Scientific Reports in Medicine

Current Developments in Small Cell Lung Cancer

SCLC treatments

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Abstract:

Small cell lung cancer (SCLC), often associated with smoking, is characterized by its aggressive biology and potential for early metastasis. It accounts for approximately 15% of all lung cancer patients. The combination of platinum-based chemotherapy and etoposide has been used for many years in the treatment of SCLC. The prognosis for patients with SCLC who are treated as a single group is still quite poor. Recent research has provided a new perspective on the biology of SCLC. A survival benefit has been demonstrated by adding immune checkpoint inhibitors to chemotherapy in patients with extensive stage SCLC.

The study of the molecular, biological, and immunological properties of the heterogeneous structure of SCLC is a promising area of research for the future. Identification of distinct gene expression profiles (ASCL1, NEUROD1, POU2F3, and YAP1) of SCLC patients may form the basis of the most effective and individualized therapeutic treatments in disease management. More research is needed to identify SCLC subtypes and develop effective treatments for this group of patients who have a poor prognosis.

Keywords: Small cell lung cancer, treatment, gene expression

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INTRODUCTION

Small cell lung cancer (SCLC) accounts for approximately 15 percent of all lung cancer cases (1). Almost all SCLC patients are related to smoking (2). SCLC is characterized by rapid proliferation, high growth fraction, and early metastasis development (3). More than two-thirds of SCLC patients are diagnosed in an advanced stage. The combination of platinum-based chemotherapy (carboplatin or cisplatin) with etoposide has been used in the treatment of SCLC for years and continues to form the backbone of modern combination methods (4). Although this treatment initially works well for most patients, many relapse in a short time. The 5-year survival rate in SCLC patients with poor prognosis is less than 7% (3). Compared to other types of lung cancer, personalized treatment for SCLC patients is limited, resulting in poor prognosis. The disease appears homogeneous. However, new studies show that immunotherapy is clinically effective in treating advanced SCLC (5).

The Genetic Structure Of Small Cell Lung Cancer

In the whole-genome analysis performed to identify somatic driver mutations that play a key role in the development of SCLC, it was determined that the tumor suppressor genes TP53 and RB1 were inactivated (6). In a study of 110 SCLC patients, almost all of the tumors showed bi-allelic inactivation of TP53 and RB1 genes (7).

Notch signaling is crucial in the development of neuroendocrine cells and is considered a tumor suppressor in Small Cell Lung Cancer (SCLC). Mutations in genes belonging to the Notch family have been found in about 25% of human SCLC cells. In a preclinical mouse model, the activation of Notch signaling was found to significantly reduce the tumor growth rate and prolong the survival of the mutant animal (7). Comprehensive genomic analyses have detected amplifications of several genes in Small Cell Lung Cancer (SCLC). The amplification of all MYC family members (16%), FGFR1 (6%), and SOX2 (27%) have been found. SOX2, which is a

transcriptional regulator for pluripotent stem cells, is usually overexpressed, particularly in the SCLC-A subtype. It is also believed that MYC amplification occurs during tumor growth and is associated with treatment resistance. Aurora kinase A and B (AURK A/B) are serine/threonine kinases that regulate mitosis. Preclinical investigations have shown the effectiveness of AURK A/B inhibitors in treating SCLC (9).

Subtype Classification In Small Cell Lung Cancer

Although SCLC is still clinically treated as a single disease, recent preclinical research has found biologically distinct SCLC subtypes. In the 1980s, cancers were classified solely by their dominant phenotype, namely "classic" and "variant" (7). NE-high and NE-low subgroups were identified and classified based on the expression patterns of various neuroendocrine markers, such as chromogranin A (CHGA), synaptophysin (SYP), neural cell adhesion molecule 1 (NCAM1/CD56), and gastrin-releasing peptide (GRP) (8). Recent studies have shown that the traditional categories used to classify small cell lung cancer (SCLC) have limited effectiveness in determining a course of treatment. However, with the help of genomics and new preclinical models, researchers have been able to study the intratumoral heterogeneity and genetic changes of this disease more effectively. As a result, a new subtype of SCLC has been identified, which is characterized by differential expression patterns. The identification of this subtype was based on extensive data from studies involving human SCLC cell lines, genetically engineered mouse models, and patient-derived xenografts. These studies have suggested the involvement of four key transcriptional regulators: ASCL1 (SCLC-A), NEUROD1 (SCLC-N), POU2F3 (SCLC-P), as well as inflammatory markers (SCLC-I) (Figure 1) (9). This novel classification of SCLC is based on various molecular profiles and neuroendocrine markers, which correlate with different clinicopathological features. It is particularly useful for prognostic and predictive
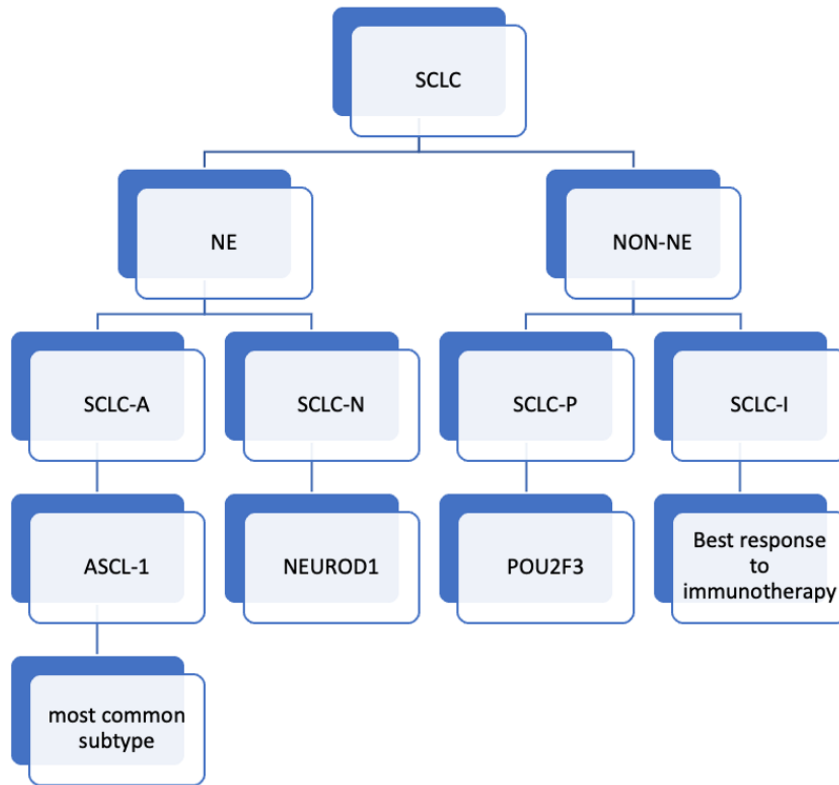
Figure 1: Neuroendocrine differentiation and molecular subtypes of SCLC

purposes (5).

SCLC, small cell lung cancer; NE, neuroendocrine; ASCL1, achaete-scute homologue 1; INSM1, insulinoma-associated protein 1; NE, neuroendocrine; NeuroD1, neurogenic differentiation factor 1; POU2F3, POU class 2 homeobox 3.

SCLC-A

SCLC-A is the most common subtype of SCLC, accounting for 40-50% of all cases. It has a classical morphology and expresses a high number of neuroendocrine markers (4). Typically, Small Cell Lung Cancer subtype A is characterized by an increase in BCL-2, EZH, DLL3, SOX2, INSM1 amplification, and a decrease in CREBBP level (5). "BCL-2" is a cellular signaling molecule that prevents cell death. It is directly controlled by the ASCL1 gene, which regulates its transcription (4). In preclinical models of small cell lung cancer (SCLC), venetoclax, a BCL2 inhibitor, has been demonstrated to cause

tumor regression (5) . The molecule DLL3 is a ligand for the Notch pathway and is an interesting target for treatment. Around 85% of small cell lung cancer (SCLC) cells have DLL3 expressed on their surface. An antibody-drug conjugate called rovalipatumab (Rova-T) has been developed to target DLL3 and has been tested on patients with SCLC that express DLL3 in the TRINITY phase 2 trial. The results have shown that the treatment has had a positive clinical response in patients who had received third-line or higher treatment (10). However, a phase 3 randomized controlled trial failed to demonstrate superiority over topotecan in second-line treatment (11).

Tarlatamab is a bispecific molecule that binds to two different proteins in cancer cells and T cells, respectively. By doing so, it activates T cells to attack and destroy cancer cells. In a phase 1 clinical trial, Tarlatamab showed promising results in treating small cell lung cancer (SCLC) that had previously been treated. The median duration of response

(mDoR) was 12.3 months, and the median overall survival (mOS) was 13.2 months. These results suggest that Tarlatamab has exceptional efficacy in treating SCLC and warrants further investigation (12). Due to the inactivation of CREBBP, SCLC-A subtype exhibits higher sensitivity to histone deacetylase (HDAC) inhibitors (4).

SCLC-N

The SCLC-N subtype is defined by the transcription factor NEUROD1, characterized by low expression of neuroendocrine markers, c-Myc amplification, increased aurora kinase (AURK) activity, and arginine biosynthesis (4). It was observed that a combination of small cell lung cancer with both neuroendocrine and non-neuroendocrine histology (SCLC-A and SCLC-N) was also identified (5).

SCLC-P

POU2F3 is a transcription factor that regulates tuft cells. The SCLC-P subtype may have originated from tuft cells due to high POU2F3 expression (13). Patients with this subtype lack neuroendocrine markers. Targeted treatment options may include nucleoside analogs, PARP inhibitors, and IGF-1R inhibitors (5).

SCLC-I

Expression of YES-associated protein (YAP) 1 was used to define the subtype SCLC-Y, which was initially proposed but not confirmed as a distinct type in human samples (5). PD-1 and PD-L1 expressions are not unique to the SCLC-Y subtype. However, YAP1 has been shown to create an immunosuppressive environment that increases PD-L1 transcripts. SCLC-Y tumor cells express both LAG-3 and CD38, making them more responsive to immune checkpoint inhibitors. Moreover, the SCLC-Y subtype is particularly sensitive to polo-like kinase (PLK), mammalian target of rapamycin (mTOR) and possibly cyclin-dependent kinase (CDK) 4/6 inhibitors (5).

It has been predicted that samples lacking significant expression of ASCL1, NEUROD1, POU2F3, or YAP1 would be classified as a quadruple negative subtype of small cell lung cancer (SCLC-QN). To determine whether this SCLC-QN subtype is comparable to the SCLC-I subtype, which is quadruple switch-transcription factor negative but exhibits inflammatory characteristics, further investigation is required. It has been observed that the SCLC-I subtype has a high response to immune therapy due to its high infiltration of cytotoxic T cells, natural killer cells, and tumor-associated macrophages, as well as its high expression of various immune checkpoint markers (5).

Staging in small cell lung cancer

Two different staging systems have been presented for small cell lung cancer: the Veterans Administration Lung Study Group (VALG) classification and the tumor-node-metastasis (TNM) staging system. The VALG classification defines an extensive stage (ES-SCLC) as disease beyond the ipsilateral hemithorax, such as malignant pleural/pericardial effusion or hematogenous metastases. On the other hand, a limited stage (LS-SCLC) describes disease that is contained within the ipsilateral hemithorax and can be safely treated within a radiation field (14). The National Comprehensive Cancer Network (NCCN) and other clinical guidelines consider TNM stages I-III as LS-SCLC and stage IV as ES-SCLC.

Strategies for treating small cell lung cancer in its limited stage (LS-SCLC)

The standard systemic therapy for LS-SCLC patients is a combination of etoposide and platinum. The use of radiation and chemotherapy together has been shown to improve local control and increase survival rates. At present, there is insufficient data to support the use of immunotherapy for LS-SCLC (1).

Treatment approaches in extensive stage small cell lung cancer (ES-SCLC)

For several years, the main treatment for ES-SCLC has been a combination of platinum-based chemotherapy (carboplatin or cisplatin) and etoposide. A recent study has shown that the use of immune checkpoint inhibitors alongside chemotherapy can improve the

survival rate of patients with ES-SCLC. Atezolizumab is a monoclonal antibody that blocks PD-L1's interaction with PD-1 and B7.1. The IMpower133 study was a phase III, double-blind, randomized controlled trial that investigated the effectiveness and safety of adding atezolizumab or placebo to first-line carboplatin and etoposide treatment in patients with extensive-stage small-cell lung cancer (ES-SCLC). The study found that the overall survival (OS) was 12.3 months for the chemotherapy + atezolizumab group and 10.3 months for the chemotherapy alone group (hazard ratio [HR] for death, 0.70; 95% CI, 0.54-0.91; P =0.007) at a median follow-up of 13.9 months. The atezolizumab plus chemotherapy arm showed a median progression-free survival (PFS) of 5.2 months, whereas the chemotherapy alone arm had a PFS of 4.3 months (HR, 0.77; 95% CI, 0.62 to 0.96; P = 0.02) (Table 1). In the group of patients who received a combination of atezolizumab and chemotherapy, 34.0% of them were still alive after 18 months. On the other hand, in the group of patients who were given a placebo along with chemotherapy, only 21.0% were still alive. The study showed that adding atezolizumab to chemotherapy was beneficial for patients, regardless of whether they had TMB or PD-L1 immunohistochemistry. In both therapy groups, a similar percentage of patients experienced adverse events (94.9% and 92.3%, respectively). Among the patients, 48 out of 196 (24.5%) in the placebo group and 79 out of 198 (39.9%) in the atezolizumab group developed immune-mediated adverse events. The study did not allow thoracic radiation therapy during the maintenance period, but prophylactic cerebral irradiation was allowed. After receiving treatment for brain metastases, there were no statistically significant differences in overall survival or progression-free survival between the two groups. However, due to the limited number of patients with brain metastases who participated in the study and the exploratory nature of the analysis, it is not possible to draw any definitive conclusions (15). The role of immunotherapy in small cell lung cancer patients with brain metastases requires further research.

Durvalumab is another type of immunotherapeutic treatment that has been proven to be effective in treating ES-SCLC. It is a human IgG1 monoclonal antibody that is selective and high-affinity, which prevents PD-L1 from binding to PD-1 and CD80. The safety and effectiveness of durvalumab in combination with etoposide plus cisplatin or carboplatin, with or without tremelimumab, for first-line therapy of patients with ES-SCLC were evaluated in the double-blind, randomized controlled, phase III CASPIAN study. Durvalumab plus platinum-etoposide resulted in a median overall survival of 13.0 months (95% CI 11.5-14.8), compared to 10.3 months (9.3-11.2%) in the platinum-etoposide group (HR, 0.73; 95% CI 0.59–0.91; p=0.0047) (Table 1). It was found that there is a significant difference in overall survival between the two groups of patients. All subgroups of patients showed an improvement in overall survival. Out of the 266 patients who received platinum-etoposide plus durvalumab, 62% (166 patients) experienced grade 3 or 4 any-cause adverse events. Similarly, out of the 265 patients who received durvalumab, 62% (163 patients) experienced grade 3 or 4 any-cause adverse events. Additionally, 5% (13 patients) and 6% (15 patients) experienced adverse events that resulted in death.(16).

Table 1: Treatments For First Line Extensive Stage Small Cell Lung Cancer			
Trial	**Treatment**	**mPFS** (months)	**mOS** (months)
IMpower133	Carboplatin+Etoposid+ Atezolizumab Carboplatin+Etoposid+Placebo	5,2 (HR:0,77; P : 0,02) 4,3	12,3 (HR:0.70; P :0.007) 10,3
CASPIAN	Cisplatin/Carboplatin+Etoposid+Durvalumab Cisplatin/Carboplatin+Etoposid+Placebo	5,1 (HR: 0,78) 4,9	13,0 (HR, 0,73;p:0.0047) 10,3

HR, hazard ratio; OS, overall survival; PFS, Progression-free survival

Adding durvalumab or atezolizumab to the platinum and etoposide combination is the current first-line treatment for ES-SCLC patients with available data.

Although SCLC patients usually respond well to first-line treatment, many of them tend to relapse. Patients who experience a relapse within three months of receiving the initial treatment are considered "refractory" and require a different treatment regimen. On the other hand, patients who experience a recurrence more than six months after the first-line treatment are referred to as "sensitive" and can be treated again with the same regimen (1). Unfortunately, the response rate in subsequent treatment steps after the initial line of treatment is reduced, and the prognosis is poor (17).

Topotecan is the only approved second-line treatment for SCLC. Prior to its discovery, anthracycline-based regimens such as CAV (cyclophosphamide-doxorubicin-vincristine) were commonly used (18). In the randomized study comparing topotecan with CAV, topotecan was found to be as effective as CAV while presenting fewer grade 4 neutropenia side effects and better symptom control (19).

Lurbinectedin, a new alkylating drug that inhibits oncogenic transcription, has been approved as a second-line therapy for metastatic SCLC patients (20). Additionally, ongoing studies are being conducted to identify new therapeutic targets and develop more effective treatment plans.

CONCLUSION

Recent research has provided a new perspective on the biology of SCLC. This cancer type is heterogeneous in structure, so ongoing research is being conducted to evaluate its molecular, biological, and immunological characteristics. By identifying distinct gene expression profiles (ASCL1, NEUROD1, POU2F3, and YAP1) of SCLC patients, the most effective and individualized therapeutic treatments can be developed for disease management. However, more study is required to understand the subgroups of SCLC. As this patient population has a very poor prognosis, it is essential to develop effective novel treatments.

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