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REVIEW ARTICLE

Progress in the diagnosis and treatment of extensive-stage small cell lung cancer

Fei Xu[1, 2], Xiaoli Ren[1], Yuan Chen[1], Qianxia Li[1], Ruichao Li[1], Yu Chen[1], Shu Xia[1] (✉)

[1] Department of Oncology, Tongji Hospital, Tongji Medical College of Huazhong University of Science and Technology, Wuhan 430030, China
[2] Department of Oncology, Affiliated Hospital of Hebei University of Engineering, Handan 056000, China

Abstract

Lung cancer, being the most common cancer type, accounts for 13% of all newly diagnosed malignant tumors globally each year. Small cell lung cancer (SCLC) accounts for approximately 15% of newly diagnosed lung cancers each year, but its annual death toll accounts for 25% of that of lung cancer. We summarized relevant clinical studies to elaborate the epidemiology, pathological and clinical characteristics and the treatment status of small cell lung cancer. This paper first described the epidemiology and the pathological and clinical characteristics of SCLC and the systematic treatment of extensive-stage SCLC and then introduced the current targeted therapy and immunotherapy for SCLC to provide clinicians and patients with a more systematic, comprehensive, and beneficial treatment regimen. We expect that these studies can provide clinicians with a clear direction in molecularly targeted therapy or immunotherapy, so that a treatment approach with better antitumor effects and longer-lasting clinical benefits can be provided to the patients.

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Epidemiology of small cell lung cancer (SCLC)

As the leading cause of death in cancer diseases worldwide, lung cancer has a continuously increasing incidence. According to the World Health Organization's statistics of tumor morbidity and mortality, in 2012, there were 18 million newly diagnosed lung cancer cases worldwide. Lung cancer ranks first in the morbidity and mortality of solid tumors in male, while in female, its incidence ranks fourth, following breast cancer, colorectal cancer, and cervical cancer. The overall mortality rate of lung cancer, on the other hand, is at the top of well-diagnosed neoplastic causes. Taking China as an example, in 2015, there were 7.2 million newly diagnosed lung cancer cases and 6.1 million related deaths in China. Lung cancer has become the malignant tumor with the highest mortality in male and female in China [1].

SCLC is a highly malignant tumor with the following characteristics: short doubling time, high invasiveness, and early metastasis [2–3]. The incidence of SCLC accounts for 15%–17% that of lung cancer. Its risk is mostly related to smoking time and intensity, and we have also found that smoking cessation is associated with the significant drop in its morbidity and mortality rates [3]. In the past two decades, the incidence of SCLC has been declining, which is likely related to recently implemented tobacco production control measures and changes in smoking behaviors [4].

Because SCLC grows fast and is highly invasive, most patients demonstrate no surgical indications at the time of diagnosis. Therefore, chemotherapy or concurrent chemoradiotherapy is the main treatment method for SCLC. Although SCLC is sensitive to chemoradiotherapy, it still progresses rapidly in most patients after they receive first-line treatment. The substantial development in the tumor genomics and molecularly targeted therapy for non-SCLC in recent years cannot be fully applied to SCLC though, causing poor prognosis in patients with SCLC. For patients with limited-stage SCLC who received treatment, the median overall survival (OS) rate was 15–20 months, and the 5-year survival rate was 10%–13%,

✉ Correspondence to: Shu Xia. Email: xiashutj@hotmail.com

while for patients with extensive-stage SCLC, the median OS rate was 8–13 months, and the 5-year survival rate was merely 1%–2% [5–6]. Therefore, there is an urgent need to find an effective method to completely cure or control the progress of SCLC.

Histopathological characteristics of SCLC

SCLC originates from the K cells with neuroendocrine functions located in the bronchial epithelial mucous gland. The K cell is an undifferentiated neuroendocrine tumor composed of small cells with either no or unclear nucleoli, whose nuclear chromosomes have little cytoplasm, unclear cell boundaries, and fine grains. Its cancer cells are relatively small and often have an oval or spindle shape, or sometimes are like lymphocytes. The nuclei are deeply stained, often with mitoses. According to their morphological characteristics, the cancer cells can be divided into three subtypes: oat cell type, intermediate cell type, and mixed cell type. SCLC is a poorly differentiated malignant tumor that belongs to high-grade neuroendocrine tumors. This type of tumors shares the same distinctive pathological and molecular characteristics, but at the same time demonstrates different biological behaviors and prognosis. For example, poorly differentiated SCLC and large cell lung cancer have similar pathological characteristics with the less invasive carcinoid [7]. Therefore, in clinical practice, immunohistochemistry is often used to detect the expressions of related proteins to distinguish between SCLC and similar tumors. SCLC immunohistochemistry reveals related neuroendocrine markers, such as neural cell adhesion molecule (CD56), neuron-specific enolase, chromogranin A, and synaptophysin. Additionally, most SCLC exhibits a positive thyroid transcription factor-1 expression [8–9].

Clinical characteristics of SCLC

Because SCLC grows fast and is highly invasive, it may develop into distant metastasis in an earlier stage. According to the staging of SCLC defined by the expert group from the US Veterans Association, approximately one-third of newly diagnosed SCLC patients are still at the limited stage, when the lesion is located on one side of the chest only, or can be covered by one radiotherapy field; the rest of the patients are defined to have extensive-stage SCLC [10]. Patients with SCLC often have nonspecific cough and dyspnea as the initial presenting symptoms, which are mostly caused by the enlarged pulmonary hilar mass and mediastinal lymph nodes. However, because some patients with SCLC already had hematogenous metastasis at the first visit, their clinical manifestations are mainly symptoms caused by the primary lesions and metastatic lesions, such as significant weight loss, bone pain, headache, and vomiting. Furthermore, it is well known that SCLC has a certain neuroendocrine origin, which leads to the occurrence of corresponding paraneoplastic syndromes [11–13], including Lambert-Eaton myasthenic syndrome, encephalomyelitis, and other sensory neuropathies. Meanwhile, the cancer secretes some peptide hormones, such as antidiuretic hormone and adrenocorticotropic hormone, causing hyponatremia and Cushing's syndrome [14–15]. Additionally, some studies have confirmed that SCLC secretes insulin growth factor in an autocrine manner [16], which can act as a stimulator of tumors and their secretions and consequently result in related symptoms.

SCLC is very sensitive to initial chemoradiotherapy, but patients eventually die due to disease progression or lack of sensitivity to further treatment [17]. In the past three decades, there has been no breakthrough in the standard treatment of SCLC. For patients with limited-stage SCLC, chemoradiotherapy is used as the major treatment method to cure the disease, while for patients with extensive-stage SCLC, systemic chemotherapy can relieve symptoms and prolong life to a certain extent. Very few patients (2%–5%) have an operative chance at the time of diagnosis, and surgery is limited to stage I SCLC patients and some stage II SCLC patients.

Systematic treatment of extensive-stage SCLC

In the past three decades, the systematic treatment of extensive-stage SCLC has not changed significantly. For patients in this stage, systemic chemotherapy is the recommended treatment option, and additional local radiation therapy can be performed in selected patients to relieve symptoms.

The standard first-line treatment option for extensive SCLC in Europe and America is the administration of etoposide combined with cisplatin or carboplatin [18–22], while in Asia, it is the administration of etoposide or irinotecan combined with cisplatin or carboplatin [23–24]. Despite the fact that around 80% of the patients are sensitive to first-line chemotherapy, 80% of patients with limited-stage SCLC and almost all patients with extensive-stage SCLC suffered from disease recurrence approximately 1 year after the treatment with the following possible reason: residual tumor cells that are insensitive to the initial chemotherapy developed drug resistance [25]. The outcome of the first-line treatment is predictive of the effectiveness of second-line treatment. Most second-line treatments have limited options and are inefficient. In the United States, among all second-line treatment options, only topotecan has been approved by

the FDA [26], while in Japan, besides topotecan, amrubicin can also be administered [27]. Treatments subsequent to second-line treatment do not have a standard treatment regimen due to the low efficiency of chemotherapy, which is possibly a result of cross-resistance when multiple drugs are administered [25, 27]. The mechanisms of drug resistance in SCLC are complex. The currently identified ones include the following: abnormalities in the intracellular enzyme system, abnormal enhancement in the anti-apoptosis and repair functions of the cells, and overexpression of some membrane proteins, such as the lung resistance protein [28–29]. At present, effective drugs for successive treatment include lacquers, topotecan, irinotecan, and gemcitabine.

More than 50% of patients with SCLC will also develop intracranial metastasis. Therefore, prophylactic cranial irradiation (PCI) is recommended for patients with limited-stage SCLC who demonstrated good disease control after the initial induction chemotherapy [30]. Alternatively, for extensive-stage SCLC, early clinical trials have found that PCI can increase the 1-year survival rate (27.1% vs. 13.3%) of patients who are relatively sensitive to initial chemotherapy and additionally reduce the associated symptoms caused by brain metastasis (14.6% vs. 40.4%) [31]. However, a study reported at the 2014 American Society of Clinical Oncology (ASCO) annual conference had an almost totally opposite conclusion. This clinical study admitted 224 patients with extensive-stage SCLC who did not have brain metastasis and combined the platinum-based chemotherapy regimen and the PCI regimen (25 Gy/10 F) [32]. The results of the study revealed that for patients who received PCI, the median progression-free survival (PFS) and OS rates were 2.3 months and 11.6 months, respectively, while for patients in the control group, the PFS and OS rates were 2.4 months and 13.7 months, respectively. PCI did not reveal any advantages in improving patient survival, although it significantly reduced the incidence of brain metastases (the 1-year brain metastasis incidence decreased from 59% to 32.9%). These two opposite authoritative findings have led to controversy over whether PCI is required for patients with extensive-stage SCLC.

Targeted therapy for SCLC

In recent years, a few clinical studies have been conducted on the administration of molecularly targeted drugs as single agents or in conjunction with other antitumor drugs in the treatment of SCLC, but most clinical trials did not achieve an effective clinical benefit. Since SCLC is a type of tumor that is sensitive to chemotherapy, the overall response rate (ORR) of platinum-based chemotherapy is already quite high (75%–95%). Therefore, in the absence of a large number of patients with SCLC, the targeted therapy clinical trials could not provide a convincing increase in the response rate [33]. However, although SCLC demonstrates a high response rate to initial chemotherapy, tumor recurrence in a short period of time is inevitable. Therefore, an effective approach is to investigate the administration of molecularly targeted drugs in maintenance treatment.

Antiangiogenesis targeted drugs

In the field of molecularly targeted therapy for SCLC, antiangiogenesis drugs are the most widely studied. However, in general, clinical trials on antiangiogenesis targeted drugs have presented disappointing results. As is known, angiogenesis makes up a big part in tumor growth, invasion, and metastasis [34]. A study has indicated that the vascular endothelial growth factor (VEGF) plays an important role in tumor cell migration and infiltration, vascular permeability increase, and angiogenesis promotion and has been shown to inhibit tumor growth and angiogenesis in some preclinical models [34]. Moreover, elevated VEGF-A levels and high blood vessel counts are believed to be closely associated with poor prognosis in SCLC [35]. All these preclinical studies have suggested that treatment for angiogenesis may be a viable option. However, to our disappointment, this type of research has barely achieved any clinical benefit.

Monoclonal antibodies

In the 2016 ASCO annual conference, the result of an Italian study was reported. The study was a stage III clinical trial (GOIRC-AIFA FARM6PMFJM) that compared the efficacy of the etoposide and cisplatin (EP) chemotherapy regimen with the bevacizumab combined with EP chemotherapy regimen as the first-line treatments of patients with SCLC [36]. The results suggested that bevacizumab combined with EP chemotherapy regimen was able to improve the patients' median PFS rate significantly, and the difference when compared to that of the chemotherapy alone group was statistically significant. The median PFS rates were 6.7 months and 5.7 months for the combined treatment group and the chemotherapy alone group (HR = 0.72, P = 0.03), respectively; the median OS rates were 9.8 months and 8.9 months for the combined treatment group and the chemotherapy alone group, respectively; and the one-year survival rates were 37% and 25%, whose difference was not statistically significant (HR = 0.78, P = 0.112), for the combined treatment group and the chemotherapy alone group, respectively. In terms of side effects, except that the combined treatment group demonstrated a higher incidence of hypertension, with the difference between the groups being statistically significant, for the rest of the toxic side effects, the two groups did not show any obvious difference. A wide view of all studies on the use of bevacizumab to treat extensive-stage SCLC showed

that the SALUTE trial also obtained positive PFS rates (5.5 months vs. 4.4 months; HR = 0.53; 95% CI, 0.32–0.86) [37], while the IFCT-0802 [38] trial only obtained negative results and was consequently terminated in advance.

Casamino acid kinase inhibitors

As a small-molecule, multitargeted drug for casamino acid kinase inhibitor, sunitinib has exhibited a certain antitumor activity in multiple clinical trials. The CALGB 30504 study assessed the efficacy of using sunitinib as the maintenance treatment regimen after the administration of EP chemotherapy. The result revealed that the OS and PFS rates for the group that received sunitinib as the maintenance treatment and the group that received placebo as the maintenance treatment were 9.0 months and 6.9 months and 3.7 months and 2.1 months, respectively, among which the advantage of sunitinib in the PFS rate was statistically significant (P = 0.02) [39]. A few studies were conducted to report the use of sunitinib as a single agent for the second-line treatment of patients with recurrent SCLC. In a phase II trial that administered sunitinib as a follow-up treatment of patients with recurrent or progressing SCLC after chemotherapy, it was found that the patients' tolerance to sunitinib was extremely poor, as 63% patients developed grade III–IV thrombocytopenia and 25% patients developed grade III–IV leukopenia [40]. Alternatively, the EORTC-08061 trial reported a patient whose partial response (PR) lasted for 10 months and another patient whose stable disease (SD) lasted for 20 months after undergoing sunitinib single-agent treatment [41]. Future research should explore the predictive factors for the effectiveness of sunitinib treatment to guide its clinical use.

DNA repair pathway-targeted therapy

The initiation and development of SCLC involves abnormalities in transcriptional regulation and DNA repair pathway. Sequencing of postoperative pathology in SCLC patients also confirmed the inactivation mutations of tumor protein 53 (TP53) and the retinoblastoma protein 1 (RB1), the amplification of Myc family members, and the mutation of histone modification [42].

Poly (ADP-ribose) polymerase (PARP) has a high level of expression in SCLC than in other types of cancers [43]. PARP repairs damaged DNAs via base excision. Additionally, in some preclinical studies, it was found that the loss of PARP1 activity resulted in DNA strand breaks, which in turn enhanced chemoradiotherapy sensitization [44]. It is known that platinum-based chemotherapy presents a higher response rate in patients with SCLC, and at the same time PARP inhibitors prevent tumor cells from repairing DNA damage. Therefore, it is suspected that by inhibiting DNA repairs, PARP inhibitors may achieve some clinical benefits when used in the maintenance treatment of patients who are sensitive to platinum. Consequently, cytotoxic drugs combined with PARP inhibitors may be a promising treatment approach. In a phase I clinical trial (E2511) that assessed the use of veliparib, a PARP inhibitor, together with EP chemotherapy as the first-line treatment of patients with extensive-stage SCLC, its antitumor effect has been preliminarily demonstrated [45]. Other clinical studies on the use of PARP inhibitors as the second-line treatment or the maintenance treatment following first-line chemotherapy of patients with SCLC have also been launched. In the future, we expect various studies to confirm the antitumor effect of PARP and will continue to explore its relevant biological predictors.

Notch signaling pathway-targeted therapy

The Notch signaling pathway is important for the growth and development of the embryo through the regulation of cell proliferation, differentiation, and apoptosis. Additionally, it also affects the developments of the hematopoietic system and the mammary gland, the maturation of the gastrointestinal epithelial cells, and the immune regulation, angiogenesis, and growth and development of neural stem cells [46]. Some clinical trials and preclinical model studies have demonstrated the role of Notch signaling pathway in maintaining the cancer stem cells (CSCs) [47–48], while these CSCs play a fundamental role in promoting tumor growth and progression and inducing drug resistance [49]. There is increasing evidence that abnormalities in the Notch signaling pathway are related to tumors in the blood system, solid tumors, and tumor angiogenesis [50–51]. Complete genome sequencing has revealed that abnormalities in the Notch family gene are detected in 25% of patients with SCLC. Additionally, the high invasiveness, easy drug resistance, and heterogeneity of SCLC all indicate that it may contain a larger number of CSCs. Based on the above mechanisms, the Notch signaling pathway is considered a potential target for the treatment of SCLC.

Treatments targeting the Notch signaling pathway mainly involve small-molecule inhibitors or monoclonal antibodies of macromolecules. These treatments have now all started clinical trials, such as a phase Ib study on the use of a Notch 2/Notch 3 humanized IgG2 antibody, tarextumab, in conjunction with EP chemotherapy as the first-line treatment of patients with extensive-stage SCLC. We look forward to the outcomes of this study and its subsequent studies.

However, a mouse model study showed that Notch pathway inhibitors could rapidly transform the intestinal proliferative cells into goblet cells, which in turn led to secretory diarrhea [52]. Therefore, the most critical and serious toxic side effect of the administration of Notch inhibitors is intractable diarrhea, which is more likely to happen when the drug is administered continuously

[53]. Therefore, the development of this type of clinical research is facing certain challenges due to the limitations of intestinal adverse reactions. In some studies, attempts were made to intermittently administer Notch inhibitors together with a certain dose of steroid hormones, which not only ensured the efficacy of the clinical treatment to a certain extent but also effectively relieved the treatment-related diarrhea [54].

Immunotherapy for SCLC

At present, immunotherapy has achieved several breakthroughs in the treatment of malignant tumors, such as melanoma, lung cancer, and kidney cancer. Recent research data have revealed that lung cancer types with a high mutational load are more sensitive to immunotherapy [such as blocking the programmed cell death-1 (PD-1) pathway] because of the formation of substantial tumor antigens, which are then presented to T cells and eventually trigger the immune responses. SCLC is the type of cancer with a high mutational load [55]; therefore, inhibiting the PD-1 pathway may be an effective treatment. Although, in principle, it is feasible to perform immunotherapy to SCLC, in practice, very few studies are available. To date, clinical trials on the immunosuppressive agents (ipilimumab, nivolumab, and pembrolizumab), interferon (IFN), and tumor vaccines have been gradually launched, with the results of immunosuppressive agent research showing the most promising clinical benefits.

Cytotoxic T-lymphocyte antigen 4 (CTLA-4) inhibitor is the first immunosuppressive agent administered to patients with SCLC. In a randomized, double-blind phase II study (NCT00527735), the safety and efficacy of ipilimumab combined with carboplatin and paclitaxel in treating newly diagnosed NSCLC or SCLC patients were observed and were compared to those patients performing chemotherapy alone. The result indicated that ipilimumab combined with chemotherapy could significantly extend the immune-related PFS rates in patients with SCLC (6.4 months vs. 5.3 months, HR = 0.64, P = 0.03) [56]. Despite the encouraging effects demonstrated in this phase II clinical trial, another phase III multicenter, double-blind clinical trial (NCT01450761) was performed using ipilimumab combined with EP chemotherapy to treat patients with extensive-stage SCLC, and the result instead prompted people to question this treatment option. In this study, when compared to the chemotherapy alone group, the combined treatment group did not successfully extend the patients' OS rates (10.97 months vs. 10.94 months, HR = 0.936, P = 0.3775). Some ongoing clinical studies are investigating the use of ipilimumab in conjunction with other treatment regimens. A phase II open study (NCT01331525) that uses ipilimumab combined with etoposide and carboplatin to treat patients with limited-stage SCLC is currently underway, and another clinical study (NCT02239900) that combines ipilimumab with stereotactic radiotherapy has also been launched.

Research on PD-1 receptors is another important direction in immunotherapy [57]. The KEYNOTE-028 (NCT02054806) study [58] revealed that pembrolizumab, as a PD-1 monoclonal antibody, exhibited a strong and prolonged antitumor effect when used on SCLC patients whose programmed death ligand-1 (PD-L1) expressions were positive (defined as the expression of the tumor cell membrane, PD-L1, larger than or equal to 1%). Of the patients whose efficacy was evaluated, 4 cases (25%) reached PR, 1 case (7%) reached SD, disease control rate (DCR) reached 31%, and no serious toxic side effects were developed. Relevant basic research has shown that CTLA-4 inhibitor upregulates the expression of PD-1 on the surface of tumor-infiltrating cells, while PD-1 inhibitor upregulates the expression of CTLA-4 on the surface of tumor-infiltrating cells [59]. These studies have provided us with a new treatment approach, that is, that blocking CTLA-4 and PD-1 simultaneously may produce synergistic antitumor effects. The CheckMate 032 (NCT01928394) study was launched on the above theoretical basis. It is an ongoing, randomized, open phase I/II study that compares nivolumab combined with ipilimumab to nivolumab alone in treating five different malignant cancers, including SCLC [60]. The primary end point of the study was objective response rate, and the secondary end point was safety. The analysis of PD-L1 as a biomarker was also included in the study. The study admitted 183 patients whose SCLC progressed after first-line or multiline treatments. The effectiveness data of the midterm analysis of the study were obtained from 55 patients who received nivolumab alone and 45 patients who received nivolumab combined with ipilimumab. The ORR were 13% and 31% and the corresponding disease control rates were 29% and 53% for patients who received nivolumab alone and for patients who received nivolumab combined with ipilimumab, respectively. The average effect onset time were 1.6 months and 2.2 months, respectively; the median OS rates were 3.6 months and 7.8 months, respectively; and the median PFS rates were 1.4 months and 3.4 months, respectively, for patients who received nivolumab alone and for patients who received nivolumab combined with ipilimumab, respectively. Interestingly, antitumor responses occurred in all patients whether they were platinum-sensitive, drug-resistant, or refractory and were irrelevant with the expression of PD-L1 (tumor cell PD-L1 expression less than 1% vs. that larger than or equal to 1%). The safety assessment revealed that the adverse reactions were under control in each treatment group, although grade III–IV treatment-related adverse reactions were more common in the combined treatment group (11%

vs. 32%). In general, in terms of response rate and tumor regression, the combined treatment was potentially more advantageous; especially in recurrent SCLC patients who demonstrated drug resistance, it exhibited a long-lasting antitumor activity. Although the combined treatment presented a higher incidence of adverse reactions, these reactions were basically controllable. Despite difficulties in comparing survival benefits across various studies, the interim result of the CheckMate 032 study appeared to be better than that of studies on other drugs used for the second-line treatment of SCLC (such as topotecan or amrubicin) [61]. More mature data are expected to further guide the use of nivolumab as a single agent or combined with ipilimumab in the treatment of SCLC patients. Furthermore, more clinical studies comparing the use of PD-1 monoclonal antibodies in the first-line, second-line, and maintenance treatments of SCLC to chemotherapy are being launched (NCT02481830, NCT02046733, and NCT02538666).

IFN, as an immunotherapy method, was first administered to patients with SCLC in the 1980s as a combined treatment. Unfortunately, some recent studies did not find a sufficient antitumor activity [62–63]. Among these, a phase II study (NCT00062010) evaluated the efficacy and safety of combined IFN-α with chemotherapy in treating patients with recurrent SCLC [62]. In the final 34 patients enrolled, 3 cases (9%) reached PR and 5 cases (15%) reached SD. The median PFS rate was 2 months (95% CI, 1.8–3.9), and the median OS rate was 6.2 months (95% CI, 4.7–9.8). Obviously, the proposed treatment regimen did not significantly improve the survival outcomes. Another phase II study combined IFN-α or IFN-γ with chemotherapy to treat limited-stage or extensive-stage SCLC patients (n = 164) [63]. Patients included in the study were randomly divided into the chemotherapy alone group (carboplatin, etoposide, or ifosfamide), the chemotherapy combined with IFN-α group, the chemotherapy combined with IFN-γ group, and the chemotherapy combined with both IFN-α and IFN-γ group (in this group, each IFN was administered in half of the dose given to the other groups). Although the OS rate of each group was not significantly different, subgroup analysis revealed that the patients with limited-stage SCLC who received IFN-α treatment demonstrated a significant increase in the median OS rate (34 months vs. 13.6–19.0 months, P = 0.039). Toxic effects were present in all treatments, especially in the group that received chemotherapy combined with both IFN-α and IFN-γ, but all effects were basically controllable. Therefore, the optimal treatment approach of applying IFN to extensive-stage SCLC and the potential benefit groups need further investigation.

Tumor vaccine, being another rare and novel immunotherapy method, has started to demonstrate certain antitumor effects in some clinical studies on SCLC, but the clinical benefits so far are limited. Binding polysialic acid to the neural cell adhesion molecules highly expressed on the surface of SCLC cells can act as a tumor vaccine; as in a SCLC phase I clinical study, it was found that this type of vaccine can produce a strong antigen-antibody reaction [64]. A common adverse reaction is the reaction at the injection site. Although in one case the patient developed peripheral neuropathy and ataxia, the adverse reaction was immediately relieved after the treatment was discontinued. Another approach exploring tumor vaccines was to utilize the P53 gene, which is known as a common mutant gene in SCLC. Transducing the adenoviruses expressing P53 to the dendritic cells induced the T cell response in 57% of patients with limited-stage SCLC, which in turn increased the clinical objective response rate to a higher level (61.9%) in the subsequent chemotherapy [65]. Another vaccine treatment approach is related to Bec2, which is an anti-idiotypic antibody highly expressed in the neuroectodermal-derived gangliosides on the SCLC cell surface. In a phase II study, a vaccine with Bec2 was used in patients with limited-stage SCLC after undergoing standard chemoradiotherapy, but it did not improve the patients' OS rates [66]. Recently, research on tumor vaccines is still in the early stages, and the vaccines have not been specifically administered to SCLC patients.

From the development of immunotherapy and the progress of multiple clinical trials, it is concluded that the exploration of effective biological predictors is important to find patients who will benefit from the immunotherapy. The expression of PD-L1 is the closest indicator we can use to somehow predict the immunotherapy's efficacy, but it still has some disadvantages [67]. Variations in lab conditions, tumor types, and previous treatments can all cause differences in PD-L1 expression. The design of a treatment plan based on the PD-L1 expression requires careful consideration, as we have also found cases whose PD-L1 expression was negative, but the treatment was effective. Therefore, when selecting an effective biological predictor to predict the treatment effect of PD-L1/PD-1 inhibitors, additional factors may need to be considered, such as the tumor antigen load. Future clinical trials should further investigate relevant content to guide individualized clinical treatment.

Antibody-drug conjugate (ADC) therapy for SCLC

In recent years, because of their high specificity and affinity, monoclonal antibodies have been used together with cytotoxic drugs for the treatment of malignant tumors and have gradually attracted people's attention since then. The antibody-drug conjugates (ADCs) can

specifically recognize antigens on the tumor cell surface and at the same time use the cytotoxic drugs they carry for tumor treatment. Therefore, this mode of drug delivery can reduce the killing and damaging effects of cytotoxic drugs on normal cells. At present, two ADCs, Adcetris and Kadcyla, have been approved by the FDA and are used for the treatment of Hodgkin's lymphoma and Her-2-positive breast cancer, respectively. However, most of the ADCs currently under investigation have a narrow therapeutic window, and future developments should focus on enhancing the therapeutic potential of ADCs.

Lorvotuzumab mertansine (LM) is an ADC formed by conjugating a humanized CD56 antibody with the tubulin-damaging factor DM-1, and it is known that approximately 76% of SCLC cells express CD56 on the surface [68]. In some preclinical model studies, LM has demonstrated some antitumor activity whether used as a single agent or in combination with chemotherapy [68]. In a phase I study of patients who developed solid tumors with a positive CD56 expression, the clinical effective rate of LM in treating 113 SCLC patients was 25% [69]. Although these initial studies have achieved encouraging results, LM has not been further developed into a drug that can be widely used to treat SCLC.

Immunohistochemistry of SCLC revealed that 72% to 85% of cells expressed delta-like 3 (DLL3), while in adenocarcinoma, this value was 3.7%; in squamous cell carcinoma, it was 0%; and in normal tissue cells, it was also 0%. Therefore, compared with normal tissues, DLL3 was overexpressed in SCLC and its transplanted tumor [70]. Rovalpituzumab tesirine is an ADC containing a humanized DLL3 monoclonal antibody that currently exhibits a certain antitumor activity in the treatment of SCLC [70]. In a study of transplanted tumor model originated from SCLC patients, it was found that treatment using rovalpituzumab tesirine could induce long-lasting antitumor responses and eliminate tumor-initiating cells, while it is well known that tumor-initiating cells did not respond well to treatment and were considered the cause of rapid recurrence or progression of SCLC [70]. A recent phase I clinical trial assessed the efficacy and safety of rovalpituzumab tesirine in treating 22 patients with recurrent SCLC. The total response rate was 22%, where 7 cases reached PR, and the disease control rate was 53%. Of the 16 patients whose DLL-3 expressions were positive, 7 cases reached PR, and 8 cases reached SD. The common grade III–IV adverse reactions were capillary leak syndrome (14%) and thrombocytopenia (6%) [71]. Consequently, the use of rovalpituzumab tesirine in treating SCLC patients whose DLL3 expression is positive may become a promising treatment approach.

Thoughts on targeted therapy and immunotherapy for SCLC

Over the past decade or so, the emergence of molecularly targeted therapies has changed the treatment management and approach of multiple malignant tumors and has consequently benefited many patients who have been screened by relevant biological predictors. Although the advantages of molecularly targeted therapy and immunotherapy have been confirmed in many solid tumors, satisfactory results have not been achieved in the exploration of SCLC. The possible reasons behind this include the following: first, most of the targeted drugs whose use in SCLC are being explored have already achieved promising effects in other malignant tumors, which indicates that these drugs are not developed on the biological characteristics of SCLC, and second, although the molecular and biological characteristics of SCLC have been further understood, the development of its targeted therapy is still in phase II studies, and most of the patients included in the study are unselected SCLC patients. Therefore, it is difficult to acquire meaningful results from these studies, and, consequently, it is challenging to proceed to phase III clinical trials.

Based on the analysis of whole exome sequencing, it is realized that translational studies on the identification of molecular and signaling pathway abnormalities that are critical for the initiation and development of SCLC are urgently needed. Combining these results with clinical outcomes is important to finding the predictors and consequently the patients who are most likely to benefit from immunotherapy and molecularly targeted therapy. During this process, the biggest challenge we face is the acquisition of the pathological tissues of SCLC, and due to insufficient pathological tissues, it is difficult to conduct related molecular studies. As a result, the development of circulating tumor cells (CTCs) or circulating plasma DNA (cpDNA) results in the deficiency of pathological tissue sources to a certain extent and can therefore be used as a method for translational research. Additionally, translational studies can explore the mechanisms of patients who develop drug resistance after undergoing targeted therapy or immunotherapy, which is another key factor in the future development of combined treatment. These approaches can potentially overcome the treatment resistance, thereby providing SCLC patients with further clinical benefits.

Consequently, in the future, there may be a novel treatment example of SCLC that includes the molecular analysis of all pathological tissues or cells before and during the entire course of the treatment, as this can help in establishing a more optimized treatment course management and in selecting the most suitable individualized treatment option based on the patient's

situation. Therefore, for patients with SCLC, pathological tissues should be obtained and examined in the early stage of diagnosis to be used for molecular analysis, and during the course of treatment, blood samples should be collected at different stages for CTCs of cpDNA analysis. Such a translational study can then predict the patient's response to treatment via the discovery of gene and molecular signaling abnormalities. Furthermore, clinical studies on cancer patients or derived from transplanted tumor CTC can to some extent be used to guide individualized treatment approaches. As a result, the acquisition of patient pathological tissues, CTCs, and cpDNA and the establishment of a transplanted tumor model during the course of treatment will play an important role in the timely monitoring of patient's disease and the continuous molecular analysis of tumor tissues. These study models have demonstrated some prospect in the treatment of SCLC patients. One of the limitations is that in SCLC patients, the establishment of the translational tumor model is time consuming, but when the disease is progressing rapidly, treatment must proceed without any delay. However, with the advancement and refinement in science and technology, time spent in the modeling process is shortening; therefore, this transplanted tumor technique may become the key to guiding treatment approaches and overcoming drug resistances and solving other problems.

In conclusion, we expect that the aforementioned translational studies can provide clinicians with a clear direction in molecularly targeted therapy or immunotherapy, so that a treatment approach with better antitumor effects and longer-lasting clinical benefits can be provided to the patients.

Conflicts of interest

The authors indicate no potential conflicts of interest.

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