Lambert-Eaton Myasthenic Syndrome is Underrecognized in Small Cell Lung Cancer: An Analysis of Real-World Data

David Morrell,[1] Benjamin Drapkin,[2] Guy Shechter,[3] Regina Grebla[4]

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

BACKGROUND

- Lambert-Eaton myasthenic syndrome (LEMS) is a rare autoimmune disorder characterized by proximal muscle weakness, loss of tendon reflexes, and autonomic dysfunction that can occur as a paraneoplastic disorder, most commonly in association with small cell lung cancer (SCLC)[1-3]
- SCLC accounts for 10-15% of lung cancers in the United States (US)[4,5]
  - LEMS symptoms often precede SCLC diagnosis and are a prognostic indicator of SCLC survival[2,6]
- LEMS was estimated to occur in 3% of patients with SCLC in prospective European studies[7-9]
  - Data on the epidemiology of SCLC-LEMS in the US is more limited. In single-center retrospective US studies, LEMS occurred in 4-6% of patients with SCLC[10,11]

Objective: To investigate the frequency of LEMS diagnoses among US patients with SCLC in the US

METHODS

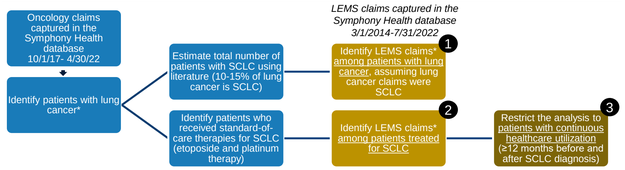
Study Design and Data Source

- Retrospective observational database cohort study using Symphony Health's PatientSource®, Anonymous Patient Level Datasets (LEMS, 3/1/2014-7/31/2022; Oncology, 10/1/2017-4/30/2022)
  - PatientSource® data include individual-level longitudinal medical and pharmacy healthcare claims for >300 million US-based commercial and Medicare Advantage enrollees

Patient Selection Criteria

- Patients with a lung cancer diagnosis (including non-small cell lung cancer (NSCLC)) were identified in the oncology dataset based on ≥2 claims ≥30 days apart[12]
  - **Treated SCLC** included receipt of etoposide and platinum (carboplatin or cisplatin) therapy
- Patients with LEMS were identified based on ≥2 claims ≥30 days apart[12]
- The earliest lung cancer claim served as the index date (**Figure 1**)

Figure 1. SCLC-LEMS identification



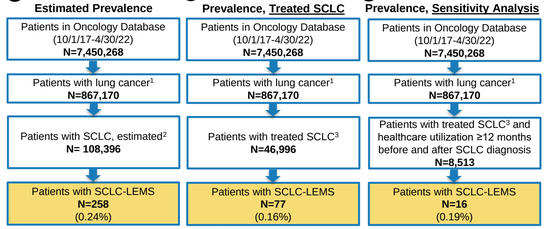
*≥2 diagnoses on two dates ≥30 days apart

Analysis

- In the absence of diagnosis codes specific for SCLC in ICD-9-CM and ICD-10-CM, the prevalence of LEMS in SCLC was estimated using 3 approaches:
  - (1) Using the number of patients with lung cancer and applying the midpoint (12.5%) of the estimated proportion of lung cancer patients with SCLC[4]
    - Because almost all cases of tumor-associated LEMS are SCLC[1], a lung cancer diagnosis was presumed to be a SCLC diagnosis among patients with LEMS
  - (2) The proportion of patients with LEMS and treated SCLC among those with treated SCLC
  - (3) The proportion of patients with LEMS and treated SCLC among those with treated SCLC and continuous healthcare utilization (≥12 months pre- and post-index SCLC claim)
- Patient demographic characteristics were assessed on index date; data were descriptive, and no statistical comparisons were performed
- The time between the earliest SCLC and LEMS diagnoses was assessed using the longitudinal LEMS dataset, which provided an additional 3 years of claims history (2014-2022)

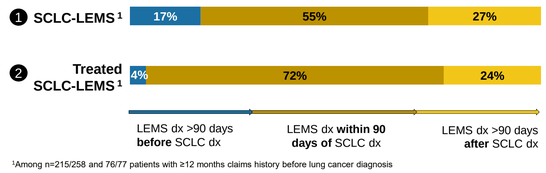
RESULTS

Figure 2. Estimated prevalence of LEMS in patients with SCLC



[1]Based on 2 lung cancer diagnoses ≥30 days apart; [2]Using midpoint estimation based on SCLC occurring in 10-15% of lung cancer patients; [3]Based on 2 lung cancer diagnoses ≥30 days apart and receipt of etoposide and platinum therapy. Note: lung cancer cases are presumed to be SCLC in the absence of a specific ICD code for SCLC.

Figure 3. Proportion of patients with SCLC-LEMS according to timing of diagnosis



[1]Among n=215/258 and 76/77 patients with ≥12 months claims history before lung cancer diagnosis

Estimated Prevalence of LEMS in Patients with SCLC

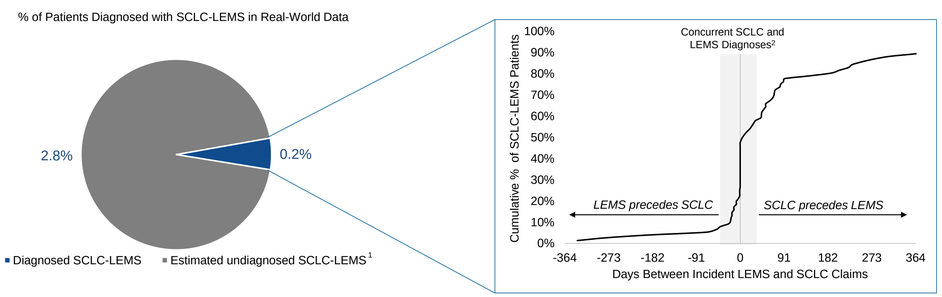
- 867,170 US patients with lung cancer claims between 2017 and 2022 were identified in the Symphony Health database; 46,996 (5.4%) received studied SCLC therapies
- 258 patients with lung cancer and LEMS claims were identified between October 2017 and April 2022 (56% female, mean age 66.1 years) (**Table 1**)
- The prevalence of LEMS among patients with SCLC in the database during this period ranged from 0.16% (treated SCLC) to 0.24% (presumed SCLC) (**Figure 2**)
  - Among the subset of 8,513 patients with treated SCLC and continuous healthcare utilization, 0.19% had LEMS claims, consistent with the primary analyses

Timing of SCLC and LEMS

- Data on the timing of diagnoses (dx) were available for 83% (n=215/258) of SCLC-LEMS* patients with ≥12 months claims history (**Figure 3**)
  - In 17%, the initial LEMS claim preceded SCLC by >90 days
  - 55% had initial SCLC and LEMS claims within 90 days
  - In 27%, the initial LEMS claim was >90 days after the index SCLC claim and the mean (median) time between diagnoses was 15.5 (12.1) months
- Among patients with treated SCLC-LEMS (n=76) with ≥12 months claims history, the diagnosis of LEMS preceded SCLC by >90 days, or occurred within 90 days, in 76%
  - LEMS lagged SCLC by ≥12 months in 12% (n=9/76) of treated SCLC-LEMS
  - Initial claims that preceded SCLC by > 2 weeks were nearly always (75%; n=9/12) associated with neurologist visits
- The diagnosed prevalence of SCLC and LEMS in this analysis was <1/10 of earlier published estimates of LEMS among patients with SCLC (**Figure 4**). This suggests the possibility that >90% of LEMS in SCLC patients was undiagnosed.

* Lung cancer cases in patients with LEMS were presumed to be SCLC in the absence of a specific ICD code for SCLC

Figure 4. Diagnosed prevalence of LEMS among patients with SCLC and timing of diagnoses



*Among n=76/77 treated SCLC-LEMS patients with 12+ months claims history before lung cancer diagnosis; [1]3% based on published literature; [2]Concurrent LEMS claims occurred ± 14 days of initial SCLC claim

Estimated patients with SCLC-LEMS in the US

- There were 603,989 prevalent US lung cancer cases in 2020[4]
- The estimated number of patients with SCLC-LEMS in the US therefore ranges from 1,800 to 2,700*, among whom >90% were undiagnosed
- Assuming SCLC-LEMS accounts for approximately 50% of LEMS overall[2], we estimate the total number of US patients with LEMS to be in the range of 3,600 to 5,400

*Assumes SCLC accounts for 10-15% of lung cancer in the US and a 3% prevalence of SCLC-LEMS

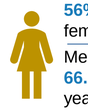
Patient Characteristics

- Most patients in this study with SCLC and LEMS were female, contrary to earlier published studies reporting most SCLC-LEMS cases were among males[13]

Table 1. Patient baseline characteristics assessed on the index date

	SCLC-LEMS[1] N=258	Treated SCLC-LEMS[2] N=77
Age, years, mean ± SD	66.1 ± 7.6	64.5 ± 7.0
Female, n (%)	144 (56)	42 (55)
Insurance coverage, n (%)[3]		
Commercial	135 (52)	48 (62)
Medicare	70 (27)	16 (21)
Medicaid	17 (7)	4 (5)
Other[4]	6 (2)	0 (0)
Unknown	30 (12)	9 (12)
Census Region, n (%)		
Northeast	53 (21)	16 (21)
Midwest	69 (27)	20 (26)
South	102 (40)	33 (43)
West	33 (13)	8 (10)
Unknown	1 (0.4)	0 (0)
Receipt of etoposide + platinum therapy, n (%)	77 (30)	77 (100)

[1]Lung cancer cases are presumed to be SCLC in the absence of a specific ICD code for SCLC; [2]For treated SCLC, which included receipt of etoposide and platinum therapy; [3]Includes patients with government-sponsored insurance (n=1) and with a combination of insurance types.



56% female

Mean age **66.1** years

40% in Southern US

52% with commercial insurance

30% received SCLC standard-of-care therapies

LIMITATIONS

- Analyses were based on observational data and unmeasured confounding is possible
- As SCLC is not associated with a unique ICD code, there is potential for misclassification of patients with NSCLC and potential overestimation of the prevalence of LEMS among patients with SCLC. Such misclassification in this analysis is unlikely because (1) LEMS is known to be associated with SCLC[1]; and (2) analyses restricted to patients who received SCLC therapy yielded similar results.
- Patients with SCLC may not survive long enough to be diagnosed with LEMS
- The requirement of claims post-SCLC diagnosis in the sensitivity analysis risks introducing survival bias; however, this enables the estimation of SCLC-LEMS in the setting of LEMS diagnostic delay

CONCLUSIONS

- LEMS is the most common neurologic paraneoplastic disorder associated with SCLC, but among US patients LEMS may be underdiagnosed, as claims are less than 1/10 the estimated prevalence
- Because some non-specific LEMS symptoms may be attributed to SCLC or its treatment, comorbid LEMS may go unrecognized
- Underdiagnosis of LEMS and other PNS could lead to undertreatment, and standardized screening and paraneoplastic antibody testing may be warranted

REFERENCES

1. O'Neill et al. *Brain* 1988;111(Pt 3):577-96
2. Titulaer et al. *Lancet Neurol* 2011;10(12):1098-107
3. Schoser et al. *J Neurol* 2017;264(9):1854-63
4. American Cancer Society. Key Statistics for Lung Cancer. 2023.
5. Rudin et al. *Nat Rev Dis Primers* 2021;7(1):3
6. Maddison et al. *Lancet* 1999;353(9147):117-8
7. Wirtz et al. J Neuroimmunol 2005;164(1-2):161-5
8. Gozzard et al. *Neurology* 2015;85(3):235-9
9. Payne et al. *J Thorac Oncol* 2010;5(1):34-8
10. Emani et al. *Thorac Cancer* 2022;13(7):925-33
11. de la Monte et al. *Am J Med* 1984;77(5):851-7
12. Khan et al. *JAMA Oncol* 2016;2(11):1507-8
13. Wirtz et al. *Clin Neurol Neurosurg* 2002;104(4):359-63

DISCLOSURES

DM – employee, shareholder of Catalyst Pharmaceuticals; BD – consulting Sonata Therapeutics; GS, RG - consultants to Catalyst Pharmaceuticals

Supported by: Catalyst pharmaceuticals

Correspondence can be addressed to: dmorrell@catalystpharma.com