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CLINICAL GUIDES IN ONCOLOGY

SEOM clinical guidelines for the treatment of small-cell lung cancer (SCLC) (2019)

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Abstract
Small-cell lung cancer (SCLC) accounts for 15% of lung cancers. Only one-third of patients are diagnosed at limited stage. The median survival remains to be around 15–20 months without significative changes in the strategies of treatment for many years. In stage I and IIA, the standard treatment is the surgery followed by adjuvant therapy with platinum–etoposide. In stage IIB–IIIC, the recommended treatment is early concurrent chemotherapy with platinum–etoposide plus thoracic radiotherapy followed by prophylactic cranial irradiation in patients without progression. However, in the extensive stage, significant advances have been observed adding immunotherapy to platinum–etoposide chemotherapy to obtain a significant increase in overall survival, constituting the new recommended standard of care. In the second-line treatment, topotecan remains as the standard treatment. Reinduction with platinum–etoposide is the recommended regimen in patients with sensitive relapse (≥ 3 months) and new drugs such as lurbinectedin and immunotherapy are new treatment options. New biomarkers and new clinical trials designed according to the new classification of SCLC subtypes defined by distinct gene expression profiles are necessary.

Keywords SCLC · Chemotherapy · Immunotherapy · Radiotherapy

Introduction

Small-cell lung cancer (SCLC) is the most aggressive subtype of lung cancer, which is strongly associated with cigarette smoking. SCLC comprises about 15% of all lung cancer cases. A decreasing trend in the incidence has recently been observed, but is still increasing in women, what might reflect changes in smoking habit [1].

SCLC is characterised by a rapid doubling time, a high growth fraction, an early development of widespread metastases, paraneoplastic endocrinopathies and sensitivity to chemotherapy and radiation. Untreated SCLC is rapidly fatal within 2–4 months. According to the classification system developed by the veterans' administration lung study group (VALSG), more than two-thirds of SCLC patients are diagnosed with extensive stage (ES) and the remaining patients are diagnosed with limited stage (LS).

In LS stage patients, 80–90% achieve a partial or complete response using a combination of chemotherapy plus radiation with a median overall survival (mOS) of 15–20 months. Not more than 10–20% of patients survive beyond 5 years. In ES, mOS is 8–13 months, with a 5-year survival rate < 2% [2].

Although favourable response rates (ORR) have been achieved using combination chemotherapy, particularly platinum–etoposide as the most widely used regimen, only a small proportion of patients survive after 5 years. Most patients relapse within 1 year of starting first-line treatment and the reasons for the intrinsic or acquired resistance to chemotherapy are still unclear.

Methodology

For the elaboration of this guideline, we have carried out an exhaustive review of the most relevant published studies to date. The Infectious Diseases Society of America grading

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system was used to assign levels of evidence and grades of recommendation [3].

Pathological diagnosis

The pathological diagnosis of SCLC should be made using the World Health Organization (WHO) classification [4]. SCLC is a type of neuroendocrine tumour (NET) of the lung that consists of small cells with scant cytoplasm, poorly defined cell borders, fine granular nuclear chromatin, and absent or inconspicuous nucleoli. The cells are round-, oval-, or spindle-shaped, and the nuclear moulding is prominent. The classic and distinctive histology on haematoxylin and eosin (H&E) may be sufficient for identifying SCLC in good-quality histologic or cytologic samples, but immunohistochemistry (IHC) may be required for confirmation, including synaptophysin, chromogranin, and NCAM/CD56. The mitotic count is high (at least 10 mitoses/2 mm^2, but averaging over 60 mitoses/2 mm^2) and the proliferative index as evaluated by Ki-67 antigen IHC is > 50%, approaching 100% in most cases.

Initial evaluation and staging

Initial assessment must include medical and smoking histories, physical examination, complete blood count, biochemistry including liver enzymes, sodium, potassium, calcium, glucose, lactate dehydrogenase levels and renal function tests, and, in the case of thoracic radiation, lung function tests.

Full staging includes computed tomography (CT) scan (with intravenous contrast) of the chest/abdomen; and brain imaging using magnetic resonance imaging (MRI) (preferred) or CT scan (with intravenous contrast). If LS is suspected, a 2-fluor-2-deoxy-D-glucose positron-emission-tomography (FDG-PET) CT could be performed to assess distant metastases. PET scans can increase staging accuracy in patients with SCLC, because SCLC is a highly metabolic disease. Approximately 19% of patients who undergo PET/CT are upstaged from LS to ES disease. PET/CT is recommended in LS patients. In patients with a solitary metastasis, its pathological confirmation is recommended to clarify the stage (III, C).

The 8th edition of the TNM staging system according to the AJCC should be used to define better prognosis and personalised treatment options (I, A) [5]. The VALSG classification could be used in clinical practice [6]. LS is defined as stage I–III (T any, N any, M0) that can be treated with definitive chemoradiation therapy. ES is defined as stage IV (T any, N any, M1a/b/c) or T3–4 due to multiple lung nodules that are too extensive or have tumour/nodal volume that is too large to be encompassed in a tolerable radiation plan (Table 1).

Limited stage

The mOS for patients with LS is 15–20 months and 5-year survival rate is 10–20%.

Stage I–IIA (T1–T2, N0, M0)

Stage I–IIA (T1–2, N0, M0) represent less than 5% of SCLC. In these patients, a mediastinal staging is necessary that should be performed by either surgery (mediastinoscopy, mediastinotomy or video-assisted thoracoscopy) or endobronchial or oesophageal ultrasound-guided biopsy (II, A). The lobectomy should be the preferred surgical procedure with a systematic lymph-node dissection (II, A). Adjuvant systemic therapy should be always considered (II, A). For patients with surgical contraindication or refusing surgery, stereotactic body radiation therapy (SBRT) may be a useful treatment (III, B). Sequential chemotherapy after SBRT yielded a mOS of 31.4 vs 14.3 months compared to SBRT alone ($p = 0.02$) [7]. Four cycles of cisplatin–etoposide are the recommended systemic adjuvant therapy (Table 2) in this subgroup of patients (II, A). Adjuvant radiotherapy, administered sequentially or concomitantly to chemotherapy, should be recommended when N1 or N2 disease has been diagnosed after surgery (II, A). There is no clear evidence of prophylaxis cranial irradiation (PCI) recommendation in surgically resected early stage patients (T1–2, N0, M0), since data from this subgroup of patients have lower risk to develop brain metastases [8]. For this reason, we do not recommend its use in T1–2, N0, MO, patients.

Stage IIB–IIIC (T3–4, N0, M0; T 1–4, N1–3, M0)

The standard treatment in these patients is concurrent chemotherapy and thoracic radiotherapy (CTRT) (IA).

Chemotherapy should be administered up to a maximum of 4–6 cycles. Cisplatin plus etoposide is the recommended chemotherapy regimen to combine with thoracic radiotherapy (I, A) [9, 10]. There is less evidence for the use of carboplatin, although a meta-analysis including 663 patients (32% with LS) demonstrated no significant differences when comparing cisplatin vs carboplatin, with an ORR of 67% vs 66%, median progression free survival (mPFS) of 5.5 vs 5.3 months, and mOS of 9.6 vs 9.4 months. However, carboplatin should be reserved only when cisplatin is contraindicated (Table 2) [11]. There is no recommendation for the use of prophylactic myeloid growth factor to avoid myelosuppression (I, A) in this setting.

Table 1 TNM classification (AJCC 8th edition)

T	N	M	AJCC stage
TX	N0	M0	Occult
Tis	N0	M0	0
T1a	N0	M0	IA1
T1b	N0	M0	IA2
T1c	N0	M0	IA3
T2a	N0	M0	IB
T2b	N0	M0	IIA
T1a–T2b	N1	M0	IIB
T3	N0	M0	
T1a–T2b	N2	M0	IIIA
T3	N1	M0	
T4	N0/N1	M0	
T1a–T2b	N3	M0	IIIB
T3–T4	N2	M0	
T3–T4	N3	M0	IIIC
Any T	Any N	M1a/M1b	IVA
Any T	Any N	M1c	IVB

The use of thoracic radiotherapy for LS-SCLC has demonstrated an improvement of 25–30% of reduction of local recurrence and a 5–7% improvement in 2-year survival rate vs chemotherapy alone. However, the optimal dose and schedule of thoracic RT has not been definitively established and different factors such as, performance status (PS), pulmonary function, target volume, comorbidities, and centre resources may underlie their election. Early concurrent CTRT has demonstrated better local control and survival results when compared to sequential treatment administration [12-14] at the cost of a higher rate of oesophageal toxicity. With respect to fractionation, both once-daily and twice-daily radiotherapy with cisplatin and etoposide have been evaluated in LS-SCLC. The ECOG–RTOG trial demonstrated a survival advantage of the twice-daily approach with higher grade 3–4 toxicity [9]. The CONVERT trial demonstrated a similar efficacy result, when comparing both strategies, with higher grade 4 neutropenia events for patients receiving twice-daily radiotherapy [10]. For once-daily radiotherapy, the recommended schedule is 2.0 Gy/day up to 60–70 Gy, and for twice-daily radiotherapy, the recommended dose is 1.5 Gy twice a day, 30 fractions up to a total dose of 45 Gy. Radiotherapy administered concomitantly to chemotherapy is the standard treatment that demonstrated superior results when compared to sequential treatment (I, A). Moreover, a shorter time elapsed from the initiation of any therapy to the end of radiotherapy has associated improved survival. Thus, radiotherapy should be started as early as with the first or second course of chemotherapy (I, A) [12]. The radiotherapy target field should be defined according to the PET/CT scan performed prior to treatment initiation and should include the involved node regions, as well as the primary tumour [15].

PCI is well established to decrease the incidence of brain metastases after systemic control and to prevent morbidity and mortality usually associated with developing brain metastases. A meta-analysis of seven randomised trials including 987 patients who achieved complete remission with systemic treatment and received PCI showed that the incidence of brain metastases was significantly lower with PCI (RR 0.46, 95% CI 0.38–0.57) and reported improvement of three years cumulative incidence of brain metastases (33% vs 59%). Furthermore, overall survival (OS) at 3 years was improved from 15.3% to 20.7% with PCI (RR 0.84, 95% CI 0.73–0.97) [16]. Moreover, a randomised trial of 720 patients with complete remission after CTRT demonstrated that 25 Gy in 10 fractions as PCI was effective, equal to higher doses, and less toxic [17]. Advance age and doses > 25 Gy have demonstrated a higher risk of chronic neuro-cognitive impairment [18]. PCI (25 Gy) should be administered after CTRT in patients without progression (I, A). Treatment algorithm for treatment of LS is shown in Fig. 1.

Extensive stage

The mOS for patients with ES-SCLC is about 8–13 months. Patients treated with platinum compound relapse within 6 months and less than 2% survive beyond 2 years [2] . Algoritm of treatment of ES SCLC is described in Fig. 2.

First-line treatment

The first-line treatment of ES-SCLC has changed recently with the use of the combination of chemotherapy and immunotherapy. Chemotherapy alone remains as an effective option in patients with contraindication for immunotherapy. Schedule regimens for systemic treatment in first-line treatment are described in Table 2.

Combined chemotherapy and immunotherapy

The combination of chemotherapy and immunotherapy is currently considered the standard first-line treatment of ES-SCLC.

In the randomised phase III IMpower 133 trial [19], 403 patients with ES-SCLC, were assigned to receive four cycles of carboplatin and etoposide with atezolizumab or placebo, followed by maintenance with either atezolizumab or placebo. This trial showed a significant benefit for atezolizumab in mOS, 12.3 vs 10.3 months, HR 0.70 (0.54–0.91, $p = 0.0069$). An updated OS was reported in ESMO 2019 after a median follow-up of 22.9 months and demonstrated

an increase in the overall survival at 18 months by 13% in the atezolizumab arm (34% vs 21%). The incidence of toxicity of any grade was similar between the two groups. Blood tumour mutation burden and PD-L1 did not show to be predictive biomarkers [20]. On March 18, 2019, the food and drug administration (FDA) approved atezolizumab in combination with carboplatin and etoposide, for the first-line treatment of adult patients with ES-SCLC, followed by the European medicines agency (EMA) on September 6, 2019 (I, A).

The phase III CASPIAN trial evaluated durvalumab plus etoposide and cis/carboplatin in first-line ES-SCLC demonstrating a statistically significant improvement in mOS: 13.0 vs 10.3 months, HR 0.73 (95% CI 0.59–0.91; $p = 0.0047$) for durvalumab. The combination of durvalumab with either cisplatin or carboplatin–etoposide could stand as a new treatment option in first-line for ES-SCLC (I, A) [21].

By contrast, ipilimumab (cytotoxic T-lymphocyte associated protein 4 antibody), when added to chemotherapy, improves PFS, but not OS in treatment-naïve ES-SCLC [22].

Chemotherapy

Carboplatin or cisplatin plus etoposide Cisplatin plus etoposide has been the standard treatment for patients with ES-SCLC (I, A) for decades. A meta-analysis that included individual patient data from four trials found no statistically significant difference in OS between carbo or cisplatin-based combinations. Carboplatin–etoposide could be an alternative regimen in patients with contraindications for cisplatin (I, A) [11].

Alternative regimens to platinum–etoposide

Camptothecin-based regimens Several clinical trials have studied the substitution of a camptothecin analogue for etoposide in combination with a platinum compound in patients with ES-SCLC. In the Japanese Cooperative Oncology Group trial (JCOG 9511), patients treated with irinotecan plus cisplatin had a significantly longer mOS compared with etoposide–cisplatin (12.8 vs 9.4 months) [23]; however, other larger trials including cisplatin or carboplatin conducted outside Japan failed to confirm this observation. A recent meta-analysis reported better OS with platinum–iri-

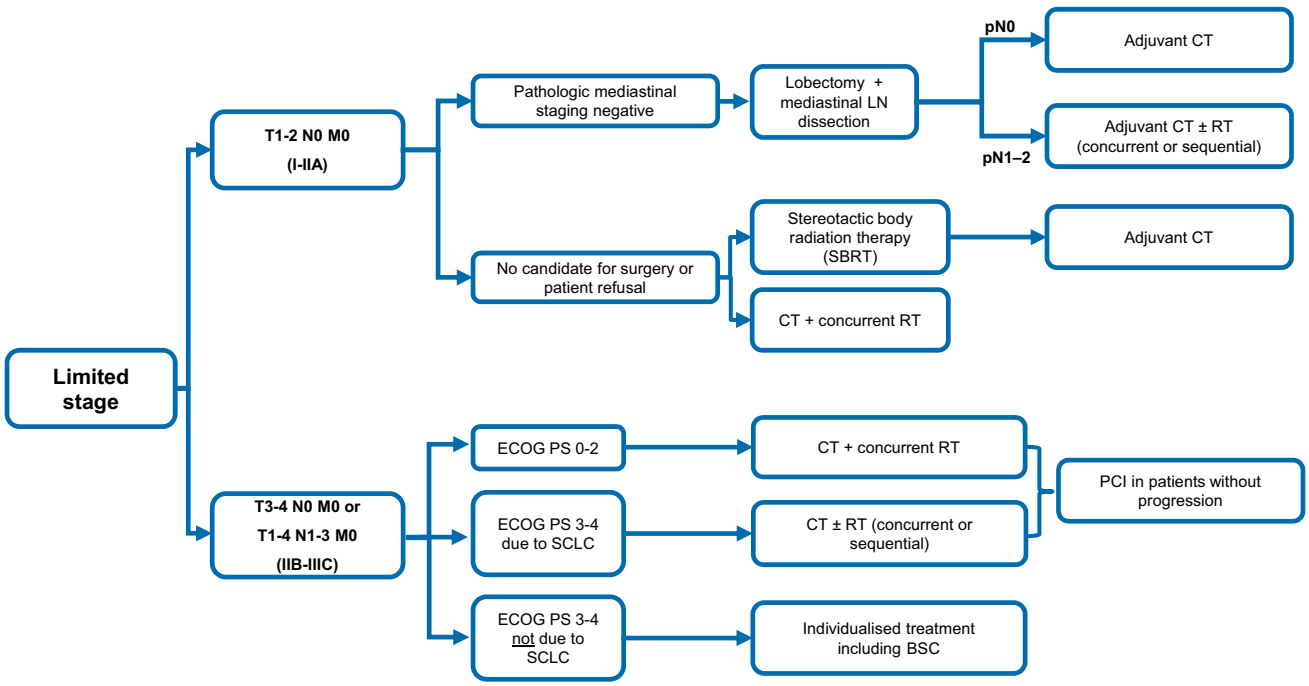

Fig. 1 Treatment algorithm for limited stage SCLC. *LN* lymph node, *CT* chemotherapy (cisplatin/etoposide, alternative carboplatin/etoposide 4 cycles), *RT* radiotherapy, *ECOG* Eastern Cooperative Oncology Group, *PS* performance status,*SCLC* small-cell lung cancer, *BSC* best supportive care, *PCI* prophylactic cranial irradiation

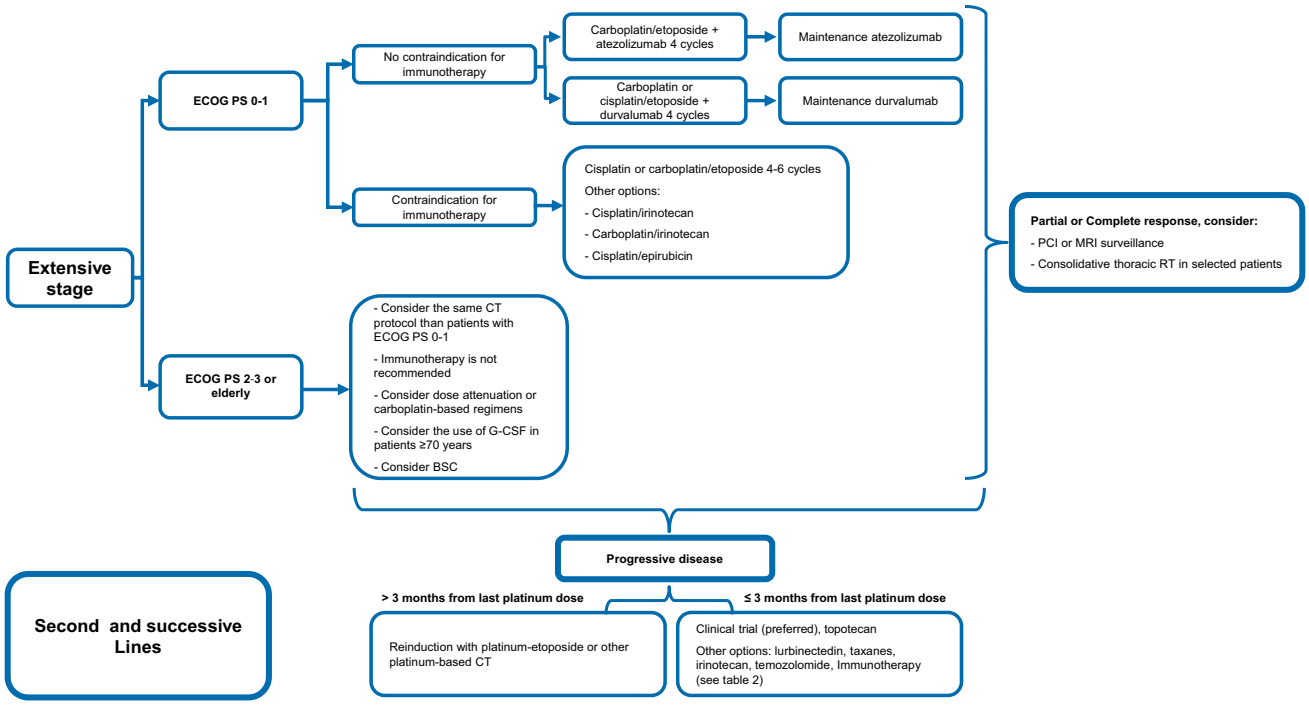

Fig. 2 Treatment algorithm for extensive stage and second or successive lines. *ECOG* Eastern Cooperative Oncology Group, *PS* performance status, *PCI* prophylactic cranial irradiation, *MRI* magnetic resonance imaging, *RT* radiotherapy, *CT* chemotherapy, *G-CSF* granulocyte colony-stimulating factor, *BSC* best supportive care

notecan, but equal ORR and PFS than platinum–etoposide with less haematologic and greater gastrointestinal toxicity with irinotecan [24].

Epirubicin plus cisplatin In a randomised phase III trial, the combination of epirubicin and cisplatin was similar to cisplatin and etoposide in ORR, mPFS (7.6 months in both arms) and mOS (10.9 versus 10.1 months) [25]. The combination of epirubicin plus cisplatin could be a reasonable alternative regimen in this setting.

Other combinations testing topotecan–cisplatin or amrubicin–cisplatin have not demonstrated an advantage over the standard platinum–etoposide combination. The addition of a third drug to platinum–etoposide regimen failed to show a significant difference in OS.

Alternative regimens are cisplatin–irinotecan, carboplatin–irinotecan, cisplatin, and epirubicin (II, B).

Duration of treatment

The optimal duration of chemotherapy for patients with ES-SCLC is not well defined; in general, 4–6 cycles are recommended. A meta-analysis reported that maintenance chemotherapy did not prolong OS [26]. No other target drugs have demonstrated benefit in OS as maintenance.

Radiotherapy in ES-SCLC

Prophylactic cranial irradiation (PCI) in ES-SCLC Prevention of cranial progression is a major concern in LS and ES-SCLC. A meta-analysis [16] suggested a benefit with PCI in responding patients, but most patients had LS-SCLC. In ES-SCLC who has responded to systemic therapy, PCI decreases the development of brain metastases. Conflicting results were obtained in two-phase III trials regarding improvement of mOS with PCI after response to systemic chemotherapy. The EORTC trial showed an OS improvement with PCI [27]. A Japanese phase III trial showed that PCI did not improve OS in patients without brain metastases at baseline MRI compared with follow-up with MRI and treatment after detection of asymptomatic brain metastases [28]. PCI may be considered in good PS responding patients (I, B). Follow-up with brain MRI is recommended for all patients regardless of the administration of PCI. Depending on individual patient factors, close MRI surveillance should be an appropriate option for ES-SCLC patients who achieve a response to initial systemic therapy.

Patients should be informed of the potential adverse effects from PCI. PCI is not recommended for patients at high risk of neurological sequelae (PS 3–4 or neuro-cognitive impairment) and should be used with caution in elderly patients.

Table 2 Recommended systemic regimens for SCLC

Systemic regimens for LS-SCLC
Chemotherapy should be administered up to a maximum of 4–6 cycles
Preferred regimen
Cisplatin 75 mg/m^2 day 1 and etoposide 100 mg/m^2 days 1–3, every 21 days
Alternative regimens
Cisplatin 25 mg/m^2 day 1–3 and etoposide 100 mg/m^2 days 1–3, every 21 days
Carboplatin AUC 5–6 day 1 and etoposide 100 mg/m^2 days 1–3, every 21 days.
Systemic regimens for ES-SCLC first line
Preferred regimens: combination of chemotherapy + immunotherapy
Carboplatin AUC 5 day 1 and etoposide 100 mg/m^2 days 1, 2, 3 and atezolizumab 1200 mg day 1 every 21 days × 4 cycles followed by maintenance atezolizumab 1200 mg day 1, every 21 days (IA)
Carboplatin AUC 5–6 day 1 and etoposide 80–100 mg/m^2 days 1, 2, 3 and durvalumab 1500 mg day 1 every 21 days × 4 cycles followed by maintenance durvalumab 1500 mg day 1 every 28 days (IA)
Cisplatin 75–80 mg/m^2 day 1 and etoposide 80–100 mg/m^2 days 1, 2, 3 and durvalumab 1500 mg day 1 every 21 days × 4 cycles followed by maintenance durvalumab 1500 mg day 1 every 28 days (IA)
Recommended regimens of chemotherapy (4–6 cycles)
Preferred regimen
Cisplatin 75 mg/m^2 day 1 and etoposide 100 mg/m^2 days 1–3, every 21 days (IA)
Alternative regimens
Carboplatin AUC 5–6 day 1 and etoposide 100 mg/m^2 days 1–3, every 21 days (IA)
Optional chemotherapy regimens (IIB)
Carboplatin AUC 5 day 1 and irinotecan 50 mg/m^2 days 1, 8, 15 every 28 days
Cisplatin 60 mg/m^2 day 1 and irinotecan 60 mg/m^2 days 1, 8, 15 every 28 days
Cisplatin 30 mg/m^2 days 1, 8 and irinotecan 65 mg/m^2 days 1, 8 every 21 days
Epirubicin 100 mg/m^2 and cisplatin 100 mg/m^2 on day 1 every 21 days
Systemic regimens for second and successive lines
Relapse ≤ 3 months
Preferred regimen
Clinical trial
Topotecan oral or IV (I, B)
Cyclophosphamide/doxorubicin/vincristine (CAV) (II, B)
Other options (II, C)
Nivolumab ± ipilimumab
Pembrolizumab
Paclitaxel
Lurbinectedin
Docetaxel
Irinotecan
Temozolomide
Vinorelbine
Gemcitabine
Bendamustine
Relapse > 3 months
Reinduction with platinum–etoposide (II, B)

Preferred schedule is 25 Gy in ten daily fractions.

Treatment of brain metastases In symptomatic brain metastases, whole-brain radiotherapy (WBRT) before systemic therapy should be administered (II, A). In patients with a small number of metastases, SBRT should be an optional treatment. In asymptomatic brain metastasis, systemic therapy should be administered as the first treatment with cranial MRI or CT with contrast evaluation during systemic therapy; WBRT may be administered after completion of systemic therapy or if brain metastases progress during systemic therapy. Preferred schedule for WBRT is 30 Gy in ten daily fractions. In patients with cranial progression after PCI: consider to repeat WBRT or stereotactic radiosurgery (preferably) if feasible.

Consider adding memantine during and after radiotherapy (PCI or WBRT).

Consolidative thoracic radiation therapy As a result of two phase III trials [29, 30], consolidative thoracic radiotherapy should be considered in selected patients with ES-SCLC who have completed chemotherapy and achieved a complete

or near complete response, especially in patients with good extrathoracic response (I, B).

Second and successive lines in ES-SCLC Despite SCLC being very responsive to initial therapy, most of the patients relapse with a mOS of 5–7 months. It is very important for the distinction of > 3 months (chemo-sensitive disease) or within 3 months (chemo-resistant or refractory disease). All patients with relapsed SCLC should be assessed for clinical trials. Decision treatment should include PS, comorbidities, toxicity, and disease-free interval from prior therapy. When a patient relapses more than 3 months after the first-line therapy, reinduction of the original regimen with platinum etoposide is recommended (II, B) [31]. If relapse occurs, 3 months or less must be considered administering single-agent therapy with IV or oral topotecan (I, B). An alternative is the combination CAV: cyclophosphamide–doxorubicin–vincristine (II, B). Other agents commonly used based on phase 2 trials are irinotecan, taxanes, gemcitabine, vinorelbine, or temozolomide [32]. Only around 20% of SCLC patients will receive the third-line therapy with modest results.

A novel cytotoxic drug is lurbinectedin, a transcription inhibitor that binds to the DNA minor groove and inhibits RNA polymerase II; is active as a single agent in second-line SCLC in a phase 2 trial for both sensitive and resistant disease (ORR 35.2%) [33], a phase 3 study in combination with doxorubicin vs chemotherapy has completed the recruitment, pending of final results (ATLANTIS trial).

Several targeted therapies have been assessed without still satisfactory results. Rovalpituzumab is an antibody–drug conjugate directed against DLL3 (Notch signalling) with positive results in an initial trial [34], but negative in a phase 3 study against topotecan (TAHOE trial). Other studies with DLL3 inhibitors are ongoing. New drugs targeting other new pathways are in development, including DNA damage and repair (e.g. PARP inhibitors), epigenetics, and cell cycle.

Immunotherapy with immune checkpoint inhibitors has demonstrated modest activity in relapsed SCLC patients (nivolumab +/− ipilimumab, pembrolizumab, atezolizumab, and durvalumab + tremelimumab) without clear predictive biomarker identification; and the only phase 3 study carried out comparing nivolumab vs standard chemotherapy (CheckMate 331) was negative [35]. New immunotherapy drugs and combinations remain promising. Patients whose progress while on immunotherapy as part of first-line therapy should not be treated with other immune checkpoint inhibitors (see Fig. 2).

Definitely, predictive biomarker-driven therapies are needed with the aim to improve the current still poor outcomes in relapsed SCLC. New classification of SCLC subtypes defined by distinct gene expression profiles could help us to design new clinical trials [36]. Schedules regimens for second and successive lines are described in Table 2.

Treatment of fragile and elderly patients

The incidence of SCLC increases with age; approximately one-third of patients are 70 years of age or older. The key to treatment is to assess whether the expected benefits of treatment are superior to the risks. In general, good performance older adult patients should receive the same doses as younger patients.

In LS-SCLC, the concurrent CTRT with modern radiotherapy techniques could be a treatment option for fit, older patients. This approach yields equivalent mOS in older vs younger patients (29 vs 30 months; $p = 0.38$) [37].

In ES-SCLC, older patients with good PS are able to tolerate commonly used chemotherapy with adequate supportive care. Randomised trials have indicated that less-intensive treatment (e.g., single-agent) is inferior to combination chemotherapy in elderly patients with good PS (0–2). Dose attenuation and carboplatin-based regimens are preferred in risk patients, although there are associated with poor therapeutic outcomes [38]. Myelosuppression, fatigue, and lower organ reserves are found more frequently in elderly patients. The most important risk factor is the development of severe neutropenia; moreover the treatment, is older age (> 65 years). The use of colony-stimulating factors (G-CSF) in the elderly patients is recommended [39].

PCI should be used with caution in elderly patients; an increased risk for cognitive decline after PCI is found in patients (≥ 60 years) [40].

There are no data that define the role of treatment in poor PS patients (PS3 or PS4) or extremes ages; it seems reasonable to offer treatment to this patient if their poor PS is due to SCLC rather than comorbidity.

Follow-up

The smoking cessation is the most important recommendation for patients with SCLC. The objective of the follow-up is to detect early relapse. There are not clinical trials evaluating the follow-up of SCLC. For LS, a CT scan is recommended every 3 months the first year, every 6 months years 2–5, and then annually (V, C). For ES every 2 months, the first year, every 3 months year 2 and 3, every 6 months year 4–5, and then annually (V, C).

Summary of recommendations is listed in Table 3.

Table 3 Summary of recommendations

Diagnosis, initial assessment and staging	Pathological diagnosis of SCLC should be made using the World Health Organization (WHO) classification Initial assessment must include medical/smoking histories, physical examination, complete blood count and biochemistry including liver enzymes, sodium, potassium, calcium, glucose, lactate dehydrogenase levels, and renal function test Lung function tests if thoracic radiation is indicated A computed tomography (CT) scan with intravenous contrast of the chest/abdomen is recommended Magnetic resonance imaging (MRI) (preferred) or CT scan (with intravenous contrast) for brain imaging 2-Fluor-2-desoxy-D-glucose positron-emission-tomography (FDG-PET CT) scan is recommended in localised disease. In patients with a solitary metastasis, its pathological confirmation is recommended (III, C) 8th edition of the TNM staging system according to the AJCC should be used (I, A). Combined use of TNM and VALSG classification is appropriate
Treatment of limited stage I–IIA (T1–T2, N0, M0)	Lobectomy with a systematic lymph-node dissection is the preferred surgical procedure after mediastinal staging (II, A) Patients with N0 disease should be recommended adjuvant chemotherapy (II, A) Patients with pN1 or pN2 disease should be recommended adjuvant chemotherapy and thoracic radiotherapy (II, A) SBRT represents an alternative for patients with stage I–IIA SCLC with surgical contraindication or refusing surgery (III, B). After completion of SBRT patients should be receive 4 cycles of adjuvant chemotherapy (II, A) PCI is not recommended in T1–T2, N0, M0 patients
Treatment of limited stage IIB–IIIC (T3–4 N0 M0; T1–4 N1–3, M0)	Patients should be treated with concurrent chemotherapy and thoracic radiotherapy (I, A) The recommended chemotherapy is the combination of 4 -6 cycles of cisplatin-etoposide (I, A). Carboplatin could replace cisplatin when contraindication (IA) 45 Gy with twice-daily fraction or 60–70 Gy with once-daily fraction are accepted treatments. Either of them should be administered concomitantly to systemic therapy (I, A) Radiotherapy should be started as early as with the 1st or 2nd course of chemotherapy (I, A) PCI (25 Gy) should be administered after CTRT in patients without progression (I, A)
First-line treatment of extensive stage IV (T1–4 N1–3, M1 a,b,c)	The recommended first-line treatment is the use of platinum–etoposide + immunotherapy (I, A) Carboplatin–etoposide–atezolizumab 4 cycles followed by maintenance atezolizumab until progression Durvalumab–carboplatin or cisplatin + etoposide 4 cycles followed by maintenance with durvalumab until progression If no candidate to receive immunotherapy the recommended treatment is chemotherapy 4–6 cycles of cisplatin-etoposide. Carboplatin could replace cisplatin when contraindication (I, A) Alternative regimens are Cisplatin–irinotecan, carboplatin–irinotecan, cisplatin, and epirubicin (II, B)
Radiotherapy in ES-SCLC	PCI (25 Gy) should be evaluated in patients with good PS who achieve a response (I, B). Depending of individual patient factors, close MRI surveillance should be appropriate in patients whose achieve a response to initial systemic therapy Consolidative thoracic radiation therapy should be considered in selected patients who have completed chemotherapy and achieved completed or near complete response (I, B)

Table 3 (continued)

Second and successive lines treatment in SCLC	Patients who progress during treatment or less < 3 months, inclusion in clinical trial is highly recommended (II, C) Topotecan is recommended in resistant or sensitive relapse (I, B). Other alternative are VAC (II, B) Patients with sensitive relapse (3 months) reinduction treatment with platinum–etoposide is recommended (II, B)
Fragile and elderly patients	Use same chemotherapy protocol than patients with PS 0–1 No immunotherapy in patients with PS 2–3 Consider dose attenuation or carboplatin-based regimens Consider the use of colony-stimulating factors (G-CSF) in PS 2–3 or age greater than or equal to 70 years In LS concurrent CTRT with modern technics could be a treatment option for fit and elderly patients In ES dose attenuation of cisplatin–etoposide or carboplatin–etoposide are adequate. Use of G-CSF recommended PCI (25 Gy) should be use with caution in elderly patients
Follow-up	LS: CT scan every 3 months the first year, every 6 months year 2–3 and then annually (V, C) Extensive Stage every 2 months the first year, every 3 months years 2 and 3, every 6 months years 4–5 and then annually (V, C)

Compliance with ethical standards

Conflict of interest MD reports lecture and advisory board from AstraZeneca, BMS and Boehringer Ingelheim, outside the submitted work. TM has nothing to disclose. DI reports personal financial interests: Consulation Honoraria from AbbVie, AstraZeneca, Bayer, BMS, Boehringer Ingelheim, F. Hoffmann-La Roche, MSD, Pierre Fabre, Pfizer, and Takeda; Speaker Honoraria from AstraZeneca, Bayer, BMS, Boehringer Ingelheim, F. Hoffmann-La Roche, MSD, Pierre Fabre and Pfizer. Institutional financial interests: Clinical Trials from AbbVie, AstraZeneca, Boehringer Ingelheim, BMS, F. Hoffmann-La Roche, Janssen, Merck, MSD, Novartis; Research Grant from BMS, F. Hoffmann-La Roche. Non-financial interests: Leadership Role from SEOM (Spanish Society of Medical Oncology): Scientific Assistant. Other: Executive Board Member of the Commission for the Approval of New Drugs, Regional Health Care Department, Spain. JLM reports honoraria from Roche, outside the submitted work. IS reports personal fees from Roche, MSD, BMS, AstraZeneca, Boehringer Ingelheim, Pfizer and Novartis, and non-financial support from Novartis, outside the submitted work. MP reports honoraria for speaking and advisory board from BMS, AstraZeneca, Takeda, Roche and Amgen, outside the submitted work. MEO has nothing to disclose. SP has nothing to disclose. AB has nothing to disclose. MC reports lecture and advisory board from AstraZeneca, BMS, Boehringer Ingelheim, outside the submitted work.

Ethical approval The current study has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Informed consent Not applicable.

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