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Future directions of diagnostic and therapeutic strategies specific to subtypes of small cell lung cancer

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Abstract

Small cell lung cancer exhibits rapid proliferation and significant metastatic potential. There are significant epidemiologic and biological associations with tobacco carcinogens. While most small cell lung cancers display neuroendocrine characteristics, a significant subset of tumors does not possess these features. Genomic profiling of small cell lung cancer demonstrates genetic instability, nearly universal inactivation of the tumor suppressor genes TP53 and RB1, and a significant mutation burden. Due to early metastasis, a limited number of patients are suitable for curative lung resection, necessitating adjuvant platinum-etoposide chemotherapy for these individuals. Consequently, most patients are presently receiving chemoradiation, with or without the addition of immunotherapy. For patients with disease localized to the chest, standard treatment comprises thoracic radiotherapy alongside concurrent platinum-etoposide chemotherapy. Patients diagnosed with metastatic disease receive treatment that combines platinum-etoposide chemotherapy with immunotherapy utilizing an anti-programmed death-ligand 1 monoclonal antibody. Small cell lung cancer initially exhibits a strong response to platinum-based chemotherapy; however, these responses are temporary due to the emergence of drug resistance. Recent years have seen an accelerated accumulation of biological insights into the disease, resulting in a redefinition of the classification scheme for small cell lung cancer. The emerging understanding of molecular subtypes in small cell lung cancer may delineate distinct therapeutic vulnerabilities. The integration of these recent findings with existing knowledge of small cell lung cancer biology and clinical management could result in significant improvements in patient care for this condition. The authors provide an overview of multimodal clinical approaches in small cell lung cancer, emphasizing recent advancements in research that may expedite clinical development.

Keywords: small cell lung cancer; future directions; therapy; diagnosis; tumor heterogeneity

Small cell lung cancer

Small cell lung cancer accounts for approximately 13%–15% of all lung cancer cases and is among the most lethal malignancies, exhibiting a 5-year survival rate of less than 7%.Small cell lung cancer is characterized by rapid proliferation, high vascularity, apoptotic imbalance, and early metastatic spread.[1] Consistent with this significant metastatic potential, two-thirds of patients exhibit tumor cell dissemination beyond the chest at the time of initial diagnosis. Consequently, a limited number of patients are suitable for potentially curative multimodality therapy.[2] Over the last ten years, genotype-directed targeted therapies that focus on mutually exclusive subtypes characterized by aberrant oncogenic drivers have significantly enhanced treatment outcomes for patients with non-small cell lung cancer.[3] Small cell lung cancer exhibits distinct biological and clinical characteristics compared to other lung cancer types, resulting in a notable disparity in therapeutic advancements relative to non-small cell lung cancer.[4] After a prolonged nihilistic period, significant advancements in the understanding of small cell lung cancer biology and tumor heterogeneity have been achieved.[4] These advancements across multiple domains may establish new pathways in management protocols and offer renewed optimism for patients with this challenging disease.

Small cell lung cancer, originating from bronchial tissue, was first characterized by Barnard in 1926, who referred to it as an atypical mediastinal oat cell sarcoma.[5] Approximately 30 years later, Azzopardi offered a light-microscopic description that differentiated small cell lung cancer from other lung cancer types. [6] The 1973 discovery that small cell lung cancer cells disseminate via lymphatic and blood vessels earlier than malignant cells of other lung cancer histotypes diminished the prominence of surgical resection. [7] The therapeutic focus shifted to radiation and chemotherapy. Small cell lung cancer tumors exhibit significant chemo-sensitivity initially. [8] Recurrence occurs rapidly, making small cell lung cancer a particularly challenging tumor type for oncologists to manage. [9] The concept of platinum-based combination chemotherapy, as currently employed, was established in the 1980s. Numerous studies indicated that concurrent administration of platinum-based chemotherapy with chest radiotherapy enhanced survival rates in patients with limited-stage small cell lung cancer. Additionally, platinum-based combinations incorporating etoposide yielded improved survival outcomes for patients with extensive-stage disease. [10] Consequently, the etoposide/platinum combination served as the standard treatment until 2019, when research indicated that the addition of anti-programmed death-ligand 1 immunotherapy to etoposide/platinum chemotherapy enhanced survival rates, resulting in a small proportion of patients remaining alive at the 3-year mark. [11] The absence of potentially targetable oncogenic drivers, coupled with the limited availability of surgically resected tissue specimens suitable for profiling studies, significantly impeded therapeutic advancements. [12] The shortage of sufficient patient materials has heightened the significance of preclinical models and patient-derived xenografts in elucidating the biology of small cell lung cancer and facilitating translational research. [12] The emergence of multimodal approaches, increased research funding, and the recent resurgence of profiling studies due to the development of representative disease models have advanced small cell lung cancer research.

Future directions

To present, the application of targeted therapies has been unsuccessful in small cell lung cancer, and the efficacy of immunotherapy in non-small cell lung cancer has not been fully observed in this malignancy. The absence of a breakthrough in the therapeutic options for small cell lung cancer is mostly due to its significant tumoral adaptability and the non-selective patient groups involved in clinical trial enrollment. Thus, categorizing patients based on their predominant molecular subtypes and particular protein-level modifications may aid in the formulation of innovative targeted approaches for this challenging disease. The infrequent use of surgery in small cell lung cancer, along with the tendency of small biopsies to inadequately represent the tumor's expression profile, renders the diagnosis of molecular states a complex concept, particularly in clinical environments. The examination of blood-derived tumor elements, including circulating tumor cells, cell-free tumor DNA, and tumor-derived extracellular vesicles, may offer alternative avenues for monitoring molecular phenotypes during the disease and evaluating biomarkers for treatment response and prognosis. [13] Recently, two autonomous, cell-free tumor DNA classifiers were reported to differentiate between subtypes of small cell lung cancer by methylation profiling.[14, 15] Notably, regardless of the varied pedagogical and training methodologies, both successfully identified small cell lung cancer subtypes with an accuracy of 90%. Due to the diagnostic significance of distinct tumor-associated proteins, comprehensive proteome profiling may provide novel insights into subtype-specific biomarkers. A total of 367 subtype-specific proteins were recently found by mass spectrometry-based proteomics, exhibiting differential expression in a specific subtype relative to all other subtypes. [16] The independent analysis of the cell pellet and culture media allows for the interpretation of the results as potential biomarkers derived from tissue and blood. Nonetheless, that study was performed on small cell lung cancer cell lines [16]; so, the clinical relevance and application of these proteins necessitate additional confirmation with human tissue and blood samples. The distinct vulnerability profiles of each small cell lung cancer subtype may establish a future paradigm for selecting the most successful treatment. This is particularly pertinent as, unlike non-small cell lung cancer, small cell lung cancer typically exhibits a loss of tumor suppressors as a primary genetic characteristic, leading to significantly restricted options for targeting oncogenic drivers. Considering the direct transcriptional relationship between achaete-scute homolog 1 and delta-like protein 3 in Notch-inactive tumor cells, the small cell lung cancer-A subtype is anticipated to exhibit sensitivity to delta-like protein 3 suppression. [17, 18] Furthermore, as previously stated, small cell lung cancer-A is significantly reliant on the levels of both BCL-2 and INSM1.6. [19] Consequently, BCL-2 inhibitors may serve as potential subtype-specific therapeutic agents for this category of small cell lung cancer, akin to LSD1 inhibitors, which interfere with the interaction between LSD1 and the transcriptional repressor INSM1, thereby suppressing the expression of neuroendocrine-associated genes, such as achaete-scute homolog 1.One hundred six CREBBP is an acetyltransferase that facilitates chromatin accessibility and functions as a significant tumor suppressor in small cell lung cancer. [20] Due to the frequent association of small cell lung cancer-A with CREBBP inactivation and the sensitivity of CREBBP-deleted tumors to histone deacetylase inhibition, histone deacetylase inhibitors such as pracinostat or tinostamustine may provide novel therapeutic options for achaete-scute homolog 1-defined tumors. [20] Inhibition of the SOX2 oncogene by hedgehog signaling cascade inhibitors e.g. sonidegib or vismodegib may constitute a promising targeted therapy strategy in small cell lung cancer-A due to the elevated expression of SOX2 in this subtype. [21] Small cell lung cancer-N is frequently linked to MYC amplification, presenting a possible target for particular MYC inhibitors, e.g. MYCi361, that interact with MYC intracellularly, break MYC/MAX dimers, and hinder MYC-mediated gene expression. Three hundred ten Furthermore, due of elevated arginine production and AURKA activity, NEUROD1-driven malignancies are hypothesized to exhibit sensitivity to arginine depletion induced by

pegylated arginine deaminase (ADI-PEG 20) and AURKA inhibition (e.g., alisertib).Small cell lung cancer-N demonstrates specific tropism for the oncolytic Seneca Valley virus. Consequently, with suitable biomarker-directed patient selection, the Seneca Valley virus may exhibit selective efficacy as either a monotherapy or in conjunction with immunotherapy. The NEUROD1-to-achaete-scute homolog 1 ratio may serve as a prognostic biomarker in this scenario. [22] Recent CRISPR screens demonstrated that tumors driven by POU2F3 exhibit susceptibility to IGF-1R deficit induced by IGF-1R inhibitors such as dalotuzumab. [23] Furthermore, PARP inhibitors such as veliparib and nucleoside analogs are expected to be highly successful in small cell lung cancer-P. Nonetheless, SLFN11 expression, recognized as a predictive biomarker for the efficacy of PARP inhibition, appears to lack correlation with the expression of subtype-defining markers. [19] The small cell lung cancer-I subtype is predominantly associated with immune blockage targeting the PD-1/PD-L1 axis due to its correlation with an inflammatory, immunological oasis phenotype and elevated expression of immune-checkpoint markers. [19] Retrospective data analysis of the IMpower study[24] has indicated that the advantageous benefits of integrating immunotherapy into the etoposide/platinum backbone were more significant in patients with small cell lung cancer-I. [19] This justifies the application of immunotherapeutic drugs in this specific subtype. Small cell lung cancer cell lines exhibiting elevated YAP1 expression demonstrate considerable sensitivity to mTOR, PLK, and CDK4/CDK6 inhibitors. [25]

Small cell lung cancer is a rare yet highly aggressive malignancy, characterized by genomic instability and early metastatic dissemination, resulting in a nearly universal fatality rate. The clinical options for small cell lung cancer patients have seen little change over the past several decades; however, recent years have brought a rapid increase in biological understanding of the disease. Surgical resection, when integrated into a multimodal treatment approach during the early stages of disease, enhances survival outcomes. Patients are often diagnosed at a more advanced disease stage, at which point platinum-based chemotherapy combined with immunotherapy is the preferred treatment strategy. The role of radiotherapy in conjunction with systemic therapy is well established in managing small cell lung cancer patients. While these therapeutic approaches show initial efficacy, a majority of patients quickly develop acquired resistance, underscoring the necessity to enhance the effectiveness and broaden the range of existing therapeutic strategies. Recent preclinical advancements over the past decade, coupled with a global resurgence in profiling studies, have led to the development of a novel classification scheme for small cell lung cancer. This emerging knowledge of small cell lung cancer molecular subtypes and the related genomic alterations have the potential to lead to the implementation of subtype-specific therapeutic approaches, with the goal of improving patient care for this once-enigmatic cancer. Further researches are required in this area to fill the gaps in the treatment of this disease.

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