Molecular and Genomic Characterization of Small Cell Lung Cancer (SCLC)

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Abstract

Introduction: Small cell lung cancer (SCLC), strongly tobacco-associated, has been described to have a heavy mutation burden, harboring high rates of TP53 and RB1 alterations. While initially responsive to radiation and chemotherapy, SCLC is characterized by eventual progression and resistance to traditional therapy. We retrospectively analyzed a molecular profiling (MP) database to identify potentially actionable alterations using a multi-platform approach which includes massively parallel sequencing.

Experimental Procedures: SCLC patient samples were referred to a central CLIA laboratory (Caris Life Sciences, AZ) for MP (immunohistochemistry [IHC] and next generation sequencing [NGS]). Expression of PD1 (MRQ-CLIA laboratory (Caris Life Sciences, AZ) for MP (immunohistochemistry [IHC] which includes massively parallel sequencing. Identification of potentially actionable alterations using a multi-platform approach

Results

246 patients with SCLC were included in the study and tested centrally at a CLIA certified laboratory. Of these, 203 patients had adequate tumor samples for MP and were included in the final analysis. The median age of patients was 65 (range: 29-88). Cancer cells expressed PD-L1 in 3% of cases (2/203) and PD1+ TILs were detected in 38% (75/197).

Background

- Nearly all cases of SCLC are attributable to cigarette smoking.
- Genomic studies have shown high rates of TP53 and RB1 mutations, leading to a loss of cell cycle control, rapid doubling time and early development of metastases.
- SCLC is highly sensitive to initial chemotherapy/radiotherapy, however most patients will experience recurrence.
- The discovery of new targets is highly desirable for this disease which is very difficult to treat in advanced stages.

Methods

- 246 patients with SCLC were included in the study and tested centrally at a CLIA laboratory (Caris Life Sciences, Phoenix, AZ). Tests included one or more of the following: gene sequencing, copy number variation (NextSeq Illumina) and protein expression (immunohistochemistry [IHC]). Antibodies and cutoffs can be obtained by request, or are provided in the figures.

Results, contd.

- As an additional 43 patients profiled after abstract submission were included in the final analysis.

Figure 1. SCLC cases selected for immune checkpoint pathway and expanded next-generation sequencing analyses.

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Figure 2. Patient demographics and tissue specimen sites submitted for profiling. (A) Distribution of gender and age of SCLC patients included in this analysis. (B) Specimen sites submitted for molecular profiling, excluding lung, mediastinal and thoracic regions.

Figure 3. Immune Checkpoint Pathway PD-1 positive TILs vs PD-1+ tumor expression rate

Conclusions

- PD-1 immune checkpoint pathway shows poorer one-third of SCLC have PD-1 positive TILs and up to 22% PD1-L1 tumor expression. Antibody doses and thresholds impact the frequencies observed in SCLC.
- Next-generation sequencing confirms previously observed high rates of TP53 and RB1 mutations, as well as NOTCH1.
- Mutations in additional, potentially actionable genes included RET, SMO, ATM, and SMARCA4.
- Genealogy may reveal mutations in known oncogenic drivers from other cancers, for example, BRCA, P53, PTEN, VHL, KEAP1, etc.
- Further efforts are needed to identify and validate new therapeutic targets in SCLC.

References


Figure 4. Most common genomic alterations in SCLC detected by next-generation sequencing.

Figure 5. Protein expression rates of select biomarkers in SCLC.

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