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Intervention and Prospects of Small Cell Lung Cancer

Fangyu Xiong

RDFZxishan school, Beijing, China
m15911023983@163.com

Abstract. Small cell lung cancer (SCLC) is a type of lung cancer. It involves the transformation of certain cells within the bronchi into cancer cells, which rapidly form tumors. Its characteristics include rapid progression, high metastasis rates, and sensitivity to radiation therapy and chemotherapy. Its onset is closely associated with external factors such as smoking. Current clinical treatment primarily employs radiation therapy and chemotherapy, but issues such as high recurrence rates remain. This article will integrate the pathogenesis, clinical characteristics, risk factors, various clinical and immunotherapy methods, and potential targeted therapies for SCLC, summarizing current research findings to provide information for basic research and clinical practice in SCLC. This article will also discuss the advantages and disadvantages of current treatment methods, explore the potential for future treatment development, and assist in better preventing this type of cancer.

Keywords: cancer, therapy, prospects

1. Introduction

SCLC is a malignant tumor originating from the bronchial mucosa or glands in the lungs. It involves the transformation of certain cells within the bronchi into cancerous cells, which rapidly form tumors. SCLC usually classified as limited or extensive, and it accounts for approximately 15% of all lung cancer cases [1]. The disease mainly affects people aged 60 to 70. In the early stages of the disease, the condition deteriorates rapidly and spreads widely, resulting in a five-year mortality rate of over 90% and an extremely high overall mortality rate. Patients diagnosed with SCLC typically have a survival period of only two to four years [2]. The pathogenesis of small cell lung cancer is closely related to smoking history. Among SCLC patients, 94% of men and 93.9% of women have a history of smoking. Secondhand smoke is even more carcinogenic. Many carcinogens in cigarettes can damage DNA, highlighting the importance of quitting smoking [3]. In early-stage cases, lung resection can achieve significant results; in the middle and late stages, chemotherapy and immunotherapy are typically used, but these therapies are prone to developing drug resistance, thereby losing its therapeutic effect. With the advancement of medical science and deeper research into the molecular subtypes of SCLC, new treatment targets may be identified in the future. Over the past few decades, patient survival rates have not improved significantly. Therefore, new therapies are particularly important [3,4].

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2. SCLC related risk factor

Smoking is the main risk factor for SCLC, accounting for more than 95% of SCLC cases [5,6]. Research data shows that among lung cancer cases in smokers, adenocarcinoma accounts for 32.5%, small cell carcinoma accounts for 19.6%, and overall, Klebsiella pneumoniae group I accounts for 57.3% among young people [7]. Cigarette smoke contains toxic carcinogens, including polycyclic aromatic hydrocarbons, N-nitrosamines, and aromatic amines, which attack lung cells and damage DNA structure. There is also a strong association between secondhand smoke exposure and the development of SCLC. According to research, the risk of developing SCLC associated with secondhand smoke is two to three times higher than that of other histological types.3 Compared to short-term heavy smoking, long-term light smoking is more harmful. Furthermore, smoking at an early age significantly increases the risk of lung cancer. The 15q25 locus' mutation, which associate with smoking, has a significant association with SCLC risk [5].

2%–3% of SCLC cases occur in non-smokers. Among these, long-term exposure to radon is the second leading risk factor. Also, engine emissions and certain heavy metals such as polycyclic aromatic hydrocarbons and crystalline silica are risk factors [3,5].

3. The mechanism of SCLC

Proteomics, transcriptomics, and genomics can help us understand the molecular characteristics of SCLC, thereby promoting clinical research and potentially improving treatment methods.

TP53 and RB genes undergo chromosomal deletions or inactivation in SCLC, making them the two most important genes responsible for SCLC [4,8]. p53 is a transcription factor that activates numerous genes involved in cell cycle arrest, senescence, apoptosis, and DNA repair. These genes collectively promote genomic integrity and tumor suppression, and activate various cell cycle regulators under their control. Due to the loss of p53 function, affected cells accumulate potential oncogenic mutations and proliferate abnormally due to cell cycle disruption. RB is a transcription co-repressor. It forms complexes with transcription factors of the E2F family to inhibit the expression of various proteins associated with the cell cycle, such as cyclins. It also possesses functions independent of its interaction with E2F proteins, and its inactivation leads to impaired cell cycle checkpoint control and disruption of cell proliferation and apoptosis signaling pathways [8,9].

There are also other abnormal genes. FAT1 gene mutations (13%) and RB1 gene deletions affect the proteome and phosphoproteome of SCLC through cis- and trans-acting mechanisms, respectively; ZFHX3 gene mutations (19%) are enriched in "immunogenic" tumors; Deletions of the long arm of chromosome 5 (5q) are also common, and 5q deletions promote tumorigenesis by regulating the expression of cell cycle-related genes. Mutation frequencies of chromatin modification enzyme-related genes, including KMT2C, KMT2D, and CREBBP, all exceed 10%. These genes participate in chromatin modification processes and influence gene expression regulation. Mutations in Notch family genes exceed 10%, encompassing NOTCH1, Notch2, and Notch3. The Notch signaling pathway plays a key role in cell development and differentiation. Other transcription regulation-related genes, such as NCOR2 and CRTC1, also have mutation frequencies exceeding 10%. These genes participate in transcription regulation processes, and mutations may affect the expression of downstream target genes, which are associated with the molecular mechanisms of SCLC. GNAS gene mutations are also present, and their mutation rates are significantly elevated in patient populations with high tumor mutational burden (TMB). These mutations may be associated with genomic instability and disease characteristics in SCLC [4,10]. The absence of YAP expression is key to SCLC cells acquiring rapid amoeboid migration and high

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metastatic potential. RB1 mutations lead to upregulation of E2F7 expression, which interacts with the RCOR complex, recruiting the complex to the YAP promoter region, inducing inhibitory histone modifications, and thereby silencing its transcription [11].

In two studies using targeted gene panels to identify molecular abnormalities in SCLC, the most common gene mutations and amplifications were PIK3CA (5% mutation and 10% amplification) and MET (4.4% mutation), respectively [12].

4. Clinic manifestations and treatment

4.1. Clinic manifestations

The clinical manifestations of SCLC usually begin to appear approximately 12 weeks before diagnosis, including local tumor growth, coughing, shortness of breath, weight loss, and fatigue. May be accompanied by other cardiopulmonary or metabolic complications. Tumors in the chest cavity may cause superior vena cava syndrome and upper body edema. As the cancer metastasizes, it can cause neurological and endocrine disorders, such as sensory neuropathy and syndrome of inappropriate antidiuretic hormone secretion(SIADH) [3,12].

4.2. Therapies

In VALG staging system, SCLC is typically divided into two stages, limited-stage disease (LD) and extensive-stage disease (ED), and is also using the tumour, node, metastasis (TNM) classification [2,3]. The limited-stage of lung cancer refers to a limited lesion in one hemithorax. Patients with both lung affected or metastasis are classified as having extensive-stage SCLC [3]. Currently, the optimal treatment regimen for limited-stage small cell lung cancer (LD-SCLC) is concurrent chemotherapy and radiotherapy [2,12]. According to research, chemotherapy and radiotherapy can significantly improve the 3-year overall survival rate. In an analysis of 82 patients, surgical resection followed by adjuvant platinum based chemotherapy reported a 5-year survival rate of 68%. Thus, in the research, concurrent chemotherapy with cisplatin and etoposide and thoracic radiation should be the initial therapy. Surgical resection therapy can also be used in cases where patients are strictly screened. Lobectomy can achieve a five-year overall survival rate of 50% [12]. Combination therapy based on platinum drugs is reliable, with treatment adjusted according to the patient's stage. Conformal radiation therapy may also be used [3].

Immunotherapy can be used alone or in combination with chemotherapy. The US Food and Drug Administration (FDA) has approved the PD-L1 inhibitor atezolizumab in combination with first-line platinum-based doublet chemotherapy for the treatment of patients with extensive-stage small cell lung cancer (ED-SCLC). Clinical trial results show that adding atezolizumab to the first-line treatment regimen significantly prolongs median progression-free survival (PFS) and overall survival (OS) [3,13]. Clinical data show that all five patients were treated with immune checkpoint inhibitors (ICIs) either in combination or as monotherapy, including durvalumab combined with the EP regimen (etoposide + platinum), resulting in tumor shrinkage and partial response (PR). Targeted treatment for PNS led to improvement in its symptoms [14]. Those demonstrates the potential of immunotherapy in improving symptoms and curing SCLC.

There are many potential epigenomic regulators could be target. DLL3, which highly expressed in SCLC-A and regulate Notch signaling pathway, may be targeted by AMG757 or AMG1193 [13]. At the same time, LSD1 and KDM5A are also involved in regulating Notch signaling, with LSD1 being overexpressed in SCLC. KDM5A inhibits Notch signaling and promotes tumor formation.

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Lademstat and ORY-1001 can inhibit LSD1, while KDM5-C70 can inhibit KDM5A.15 MYC, which associated with SCLC-N, overexpressed in SCLC, and C-MYC can activate the Notch pathway [3,15]. SCLC-I has elevated expression of immune checkpoint-related genes and leukocyte antigen genes [3].

4.3. Limitations

Despite the variety of treatment options, the prognosis for SCLC remains poor, especially for patients with ED-SCLC. In first-line treatment, the median OS for patients with LD-SCLC is 17.3 months, with a median PFS of 11.6 months until the disease progresses to a specific stage; For patients with ED-SCLC, the median OS was only 8.8 months, significantly shorter than that of LD-SCLC patients, with a median PFS of 6.1 months. This indicates that ED-SCLC patients experience faster disease progression and poorer survival outcomes. For patients who initiated second-line treatment, the median OS was 6.6 months; for patients initially diagnosed with ED-SCLC, the OS calculated from the start of second-line treatment was only 5.1 months [2]. According to research, thoracic radiotherapy can prolong progression-free survival in patients with distant metastases. However, in a secondary analysis, patients still had multiple metastatic lesions, so the benefits of thoracic radiotherapy are limited. Immunotherapy and targeted therapy have also not achieved breakthrough progress, most drugs still in the clinical trial stage, and require further research [3].

5. Disscusion

The clinical treatment of SCLC has become relatively mature, but there are still many shortcomings, such as relatively low survival rates. Due to the highly invasive and metastatic nature of SCLC, early-stage patients can use surgical resection therapy, but most patients are diagnosed at an advanced stage. There are numerous external factors that can trigger SCLC, making prevention particularly important. Given the strong association between SCLC and smoking, the importance of quitting smoking cannot be overstated.

Since each subtype of SCLC mutation has unique genetic characteristics, continued research into the molecular characteristics of SCLC subtypes, along with in-depth studies in genomics and proteomics, may lead to new breakthroughs in treatment. If precise, personalized treatment plans can be developed by analyzing the varying conditions of different patients, and targeted therapy, immunotherapy, chemotherapy, and radiotherapy can be effectively combined, this may significantly improve patient outcomes.

6. Conculsion

Current clinical data confirm that while effective therapeutic modalities—primarily radiotherapy and chemotherapy—exist to manage small cell lung cancer (SCLC) in practice, smoking cessation unequivocally remains the most critical and impactful preventive intervention to curb its incidence. Consequently, for primary prevention, it is imperative that smokers actively engage in and implement comprehensive smoking cessation programs, which constitute the cornerstone of public health strategies against SCLC. However, the management of SCLC is markedly hampered by significant challenges, including the rapid development of treatment resistance, a high propensity for relapse, and an exceedingly poor prognosis, particularly for patients diagnosed at advanced stages. These formidable obstacles underscore the urgent necessity to develop novel and more effective therapeutic strategies. To this end, ongoing research is intensely focused on deciphering the intricate

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molecular characteristics and heterogeneous subtypes of SCLC. A deeper understanding of its tumorigenesis pathways, immune evasion mechanisms, and genetic drivers is fundamental to identifying new vulnerabilities and biomarkers. Translating these preclinical discoveries into tangible clinical benefits necessitates a robust pipeline of clinical trials. These trials are crucial for evaluating promising new interventions, such as targeted therapies, immunotherapies (including immune checkpoint inhibitors), and innovative combination regimens. Ultimately, this multi-faceted approach—ranging from primary prevention and enhanced disease control with existing tools to the development of next-generation therapies—is key to fundamentally improving long-term survival rates and quality of life for patients afflicted with this aggressive malignancy.

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