

MINI REVIEW

Comparison and discussion of the treatment guidelines for small cell lung cancer

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Introduction

Small cell lung cancer (SCLC) is one of the leading causes of cancer-related death worldwide.¹ More than 130 000 new diagnoses of SCLC and 100 000 deaths from the disease were estimated to have occurred in China in 2013.² Traditional treatment guidelines for SCLC are based on the two-stage method of the American Veterans Administration Lung Study Group (VALG), which focuses mainly on the importance of radiotherapy to treat SCLC.³ The International Association for the Study of Lung Cancer (IASLC) staging project recently showed that tumor node metastasis (TNM) staging of SCLC, combined with the VALG two-stage method, provides more accurate prognoses and treatment options.⁴ Thus, the recommended guidelines for the diagnosis and treatment of SCLC worldwide are now based on TNM staging. Because of the regional differences in economic and medical capabilities, different regional medical guidelines have been developed with reference to the new staging system. In order to understand the current status of SCLC treatment in more detail, we identified the similarities and differences between the latest National Comprehensive Cancer Network (NCCN) Clinical Practice

Abstract

Small cell lung cancer (SCLC), which accounts for 15% to 17% of all lung cancers, is one of the leading causes of cancer-related death worldwide. More than 130 000 new diagnoses of SCLC and 100 000 deaths from the disease were estimated to have occurred in China in 2013. The existing guidelines of SCLC therapeutic principles differ by region. In recent years, new immunotherapy and targeted therapy treatments have been lacking. In order to understand the current status of SCLC treatment in more detail, we identified the similarities and differences among the latest National Comprehensive Cancer Network Clinical Practice Guidelines for SCLC, the Chinese Society of Clinical Oncology Lung Cancer Guidelines, and the European Society for Medical Oncology Clinical Practice Guidelines for Metastatic SCLC, and present a reference of treatment strategies that should prove beneficial for the treatment of patients with SCLC.

Guidelines for SCLC, Chinese Society of Clinical Oncology (CSCO) Lung Cancer Guidelines, and the European Society for Medical Oncology (ESMO) Clinical Practice Guidelines for Metastatic SCLC.^{5–7}

The precursors of SCLC, which is characterized by rapid growth, are neuroendocrine cells. With recent advances in medical imaging technology, SCLC tumors are being detected earlier and overall, the diagnosis and treatment of SCLC has shown great progress. During the 21st century, concurrent chemotherapy has improved the survival of patients with SCLC. Prophylactic cranial irradiation (PCI) might markedly reduce the risk of SCLC brain metastasis, and surgery has been re-established as a treatment option for SCLC. With the introduction of targeted therapy and immunotherapy, SCLC treatment has entered a new chapter. The specific characteristics of different regions have resulted in varying criteria for staging.

The NCCN is a nonprofit academic organization, consisting of the 21 most highly regarded cancer centers. The NCCN Clinical Practice Guidelines for SCLC are globally recognized and have been instrumental in promoting the standardization of SCLC treatment. The Chinese Lung Cancer Guidelines for non-small cell lung cancer (NSCLC)

and SCLC, which are based on clinical research and clinical practice in China, were promulgated by the CSCO. The authors are experts from established cancer centers in China who focused on data from the latest scientific investigations and clinical experience in the field of lung cancer. ESMO is the leading European professional organization committed to advancing the specialty of medical oncology and promoting a multidisciplinary approach to cancer treatment and care. The ESMO clinical recommendations are clinical practice guidelines intended to provide the user with a set of requirements for basic standards of cancer care. To improve the basic standard of care for treating SCLC, we compared SCLC guidelines from China, Europe, and the United States (US).

Incidence and epidemiology

An estimated 1.6 million new lung cancers are diagnosed worldwide each year. In the US, an estimated 31 000 new cases of SCLC were estimated to occur in 2017. Although the overall incidence of SCLC in the US has decreased, the incidence in women is increasing, with a male-to-female incidence ratio of 1:1. In Europe, the highest incidence rates in men are observed in Central, Eastern, and Southern Europe, whereas in women the highest rates are found in Northern Europe. The five-year survival rates of lung cancer patients have only slightly improved during the past decade, and remain low at 10%. Epidemiological data for lung cancer in China are missing from the latest Chinese guidelines, but official data show that the incidence of lung cancer in China has increased over recent years. All guidelines report that the development of SCLC is associated with cigarette smoking, the rates of which vary across different populations. Smoking cessation not only reduces the risk of SCLC but has also been shown to decrease the risk of death by almost 50% in patients with localized SCLC.

Diagnosis

According to the NCCN guidelines, although screening with low-dose computed tomography (CT) can detect early-stage NSCLC, it does not seem to be useful for detecting early-stage SCLC. For patients with a clinical diagnosis of SCLC, the pathological diagnosis and evaluation of tumor stage is very important to design an appropriate treatment plan. The NCCN guidelines recommend that complete staging include contrast-enhanced CT of the chest, liver, and adrenal glands, and brain imaging by magnetic resonance imaging (preferred) or CT. If the patient is diagnosed with advanced-stage disease, further staging, such as examination of bone marrow aspirates and positron emission tomography (PET)-CT is optional. The ESMO guidelines recommend assessment of the brain and bone after estimating the stage by assessing the

chest and abdomen. By contrast, the CSCO recommends the addition of cervical ultrasonography to the required contrast-enhanced CT for the chest and abdomen. All guidelines indicate that PET-CT can increase staging accuracy for patients with SCLC. A review reported a median of 13% of patients with SCLC in a stage migration, in which 9% of patients are up-staged from LS (limited stage) to ES (extensive stage) and 4% are down-staged from ES to LS by PET-CT compared to conventional imaging, which included bone scintigraphy and brain imaging.⁸ Thus, PET-CT has a major diagnostic role in the assessment of patients with SCLC. However, PET-CT is inferior to magnetic resonance imaging and CT for the detection of brain metastases. Although PET-CT seems to improve the staging accuracy in SCLC, histopathologic confirmation is still required.

ESMO presents different views on solitary metastases. Histopathological confirmation of a solitary metastasis should not delay the initiation of treatment for SCLC patients, and the size of a solitary metastatic lesion should be re-evaluated after two treatment cycles, which also allows further judgment as to whether it is a true metastatic site. For example, if pleural or pericardial effusion is the only site of an M1 SCLC, no malignant cells are identified in the pleural fluid, and a plausible explanation other than tumor involvement is clinically suspected, the initial treatment should be based on treatment for an M0 tumor.

Staging

The NCCN, CSCO, and ESMO panels have adopted a combined approach for staging SCLC using both the American Joint Committee on Cancer TNM staging system and the older VALG protocol for SCLC. The approach suggests that the methods of assessment and treatment planning should both be based on the two-stage system, but that the choice of surgery and radiotherapy should be based on the TNM system. However, the definition of the two-stage system is not consistent among guidelines. NCCN is in accordance with CSCO with regard to LS and ES disease, while ESMO refers to localized and metastatic disease. The primary distinction concerns $T_{3-4}N_xM_0$ -stage disease, which NCCN and CSCO consider to be ES disease because of multiple lung nodules that are too extensive or because the volume of tumor or lymph nodes is too large to be included in a tolerable radiation field.

Surgery

The SCLC guidelines disagree on the use of surgery. The NCCN and CSCO guidelines state that surgery should only be considered for patients with $T_{1-2}N_0M_0$ SCLC without lymph node involvement, confirmed by biopsy. The ESMO guidelines state that patients with $T_{1-2}N_{0-1}M_0$ SCLC, which

includes negative lymph nodes on imaging, should undergo surgery, and biopsy is not required before surgery. Wakeam *et al.* recently investigated patients with $T_{1-2}N_0M_0$ SCLC from 2004 to 2013 in the US National Cancer Database, which showed that only 22.7% underwent surgery: 64.3% lobectomy, 33.4% sublobar resection, and 2.3% pneumonectomy. The resection rates increased over the time of the study from 9.1% to 21.7%, but two-thirds of potentially eligible patients did not undergo surgery.⁹ Postoperative chemotherapy (PORT) is required by the guidelines. PORT can significantly improve the survival of combined SCLC patients with resected pathological pN2 stage. For patients with a large percent of metastatic lymph nodes, PORT can also improve survival.¹⁰ Patients with N_{1-2} disease obtained longer survival after radiotherapy than those not treated with radiotherapy, a result that further confirms the value of postoperative radiotherapy. However, neither the NCCN, CSCO, nor ESMO guidelines present recommendations for surgery for patients with higher than stage I disease that have undergone induction chemotherapy. Further study to address the lack of concordance between guidelines and practice is needed.

Concurrent chemoradiotherapy

For SCLC patients who cannot undergo surgery, chemoradiotherapy is undoubtedly the most effective weapon. The ESMO guidelines provide broad indications, suggesting that patients with $T_{1-4}N_{2-3}M_0$ or $T_{1-4}N_{1-3}M_1$ (solitary or unconfirmed) disease with good performance status (PS) need concomitant chemoradiotherapy. By contrast, the NCCN guidelines recommend that patients with LS SCLC ($T_{0-4}N_{0-3}M_0$) or excess $T_{1-2}N_0M_0$ with good PS undergo treatment consisting of chemotherapy with concurrent thoracic radiotherapy. The CSCO guidelines are basically consistent with the NCCN guidelines. All of the guidelines agree that thoracic radiotherapy should be initiated as early as possible, beginning with the first or second chemotherapy cycle when cisplatin-based chemotherapy is used. Moreover, recent studies have shown that super-partition radiotherapy is better than conventional radiotherapy, and can improve patient compliance, shorten the duration of radiotherapy, and decrease the total radiation dose.^{11,12}

Sequential chemoradiotherapy

The majority of SCLC patients with ES disease must undergo chemotherapy so that a determination, which is based on response to chemotherapy, can be made about the need for sequential thoracic radiotherapy (TRT). The ESMO guidelines recommend four to six cycles of etoposide and carboplatin/etoposide and cisplatin (EC/EP) chemotherapy. The NCCN guidelines recommend EP/EC/irinotecan and

cisplatin (IP)/irinotecan and carboplatin (IC) as first-line chemotherapy. Beyond the NCCN guidelines, the CSCO guidelines add VP-16/lobaplatin as a first-line chemotherapy regimen, based on the results of a randomized, multicenter phase III study of lobaplatin/etoposide versus EP.¹³ Chinese investigators have also discussed the possibility of aminospine/cisplatin as first-line chemotherapy for patients with ES-SCLC. Although the effect is similar to EP, aminospine/cisplatin is not used in practice because of the excessive side effects.¹⁴ Studies have shown that sequential TRT improves the two-year survival rate and reduces the risk of disease progression. Both the NCCN and CSCO guidelines suggest administering sequential TRT, but the ESMO guidelines do not provide any recommendations.^{15,16} Findings from the latest ColoRectal Stenting Trial suggest that patients with fewer than three distant metastases and no liver metastases receive increased benefits from TRT; thus, radiotherapy should focus on such ES-SCLC patients.¹⁷

Prophylactic cranial irradiation

Prophylactic cranial irradiation has consistently resulted in a marked decrease in the risk of symptomatic brain metastases and increased overall survival (OS). All SCLC patients with poor PS and impaired neurocognitive functioning who respond to first-line treatment should be evaluated for PCI. PCI should not be administered concurrently with systemic chemotherapy. The total radiotherapy dose should not be so high as to cause an increased risk of neurotoxicity. The highest total radiotherapy dose recommended by the NCCN and CSCO guidelines is 25 Gy in 10 daily sessions, which correspond with the ESMO guidelines that recommend two radiotherapy programs: 25 Gy in 10 daily sessions or 20 Gy in five fractions. A recent Japanese trial reported no difference in OS between ES-SCLC patients who underwent PCI and those that did not, which suggests that patients with ED-SCLC should be evaluated carefully before deciding to administer PCI.¹⁸

Second-line therapy

Although SCLC is very responsive to initial treatment, most patients relapse with relatively resistant disease. Second-line chemotherapy provides significant palliation for many patients, and the likelihood of response is highly dependent on the time from the response to initial therapy to relapse. There are several choices for second-line therapy from the three guidelines.

European Society for Medical Oncology

The outcomes are poor for refractory patients (patients that do not respond or progress during chemotherapy)

and resistant patients who experience early relapse (progression-free interval < 6 weeks), and the clinical benefit of further systemic therapy is uncertain. The recommendations for these patients include participation in a clinical trial or best supportive care. The recommendation for resistant patients (progression-free interval < 3 months) and sensitive patients (progression-free interval > 3 months) is topotecan. Only patients with chemotherapy-sensitive disease derive benefits from re-administration of first-line therapy (usually platinum-etoposide).

National Comprehensive Cancer Network

The recommendations for patients with a PS 0–2 who relapse < 6 months after treatment are topotecan (PO or IV), irinotecan, paclitaxel, docetaxel, temozolomide, nivolumab ± ipilimumab, vinorelbine, oral etoposide, gemcitabine, cyclophosphamide/doxorubicin/vincristine (CAV),

or bendamustine. By contrast, the recommendation for patients who relapse > 6 months after treatment is the original regimen.

Chinese Society of Clinical Oncology

Topotecan is the first choice for patients who relapse < 6 months after treatment, while the original regimen is recommended for patients who relapse > 6 months after treatment. Irinotecan, paclitaxel, docetaxel, and gemcitabine are second-line treatments for resistant patients who experience early relapse. Irinotecan, docetaxel, gemcitabine, oral etoposide, and navelbine are second-line treatments for sensitive patients who relapse.

Clinical trials of new chemotherapeutic agents such as lurbinectedin and NKTR-102 are currently underway and are expected to bring new good news to patients with SCLC.¹⁹

Table 1 Recent clinical trials of immunotherapy for SCLC

Patients	Clinical trial	Agent	ORS	1-year OS	OS (m)	Trial state	Phase
Second line (ED)	Checkmate032	Nivo	10%	27%	4.1	Closed	I/II
		Nivo + IPI	23%	40%	7.8		
	KEYNOTE028	Pemb	33%	33.7%	9.7	Closed	I
	PCD4989g	Atezo	6%		5.9	Closed	I
	CheckMate331	Nivo				Enrolling	III
		vs. Topotecan or Amrubicin					
	NCT02963090	Pemb				Enrolling	II
		vs. Topotecan					
	MISP-MK3475	Pemb + paclitaxel				Enrolling	II
	NCT03059667	Atezo				Enrolling	II
	vs. chemotherapy						
NCT02701400	Radiotherapy + Treme + durva vs. treme, + durva				Enrolling	II	
NCT02937818	Durva + Treme				Enrolling	II	
	vs. AZD1775 + carboplatin						
MEDIOLA	Olaparib (PARP) + Durva				Enrolling	I/II	
Maintenance (ES)	NCT02359019	Pemb			9.2	Closed	II
	CheckMate451	Nivo				Enrolling	III
First line (ES)	NCT02402920	Pemb + Radio-chemotherapy				Enrolling	I
	KEYNOTE-011	Pemb + EC				Enrolling	I
	REACTION	Pemb + chemotherapy				Enrolling	II
		vs. chemotherapy					
	KEYNOTE-604	Pemb + EP				Enrolling	III
		vs. placebo + EP					
	Impower133	Atezo + EC				Enrolling	III
		vs. placebo + EC					
	NCT02748889	Atezo + chemotherapy				Enrolling	II
		vs. chemotherapy					
NCT03041311	Trilaciclib + EC + Atezo				Enrolling	II	
	vs. Placebo + EC + Atezo						
Caspian	Durva + treme + EP				Enrolling	III	
	vs. Durva + EP						
	vs. EP						

Atezo, atezolizumab; durva, durvalumab; EC, etoposide and carboplatin; EP, etoposide and cisplatin; ES, extensive disease; IPI, ipilimumab; nivo, nivolumab; OR, odds ratio; OS, overall survival; pemb, pembrolizumab; SCLC, small-cell lung cancer; treme, tremelimumab.

Targeted therapy

Because of slow progress in the development of targeted therapy for SCLC and the lack of relevant data, the guidelines do not include any recommendations. However, researchers in various countries continue to investigate, especially antiangiogenic targeted therapy. A European study evaluated the efficacy and tolerability of the second-line agent pazopanib for SCLC. Pazopanib is a tyrosine kinase inhibitor (TKI) with antiangiogenic effects that has shown promising activity as second-line treatment for patients with platinum-sensitive SCLC.²⁰ The European study is the first to report that antiangiogenic TKIs have demonstrated substantial and clinically relevant efficacy.²¹ In a Chinese study that enrolled 10 ES-SCLC patients administered apatinib from November 2016 to June 2017, one patient achieved a partial response (PR), eight stable disease (SD), and one progressive disease (PD) with metastasis to the liver. All of the target lesions were reduced. The use of apatinib for advanced SCLC is expected. Further clinical trials are needed to verify the role of targeted antiangiogenic therapy for the treatment of SCLC.

DLL3, an atypical inhibitor of the Notch ligand, has been identified in tumor-initiating cells isolated from SCLCs. It is expressed in about 85% of patients on the surface of tumor cells with neuroendocrine cancer, but not in healthy tissues. DLL3 is a novel and promising target for the development of specific inhibitors for treating patients with SCLC.^{22,23} Rovalpituzumab tesirine, which is a first-in-class antibody-drug conjugate directed against DLL3, was used for a phase I open-label study at 10 US cancer centers. Rovalpituzumab tesirine has shown encouraging single-agent antitumor activity and a manageable safety profile. Further development of rovalpituzumab tesirine for DLL3-expressing malignant diseases is warranted.

Immunotherapy

The development of immunotherapies for SCLC is not a novel endeavor, and the recent successes in this field for other cancer types suggest that this approach may provide a degree of prolonged clinical benefit that has not yet been achieved for SCLC patients by traditional treatments. Immunotherapy has already changed the clinical treatment of SCLC, and is included in the NCCN guidelines. PD-1/PD-L1 are undoubtedly the hot topics of SCLC immunotherapy. The limitations of studies on immunotherapy for SCLC include the lack of a standard “current practice” comparator because of the absence of established effective treatments in this setting, small sample sizes, and relatively short follow-up periods, precluding further insights into the impact of immunotherapy on the long-term survival of patients with SCLC.²⁴ A number of clinical immunotherapy trials for SCLC patients are shown in Table 1.^{25,26}

Conclusion

No major advances in the treatment of SCLC have occurred over the past 30 years.²⁷ We analyzed the similarities and differences between the treatment guidelines for SCLC from different countries to clarify the status of treatments. All of the guidelines suggest that we should be inspired by the efficacy of controlling tobacco use to reduce the incidence of SCLC, and that the value of surgery should be re-evaluated in the role of SCLC treatment. SCLC has a high propensity for early spread and characteristically shows high initial responsiveness to cytotoxic chemotherapy, which is usually followed by the rapid development of resistance. Although new agents, protocols, and treatment modalities have been explored worldwide during the last two decades, the EP regimen as first-line standard of care for SCLC has not yet been replaced. The treatment of drug-resistant SCLC remains a key clinical problem, and a promising breakthrough has not yet occurred. Targeted antiangiogenesis therapy may become established in this field. Immunotherapy has obtained good results for treating NSCLC, but more clinical evidence is needed before it can be recommended for SCLC.

Different countries and regions are constantly exploring their own basic and clinical research endeavors to develop SCLC treatment guidelines for the clinical situation and disease characteristics. Distinctive treatment guidelines are more dependent on the regional scale, and clinical trials provide more evidence in the era of individualized treatment.

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Disclosure

No authors report any conflict of interest.

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