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The genomic landscape of small cell lung cancer in never smoking patients

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Background

Small cell lung cancer (SCLC) predominantly develops in patients with significant smoking history, but 6-8% of patients in recent SCLC datasets have no tobacco exposure. Prior reports have suggested that SCLC in never smoking patients may have unique genomic traits.

Methods

We retrospectively analyzed records from SCLC patients reporting “never smoking” (NS, n = 54) or “current/former smoking” (C/FS, n = 609) status. Tumors were sequenced with the Tempus xT assay, including a targeted DNA panel (595-648 genes) and whole exome capture RNA-seq. Tumor immune cell infiltration was estimated from RNA expression data. PD-L1 positivity was defined by tumor expression > 1% using 22C3 pharmDx IHC. Statistical significance was assessed with Pearson’s chi-squared test or Fisher’s exact test, using a threshold of $p < 0.05$ or false discovery rate-adjusted $q < 0.05$.

Results

Compared with CF/S patients, NS patients were more likely to be female (70% vs 55%, $p = 0.031$). Tumors of NS patients had a lower prevalence of *TP53* mutations (59% vs 85%, $q < 0.001$) but no significant difference in *RB1* mutations (57% vs 63%, $q = 0.600$). Meanwhile, NS patients had a higher prevalence of *EGFR* (26% vs 2.6%, $q < 0.001$) and *PIK3CA* (15% vs 3.6%, $q = 0.022$) mutations. We also observed a trend towards higher rates of mutations in *FGF4* (7.4% vs 1.6%, $q = 0.100$) and *NF1* (7.4% vs 1.3%, $q = 0.092$). Gene fusions were infrequently found, with no notable difference across cohorts. With regard to the immune environment, NS patients had lower tumor mutation burden (2.59/Mb vs 4.99/Mb, $p < 0.001$) and a trend towards higher PD-L1 positivity (20% vs 9%, $p = 0.086$). NS tumors also had decreased immune cell infiltration (median 2% vs 10%, $p = 0.008$), and specifically a lower proportion of CD4+ and CD8+ T cells and higher proportion of macrophages.

Conclusions

The mutational landscape of SCLC in NS patients significantly differs from that of C/FS patients. Tumors of NS patients were more likely to harbor mutations in oncogenic drivers – such as *EGFR* and *PIK3CA* – and exhibited lower TMB and immune cell infiltration. These findings suggest that the occurrence of SCLC in NS patients may represent a distinct genomic entity and treatment implications should be further explored.

Legal entity responsible for the study

The authors.

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Disclosure

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