Small cell lung cancer: new clinical recommendations and current status of biomarker assessment

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Abstract

Small-cell lung carcinomas (SCLC) represent 15–18% of all lung cancers. As SCLC has a high propensity for early metastatic dissemination, less than a third of patients have limited disease (T0–4N0–3M0). The new TNM classification should now be used also for SCLC. Platin- and etoposide-based chemotherapy is the cornerstone treatment. Response rates to both chemotherapy and radiotherapy are impressive but relapses are frequent. The current state-of-the-art treatment for M0 patients involves platin–etoposide-based chemotherapy, combined with early thoracic radiotherapy. Because of the high risk of brain metastases, prophylactic cranial irradiation is indicated in responders and should be part of the standard management. The 5-year survival rate may reach 25% in M0 patients, but does not exceed 10% at 2 years in metastatic patients. Most patients relapse within the first two years, and there are few treatment options in second line as opposed to NSCLC. Many issues are subject for further clinical research such as the biology of this disease to better identify pathways that could be targeted with new drugs, optimisation of systemic treatments and radiotherapy. Pursuing clinical trials at all stages constitutes a challenge for thoracic researchers and oncologists.

Introduction

Lung cancer is the most common cancer worldwide with 1.35 million cases (12.4% of all cancers). It is the leading cause of death due to cancer, with more than 1 million deaths worldwide each year (17.6% of cancer mortality) [1]. In Europe, in 2008, there were 391,000 cases of lung cancer (12.2% of cancers, or the third cancer by frequency) and 342,000 deaths (19.9% of cancers, or the leading cancer by death). Small cell lung cancer (SCLC) represents 15–18% of all lung cancers and is closely associated with smoking. The change in number of cases of SCLC reflects cigarette consumption in the population in the previous 20 years. In the USA, the incidence of SCLC has decreased in men over the past 10 years but continues to increase in women.

Rapid metastatic dissemination is common, so that two-thirds of patients have disseminated disease at the time of diagnosis. These tumours are very sensitive to cytotoxic treatments (chemotherapy and radiotherapy), but are characterised by the relatively rapid appearance of chemo/radioresistance, and relapses are common. Five-year survival is around 20–25% for limited forms of the disease and 5% for disseminated forms [2,3]. Therapeutic developments in terms of systemic treatment over the past 10 years have been disappointing and have only resulted in better integration and combinations of different treatments.

Histopathology and biological factors

The pathological diagnosis relies on a biopsy taken either by bronchial endoscopy (tumour generally central and easily accessible), or from a lymph node (by bronchial or transoesophageal endoscopy, supraclavicular node biopsy or mediastinoscopy), or from a metastasis (subcutaneous, hepatic, bone, ...). The histological classification of bronchial and pleural tumours was updated by OMS in 1999 [4]. Neuroendocrine tumours of the lung form a subgroup of tumours that share common morphological, immunohistochemical and molecular characteristics. Several types can be distinguished: typical carcinoid, atypical carcinoid, large cell neuroendocrine cancer and SCLC.

The histological criteria of SCLC include: the small size of the cells, limited cytoplasm, a nucleus with fine granulation without a nucleolus, a high level of mitosis (more than 11 per 2 mm^2 field) and frequent areas of necrosis. The most reliable markers of neuroendocrine

differentiation are chromogranin and synaptophysin. NSE (neuron-specific enolase) is not specific as it binds to two-thirds of non-SCLCs. Immunolabelling with TTF1 (thyroid transcriptase factor 1) is generally positive (in >85% of cases).

Assessment of tumour spread and prognostic factors

The aim is to establish the extent of the disease in order to guide treatment and to define prognostic factors.

Stage

Classification by stage has important prognostic value. For years, the TNM classification was mainly used for non-SCLCs. For SCLCs, the therapeutic modalities (non-surgical) have led to the distinction of two stages: limited and disseminated, according to the Veterans Administration Lung Cancer Study Group classification. Limited disease was defined as confined to a hemithorax and the regional lymphatic nodes (mediastinum, homolateral and contralateral hilar regions, homolateral supraclavicular fossa), thus theoretically accessible to radiotherapy. Limited disease represents about a third of patients. Even though this classification has been used for many years, the International Association for the Study of Lung Cancer (IASLC) has recently published the 7th edition of the TNM classification which seems more accurate in identifying patient subgroups. Limited disease should now be based on this classification, corresponding to TxNxM0 patients [5]. Extensive disease corresponds to TxNxM1a and TxNxM1b. It should be underlined that most studies did not use the TNM classification.

Assessment of spread

Only one-third of patients with SCLC present with TxNxM0 disease. Radiological staging procedures should include a thoracic and an abdominal CT scan exploring liver and adrenal glands. Bone scintigraphy and/or bone MRI may be proposed in case of suspicion of bone metastases. The presence of brain metastases should be investigated systematically by a scan or MRI. The role of FDG PET-CT is becoming more important but it is not as well validated as in non-SCLC. It can be useful in patients eligible for chemoradiation. The biological assessment should include complete blood cell count, liver, lung and renal function tests as well as sodium levels and lactate dehydrogenase (LDH) level.

Prognostic factors

Clinical, radiological or biological factors determined before any treatment may be prognostic factors. The main factor is limited disease spread. Other favourable prognostic factors include a good performance status (PS), female gender, age <60 years and a normal level of LDH.

Clinical presentation and specificities (paraneoplastic syndromes)

Typical clinical presentation is a 65–70 year-old male, heavy smoker, presenting with symptoms due either to intrathoracic growth with bulky mediastinal disease on chest X-ray, extrathoracic spread and/or paraneoplastic syndrome. Because of the rapid growth of SCLC, most patients present with bulky limited disease or metastatic disease. Early-stage SCLC is rare, so that very few patients are eventual surgical candidates. SCLC has long been associated with paraneoplastic syndromes. Endocrine paraneoplastic disorders are characterised by ectopic production of peptide hormones and the neurological complications are related to antibody-mediated damage to the central nervous system. The three most common paraneoplastic syndromes are hyponatremia (up to 15% of patients), due to production of antidiuretic hormone, Cushing's syndrome (2–5% of patients), caused by ectopic production of corticotropin by tumour cells, and Lambert–Eaton myasthenic syndrome (3% of patients), caused by autoantibodies directed against P/Q-type voltage-gated calcium channels. SOX and Hu antibodies are common in SCLC with and without paraneoplastic syndrome and can serve as serological tumour marker: about two thirds of SCLC patients with Lambert–Eaton myasthenic syndrome patients have antibodies to one of the SOX or Hu proteins with no relation to survival however.

Molecular abnormalities and biomarkers of SCLC

Various genetic abnormalities associated with the development of SCLC, as well as signalling pathways have been identified over the past few decades. These abnormalities have prognostic value and represent potential therapeutic targets.

Proto-oncogenes and tumour-suppressor genes

Different abnormalities such as amplification of oncogene *myc* (15–30%), *P53* mutation (~75%) or deletion of tumour-suppressor genes such as fragile histidine triad (*FHIT*) gene (abnormal in 80%), RAS effector homologue (*RASSF1)* (abnormal in >90%), retinoic

acid receptor β (abnormal in 72%), *FUS1*, *TP53* (abnormal in >75%), retinoblastoma gene (*RB1*) (abnormal in >90%), phosphatidylinositol triphosphate PTEN (abnormal in 8%) are found in SCLC [6,7].

Cell signalling pathways

Activation of tumour cells often occurs due to autocrine secretion of neuropeptides such as gastrin, neuromedin B and gastrin-releasing peptide (GRP) which can act on DNA synthesis and cell proliferation via protein-kinase C by a paracrine loop [8].

Apoptosis pathways

Overexpression of antiapoptotic proteins such as Bcl-2, Bcl-xl, Bcl-w and Mcl-1 in cell lines leads to an increase in resistance to radiation and chemotherapy. It is estimated that around 80% of SCLCs overexpress Bcl-2. Telomerase, an enzyme that is overexpressed in >90% of SCLCs, is implicated in unlimited replication through its ability to stabilise the end of the chromosomes (telomeres).

Angiogenesis

Tumour growth is stimulated by angiogenic factors such as vascular endothelial growth factor (VEGF) and matrix metalloproteinases (MMP), and inhibited by interferons and inhibitors of MMP. The observation of high-density microvascularisation and increase of VEGF, MMP-3, MMP-11 and MMP-14 in SCLCs has justified the development of angiogenesis inhibitors in this disease.

Biomarkers and SCLC

Although the majority of patients with small cell lung cancer respond to initial chemotherapy or chemoradiotherapy, many relapse within the first 2 years. Development of resistance is the main cause of poor outcome. There is a need for predictive biomarkers, in designing future clinical trials that better stratify patients beyond standard clinical and laboratory parameters, and to identify potential new treatments. In NSCLC, great progress has been achieved in the past years to identify subpopulations that may benefit from targeted agents. In SCLC, several studies have investigated the prognostic and or predictive significance of different biomarkers such as P53, β1-integrin, bcl-2, microRNA92a-2, ERCC1, RRM1, IL-2, bax, breast cancer resistance protein (BCRP) and c-kit, with conflicting results and no implications for SCLC management at present.

New clinical recommendations for treatment of M0 patients

Even though responses rates (RR) to chemotherapy are impressive (between 70% and 90%), when used alone, there is a high rate of local recurrence, of about 50%, which can be divided by 2 or 3 when thoracic radiotherapy (TR) is added to chemotherapy [2,3]. Combination of chemotherapy and radiotherapy has become the standard treatment in the early 1990s after the publication of 2 meta-analyses. In the meta-analysis of Pignon and colleagues in 1992, based on individual data, TR significantly improved overall survival (OS) with an absolute benefit of 5.4% (3-year OS 8.9% *versus* 14.3% in the combination arm) [9]. The meta-analysis of Warde and Payne led to an overall benefit of TR on 2-year survival of 5.4%, and a better 2-year intrathoracic tumour control (from 16.5% to 34.1% in the combined modality arm) [10].

However, there are different ways to combine treatments: TR and chemotherapy can be combined concurrently, sequentially, or in an alternating fashion. Furthermore radiation can be administered early or late in the overall course of treatment. Sequential treatments are not recommended as there is a potential risk of developing chemoresistant clones, which can also become radioresistant, as well as a risk of tumour repopulation. Alternating regimens, interdigitating weeks of radiotherapy with weeks of chemotherapy, offer a good toxicity profile and have resulted in a 5-year survival rate of 26% in a phase III trial [11]. However, these good results could not be reproduced in a EORTC study comparing alternating to sequential regimen [12]. There was no difference of survival between the 2 groups (3-year overall survival in the alternating and sequential arms of 12% and 15%, respectively), but the haematological toxicity was higher in the alternating arm. It should be underlined that chemotherapy was not platin based and that compliance to treatment was quite poor. The study of Lebeau and colleagues, which also compared two non-platin-based regimen (concurrent versus alternating), did not find any difference between the 2 modalities (median survival 13.5 months and 14 months, respectively) [13].

Concomitant approaches have the advantage of shortening the whole duration of treatment time, at the cost of an increased rate of acute toxicities, especially oesophageal, that are manageable. Concomitant chemoradiation has now been evaluated in many trials with good results, so that it has become the standard of care in fit patients [2,3,14,15]. In the randomised trial of Takada and colleagues

Table 1
Phase III studies exploring timing [16,17]

Author	n	Dose/Fr (Gy)	CT	TR Timing	MS	2-OS	3-OS	p
Perry 1987	270	50/2 OD	Non-platinum combination	conc C1 (D1)	13	24	7.2	NS
				conc C4 (D64)	14.5	31.7	13.8	$P = 0.144$
Murray 1993	308	40 /2.67 OD	Non-platinum combination alternating with PE	conc C2 (D22)	21.2	40	29.7	S
				conc C6 (D106)	16	33.7	21.5	$P = 0.008$
Work 1997	199	40–45/2 OD Split course	Combination of PE and non-platinum combination	seq C1 (D1)	10.5	20.2	13.1	NS
				seq C6 (D127)	12	19	12	
Jeremic 1997	107	54 /1.5 BD	CbE during RT, then 4 PE	conc C1 (D1)	34	71.2	48.1	NS
			CbE during RT with PE before and after RT	conc C3 (D36)	26	52.9	39.2	$P = 0.052$
Skarlos 2001	81	45 /1.5 BD	CbE × 6	conc C1 (D1)	17.5	35.7	21.4	NS
				conc C4 (D63)	17	28.2	12.8	
Spiro 2006	325	40 /2.67 OD	Non-platinum combination alternating with PE	conc C2 (D22)	13.7	22	16	NS
				conc C6 (D106)	15.1	31	22	

BD; twice daily; CbE: carboplatin–etoposide; conc: concurrent; D, day; OD: once daily; NS: not significant; PE: cisplatin–etoposide; seq, sequential.

comparing concurrent and sequential schedules, the results favoured the concurrent schedule with a median survival of 19.7 months in the sequential arm and 27.2 months in the concurrent arm, but with no significant difference as the trial was underpowered ($P = 0.097$) [14].

Timing issues

Several trials have compared combined modality treatments in which radiotherapy was administered early or late [16,17]. As shown in Table 1, results were highly variable from one study to the other, some favouring early and others late TR. Considering these inconclusive results, 2 meta-analyses based on published data have investigated timing in SCLC combined modality treatments. They both demonstrated that a short time between the initiation of chemotherapy and the initiation of TR was prognostic for survival, however the delay chosen to define early and late TR differed in the two studies. Late TR was defined as beginning 9 weeks after initiation of chemotherapy or after completion of the third cycle of chemotherapy in the meta-analysis by Fried, with a statistically significant benefit of 5% of early TR over late TR in terms of 2-year OS but not at 3 years [16]. The benefit seemed greater with hyperfractionated (twice daily) radiotherapy and platinum-based chemotherapy. In the second meta-analysis, early TR was defined as beginning within 30 days after the start of chemotherapy [17]. When the only trial that delivered non-platinum-based chemotherapy concurrently with TR was excluded, the 5-year overall survival became significantly in favour of early TR, representing a 5-year survival rate of 20.2% for early versus 13.8% for late TR. As both overall treatment time of radiotherapy and timing of chest radiation are of importance, De Ruysscher and colleagues hypothesised that start of any treatment until the end of radiotherapy (SER) was important to consider [18]. A short time between the initiation of chemotherapy and the subsequent completion of TR was prognostic for survival (5-year OS rate of 20% when SER was less than 30 days) in their study. This SER concept should certainly be further evaluated and considered in designing new studies. However these

Table 2
Phase III trials evaluating altered fractionation

Author	n	Total dose (Daily dose)	Treatment combination	MS	2-OS	5-OS	p
Bonner 1999	311	50.4 Gy/28fr (1×1.8 Gy/day)	3 induction PE then ccCTRT starting cycle 4	20.6 mo	47%	21%	0.68
Schild 2004 [19]		24 Gy (2 × 1.5/day) Split course of 2.5 weeks	3 induction PE then ccCTRT starting cycle 4	20.6 mo	45%	22%	
Turrisi 1999 [15]	417	45 Gy/25fr (1 × 1.8 Gy/day)	Cc CTRT with PE starting cycle 1	19 mo	41%	16%	0.04
		45 Gy/30 fr (2 × 1.5 Gy/day)	Cc CTRT with PE starting cycle 1	23 mo	46%	26%	

2-OS: 2-year overall survival; 5-OS: 5-year overall survival; cc: concurrent; CT: chemotherapy regimen; CTRT chemo-radiotherapy; Gy: Gray; MS: median survival, mo: months; N: number of patients; PE: cisplatin and etoposide; TRT: thoracic radiotherapy.

results favouring early TR are not very robust, and the results of an upcoming meta-analysis based on individual patient data may help solving some of these issues.

Fractionation and dose issues

Because of SCLC's high kinetics of tumour proliferation and its ability of tumour repopulation between fractions, hyperfractionated accelerated radiotherapy has been investigated, leading to two phase III studies comparing conventional radiotherapy to hyperfractionated accelerated twice daily radiotherapy with concomitant chemotherapy in both arms [15,19]. The results of these 2 studies are detailed in Table 2. In the North Central Cancer Treatment Group study, TR started after 3 cycles of chemotherapy and was given split-course in the investigational arm (48 Gy in 32 twice-daily fractions of 1.5 Gy) [19]. Therefore, the overall treatment time (OTT) was similar in the two arms (5.5 weeks). Both overall rate of local progression and overall survival at 5 years (21% and 22% respectively) were not statistically different. The same OTT in the 2 arms and split course TR might explain the lack of difference between the two schedules. In the Intergroup study, radiotherapy started upfront during the first cycle of chemotherapy [15]. The overall survival was significantly improved ($P = 0.04$) with twice-daily radiotherapy: 5-year overall survival was 16% in the control arm versus 26% in the investigational arm. As expected, grade III oesophagitis was more frequent with hyperfractionated accelerated radiotherapy (27% *versus* 11%).

Given its perceived intrinsic radiosensitivity, SCLC has historically been treated with lower doses of radiation than non-SCLC (45–56 Gy). However, the local control is about 30–50%, and a higher dose could improve local control, and, possibly, overall survival. Higher doses have been explored given concomitantly to chemotherapy in phase I, II studies [20,21]. Therefore, it appears necessary to compare within randomised studies, the hyperfractionated accelerated approach of the North American Intergroup study (45 Gy, 1.5 Gy twice-daily over 3 weeks) with dose-escalated once-daily TR (66–70 Gy). This is the aim of a large European collaborative phase III trial, CONVERT, and a 3-arm intergroup phase III North American study (CALGB 30610, RTOG 0538, NCT00632853).

Volume issues

Traditionally, elective nodal irradiation was used for SCLC. However, due to the effectiveness of systemic treatments and the high relapse rate in the initially involved tumour bulk, recent studies have explored whether treating only the tumour and the involved nodes would be appropriate. The involved-fields approach, by reducing the treated volume, could reduce toxicity and possibly allow delivering higher doses. Phase II studies assessing involved-field radiotherapy concluded this approach was feasible [22,23]. Because of the low number of patients in these studies, no definitive conclusion can be drawn concerning the radiotherapy volume to be used, however it seems PET-CT is of value to decrease the risk of nodal failure [23].

Any place for chemotherapy intensification

Chemotherapy dose-intensification has been explored in SCLC with contrasting results. A small phase III study using an alternated chemo-radiation combination in 105 patients with limited disease suggested that a rather mild early dose-intensification during the first cycle could lead to a survival improvement [11].

The 5-year survival rate was 26% in the higher-dose group, versus 8% in the lower-dose group ($P = 0.03$). A very intensive regimen testing the role of early intensification compared high-dose ICE (iphosphamide, carboplatin, etoposide) to standard-dose ICE, in a multicentric randomised study including 97 patients with limited disease and 43 with extensive disease [24]. TR was delivered sequentially at the end of chemotherapy. The results were quite disappointing and the authors concluded this strategy should be abandoned.

Several new chemotherapy combinations have been explored in M0 patients, and some of them seemed promising, especially with paclitaxel and irinotecan. However, none has shown superiority in terms of efficacy or tolerance to the platin-based and etoposide regimen which remains the standard combined to TR.

Prophylactic cranial irradiation (PCI)

Brain metastases (BM) are frequent in SCLC and responsible for serious impairment in patient's survival and quality of life. PCI was therefore introduced in the early 1980s to prevent BMs, and several randomised trials compared PCI to no PCI. Even though they showed a significant decrease of BM incidence among patients who received PCI, no trial individually could demonstrate a positive effect on survival. Thus a meta-analysis was undertaken, based on individual data of 987 patients included in 7 phase III studies testing PCI in complete responders [25]. Complete remission corresponded to normalisation of chest X-ray in most of these trials. This meta-analysis had an impact on the standard of care for SCLC as it confirmed the decreased incidence of BM (59% at 3 years in the control arm *versus* 33% in the PCI group ($P < 0.001$), but also showed a 5% absolute benefit in terms of 3-year overall survival (15% in the control group and 21% in the PCI group). As complete response was assessed with chest X-ray, one can extrapolate that complete and good responders based on CT scan evaluation can be considered eligible for PCI. The selection of an optimal dose for PCI that would lead to a further decrease in brain metastasis incidence with minimal toxicity was one of the challenges raised by the meta-analysis. A phase III trial has addressed the question of dose effect for the prevention of metastases in patients with limited disease. It compared a standard dose of 25 Gy in ten fractions to a higher dose of 36 Gy (36 Gy/18 fractions or 36 Gy in 24 twice-daily fractions) [26]. Patients who received a higher PCI dose had a non-significant decrease in brain metastases. Incidence of brain metastases at two years was 29% in the standard-dose group and 23% in the higher-dose group ($P = 0.18$). Thus, PCI at 25 Gy in ten fractions is now recommended for limited-disease SCLC good responders.

Even though there are strong data showing that PCI reduces the incidence of BM and improves overall survival in SCLC, its indications should also be considered in the light of its potential neurotoxicity. Acute toxicity is generally manageable and consists mostly in alopecia, headache, fatigue, nausea and vomiting. Long-term toxicity is of concern, since sequelae such as severe memory loss, intellectual impairment or even dementia, ataxia or seizures have been reported in retrospective studies and attributed to PCI. It should be outlined that in the two largest randomised trials included in the meta-analysis, a prospective neurological evaluation did not show any significant difference in neurological functions between the PCI and no PCI groups, with a follow-up limited to 30 months. In the Intergroup phase III trial comparing two different PCI doses, clinical neurological outcome and quality of life were also evaluated prospectively; a mild deterioration across time of memory, communication and intellectual deficit was observed [27]. Patients should be informed of these potential adverse effects, and they should be balanced with the benefit of PCI on survival and BM.

New clinical recommendations for treatment of M1 patients

Around 70% of SCLCs are metastatic at diagnosis. As specified in both North American and European clinical recommendations, treatment relies mostly on chemotherapy [2,3]. Tables 3, 4 and 5 describe different chemotherapy schedules.

Conventional first-line chemotherapy (Table 3)

The etoposide–platin (EP) combination currently remains the standard first-line treatment for SCLC [2, 3,28]. The dominant role of cisplatin and vepeside has been confirmed in two meta-analyses [29,30]. EP and CAV (cyclophosphamide, doxorubicin and vincristine) are difficult to administer in elderly or poor-performance patients due to their high level of toxicity.

Carboplatin

The RR of etoposide and carboplatin (EC) is around 60%, with a median survival of 8–9 months. A comparison between EC and EP showed equivalence of the two treatments in a small study, but EC was less

Table 3
Comparison of chemotherapy combinations as first-line treatment

Protocol	Cytostatic	No. of patients[a]	Response rate (%)	Median survival (months)
Roth et al. (1992) [28], 3 weeks	CAV: CPM 1000 mg/m^2, ADM 40 mg/m^2, VCR 1 mg/m^2, day 1	140	51	8.6
	EP: CDDP 20 mg/m^2, day1–5 VP16 80 mg/m^2, day 1–5	140	61	8.3
	CAV/EP	138	59	8.1 (NS)
Pujol et al. (2001) [31], 4 weeks	EP: Etoposide 100 mg/m^2, day 1–3, CDDP 100 mg/m^2, day 2	109	61	9.3
	PCDE: Etoposide 100 mg/m^2, day 1–3, CDDP 100 mg/m^2, day 2, CPM 400 mg/m^2, day 1–3, 4′-epidoxorubicin 40 mg/m^2, day 1	117	76	10.5 ($P = 0.0067$)
Noda et al. (2002) [32], 4 weeks	Etoposide 100 mg/m^2 ×3 – cisplatin 100 mg/m^2 ×1 (day 21)	154	67.5	9.4
	Irinotecan 60 mg/m^2 ×3 – Cisplatin 60 mg/m^2 ×1 (day 28)		84.4 ($P = 0.02$)	12.8 ($P = 0.002$)
Hanna et al. (2006) [33], 3 weeks	Etoposide 120 mg/m^2 ×3 – Cisplatin 60 mg/m^2 ×1 (day 21)	331	48 (NS)	10.2
	Irinotecan 65 mg/m^2 ×2 – Cisplatin 30 mg/m^2 ×2 (day 21)		43.6	9.3 ($P = 0.74$)
Lara et al. (2009) [34], 3 weeks	Etoposide 100 mg/m^2 ×3 – Cisplatin 80 mg/m^2 ×1 (day 21)	671	57 (NS)	9.1
	Irinotecan 60 mg/m^2 ×3 – Cisplatin 60 mg/m^2 ×1 (day 28)		60	9.9 ($P = 0.71$)

ADM: doxorubicin; CDDP: cisplatin CPM: cyclophosphamide; NS: not significant; VCR: vincristine; VP16: etoposide.
[a] Patients with disseminated disease.

toxic [35]. EC has a better toxicity profile and should be preferred in frail patients.

Oral etoposide

In combination with cisplatin, oral etoposide gives similar results to traditional EP, but with more haematological toxicity.

Intensification of first-line therapy

Faced with a tumour that is generally extremely chemosensitive but rapidly becomes chemoresistant, different approaches have been studied to increase the dose intensity and clinical benefit.

Increase in doses of chemotherapy

Many studies have compared chemotherapy administered at classic doses with the same chemotherapy given at higher doses; the higher doses resulted in higher response but also toxicity rates, and did not benefit overall survival. Such an approach cannot be recommended [6,24].

Increased number and alternating drugs

The addition of other agents such as iphosphamide, cyclophosphamide and epirubicin to standard EP treatment has been evaluated in large randomised studies. This approach resulted in a modest benefit in survival but at the cost of increased toxicity so that it should only be proposed to selected patients [31,36].

Increase in number of cycles of chemotherapy

Four to six cycles are recommended for SCLC patients. Continuing chemotherapy beyond 4–6 cycles increased the time to progression, but had no impact on overall survival [31,37]. No benefit has been reported for consolidation treatment with topotecan after 4 cycles of EP [37].

New cytotoxic agents as first-line therapy

Several new drugs or combinations were tested with RRs over 50% in phase II studies, but these results were not confirmed in phase III trials (Table 3).

Irinotecan

There was much enthusiasm around irinotecan following the results of the Japanese Clinical Oncology Group trial, which demonstrated a benefit in terms of survival with cisplatin–irinotecan compared to EP (12.8 vs. 9.4 months, $P = 0.002$) [32]. Other phase III studies, performed in North America, could not confirm these results, emphasising the importance of pharmacogenomics [33,38]. A recent meta-analysis has however suggested equivalence between irinotecan/platinum and EP in metastatic patients [39].

Table 4
Treatments after one line of treatment

Author	Cytostatic	Number of patients[a]	Response rate (%)	Median survival (weeks)
von Pawel et al. (1999) [45]	CPM 1000 mg/m^2, ADM 45 mg mg/m^2, VCR 2 mg on day 1/3 weeks	104	18.3	24.7
	Topotecan 1.5 mg/m^2, day 1–5/3 weeks	107	24.3	25
Eckardt et al. (2007) [46]	Topotecan IV 1.5 mg/m^2 × 5/3 weeks	309	21.9	35 ($P = 0.98$)
	Topotecan oral 2.3 mg/m^2 × 5/3 weeks		18.3	33
O'Brien et al. (2006) [47]	Topotecan oral 2.3 mg/m^2 × 5/3 weeks	141	7	25.9 ($P = 0.010$)
	Supportive care			13.9
Inoue et al. (2008) [48]	Amrubicin 40 mg/m^2, day 1–3/3 weeks	29	38	32
	Topotecan 1.0 mg/m^2, day 1–5/3 weeks	30	13	34
Jotte et al. (2011) [49]	Amrubicin 40 mg/m^2, day 1–3/3 weeks	50	44	9.2 (months)
	Topotecan 1.5 mg/m^2, day 1–5/3 weeks	26	15.4	4.5 (months)

ADM: doxorubicin; CPM: cyclophosphamide; IV: intravenous; VCR: vincristine.
[a] Patients with recurring SCLC, as second-line.

Topotecan

The combination of oral topotecan and cisplatin appears to be as effective as EP, but time to progression was longer in the EP arm. Thus topotecan is not currently used as first-line therapy [40].

Paclitaxel

Paclitaxel, in combination with etoposide and platinum, has given encouraging results in phase II studies, but these were not confirmed in two phase III studies comparing paclitaxel–etoposide–cisplatin (TEP) and EP (increased number of toxic deaths in the TEP arm) [41,42].

Pemetrexed

The promising results of a phase II study combining pemetrexed and carboplatin could not be confirmed in a phase III study (carboplatin–pemetrexed vs. carboplatin–etoposide) which resulted in lower RR and survival rates for carboplatin–pemetrexed (10.6 *versus* 8.1 months, $P < 0.01$) [43]. There is therefore no indication to use pemetrexed in SCLC.

Amrubicin

Amrubicin (anthracycline) showed promising results as first-line therapy, notably as monotherapy in a population of Asian subjects [44]. It is currently being developed as second-line treatment in Caucasian patients.

Second-line chemotherapy

Most patients experience relapse after their initial treatment, with a median survival of 2–3 months without second-line therapy. In the decision for second-line therapy, it is important to take into account the quality of the response to first-line treatment and the disease-free interval that separates the end of treatment and the relapse (Table 4). Thus, patients who respond to first-line treatment and relapse after a disease-free interval of at least 90 days are usually called "sensitive". Conversely, patients who do not respond and who progress within 90 days after end of treatment are called "resistant". However, this time interval remains relatively arbitrary. Finally, the last category concerns "refractory" patients who never responded or progressed during first-line therapy. In "sensitive" patients, the reintroduction of initial treatment (EP or carboplatin–etoposide) is generally recommended.

Topotecan or CAV

Topotecan, an inhibitor of topoisomerase I, has been shown to be superior as monotherapy compared to supportive care only (OS 26 *versus* 14 weeks, $P = 0.010$) [47]. The antitumour activity of both topotecan and CAV was similar at the time of relapse after EP [45]. Oral topotecan appears to be equivalent to the IV form [46]. As CAV, topotecan can be prescribed as second-line treatment for SCLC.

Amrubicin

Amrubicin has shown encouraging results compared to topotecan as second-line therapy both in Asian

Table 5
Chemotherapy and anti-angiogenic combinations as first-line therapy

Author	Treatments	Number of patients	Objective response (%)	Median survival (months)
Jett [51]	CT-TR-PCI then IFN-gamma	51	–	13.3 ($P = 0.43$)
	CT-TR-PCI then observation	59		18.8
Kelly [52]	CT then IFN-alpha	64	–	13 ($P = 0.72$)
	CT then observation	68		16
Shepherd [53]	CT + marimasta	266	–	9.3 ($P = 0.90$)
	CT + placebo	266		9.7
Pujol [54]	PCDE + thalidomide	49	81.5	10.2 ($P = 0.16$)
	PCDE	43	81.5	10.5
Lee [55]	EP + thalidomide	49	87	8.7 ($P = 0.24$)
	EP + placebo	43	84	11.7
Horn [56]	CDDP-etoposide + bevacizumab	63	63.5	10.9
Ready [57]	CDDP-irinotecan + bevacizumab	68	62	11.7
Spigel [58]	Carboplatin–irinotecan + bevacizumab	51	84	12.1
Arnold [59]	CT then vandetanib	53	–	10.6 ($P = 0.90$)
	CT then placebo	54		11.9

CT: chemotherapy; EP: etoposide, cisplatin; PCDE: etoposide, cisplatin, cyclophosphamide and 4′-epidoxorubicin; PCI: prophylactic cranial irradiation; TR: thoracic radiotherapy.

patients (one-third being resistant to platinum) and in non-Asian patients [48–50]. The RR was higher for amrubicin in both sensitive (21% *versus* 53% in the amrubicin arm) and resistant (0% *versus* 17% in the amrubicin arm) Asian patients [48]. Among sensitive non-Asian subjects, amrubicin significantly increased the RR in comparison with topotecan (15% *versus* 44%, $P = 0.021$) with a tendency towards a better PFS and OS [49]. These results need to be confirmed.

Targeted therapies as first-line or later (Table 5)

Interferon, marimastat and thalidomide

Maintenance treatments such as interferon alpha or marimastat (inhibitor of metalloproteinases) have failed to demonstrate any clinical benefit in SCLC. Thalidomide was also evaluated as maintenance treatment in a phase III setting with no benefit on survival.

Bevacizumab

Bevacizumab (monoclonal anti-VEGF antibody) has been studied in extensive-disease patients, combined to EP, cisplatin–irinotecan or carboplatin–irinotecan with promising results (OS of 10.9, 11.7 and 12.1 months, respectively) [56,58]. Different inter-group validation studies are currently ongoing (CALGB, ECOG, IFCT).

Vandetanib

Vandetanib, a tyrosine kinase inhibitor of EGFR and VEGFR, has not shown any efficacy as maintenance treatment [59].

Anti-sense therapies

Bcl2, a powerful anti-apoptotic frequently overexpressed in SCLC, could possibly be responsible for an increase in chemoresistance, thus targeting Bcl-2 could provide therapeutic benefit. The results of a phase II study evaluating the addition of an antisense bcl2 oligonucleotide (oblimersen) to carboplatin–etoposide as first-line treatment were disappointing as the addition showed no benefit on OS and survival without relapse [60]. Other novel Bcl-2 family inhibitors, such as ABT-263, are currently being studied, including an oral inhibitor, with encouraging preliminary results [61].

Inhibitors of mTOR

Although RAD001 was not effective as second-line therapy in a phase II study, trials are currently underway combining RAD001 with EP.

Inhibitors of proteasome and inhibitors of EGFR

Bortezomib as well as tyrosine kinase inhibitors of EGFR (gefitinib, erlotinib) do not appear to be active in SCLC [62,63].

Inhibitor of c-Kit

SCLCs express the receptor tyrosine kinase c-Kit in around 35% of cases. Phase II studies, carried out in relapsed or refractory patients identified as c-Kit positive by immunohistochemistry, failed to demonstrate either an objective response or tumour stabilisation [64].

Thus, to date, most targeted therapies evaluated have failed to demonstrate any therapeutic benefit in SCLC. Many other studies are underway, but it appears important to better define the molecular abnormalities in SCLC in order to possibly develop specific targeted agents.

Role of radiotherapy in M1 patients (PCI and TR)

As the meta-analysis supported PCI in extensive disease for complete responders, a EORTC study was undertaken to address the question of PCI in patients with extensive disease who had a response to chemotherapy [65]. The results strongly support PCI as it significantly reduces the risk of symptomatic brain failure (14.6% at 1 year in the PCI arm versus 40.4% in the control arm) but also improves survival (1-year survival rate of 27.1% in the PCI arm versus 13.3% in the control arm; $P = 0.003$). PCI has now become a standard treatment also among metastatic patients who respond to first-line treatment.

TR cannot not be considered as a standard treatment for patients with extensive disease. There are however ongoing studies addressing the question of TR in extensive disease both in North America and in the Netherlands.

Conclusion

SCLC remains a disease with a poor prognosis. A platinum salt in association with vepeside is currently the reference combination as first-line therapy; however other drugs can be added to this for patients in good general state (PCDE protocol). Despite the high chemosensitivity of these tumours, >90% of metastatic patients will present with a relapse after a response and poor therapeutic possibilities. Furthermore, despite therapeutic progress, the clinical benefit of new targeted therapies has been disappointing in SCLC. It is imperative to evaluate the new cytostatic and biological approaches in phase III studies, and patients should be included in therapeutic trials. The treatment of localised forms depends on a combination of radio- and chemotherapy. Prophylactic cerebral irradiation is now an integral part of treatment of all patients with SCLC, whether limited or disseminated. The optimal modalities of radiotherapy–chemotherapy such as the chronology, doses and fractions of thoracic radiotherapy should continue to be the object of clinical studies. Finally, more than ever, emphasis should be placed on the prevention of smoking, the major cause of SCLC.

Conflict of interest statement

The authors disclose they have no financial and personal relationships with other people or organisations that could inappropriately influence (bias) their work.

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