from an online survey of patients with solid tumors. *Adv. Ther.* 37(8), 3606–3618 (2020).

- **Analysis of an online survey of participants with breast, lung, or colorectal cancer recently treated with chemotherapy. The authors reported substantial real-world impact of chemotherapy-induced myelosuppresion despite patient-focused approach and various methods to address chemotherapy-induced myelosuppresion.**

26. Roe H, Lennan E. Role of nurses in the assessment and management of chemotherapy-related side effects in cancer patients. *Nurs.: Res. Rev.* 2014(4), 103–115 (2014).

27. Epstein RS, Nelms J, Moran D, Girman C, Huang H, Chioda M. Treatment patterns and burden of myelosuppression for patients with small cell lung cancer: A SEER-medicare study. *Cancer Treat. Res. Commun.* 31(2022), 100555 (2022).

•• **Descriptive, restrospective analysis of the Surveillance, Epidemiology, and End Results (SEER)-Medicare data for patients with small cell lung cancer. The authors reported that only half of patients completed recommended chemotherapy cycles and health care resource utilization associated with myelosuppreion was prominent.**

28. Epstein RS, Weerasinghe RK, Parrish AS, Krenitsky J, Sanborn RE, Salimi T. 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(1), 108–118 (2022).

•• **Retrospective, observational analysis of electronic medical records for patients with small cell lung cancer. The authors reported substantial real-word burden of chemotherapy-induced myelosuppresion for patients with small cell lung cancer in the community cancer care setting.**

29. National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE). Version 5.0 (2017). Available from: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf (Accessed 2 June 2022).

30. Bureau of Labor Statistics. Medical care consumer price index (2021). Available from: www.bls.gov/cpi/factsheets/medical-care.htm (Accessed 7 October 2021).

31. Rudin CM, Brambilla E, Faivre-Finn C, Sage J. Small-cell lung cancer. *Nat. Rev. Dis. Primers.* 7(1), 3 (2021).

32. Bogart JA, Wang XF, Masters GA *et al.* Phase III comparison of high-dose once-daily (QD) thoracic radiotherapy (TRT) with standard twice-daily (BID) TRT in limited stage small cell lung cancer (LSCLC): CALGB 30610 (Alliance)/RTOG 0538. *J. Clin. Oncol.* 39(Suppl. 15), 8505–8505 (2021).

33. American Cancer Society. Lung Cancer Survival Rates (2022). Available at: www.cancer.org/cancer/lung-cancer/detection-diagnosis-staging/survival-rates.html (Accessed 22 September 2022).

34. Paz-Ares L, Chen Y, Reinmuth N *et al.* Durvalumab, with or without tremelimumab, plus platinum-etoposide in first-line treatment of extensive-stage small-cell lung cancer: 3-year overall survival update from CASPIAN. *ESMO Open.* 7(2), 100408 (2022).

35. Thomas K, Martin T, Gao A, Ahn C, Wilhelm H, Schwartz DL. Interruptions of head and neck radiotherapy across insured and indigent patient populations. *J. Oncol. Pract.* 13(4), e319–e328 (2017).

36. Claessens AKM, Erdkamp FLG, Lopez-Yurda M *et al.* Secondary analyses of the randomized phase III Stop&Go study: efficacy of second-line intermittent versus continuous chemotherapy in HER2-negative advanced breast cancer. *Acta Oncol.* 59(6), 713–722 (2020).

37. Bese NS, Sut PA, Ober A. The effect of treatment interruptions in the postoperative irradiation of breast cancer. *Oncology* 69(3), 214–223 (2005).

38. Cramer-Van Der Welle CM, Schramel F, Van Leeuwen AS, Groen HJM, Van De Garde EMW. Real-world treatment patterns and outcomes of patients with extensive disease small cell lung cancer. *Eur. J. Cancer Care. (Engl.).* 29(5), e13250 (2020).

39. Lyman GH, Kuderer NM, Aapro M. Improving outcomes of chemotherapy: established and novel options for myeloprotection in the COVID-19 era. *Front. Oncol.* 11, 697908 (2021).

40. COSELA (trilaciclib) for injection, for intravenous use. *Prescribing information.* G1 Therapeutics, Inc (2022).

41. Weiss JM, Csoszi T, Maglakelidze M *et al.* 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(10), 1613–1621 (2019).

42. Daniel D, Kuchava V, Bondarenko I *et al.* 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(10), 2557–2570 (2020).

43. Hart LL, Ferrarotto R, Andric ZG *et al.* 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(1), 350–365 (2021).

44. Gueyffier F, Cucherat M. The limitations of observation studies for decision making regarding drugs efficacy and safety. *Therapie.* 74(2), 181–185 (2019).

45. Boyko EJ. Observational research – opportunities and limitations. *J. Diabetes Complications* 27(6), 642–648 (2013).