Autonomic Symptoms May Suggest Paraneoplastic Neurological Syndromes in Small-Cell Lung Cancer

Guy Shechter[1], David Morrell[2], Regina Grebla[3], Steven Vernino[4]

[1]MedTech Analytics, LLC, Lexington, MA, USA, [2]Catalyst Pharmaceuticals, Coral Gables, FL, USA; [3]Northeast Epi, LLC, Bradford, NH, USA; [4]University of Texas Southwestern Medical Center, Dallas, TX, USA

Background

- Patients with small-cell lung cancer (SCLC) have a 3-5% chance of developing a paraneoplastic neurological syndrome (PNS), the most common types being Lambert-Eaton myasthenic syndrome (LEMS), sensory neuropathy, and limbic encephalitis.[1,2]
  - In some patients with PNS, autonomic symptoms (dry mouth, difficulty swallowing, orthostatic hypotension, impotence) occur[4] and may help identify patients with an increased risk of SCLC.
- Awareness of PNS in SCLC and screening for suspected PNS in patients with autonomic symptoms can lead to earlier diagnosis of both conditions, potentially leading to improved prognosis and quality of life for patients.

Objective

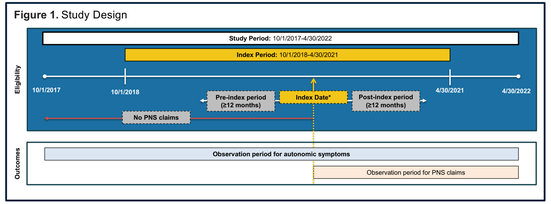
To evaluate whether the presence of autonomic symptoms can help identify SCLC patients at risk of comorbid PNS.

Methods

Study data and design

- Healthcare claims from a US de-identified dataset (Symphony Health's PatientSource®, 10/2017-4/2022) were analyzed.
- Eligible SCLC patients were identified based on ≥2 lung cancer claims ≥30 days apart, receipt of SCLC-associated therapies (etoposide and platinum-based chemotherapy; "treated SCLC"), continuous healthcare utilization (≥12 months pre- and post-first observed SCLC claim), and the absence of PNS claims before the index SCLC claim.
  - The first observed lung cancer claim served as the patient's index date. **(Figure 1)**
    - In the absence of diagnosis codes specific for SCLC in ICD-9-CM and ICD-10-CM, a lung cancer diagnosis was presumed to be SCLC among patients who received SCLC-associated therapies.

Figure 1. Study Design



Outcomes

- Autonomic symptoms were defined as ≥2 claims ≥30 days apart for autonomic nervous system disorders, orthostatic hypotension, and/or hypotension.[4]
- Neurological PNSs were defined as ≥2 claims ≥30 days apart for LEMS, paraneoplastic neuropathy, cerebellar degeneration, cerebellar ataxia, or opsoclonus-myoclonus. Paraneoplastic encephalomyelitis and limbic encephalitis had overlapping ICD-9-CM and ICD-10-CM codes and were combined. Although myasthenia gravis (MG) is not a PNS commonly associated with SCLC, its symptoms are often confused with LEMS symptoms.
- Patient demographic characteristics were assessed on index date; data were descriptive, and no statistical comparisons were performed.
- The proportions of SCLC patients with PNS with and without autonomic symptoms (including autonomic disorders, and hypotension) were compared. P values <.05 were considered statistically significant.

Results

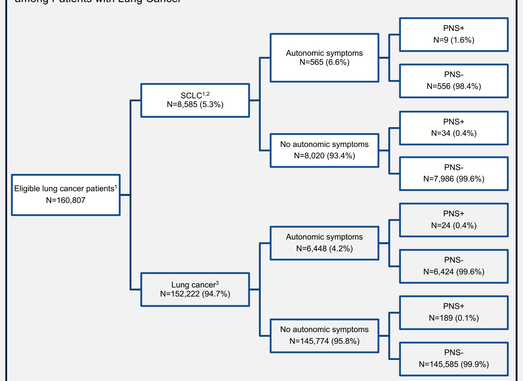
Patient Characteristics

- In total, 160,807 eligible patients with lung cancer were identified during the study period. Among them, 7,013 patients (4.4%) had claims associated with autonomic symptoms, including a diagnosis of autonomic disorders (n=1,024), orthostatic hypotension (n=1,594), and/or hypotension (n=4,913). **(Figure 2)**
- Overall, 256 (0.16%) patients had ≥1 neurological PNS following the index lung cancer diagnosis, including MG (n=77), LEMS (n=33), paraneoplastic encephalomyelitis or limbic encephalitis (n=23), paraneoplastic neuropathy (n=61), cerebellar degeneration (n=7), cerebellar ataxia (n=26), or opsoclonus-myoclonus (n=44).

Treated SCLC Cohort

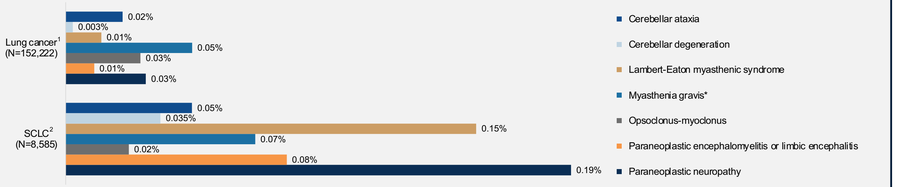
- 8,585 (5.3%) patients received SCLC-associated therapies.
- Patients with SCLC were mostly (56.3%) female, mean age of 71.1 ± 8.6 years at the index date, and 42.1% were from the Southern US Census region. **(Table 1)**
  - No meaningful differences were observed in measured demographic characteristics among SCLC patients with autonomic symptoms.
- Claims related to autonomic symptoms (n=565) were more frequent among patients with presumed SCLC than in patients with lung cancer who did not receive SCLC-associated therapies (6.6% vs 4.2%; p<0.0001; **Figure 2**).
  - Neurological PNSs after the index lung cancer diagnosis were observed in n=43/8,585 patients (0.5%).
  - **Figure 3** shows the distribution of individual neurological PNSs among patients with treated SCLC and among patients with lung cancer who did not receive SCLC-associated therapies.
- 1.6% (n=9/565) of patients with SCLC and autonomic symptoms had subsequent neurological PNS claims. **(Figure 4)**
  - In comparison, the rate of neurological PNS in patients without autonomic symptoms was four-fold lower (n=34/8,020; 0.4%; p<0.0002).
  - The proportion of patients with subsequent LEMS (5/565; 0.9%) in patients with autonomic symptoms was 9 times higher than in those without autonomic symptoms (8/8,020; 0.1%; p<0.00001).
  - The proportion of patients with subsequent paraneoplastic encephalomyelitis or limbic encephalitis (3/565; 0.5%) was 9 times higher in patients with SCLC with autonomic symptoms than in patients without autonomic symptoms (4/8,020; 0.05%; p<0.0002).
  - No significant differences were observed in the frequency of MG, paraneoplastic neuropathy, cerebellar degeneration, cerebellar ataxia, or opsoclonus-myoclonus among patients with SCLC according to the presence of autonomic symptoms.
- The findings in the primary analysis were similar among patients with lung cancer who did not receive etoposide and platinum-based therapies, where a diagnosis of a neurological PNS post-index was more common among patients with autonomic symptoms (p<0.0001).

Figure 2. Frequency of Autonomic Symptoms and Neurological Paraneoplastic Syndromes Overall among Patients with Lung Cancer



[1]Based on 2 lung cancer diagnoses ≥30 days apart; [2]Defined as the receipt of SCLC-associated therapies (etoposide and platinum-based chemotherapy); [3]Includes lung cancer claims without SCLC-associated therapies. Abbreviations: PNS, paraneoplastic syndromes; SCLC, small-cell lung cancer. Notes: Lung cancer cases are presumed to be SCLC in the absence of a specific ICD code for SCLC. PNSs were incident following the index lung cancer diagnosis.

Figure 3. Distribution of Neurological Paraneoplastic Syndromes Following Lung Cancer Diagnosis



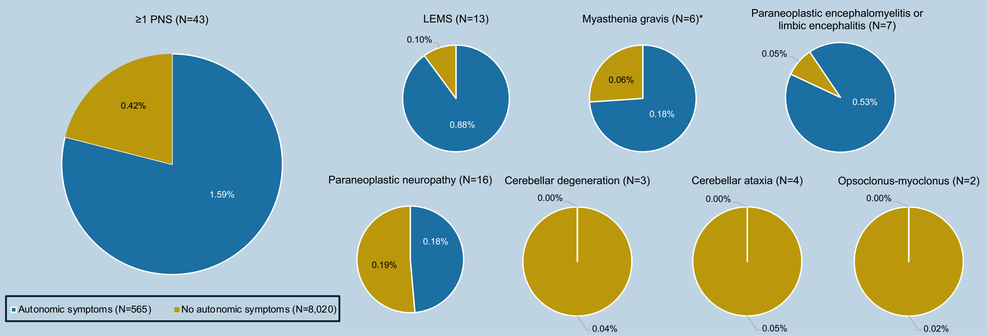
[1]Includes lung cancer claims without SCLC-associated therapies (etoposide + platinum-based chemotherapy). [2]Defined as the receipt of SCLC-associated therapies. Abbreviations: PNS, paraneoplastic syndromes; SCLC, small-cell lung cancer. Notes: Lung cancer cases are presumed to be SCLC given no specific ICD code for SCLC. Patients could have >1 PNS. *Although MG is not a PNS commonly associated with SCLC, its symptoms are often confused with LEMS symptoms.

Table 1. Patient Baseline Characteristics Assessed on the Index Date

	SCLC[1,2] N=8,585	SCLC without autonomic symptoms[1,2] N=8,020	SCLC with autonomic symptoms[1,2] N=565
Age, years, mean ± SD	71.1 ± 8.6	71.1 ± 8.6	71.6 ± 7.8
Female, n (%)	4,837 (56.3)	4,539 (56.6)	298 (52.7)
Census Region, n (%)			
Northeast	1,532 (17.8)	1440 (18.0)	92 (16.3)
Midwest	2,375 (27.7)	2204 (27.5)	171 (30.3)
South	3,613 (42.1)	3373 (42.1)	240 (42.5)
West	1,038 (12.1)	977 (12.2)	61 (10.8)
Unknown	27 (0.3)	26 (0.3)	1 (0.2)

Abbreviations: SCLC, small-cell lung cancer. [1]Based on 2 diagnoses ≥30 days apart; [2]Lung cancer cases were presumed to be SCLC in the absence of a specific ICD code for SCLC.

Figure 4. Neurological Paraneoplastic Syndromes According to the Presence of Autonomic Symptoms among Patients with Treated Small-Cell Lung Cancer



Abbreviations: LEMS, Lambert-Eaton myasthenic syndrome; PNS, paraneoplastic syndromes; SCLC, small-cell lung cancer. Patients could have >1 PNS. *Although MG is not a PNS commonly associated with SCLC, its symptoms are often confused with LEMS symptoms.

Limitations

- The claims data used in this analysis relies upon ICD coding and may not capture all diagnoses or symptoms. In addition, cash-paying and uninsured patients are not captured in the database.
- As SCLC is not associated with a unique ICD code, there is potential for inclusion of patients with other types of lung cancer. However, this analysis was restricted to patients who received etoposide and platinum-based therapies associated with SCLC to address this risk.
- The requirement of healthcare utilization post-index risks introducing survival bias as patients with SCLC may not survive long enough to be diagnosed with a PNS; however, this enables the identification of PNS in an observational setting where diagnostic delays may occur.

Conclusion

In this retrospective observational study, the presence of autonomic symptoms among US patients with SCLC was associated with a higher likelihood of PNS diagnosis, specifically LEMS and paraneoplastic limbic encephalitis.

References

1. Erlington et al. J Neurol Neurosurg Psychiatry 1991;54(9):764-7.
2. Dalmau et al. Lancet Neurol 2008;7(4):327-40.
3. Honnorat J and Antoine JC. Orphanet J Rare Dis 2007;2:22.
4. Titulaer et al. Lancet Neurol 2011;10(12):1098-107

Financial support: This study was funded by Catalyst Pharmaceuticals (Coral Gables, FL, USA).

Supported by: Catalyst pharmaceuticals

National Comprehensive Cancer Network Annual Conference. April 5-7, 2024. Orlando, FL, USA.
Correspondence can be addressed to: dmorrell@catalystpharma.com