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Research Paper

Research progress in the treatment of small cell lung cancer

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Abstract

Small cell lung cancer (SCLC) accounts for approximately 10-15% of all lung cancers. No significant improvement has been made for patients with SCLC in the past several decades. The main progresses were the thoracic radiation and prophylactic cranial irradiation (PCI) that improved the patient survival rate. For patients with limited disease and good performance status (PS), concurrent chemoradiotherapy (CCRT) followed by PCI should be considered. For extensive disease, the combination of etoposide and platinum-based chemotherapy remains the standard treatment and consolidative thoracic radiotherapy is beneficial for patients who have a significant respond to initial chemotherapy. However, the prognosis still remains poor. Recently, efforts have been focused on molecular targets and immunotherapy. But numerous molecular targets methods have failed to show a significant clinical benefit in patients with SCLC. It is anticipated that further development of research will depend on the on-going trials for molecular targeted therapy and immunotherapy which are promising and may improve the outcomes for SCLC in the next decade.

Key words: Immunotherapy; Molecular targets; Prophylactic cranial irradiation; Radiotherapy; Small cell lung cancer.

Introduction

Lung cancer is the leading cause of cancer death worldwide.[1] Small cell lung cancer (SCLC) represented approximately 10-15% of all lung cancers.[2,3] Smoking is the main risk factor for SCLC, approximately 95% of these patients were smokers.[4] SCLC is characterized by the low degree of differentiation, shorter doubling time and high sensitivity to chemotherapy and radiotherapy. According to the Veterans' Administration Lung Group, SCLC is currently divided into limited disease (LD) and extensive disease (ED). LD-SCLC, diagnosed in approximately 30-40% of SCLC patients, is defined as tumor in the side of one chest and coverage within a single radiation field. ED-SCLC, diagnosed in approximately 60-70% of SCLC patients, is defined as tumor that extends beyond the boundaries of a single radiation field, including distant metastases and malignant pleural effusion. According to the International Association of the Study of Lung Cancer, TNM staging is recommended, based on tumor, node, and metastasis staging, it is useful for the patients who are candidate for surgery. In recent years, treatment of SCLC remains a tremendous challenge for oncologists. The prognosis is still not ideal, with the median survival time ranging from 15 to 20 months for LD-SCLC and 8 to 13 months for ED-SCLC.[2,5]

This review aims to summarize the available treatments for SCLC, discussing several issues associated with the timing of radiotherapy (early vs.

late), radiation dose and fractionation, target volumes, prophylactic cranial irradiation (PCI) and progress in molecular targeted therapy and immunotherapy for SCLC.

Radiotherapy for LD-SCLC

Timing of Radiation (early vs. late)

In 1990s, two meta-analyses have shown that chemotherapy combined with definitive thoracic radiation has improved overall survival (OS) compared with chemotherapy alone in LD-SCLC patients.[6,7] Many studies found that CCRT is preferred to sequential chemoradiotherapy.[8,9] Although it has been proven that the concurrent chemoradiotherapy (CCRT) has a significant survival benefit, but the optimal timing of radiotherapy (early vs. late) combined with chemotherapy is still controversial. Most of the studies supported the radiotherapy should be started early after the first or second cycle of chemotherapy.[10,11] Fried et al. systematically reviewed the timing of thoracic radiotherapy for LD-SCLC. Patients received the early radiation (before the third cycle of chemotherapy) had a significant improvement in 2-year OS compared with late radiotherapy (after the beginning of the third cycle of chemotherapy).[10] Also, Pijls-Johannesma et al. showed 5-year OS was significantly higher when radiotherapy was started within 30 days after the start of chemotherapy for SCLC (P=0.02).[11] Recently, a randomized phase III trial of CCRT with either first-cycle or third-cycle chemotherapy showed that late radiotherapy was not inferior to early radiotherapy. No significant difference was found in the median OS (early vs. late, 24.1 vs. 26.8 months; P=0.69) and median progression-free survival (PFS) (early vs. late, 12.4 vs. 11.2 months; P=0.6), but the toxicities in the late radiotherapy group had less grade 3-4 neutropenia.[12] The National Comprehensive Cancer Network (NCCN) recommend that radiotherapy should be started with the first or second cycle of chemotherapy. But it has some limitations. Early CCRT is not suitable for all patients, because most of patients have large volume of the tumor. If the tumor has no obvious shrink after chemotherapy, early radiotherapy may increase the acute or late toxicities.

Radiation Dose and Fractionation

For LD-SCLC patients, the optimum radiotherapy dose and fractionation have not been established (Table 1). Yee et al. evaluated the radiotherapy dose for LD-SCLC patients who treated with different radiation doses: 54, 58, 62 or 65 Gy, respectively, and delivered in 25 daily fractions. The maximal tolerance dose in this trial was 58 Gy.[13] However, some trials investigated that accelerated hyperfractionated (twice-daily) radiation therapy schedule can improve the outcomes for LD-SCLC patients, which may obtain a better control in the rapidly proliferating small cell tumor.[14-16]

Table 1. Selected radiation dose and fractionation in clinical trials with LD-SCLC.

Clinical trial	Radiotherapy	Phase	Median OS (months)	P value
INT 0096(14)	45Gy/1.5Gy bid	III	23	0.04
	45Gy/1.8Gy qd		19	
RTOG0239(15)	61.2Gy 1.8Gy qd +1.8Gy bid	II	20	
Schildet et al.(21)	42Gy/1.4Gy bid	II	25.1	0.61
	45Gy/1.5Gy qd		18.8	
EORTC 0807 22)	45Gy/1.5Gy bid	III	25	0.15
	66Gy/2Gy qd		30	

INT: Intergroup Trial; RTOG: Radiation Therapy Oncology Group; EORTC: European Organisation for Research and Treatment of Cancer; bid: twice daily; qd: once daily.

The Intergroup Trial 0096 have delivered a total dose of 45 Gy either twice-daily over 3 weeks or once-daily over 5 weeks with CCRT. The twice-daily regimen greatly improved OS compared with once-daily regimen. The main problem seems to be the increase of acute toxicity of grade 3 esophagitis in the twice-daily group (27% vs. 11%, P<0.001).[14] There was an obvious defect of this study, the biologically equivalent dose (BED) in the two groups were different, which may affect the results. In the Radiation Therapy Oncology Group (RTOG) 0239 study, patients with LD-SCLC were given radiation dose to a total of 61.2 Gy over 5 weeks with CCRT. The results showed 2-year OS has no improvement compared with intergroup trial 0096, but the grade 3 esophagitis was significantly lower (18% vs. 27%).[15] A phase II study reported a favorable outcome for LD-SCLC patients with CCRT(30 Gy/20 fraction twice-daily, a 2-week break, and another 30 Gy/20 fraction twice-daily). For the 76 assessable patients, the median OS was 20 months, 5-year survival rate was 24%, and the toxicities were acceptable.[16] Another study conducted a dose escalation model for LD-SCLC and indicated a treatment of twice-daily with durations of 3 weeks as an optimal schedule.[17] Recently, a randomized phase II trial compared the thoracic radiotherapy of 42 Gy in 15 fractions (twice-daily) with 45 Gy in 15 fractions (once-daily) in 3 weeks. Even though there were no differences in OS, PFS and severe toxicities, the median OS in the twice-daily arm was more than 6 months longer.[18] Higher doses of 60-70 Gy should be delivered in 6 to 7 weeks when using once-daily fraction.[19-21] In order to evaluate the efficiency difference between a total radiation dose 60-70 Gy delivered once-daily with 45

Gy delivered twice-daily, a clinical trial of EORTC 08072 (CONVERT) reported the median OS in once-daily and twice-daily groups were 25 months and 30 months, respectively (P=0.15), the median PFS were 14 months and 15 months, respectively (P=0.26). The toxicities also have no statistical difference between the two groups. These results supported that the two regimens were suitable for LD-SCLC patients with good PS.[22] Another phase III randomized trial of Cancer and Leukemia Group B (CALGB) 30610/ RTOG 0538 is ongoing (clinicaltrials.gov: NCT00632853). This study evaluated three different radiotherapy schemes for LD-SCLC patients who received 70 Gy delivered once-daily over 7 weeks or 61.2 Gy delivered 1.8 Gy once-daily for first 16 fractions followed by 1.8 Gy twice-daily for last 9 fractions or 45 Gy delivered twice-daily in 3 weeks, respectively. We are looking forward to the results of this clinical trial.

Radiation Target Volume

Locoregional (LR) failure still plays an important role and the pattern of failure and seems preventable in patients with LD-SCLC. However, reasonable radiation target volume and the use of omitting elective node irradiation (ENI) remain controversial.[23] Although this method is widely used in clinical trials and ordinary treatment, there was still not enough evidence to support the practice of omitting ENI. In 2006, two phase II trials evaluated the patterns of recurrence when patients were treated with omitting ENI based on CT scan radiotherapy.[24,25] Baas et al. reported the results of 36 patients, two patients (5.5%) was observed isolated nodal failure (INF).[24] Nevertheless, another prospective study found that 26% (7/27) patients developed a local recurrence, 11% (3/27) of them developed INF. The recurrence and failure rates were higher than the expectation. But the small sample size and short follow-up (median 18 months) limited the conclusion in this study.[25] In a retrospective involved-field radiotherapy based on CT scan study with a slightly larger sample size, Xia et al. showed a low rate of INF (4.6%), and the recurrence were all limited in the ipsilateral supraclavicular area.[26] These different results are confusing. Inoue et al. have reported that clinical stage based on CT underestimates the nodal stage in 30.6% compared with the pathologic stage for SCLC patients.[27] Positron emission tomography/computed tomography (PET/CT) has been shown to improve the accuracy in the staging for LD-SCLC patients and could potentially identify involved nodal sites obviously.[28,29] So several studies have evaluated the impact of PET/CT scan on involved nodal irradiation. These results reported a low rate of INF when omitting ENI was based on PET/CT.[30-33] Van Loon et al. showed that PET-based involved nodal irradiation resulted in a rate of 3% INF and lower radiation-related toxicities.[30,31] Shirvani et al. showed that only 2% of patients experienced INF when PET/CT guided omitting ENI.[32] Also for PET-based omitting ENI, Reymen et al. reported similar outcomes and concluded the total gross tumor volume (GTV) was an independent risk factor of survival.[33] Although few studies compared involved nodes irradiation with ENI directly, according to the evidences which verified the safety and efficacy of omitting ENI for SCLC patients, omitting ENI remains the recommend approach in clinical trials and routine treatment.

PCI

The brain is the most common metastasis sites in SCLC patients, and more than 50% of patients have found brain metastases.[34] At present, there is no effective treatment for the brain metastasis in SCLC patients.[35] PCI should be considered for patients who have a good response to chemoradiotherapy and do not have metastatic disease to the brain. A retrospective study found that PCI significantly improved the 2 years, 5 years, and 10 years OS compared with those who did not receive PCI for LD-SCLC patients ($P < 0.001$).[36] The optimum radiotherapy does and fractionation PCI still have controversy. Auperin et al. have compared the effect of different total doses (8 Gy, 24 to 25 Gy, 30 Gy, and 36 to 40 Gy) for SCLC patients indirectly. The reduction rate of brain metastases was 24%, 48%, 68% and 73%, respectively. It was found that the higher dose could decrease the risk of brain metastasis, but there was no significant difference in survival.[37] Subsequently, a randomized clinical trial compared the effect of PCI at 25 Gy/10 fractions vs. 36 Gy/18 fractions or 36 Gy/24 fractions for SCLC patients who achieved complete response (CR) or good partial response (PR) after chemoradiation. There was no significant difference in the incidence of brain metastasis between these groups. The incidence rate of brain metastasis in 2 years was 29% vs. 23% (P=0.18). Nonetheless, the 2-year survival was higher in the 25 Gy/10 fractions group (P=0.05).[38] In RTOG 0212, the results indicated that PCI at a total dose of 36 Gy increased the incidence of chronic neurotoxicity significantly compared with 25 Gy (P= 0.02).[39] A retrospective study also reported that 25 Gy/10 fractions significantly increased the survival compared with 30 Gy/15 fractions ($P = 0.018$).[40] So PCI at 25 Gy/10 fractions should remain the standard

treatment for LD-SCLC patients with good PS and a good response to initial therapy.

Radiotherapy for ED-SCLC

Consolidative Thoracic Radiotherapy

For ED-SCLC patients, the combination of etoposide and platinum-based chemotherapy for four to six cycles remains the standard treatment.[41] However, the prognosis remains poor with the median OS of 8-13 months.[5] Many approaches have been researched to improve the survival. The results demonstrated that consolidative thoracic radiotherapy is beneficial for ED-SCLC patients who have a good respond to chemotherapy (Table 2). A retrospective study demonstrated consolidative thoracic radiotherapy was well tolerated in selected patients with ED-SCLC. The incidence of LR and distant failure in 2 years was 39% and 74%, respectively. The median OS was 14 months. Most of the patients had minimal acute toxicity and no patients had radiation pneumonitis.[42] In another retrospective review of 119 patients, the addition of thoracic radiotherapy to chemotherapy improved the OS compared with chemotherapy alone for ED-SCLC patients. The overall response rate (ORR) were 86.7% and 62.7% in the chemotherapy plus radiotherapy group and chemotherapy alone group, respectively (P=0.003). In the chemotherapy and radiotherapy group, the median OS, 2-year and 5-year OS rates were 17 months, 35%, and 7.1%, respectively and in the chemotherapy alone group were 9.3 months, 17%, and 5.1%, respectively (P=0.014).[43] Yee et al. conducted a prospective non-randomised phase II study, the results demonstrated that consolidative thoracic radiotherapy for ED-SCLC patients were associated with a lower symptomatic thoracic recurrence rate (5/32).[44] Recently, Slotman et al. conducted a phase III randomised controlled trial of 498 patients with ED-SCLC who responded to chemotherapy. The results indicated that there were significantly different between the consolidative thoracic radiotherapy group and the control group. The 2-year OS were 13% and 3% (P=0.004), respectively. The 6 months PFS were 24% and 7% (P=0.001), respectively.[45] These results demonstrated that consolidative thoracic radiotherapy should be considered for selected patients with ED-SCLC with good respond to initial chemotherapy.

PCI

PCI decreased the incidence of brain metastases and is recommended in patients with LD-SCLC or ED-SCLC who had a good response to initial treatment in previous studies. In a randomized trial from the European Organization for Research on Treatment of Cancer (EORTC), Slotman et al. assessed 283 patients with ED-SCLC who had response to initial treatment. Patients in the PCI group have reduced the symptomatic brain metastases compared with non-PCI group (14.6% vs. 40.4%, P<0.001) and increased the median survival (6.7 months vs. 5.4 months, P = 0.003).[46] However, the interim analysis from a Japanese phase III study investigated the efficacy of PCI for ED-SCLC patients. The results found that PCI group was not superior to non-PCI group, and the median OS of non-PCI group seems to be longer than PCI group (15.1 months vs. 10.1 months, P=0.091).[47] According to the different results in these studies, the recommendation for PCI might be adjusted in patients with ED-SCLC.

Table 2. Consolidative thoracic radiotherapy in studied with ED-SCLC.

Author	Therapy	Results	P value
Giuliani et al. (42)	chemotherapy + TRT	14 months(median OS)	
Zhu et al. (43)	chemotherapy + TRT	17 months(median OS)	0.014
	chemotherapy along	9.3 months(median OS)	
Yee et al.(44)	chemotherapy + TRT	8.3 months(median OS)	
Slotman et al. (45)	chemotherapy + TRT	13% (2-year OS)	0.004
	chemotherapy along	3% (2-year OS)	

OS: overall survival; TRT: consolidative thoracic radiotherapy.

Novel Treatment Strategies of SCLC

Molecular Targeted Therapy

The rapid progress of molecular targeted therapy has improved the survival in non-small cell lung cancer (NSCLC) patients. Several methods have been explored in molecular targeted therapy for SCLC (Table 3). There were numerous receptor tyrosine kinases (RTKs) have been studied in SCLC, including epidermal growth factor receptor (EGFR), C-kit and type-1 insulin-like growth factor (IGF-1R).

EGFR mutations mostly occur in lung adenocarcinoma[48] and EGFR tyrosine kinase inhibitor (TKIs) have shown clinical benefits compared with chemotherapy in NSCLC patients who were EGFR mutations.[49,50] Only about 4% patients with EGFR gene mutations in SCLC patients.[51] A previous study suggested that EGFR-TKIs was potentially effective in SCLC with low EGFR expression.[52] However, in a phase II trial, the EGFR-TKIs (gefitinib) failed to demonstrate benefit in 19 patients with relapsed SCLC. It seems that this negative result was caused by the less EGFR mutations in unselected SCLC patients.[53] Interestingly, Sequist et al. reported 14% patients transformed NSCLC into SCLC who became resistant to EGFR-TKIs and sensitive to standard SCLC therapy.[54]

Table 3. Selected molecular targeted therapy in clinical trials with SCLC.

Author	Target	Drugs	Phase	Results
Moore et al.[53]	EGFR	Gefitinib	II	21% (1-year OS)
Dy et al.[56]	C-kit	Imatinib	II	Arm A[a]: 3.9 months (median OS)
				Arm B[b]: 5.3 months (median OS)
Spigel et al.[57]	C-kit	Imatinib	II	8.4 months (median OS)
				5.4 months (median PFS)
Schneider et al.[58]	C-kit	Imatinib	II	7.8 months (median OS)
				4.3 months (median PFS)
Miller et al.[59]	C-kit	Dasatinib	II	17.0 weeks (median OS)
				5.9 weeks (median PFS)
Ellis et al.[62]	IGF-1R	Dalotuzumab	I	67% (ORR)
Belani et al.[63]	IGF-1R	EP vs. EP + V vs. EP + Cixutumumab	II	9.1 vs. 9.8 vs. 10.1 months (median OS, P < 0.05)
Spigel et al.[64]	VEGF	Bevacizumab	II	12.1 months (median OS)
				9.13 months (median TTP)
Ready et al.[65]	VEGF	Bevacizumab	II	11.6 months (median OS)
				7.0 months (median PFS)
Jalal et al.[66]	VEGF	Bevacizumab	II	30.0 weeks (median OS)
				14.7 weeks (median PFS)
Trafalis et al.[67]	VEGF	Bevacizumab	II	6.0 months (median OS)
				3.0 months (median PFS)
Marcello et al.[68]	VEGF	Bevacizumab + EP/EC vs. EP/EC	III	8.9 vs. 9.8 months (median OS, P= 0.113)
				5.7 vs. 6.7 months (median PFS, P = 0.03)
Han et al.[69]	VEGF	Sunitinib	II	5.6 months (median OS)
				1.4 months (median PFS)
Sharma et al.[70]	VEGF	Sorafenibin	II	7.4 months (median OS)
Arnold et al.[71]	VEGF	Vandetanib vs. placebo	II	10.6 vs. 11.9 months (median OS, P= 0.90)
				2.7 vs. 2.8 months (median PFS, P = 0.51)
Ramalingam et al.[72]	VEGF	Cediranib	II	6.0 months (median OS)
				2.0 months (median PFS)
Lee et al.[73]	VEGF	EC + Thalidomide vs. EC + placebo	II	10.1 vs. 10.5 months (median OS, P= 0.28)
Owonikoko et al.[76]	PARP1	Veliparib + EP	I	71.4 % (ORR)
Maria et al.[77]	PARP1	TMZ + Veliparib vs. TMZ + placebo	II	8.2 vs. 7.0 months (median OS, P= 0.50)
Charles et al.[80]	DLL3	Rova-T	II	8.0 months (median OS)[c]

EGFR: epidermal growth factor receptor; PFS: progress free survival; IGF-1R: insulin-like growth factor-1 receptor; ORR: objective response rate; VEGF: vascular endothelial growth factor; TTP: time to progression; EP: etoposide-cisplatin; EC: etoposide-carboplatin; PARP1: Poly-(ADP-ribose) polymerase 1; TMZ: temozolomide; DLL3: Delta-like ligand 3; Rova-T: Rovalpituzumab tesirine;

[a] Disease progression < 3 months after previous treatment.

[b] Disease progression ≥3 months after previous treatment.

[c] Among patients with available archive tissue specimens and ≥ 50% of cells expressing DLL3.

The expression of C-kit and its ligand stem cell factor are high in SCLC.[55] Many studies have investigated the imatinib, an inhibitor of C-kit for SCLC patients. Unfortunately, the results of these clinical trials were disappointing that imatinib did not improve the outcomes in SCLC.[56-58] Dasatinib is another inhibitor of C-kit. A phase II trial of dasatinib in 45 patients with chemotherapy sensitive relapsed SCLC. The results indicated the efficacy did not reach the specified criteria and the trial was terminated. Lack of C-kit mutations gene in SCLC may be the reason for the negative results.[59]

The IGF-1R is commonly over-expressed in lung cancer and under investigation in SCLC.[60] IGF-1R targeting can increase the efficacy of chemotherapy and radiotherapy in SCLC.[61] Currently, some clinical trials about the IGF-1R tyrosine kinase inhibitors are carrying out in SCLC, such as linsitinib (OSI-906, clinicaltrials.gov:NCT00887159), and humanized monoclonal antibodies, dalotuzumab (MK-0646, clinicaltrials.gov:NCT00869752) and cixutumumab (IMC-A12, clinicaltrials.gov:NCT1533181). A phase I trial demonstrated that the toxicities of dalotuzumab (MK-0646) combined with standard chemotherapy of cisplatin/etoposide in ED-SCLC was accepted, but the addition of dalotuzumab to chemotherapy did not bring a clinically improvement in ORR (67%) compared standard chemotherapy alone.[62] In a randomized phase II trial, chemotherapy plus concurrent and maintenance cixutumumab compared with chemotherapy alone for ED-SCLC patients. The results showed that there was no significant improvement in efficacy between the groups.[63]

Angiogenesis is an important pathogenetic mechanism of disease progression in SCLC and vascular endothelial growth factor (VEGF) is a key mediator in angiogenic pathways. Several trials have studied the relationships between VEGF and SCLC. Bevacizumab, a humanized monoclonal antibody against VEGF has been evaluated for SCLC patients.

In some phase II studies, bevacizumab combined with standard chemotherapy showed efficacy as a first line treatment in ED-SCLC.[64, 65] But the results of bevacizumab combined with paclitaxel as a second line treatment did not improve outcomes in relapsed chemotherapy sensitive SCLC.[66] However, a phase II study of bevacizumab plus irinotecan demonstrated low toxicity and promising efficacy in relapsed chemotherapy resistant SCLC.[67] A phase III randomized trial was assessed the efficacy of cisplatin-etoposide with or without bevacizumab as the first-line treatment in ED-SCLC. Even though the addition of bevacizumab to chemotherapy leads to a statistically significant improvement in PFS, but there was not statistically significant improvement in the OS.[68] Other anti-angiogenic agents have been assessed the safety and efficacy in SCLC, such as sunitinib, sorafenib, vandetanib, cediranib, thalidomide.[69-73] However, these agents did not indicate promising outcomes. Further researches should be warranted in the area of angiogenesis therapy of SCLC.

Targeting the DNA repair seems to be a novel therapeutic for SCLC patients. Poly-(ADP-ribose) polymerase 1 (PARP1), a DNA repair protein, has been studied recently. Lauren et al. reported that the PARP1 inhibitor was a potential target and efficacious in a preclinical testing in SCLC.[74] Talazoparib (BMN 673) is a highly potent PARP inhibitor. Sensitivity to talazoparib was associated with the expression levels of DNA repair proteins and the baseline activation of the PI3K/Mtor (PAM) pathway for SCLC.[75] In a phase I study, veliparib (a PARP inhibitor) combined with cisplatin and etoposide showed safety and efficacy in ED-SCLC.[76] For relapsed SCLC patients, a phase II study comparing temozolomide (TMZ) plus either veliparib or placebo as second or third-line therapy. The preliminary result indicated that response rate was higher with veliparib/TMZ compared to TMZ alone (39% vs. 14%, P=0.016). But the median OS has no difference between the veliparib arm and placebo arm (P=0.50). Hematologic toxicity more commonly occurred in the veliparib/TMZ arm.[77]

The Notch signaling pathway is an important pathway related to not only stem cell biology but also cancer.[78] Delta-like ligand 3 (DLL3) protein is a part of the Notch signaling pathway and inhibiting tumor initiating (stem) cells which is expressed on the surface of tumor cells. A DLL3-targeted antibody-drug conjugate (ADC), rovalpituzumab tesirine (Rova-T; SC16LD6.5), effectively targets and eradicates the level expression of DLL3-expressing in SCLC.[79] Charles et al. reported the results of single-agent Rova-T in recurrent or refractory SCLC. 25% (15/61) patients achieved PR or CR, and 72% (44/61) achieved clinical benefit (best response of at least stable disease). For the patients who have available archive tissue specimens, among them ≥ 50% of cells expressing DLL3, 12/22 (55%) achieved PR or CR, and 20/22 (91%) achieved clinical benefit. The median OS was 8 months. Rova-T demonstrated encouraging efficacy and safety in recurrent or refractory SCLC.[80]

Tarextumab (OMP-59R5) is a fully human monoclonal antibody that inhibits the Notch 2/3 receptors. In a phase Ib study, tarextumab combined with etoposide and platinum chemotherapy in ED-SCLC demonstrated a promsing outcome, with 13 of 16 patients (81.3%) achieved PR and 3 (18.8%) achieved stable disease.[81] A phase II study is carrying out (ClinicalTrials.gov:NCT01859741).

Immunotherapy

Recently, immunotherapy is becoming a promising strategy of treatment in various solid tumors. Therefore, a large number of trials are focused on immunotherapy in SCLC patients (Table 4).

Several tumor vaccines have been investigated in SCLC, but they may have limited efficacy. BEC2 is a monoclonal antibody that targets ganglioside antigen GD3 which is highly expressed in SCLC. In the early clinical trial, Grant et al. evaluated the BEC2 and Bacillus Calmette-Guerin (BCG) vaccine therapy after standard treatment in SCLC, and the results showed a longer survival and relapse-free survival than previous study of similar patients.[82] Based on these promising results, a phase III trial was conducted to evaluate the adjuvant vaccination with BEC2 plus BCG in responding patients with LD-SCLC. The median OS in the observation group and vaccination group was 16.4 and 14.3 months (P=0.28), respectively. The OS failed to achieve significant difference. However, in the subgroup of analysis among vaccinated patients (n=55), the median survival of humoral responders showed a trend of improvement compared with non-responders (19.2 vs. 13.9 months; P =0.0851).[83] A study of 29 patients who had received p53 vaccine combined with chemotherapy treatments in ED-SCLC showed a high ORR. Despite a response to p53 cancer vaccine in this study, the optimal treatment may not take vaccination as single modality. It should be combined with chemotherapy directly.[84] A phase I/II study reported that the p53-modified adenovirus-tranduced dendritic cell vaccine (INGN-225) was well tolerated and induced in a significant immune response (40-50%).[85]

Table 4. Selected immune therapy in clinical trials with SCLC.

Author	Target	Drugs	Phase	Results
Grant et al.[82]	Vaccine	BEC2/BCG	II	11 months (median RFS) for ED-SCLC
Giaccone et al.[83]	Vaccine	BEC2/BCG vs. observation	III	14.3 vs. 16.4 months (median OS, P = 0.28)
Antonia et al.[84]	Vaccine	P53	I	11.8 months (median OS)
Chiappori et al.[85]	Vaccine	INGN-225	I/II	8.8 months (median OS)
Zarogoulidis et al.[86]		CT vs. CT + IFN-α vs. CT+ IFN-γ vs. CT + IFN-α + IFN-γ	II	19.0 vs. 34.0 vs. 17.0 vs. 13.6 months (median OS, P<0.05) for LD-SCLC
Pillai et al.[87]		IFN	II	6.2 months (median OS) 2.0 months (median PFS)
Ott et al.[93]	PD-1	Pembrolizumab	I	35% (ORR)
Antonia et al.[95]	PD-1/CTLA-4	Nivolumab 1 mg/kg + Ipilimumab 3 mg/kg	I/II	23% (ORR)
Reck et al.[97]	CTLA-4	[d] Control vs. Concurrent Ipilimumab vs. Phased Ipilimumab	II	9.9 vs. 9.1 vs. 12.9 (median OS) 5.3 vs. 5.7 and 6.4 (median irPFS)

BCG: Bacillus Calmette-Guerin; RFS: relapse-free survival; ED-SCLC: extensive disease small cell lung cancer; CT: chemotherapy; LD-SCLC: extensive disease small cell lung cancer; IFN: Interferon; PD-1: programmed death-1; CTLA-4: cytotoxic T-lymphocyte antigen-4; irPFS: immune-related progression-free survival.
[d] Control (paclitaxel-carboplatin + Ipilimumab + placebo); concurrent Ipilimumab (Ipilimumab+ paclitaxel-carboplatin followed by placebo + paclitaxel-carboplatin); Phased Ipilimumab (placebo + paclitaxel-carboplatin followed by Ipilimumab+ paclitaxel-carboplatin).

Interferon (IFN) was one of the first immunotherapies cytokines to be studied in anticancer. A phase II, randomized study evaluated the effect of IFN in SCLC, a total of 164 patients with SCLC were assigned to four groups as follows: chemotherapy alone, or a combination of chemotherapy and IFN (IFN-α, IFN-γ, IFN-α plus IFN-γ). The results showed a significant survival benefit for chemotherapy plus IFN-α compared with chemotherapy alone (P<0.05).[86] But an Eastern Cooperative Oncology Group (ECOG) 6501 study showed the addition of IFN-α and 13-cis-retinoic to paclitaxel did not improve the outcomes for recurrent SCLC patients.[87] So we need further trials to verify the role of the IFN-α as a potential therapy in patients with SCLC.

Immune checkpoint inhibitors offer wider application in various solid tumors such as melanoma, head and neck, NSCLC, and bladder carcinomas.[88-91] The results of these inhibitors demonstrated this treatment was more beneficial than vaccines for SCLC in the last few years.[92] The immune checkpoint receptors are antigen independent and down-regulate T-cell including the programmed death-1 (PD-1), programmed death ligand-1 (PD-L1) and cytotoxic T-lymphocyte antigen-4 (CTLA-4).

PD-1 is the major immune checkpoint receptor that inhibits T-cell activation and regulates immunosuppression through binding of its ligand, PD-L1. Pembrolizumab is an anti-PD-1 monoclonal antibody that blocks the PD-1/PD-L1 pathway. In the Keynote 028 trial, the interim analysis reported that 24 patients with ED-SCLC received the pembrolizumab who had progressed on chemotherapy and expression of PD-L1. The ORR was 35% and durable responses were more than 16 weeks. However, the drug related adverse event rate was 53%.[93] The safety and efficacy of pembrolizumab for PD-L1 positive patients with SCLC were similar to other carcinoma. Ishii et al. conducted a study to investigate the expression of PD-L1 in 102 patients of SCLC that was evaluated by immunohistochemical analysis. 71.6% of SCLC patients expressed PD-L1 and was significantly correlated with LD-SCLC. The median OS was 16.3 months in the PD-L1-positive group and 7.3 months in the PD-L1-negative group ($P < 0.001$).[94] Some prospective clinical trials are investigating pembrolizumab plus chemotherapy or pembrolizumab plus chemotherapy and radiotherapy for SCLC patients (ClinicalTrials.gov:NCT02359019 and NCT02403920). We expect the results of these combination treatment to be beneficial for SCLC patients. In addition, a phase I/II clinical trial of nivolumab (anti-PD-1 monoclonal antibody) combined with or without ipilimumab (anti-CTLA-4 monoclonal antibody) for treatment of recurrent SCLC. The results presented that nivolumab plus ipilmumab and nivolumab alone showed beneficial effect to SCLC and the adverse events were tolerable.[95] A phase III clinical trial of nivolumab or nivolumab plus ipilimumab in SCLC should be carrying out.

CTLA-4 is another well-studied immune checkpoint protein that expressed on activated T cells whose function is to down-regulate T-cell activity.[96] A randomized phase II study reported the ipilimumab combined with paclitaxel and carboplatin as the first-line treatment in ED-SCLC. The results demonstrated that phased ipilimumab (chemotherapy plus placebo followed by ipilimumab plus chemotherapy) improved PFS compared with concurrent ipilimumab plus chemotherapy followed by chemotherapy plus placebo (P=0.03), and OS were 12.5 months and 9.1 months, respectively, with a trend of improvement although there was no

significant differences between the two groups (P=0.13).[97] Based on these results, a randomized phase III clinical trial of ipilimumab plus chemotherapy compare with chemotherapy alone in ED-SCLC patients is ongoing (ClinicalTrials.gov: NCT01450761).

Conclusions

In summary, the main progresses were the chemoradiotherapy and PCI improved the survival for SCLC patients in the past decades. Recently, investigators focus on the molecular targeted therapy and immunotherapy. The preliminary results showed some little therapeutic breakthroughs from some clinical trials. We expect these treatment strategies can improve the outcomes for SCLC.

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Conflict of Interest

There authors have no conflict of interest.

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