EP13.04: Treatment-Related Pneumonitis in Extensive-Stage Small Cell Lung Cancer According to Immune Checkpoint Inhibitor Use and Pre-existing Interstitial Lung Abnormalities

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INTRODUCTION

・Treatment-related pneumonitis represents a clinically significant complication of systemic therapy for extensive-stage small cell lung cancer (ES-SCLC), attributable to both cytotoxic chemotherapy and immune checkpoint inhibitors (ICIs).

・Pre-existing interstitial lung abnormalities (ILA) and interstitial lung disease (ILD) are major risk factors for drug-induced lung injury in this population. Baseline ILA is more prevalent in patients developing drug-induced ILD[1], predicts checkpoint inhibitor-related pneumonitis and poorer survival[2], and fatal cases have been documented even in mild fibrosing interstitial pneumonia receiving durvalumab.[3]

・Real-world cohorts receiving chemo-immunotherapy have demonstrated a measurable incidence of ILD-related adverse events[4], and the incidence of on-treatment ILD may vary between ICI agents despite comparable overall survival[5], although direct comparisons have not revealed consistent differences in immune-related adverse event frequency.

・Nevertheless, no study to date has concurrently evaluated treatment-related pneumonitis according to **both** ICI exposure and baseline ILA/ILD status within a single cohort that includes ICI-untreated individuals.

・**Objective:** To characterise the association between baseline ILA/ILD and treatment-related pneumonitis in ES-SCLC, accounting for ICI exposure, in a single-centre retrospective cohort.

METHODS

Study design and population： We conducted a single-centre retrospective cohort study of individuals diagnosed with Stage IVA or IVB small cell lung cancer between January 2019 and October 2025. Data were abstracted from medical records in July 2026. The study was designed as a prognostic investigation; causal inference was not intended.

Exposure： Baseline ILA/ILD was assessed on pre-treatment computed tomography in accordance with the Fleischner Society 2020 position statement. Immune checkpoint inhibitors, where administered, were initiated as part of first-line therapy.

Outcome： Treatment-related ILD was defined as drug-induced lung injury, radiation pneumonitis, or acute exacerbation of pre-existing interstitial pneumonia, adjudicated following exclusion of infection, cardiac failure and tumour progression.

Statistical analysis： Cumulative incidence was estimated with death treated as a competing event and compared using Gray's test. Crude incidence was compared using Fisher's exact test.

DISCUSSION AND CONCLUSION

Key Message

•Baseline ILA/ILD was associated with a markedly increased incidence of treatment-related pneumonitis in ES-SCLC (1-year cumulative incidence 26.7% vs 0%; Gray's test, p=0.003), irrespective of ICI exposure — which was in fact less frequent among individuals with ILA/ILD, arguing against confounding by treatment selection.

Interpretation

•These findings are consistent with prior reports of baseline ILA being over-represented among individuals developing drug-induced ILD under chemo-immunotherapy[1], and extend them to a cohort including ICI-untreated individuals, suggesting that parenchymal vulnerability, rather than the specific agent, is the principal determinant of risk.

•Concordant elevation of KL-6 supports the biological validity of the CT-based classification and suggests that serum biomarkers may complement imaging.

Clinical Implications

•Systematic ILA/ILD assessment on pre-treatment CT (Fleischner Society criteria) is feasible in routine practice and may facilitate risk stratification before initiating systemic therapy.

•In individuals with ILA/ILD, closer respiratory monitoring, a lower threshold for CT re-evaluation, and shared decision-making regarding treatment intensity may be warranted.

Conclusions and Future Directions

•Baseline ILA/ILD identifies a subgroup at substantially elevated risk of treatment-related pneumonitis. These findings are hypothesis-generating; validation in a prospective, multicentre study with blinded adjudication of both ILA and outcome is warranted.

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RESULTS

Of the eligible cohort, two individuals were excluded (absence of pre-treatment CT, n=1; insufficient clinical data, n=1), yielding a final analytic cohort of **50 individuals**, of whom 16 (32%) exhibited baseline ILA/ILD.

Treatment-related pneumonitis occurred in six individuals (12%). Crude incidence was substantially higher in the presence of baseline ILA/ILD than in its absence (31.2% [5/16] vs 2.9% [1/34]; Fisher's exact test, p=0.010), corresponding to a relative risk of 10.6 (95% CI 1.3–83.6).

Accounting for death as a competing event, the 1-year cumulative incidence was 26.7% among individuals with ILA/ILD versus 0% among those without (Gray's test, p=0.003). The majority of events occurred within approximately six months of treatment initiation.

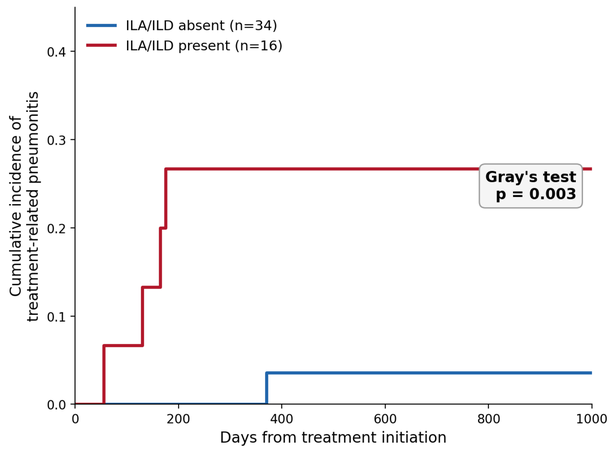
ICI exposure was less frequent in the ILA/ILD-present group (25.0% vs 47.1%), indicating that the observed association is not attributable to differential ICI use. Baseline KL-6 was significantly elevated in the ILA/ILD-present group (median 368 vs 265 U/mL; p=0.010), supporting the validity of the radiological classification.

Table 1. Baseline characteristics by ILA/ILD status

Characteristic	ILA/ILD absent (n=34)	ILA/ILD present (n=16)	p
Male sex, n (%)	27 (79)	12 (75)	0.73
Smoking history, n (%)	33 (97)	16 (100)	1.00
Pack-years, median	57	51	0.41
ECOG PS 0-1, n (%)	28 (82)	15 (94)	0.79
COPD, n (%)	7 (21)	4 (25)	0.73
ICI use, n (%)	16 (47)	4 (25)	0.22
Thoracic RT, n (%)	4 (12)	1 (6)	1.00
KL-6, median (U/mL)	**265**	**368**	**0.010**
Death during follow-up, n (%)	27 (79)	12 (75)	0.73

Data are n (%) or median.
Abbreviations: ILA, interstitial lung abnormality; ILD, interstitial lung disease; ECOG PS, Eastern Cooperative Oncology Group performance status; COPD, chronic obstructive pulmonary disease; ICI, immune checkpoint inhibitor; RT, radiotherapy; KL-6, Krebs von den Lungen-6.

Figure 1. Cumulative incidence of treatment-related pneumonitis with death as a competing event, by baseline ILA/ILD status. Curves separate early (< 6 months).



LIMITATIONS

•This was a single-centre retrospective study with a limited number of events (n=6), precluding multivariable adjustment for potential confounders.

•Baseline ILA/ILD and treatment-related pneumonitis were assessed by a single reviewer without blinding; differential misclassification cannot be excluded, and the effect size may be overestimated.

•Wide confidence intervals reflect the pilot nature of the study, which was underpowered by design.