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Treatment of extensive-stage small cell lung carcinoma: current status and future prospects

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ABSTRACT: Small cell lung cancer (SCLC) is an aggressive lung tumour strongly associated with cigarette smoking, with patients often presenting with metastatic disease at the time of diagnosis. Although SCLC is very chemoradiosensitive and high response rates are obtained with treatment, relapse rates are high and the prognosis remains very poor.

In limited-stage SCLC, the overall survival rate has been significantly improved by adding dose-hyperfractionated thoracic radiotherapy and prophylactic cranial irradiation to systemic chemotherapy. In contrast, little progress has been made in the treatment of extensive-stage SCLC (ES-SCLC), apart from the recently documented survival gain by the addition of prophylactic cranial irradiation.

First-line therapy in ES-SCLC currently consists of chemotherapy, combining a platinum drug with either etoposide or irinotecan as a possible alternative.

New treatments are needed in order to improve the prognosis of ES-SCLC, as median survival with current standard treatment is still only 9–10 months from diagnosis. The present review focuses on the management of ES-SCLC, with special attention to the development of new treatment options.

KEYWORDS: Chemotherapy, extensive disease, radiotherapy, small cell lung cancer, treatment

Small cell lung cancer (SCLC) is an aggressive malignant disease, with the majority of patients presenting with distant metastasis at diagnosis. A separate staging system has been developed for SCLC, classifying SCLC as limited or extensive disease [1]. The International Association for the Study of Lung Cancer defines limited-stage SCLC (LS-SCLC) as: ''disease restricted to one hemithorax with regional lymph node metastases, including hilar, ipsilateral and contralateral mediastinal, and ipsilateral and contralateral supraclavicular nodes and should also include patients with ipsilateral pleural effusion independent of whether cytology is positive or negative'' [2]. Patients with SCLC who do not fit this definition are considered to have extensive-stage SCLC (ES-SCLC). This staging system was used to select the appropriate treatment regimen: chemotherapy in combination with thoracic radiotherapy in patients with LS-SCLC, and chemotherapy alone in patients with ES-SCLC. Recent data suggest that the tumour, node, metastasis classification traditionally reserved for the staging of nonsmall cell lung cancer (NSCLC) can also be applied for the staging of SCLC [3].

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The present review addresses the systemic tumour-directed treatment of ES-SCLC. Recently, prophylactic cranial irradiation (PCI) has been shown to improve outcome in patients with ES-SCLC [4], but only small advances have been made otherwise.

FIRST-LINE TREATMENT OF ES-SCLC

Advances in imaging techniques have led to more accurate staging of SCLC, with a stage shift towards an increase in ES-SCLC over LS-SCLC as more occult metastases are detected. If left untreated, patients with SCLC rarely survive longer than a few months [5], but chemotherapy dramatically prolongs survival compared to the best supportive care [6]. For patients with ES-SCLC, 60–80% respond to chemotherapy, although complete remission is observed in only 15–20%. From the time of diagnosis, the reported median survival range for ES-SCLC is 8–13 months (fig. 1).

As SCLC is a very chemosensitive tumour, rapid responses, with symptomatic improvement, are often seen with chemotherapy. This has important clinical implications as, in contrast to advanced-stage NSCLC, chemotherapy can also be offered to patients with SCLC and a poor or bad performance status (World Health Organization performance status of 2–3), since a rapid amelioration of the patient's symptoms and general condition can be expected together with an improved outcome [7]. However, the risk of toxicity is greater in this group than in patients with good performance status.

The first-line treatment of ES-SCLC currently consists of chemotherapy with a platinum derivative and etoposide, a combination that was first reported to be effective in the treatment of SCLC in 1985 [8, 9]. The superiority of the platinum/etoposide combination as first-line standard treatment is confirmed by two meta-analyses reporting a significant survival benefit of platinum-based chemotherapy [10, 11] compared to chemotherapy without platinum compounds, contrary to the results of a third meta-analysis [12]. PUJOL *et al.* [10] evaluated 19 trials (>4,000 patients) and concluded that a platinum-containing regimen yields a higher response rate (odds ratio 1.35; 95% confidence interval (CI) 1.18–1.55; $p<1\times10^{-5}$) and reduction of risk of death at 1 yr (odds ratio 0.80; 95% CI 0.69–0.93; p=0.002) compared to chemotherapy involving other nonplatinum alkylating agents. These benefits were obtained without a significant increase in the rate of toxic deaths. These findings were confirmed by data from the European Lung Cancer Working Party (ELCWP) showing a survival benefit for patients treated with a combination of etoposide and cisplatin (EP) [11]. In this meta-analysis of 7,173 patients from 36 trials, the authors also demonstrated a survival benefit for treatment combinations with etoposide compared to a treatment without etoposide. Moreover, treatment regimens with cisplatin but without etoposide are probably not significantly better than regimens using neither drug, but only one trial in the meta-analysis formally compared these two treatments, and thus the clinical relevance of this finding is unclear [11].

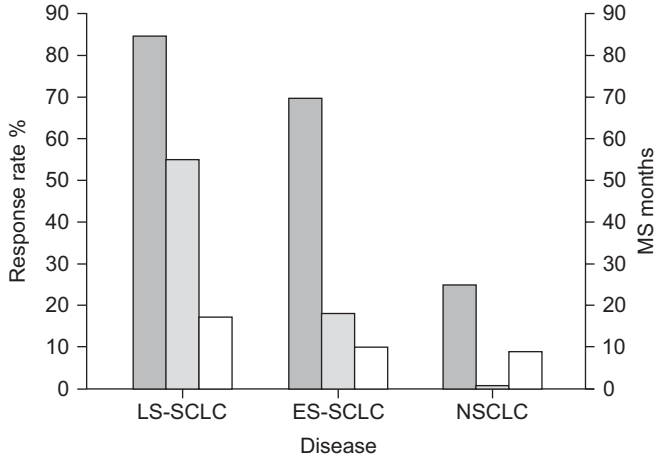

FIGURE 1. Response rates and median survival (MS; □) in small cell lung cancer (SCLC) and nonsmall cell lung cancer (NSCLC). Response rates in SCLC are much higher than in NSCLC, although MS remains poor. The overall response (■) ranges 80–90% in limited-stage SCLC (LS-SCLC), 60–80% in extensive-stage SCLC (ES-SCLC) and 20–28% in advanced-stage NSCLC. Complete responses (■) are noted in SCLC (50–60% in LS-SCLC and 15–20% in ES-SCLC), whereas this is almost never the case in NSCLC. Despite these impressive response rates, MS is only 14–20 months in LS-SCLC and 8–13 months in ES-SCLC, compared to 8–11 months in advanced-stage NSCLC.

In contrast with these findings, a recent meta-analysis in 5,530 patients from 29 trials by the Cochrane Collaboration suggested no significant benefit of platinum-based chemotherapy regimens compared with nonplatinum-based regimens [12]. There was no significant difference between the two treatment groups in terms of survival at 6, 12 and 24 months. There was also no significant difference in terms of overall tumour response. However, platinum-based treatment regimens did have a significantly higher rate of complete response. Platinum-based chemotherapy regimens had significantly higher rates of nausea and vomiting, anaemia and thrombocytopenia [12]. Whereas the ELCWP meta-analysis [11] showed a survival benefit with EP, the Cochrane meta-analysis did not formally compare EP with other platinum-based regimens, providing a possible explanation for the divergent conclusions between the two meta-analyses. Importantly, neither of these meta-analyses used individual patient data from the original trials, and hence should be interpreted with caution. In a randomised phase III trial published in 2002 (and thus not included in the meta-analyses of PUJOL *et al.* [10] and MASCAUX *et al.* [11]), SUNDSTRØM *et al.* [13] compared treatment with EP to that with cyclophosphamide, epirubicin and vincristine, and documented significantly higher 2- and 5-yr survival rates in the EP arm in LS-SCLC. A trend in survival benefit was seen in the patients with ES-SCLC, with a median survival of 6.5 months in the cyclophosphamide, epirubicin and vincristine group compared to 8.4 months in the EP group.

A well-known and important side-effect of cisplatin is its nephrotoxicity, for which prevention hyperhydration is required. This can be problematic in the more fragile and elderly patient or in patients with cardiac or renal comorbidity. This led several authors to investigate whether an association of etoposide with carboplatin, which is less toxic than cisplatin, has a comparable outcome to EP. Only one randomised phase III trial directly compared these two treatment regimens. The Hellenic Cooperative Oncology Group conducted a randomised phase III trial that compared the efficacy and toxicity of EP *versus* etoposide/carboplatin in previously untreated patients

with SCLC (both LS- and ES-SCLC) [14, 15]. These authors demonstrated that carboplatin in combination with etoposide was as effective as, but less toxic than, EP. They concluded that these results provide a rationale for the use of the etoposide/carboplatin combination over EP because of similar efficacy and decreased toxicity.

There is some controversy as to whether etoposide should preferably be administered intravenously or as on oral formulation. Although an oral formulation of etoposide exists and seems an attractive alternative at first sight, several studies have demonstrated that oral etoposide was less effective and sometimes more toxic than using intravenous administration. Two randomised trials were prematurely stopped because of inferior survival with oral etoposide at the interim analysis [16, 17]. Unpredictable events may be linked to variable bioavailability of the oral formulation.

ALTERNATIVES TO PLATIN/ETOPOSIDE

Despite the high response rates in patients with SCLC treated with cis- or carboplatin in combination with etoposide, relapse rates are high and the overall prognosis remains poor (fig. 1). The most likely explanation for this problem is the rapid development of drug resistance, probably due to the selection of a small number of residual tumour cells that are not sensitive to the initial chemotherapy. The fact that response rates during second-line chemotherapy are much lower is attributable to cross-resistance between the different drugs used.

For this reason, several other therapeutic regimens have been evaluated in the treatment of ES-SCLC. Anthracyclines, camptothecins, antifolates and taxane have all been tested as possible alternatives in the first-line treatment of ES-SCLC (table 1).

Doxorubicin-containing regimens have been used for a long time in the treatment of SCLC. However, recently published phase III randomised trials failed to demonstrate better overall survival with these regimens compared to platinum-based chemotherapy [29, 30].

Importantly, haematological toxicity was significantly higher with doxorubicin-containing regimens, leading to more episodes of febrile neutropenia and more hospital admissions. It should be mentioned that these side-effects can be managed much better nowadays, with the use of prophylactic antibiotics and growth factors.

Epirubicin, a modified anthracycline that is less cardiotoxic than doxorubicin [31], has demonstrated significant activity as a single agent in SCLC in phase II studies. A randomised phase III trial, including 207 patients with LS-SCLC and 192 patients with ES-SCLC, comparing cisplatin/epirubicin (100 $mg \cdot m^{-2}$) to EP demonstrated similar overall objective response rates, median time to progression and median survival, whereas haematological toxicity was lower in patients treated with epirubicin [22]. The combination of epirubicin and cisplatin is considered a reasonable alternative regimen for the treatment of patients with SCLC. A practical advantage is that epirubicin can be administered in 1 day, whereas etoposide is administered over 3 days consecutively.

Promising results in the treatment of ES-SCLC have been obtained in phase I and phase II trials (mainly in Japan) with amrubicin, another synthetic anthracycline [32, 33]. Randomised trials are currently recruiting patients in order to confirm these findings and to evaluate whether there is a role for amrubicin, in first-line therapy as well as in relapsed disease [34, 35].

Promising results were obtained with irinotecan, a camptothecin that acts as a topoisomerase I inhibitor. In 2002, a Japanese phase III trial suggested that the combination of cisplatin plus irinotecan

TABLE 1 Outcome of first-line platinum-based combination chemotherapy phase III trials in extensive-stage small cell lung cancer

	Year	Subjects n	Response %		Survival		Toxicity CTC 3/4 %				[Ref.]
			OR	CR	Median months	At 1 yr %	NP	Anaemia	TP	Other	
Cisplatin–etoposide	1985	20	88	29	9.1	30	18				[8]
Cisplatin–etoposide	1992	159	61	10	8.6	30	70	35	13	6#	[9]
Cisplatin–irinotecan (JCOG 9511)	2002	154	84	3	12.8	58	65	27	5	16¶	[18]
Cisplatin–irinotecan	2006	331	48		9.3	35	36	5	4	21¶	[19]
Carboplatin–irinotecan	2008	209		17	8.5	34	33	5	15	11¶	[20]
Cisplatin–irinotecan (S0124)	2008	671	59	4	9.7	39	33	6	4	19¶	[21]
Cisplatin–epirubicin	2004	195	74		10.9		42				[22]
Cisplatin–topotecan (oral)	2006	784	63	6	10.0	31	59	38	38		[23]
Cisplatin–topotecan (intravenous)	2008	795	55	10	10.3	40	36	12	19		[24]
Carboplatin–pemetrexed	2008	733	25		7.3		9	10	10		[25]
Cisplatin–etoposide–paclitaxel	2005	587	75	16	10.6	38	44	19	22		[26]
Cisplatin–etoposide–ifosfamide	1995	171	73	21	9.0	36	52	52	35		[27]
Cisplatin–etoposide–cyclophosphamide–epirubicin	2001	226	76	21	10.5	40	99	51	78	22+	[28]

OR: overall response; CR: complete response; CTC: common toxicity criteria; NP: neutropenia; TP: thrombocytopenia; JCOG: Japanese Clinical Oncology Group. #: nausea/vomiting; ¶ diarrhoea; +: infections.

was significantly more effective than EP [18]. Indeed, this trial was prematurely stopped because, at an interim analysis, the 154 patients treated with irinotecan plus cisplatin showed a significantly higher response rate (84 *versus* 68%), longer median survival (12.8 *versus* 9.4 months) and higher 2-yr survival rate (19 *versus* 5%) than those with the etoposide-based regimen. Although haematological toxicity was less pronounced with irinotecan, significantly more grade 3 or 4 diarrhoea was reported in this group. However, these results could not be confirmed in a large phase III trial in patients from the USA, Australia and Canada [19]. This study included 322 patients and could not safely administer the same doses as in Japan and thus used a different regimen for the administration of both EP and cisplatin/irinotecan but with a similar if not higher dose intensity. In order to rule out an effect due to these differences in the treatment schedule, the Southwest Oncology Group (SWOG) trial S0124 randomly assigned 671 patients with ES-SCLC to regimens identical to those used in the Japanese trial. The results of this trial were published recently [21]; no significant differences were found in overall objective response rates, overall survival or 1-yr survival between the two treatment arms. Finally, a fourth study from Norway addressing this issue was published in 2008, reporting a moderate benefit of a treatment with carboplatin and irinotecan over carboplatin with oral etoposide [20]. In summary, conflicting results have been obtained with the combination of platinum and irinotecan, probably due to pharmacogenomic differences between study populations, as well as differences in the studied treatment regimens and their pharmacokinetics. Especially with regard to the toxicity of irinotecan, genetic differences in, for example, the metabolic enzyme uridine-diphosphate glucuronosyltransferase (UGT) 1A1, might influence the degree of expected drug toxicity. In the SWOG S0124 trial, pharmacogenomic analysis showed that the TT genotype of the 3435C>T *ABCB1* (ATP-binding cassette, subfamily B (MDR/TAP), member 1 gene) polymorphism (membrane transport) was associated with cisplatin/irinotecan-related diarrhoea, whereas the AA genotype of the -3156G>A *UGT1A1* polymorphism (drug metabolism) was associated with cisplatin/irinotecan-related neutropenia. However, recent data question the validity of measuring a single polymorphism (*UGT1A1*) to predict drug elimination and toxicity, since other polymorphisms and single nucleotide polymorphisms also influence the disposition of irinotecan [36]. Moreover, in this series, half of the variation in toxicity and drug exposure remains unexplained by the UGT1A1 genotype.

Topotecan, another member of the camptothecin family, has been evaluated in several phase II and III trials as first-line therapy for ES-SCLC in comparison with the standard treatment of EP [23, 24, 37]. These trials concluded noninferiority of cisplatin/topotecan compared to EP with regard to overall survival. ECKARDT *et al.* [23] demonstrated that both regimens were similarly tolerable. Grade 3/4 neutropenia occurred more frequently with EP (84 *versus* 59%), whereas grade 3/4 anaemia and thrombocytopenia occurred more frequently with cisplatin/topotecan (38 *versus* 21% and 38 *versus* 23%, respectively). In the study of HEIGENER *et al.* [24], increased haematological toxicity was observed with topotecan. The number of toxicity-related deaths was numerically higher with cisplatin/topotecan (5%) compared to EP (3%). Moreover, a third treatment arm with the combination of topotecan and etoposide was abandoned due to an increased number of treatment-related deaths.

Belotecan, a new camptothecin analogue, has shown activity in SCLC in phase II trials [38]. Currently, a phase III trial comparing EP with cisplatin/belotecan in patients with previously untreated ES-SCLC is running in Asia [39].

Pemetrexed, a folic acid metabolism antagonist that has a place in the first-line treatment of malignant mesothelioma and possibly also of nonsquamous NSCLC, has also been evaluated in the treatment of SCLC. Data from phase I and II trials suggested antitumoural activity and toxicity comparable to standard treatment regimens with EP or cisplatin/irinotecan [25]. However, an interim analysis of a phase III trial revealed inferiority of carboplatin/pemetrexed compared to carboplatin/etoposide and led to the interruption of that trial [40].

Paclitaxel, a member of the taxane family, has also been investigated in the treatment of SCLC. There is some evidence of non-cross-resistance to paclitaxel from phase II studies, which described a 29% response rate to paclitaxel in chemotherapy-refractory ES-SCLC [41]. The combination of carboplatin and paclitaxel was compared to a treatment with cyclophosphamide, doxorubicin and etoposide by DE JONG *et al.* [29], but did not result in better survival, whereas haematological toxicity was significantly lower with carboplatin/paclitaxel compared to cyclophosphamide, doxorubicin and etoposide. The addition of paclitaxel to first-line treatment with EP did not improve the time to progression or survival in patients with ES-SCLC compared with EP alone, and was associated with unacceptable toxicity [26, 42]. At present, there are no data available that directly compare the combination of paclitaxel and a platinum compound to the standard treatment with platinum and etoposide.

The addition of ifosfamide [27] or even a combination of cyclophosphamide and epirubicin [28] to the standard treatment with EP has led to higher response rates and modestly prolonged survival, but at the cost of increased toxicity. At present, there are insufficient data to justify the addition of a third or even fourth drug to the platinum–etoposide backbone for ES-SCLC.

DOSE MODIFICATION AND SEQUENCE ALTERATION

Increasing dose intensity

Some groups have tried to eradicate all malignant cells by increasing the dose intensity of chemotherapy, exploiting the concept that the dose–response relationship in SCLC might be linear [43, 44]. This increase can be achieved by either increasing the total drug dose for one or more cycles, decreasing the interval between drugs or cycles or a combination of the two. In all approaches, myeloid growth factors can be used to avoid excessive haematological toxicity. This strategy can be pushed to the limits by administering chemotherapy at myeloablative doses, followed by bone marrow reconstitution with autologous haematopoietic stem cells.

IHDE *et al.* [45] compared high- and standard-dose EP chemotherapy in patients with ES-SCLC. Despite the higher relative dose intensity that was given in the high-dose chemotherapy group, complete response rates (23 *versus* 22%; $p=0.99$) and median survival (10.7 and 11.4 months, respectively; $p=0.68$) were almost identical, whereas significantly

more haematological toxicity was noted in the high-dose chemotherapy group. In order to overcome the problem of increased haematological toxicity, the use of myeloid growth factors has been proposed and evaluated in several phase III trials. Using myeloid growth factors permits the administration of higher dose intensities, but has not unequivocally been demonstrated to result in increased overall survival, and haematological toxicity remains significantly higher [46, 47]. A meta-analysis on this topic concluded that there is no place for the routine use of haematological colony-stimulating factors in the treatment of SCLC for the purpose of increasing dose intensity [48], although there is a role for growth factors for the prevention of infection. Two phase III trials, including both patients with LS- and with ES-SCLC, demonstrated increased haematological toxicity but no improved survival when combining myeloablative chemotherapy with autologous haematopoietic stem cell reinfusion [49, 50].

A last theoretical concept for avoiding rapid relapse is the consolidation of an initially favourable response by the continued administration of the initial drug (maintenance) [51] or the immediate administration of a second drug directly after the first chemotherapy regimen (early second line) [52]. Once again, clinical trials have failed to show a clear benefit for these at-least-theoretically promising strategies. Two meta-analyses evaluated the potential use of maintenance chemotherapy in SCLC. SCULIER *et al.* [53], in 1998, selected 13 published randomised trials, of which only one showed a significant difference in survival in favour of maintenance. Five trials described some survival advantages in subgroups of patients, one showed a significantly shorter survival with maintenance and, in six studies, there was no difference between the two arms. The overall quality of the trials was considered poor, and a quantitative meta-analysis was not possible because of the lack of data for calculation of the odds ratio and because of the heterogeneity in the design of the studies. BOZCUK *et al.* [54], in 2005, analysed 14 trials (11 of these were also included in the meta-analysis of SCULIER *et al.* [53]), of which only four resulted in significant differences as far as direct comparisons between maintenance and follow-up arms were concerned; three trials documented better overall survival with maintenance chemotherapy and one showed worse overall survival with maintenance chemotherapy, whereas 10 did not find significant differences regarding overall survival. However, in the meta-analysis of BOZCUK *et al.* [54], including 2,550 patients, both 1- and 2-yr mortality were reduced with maintenance/consolidation chemotherapy. Importantly, some of the trials showed increased toxicity (mostly myelosuppression) with the use of maintenance regimens, indicating that the benefit and toxicity from this approach should be balanced carefully [53, 54]. The authors of both meta-analyses concluded that maintenance chemotherapy could be useful in SCLC, but that new randomised clinical trials of high quality are required in order to further resolve this question. Analogous to the treatment of advanced NSCLC [55], maintenance treatment for SCLC must still be considered investigational.

Alternating or sequential administration of chemotherapy

Another approach to avoiding cross-resistance is the use of presumed non-cross-resistant regimens that are effective against SCLC in an alternating or sequential manner. However, several phase III trials have failed to demonstrate a significant survival benefit using this approach [9, 56]. In the European Organization for Research and Treatment of Cancer (EORTC) trial of POSTMUS *et al.* [56], the use of two alternating regimens with a proven degree of non-cross-resistance did not result in any improvement in survival in patients with ES-SCLC.

OTHER APPROACHES: ADDITION OF AGENTS WHOSE PRIMARY ACTIVITY IS NOT ANTITUMOURAL

Treatment with anticoagulants might improve outcomes in cancer patients through an antitumour effect in addition to their antithrombotic effect. A Cochrane analysis concluded that there is no mortality benefit from oral anticoagulation in patients with cancer in general. In patients with SCLC, however, the evidence suggested a potential mortality benefit from warfarin at 6 months, particularly in extensive disease, but this occurred at the cost of an increased risk of major and minor bleeding [57]. A more recent review suggested a survival benefit of parenteral anticoagulation with heparin in cancer patients in general, and in patients with LS-SCLC in particular [58]. A randomised phase III trial investigating the use of enoxaparin in SCLC is currently recruiting patients in Sweden [59], and the FRAGMATIC trial in the UK includes both patients with NSCLC and with SCLC in order to evaluate whether the addition of dalteparin to standard treatment increases overall survival [60].

In preclinical studies of SCLC, simvastatin suppresses growth, induces apoptosis and enhances sensitivity to etoposide [61]. Pravastatin may stop the growth of tumour cells by blocking some of the enzymes needed for cell growth and by making tumour cells more sensitive to chemotherapy [62, 63]. A randomised controlled phase III trial investigating the addition of pravastatin to standard first-line treatment in SCLC is currently accruing in the UK [64].

NEW DRUGS

Picoplatin is a platinum analogue designed to overcome platinum resistance, with some activity in relapsed SCLC, as shown in a previous phase II trial conducted in refractory resistant and sensitive patients [65]. Compared to other platinum agents, picoplatin causes much less nephro-, neuro- and ototoxicity in phase I and II trials [66]. A phase III study (the Study of Picoplatin Efficacy After Relapse (SPEAR) trial) is currently evaluating picoplatin plus best supportive care *versus* best supportive care alone in both refractory and relapsed patients [67].

New approaches to targeting SCLC in order to improve drug delivery to malignant cells are also being evaluated in clinical trials. CD56, for example, is a cell surface protein expressed on the majority of SCLC cells. A phase II clinical trial evaluating the efficacy of an anti-CD56 antibody conjugated to a cytotoxic drug, maytansinoid, is underway.

Obatoclax, a Bcl-2 inhibitor, is currently being evaluated in phase I/II trials including patients with SCLC [68, 69].

Temozolamide is an oral alkylating agent with proven efficacy in the treatment of malignant glioma. It is currently being

TABLE 2 Randomised trials of second-line treatment of small cell lung cancer

Regimen	Year	Phase	Patients n	Response rate %				TTP weeks	Survival weeks	[Ref.]
				OR	CR	PR	SD			
CAV *versus* topotecan	1999	II	104/107	18/24	1/0	17/24	12/20	–/–	25/25	[71]
Topotecan, oral *versus* intravenous	2001	II	52/54	23/15	2/4	21/11	19/30	15/13	32/25	[75]
Topotecan, oral *versus* intravenous	2007	III	155/154	18/22	1/0	17/22	18/23	12/15	33/35	[74]
Oral topotecan/BSC *versus* BSC alone	2006	III	71/70	7/–	0/–	7/–	44/–	16/–	26/14	[73]

Time to progression (TTP) and survival are presented as medians. OR: overall response; CR: complete response; PR: partial response; SD: stable disease; CAV: cyclophosphamide, doxorubicin and vincristine; BSC: best supportive care.

evaluated in a phase II trial as a treatment for patients with relapsed SCLC [70].

SECOND-LINE TREATMENT FOR ES-SCLC

As mentioned above, high relapse rates are typical for SCLC. Different patterns of relapse have been described, classifying patients into three different groups, although the validity and utility of this has been questioned recently. Sensitive patients are those with a response to first-line therapy and a treatment-free interval of $\geqslant$90 days, whereas resistant patients relapse within 90 days following an initial response. Refractory patients do not respond at all to first-line treatment.

Single-agent topotecan is currently the only approved drug for the treatment of patients with SCLC who have failed or relapsed after first-line chemotherapy, and a combination of cyclophosphamide, doxorubicin and vincristine may also be used following first-line treatment with EP [71, 72].

Topotecan is available as an intravenous and, more recently, an oral formulation. VON PAWEL *et al.* [71] compared single-agent intravenous topotecan with the cyclophosphamide, doxorubicin and vincristine regimen in sensitive patients. Results with both types of treatment were comparable; the response rates were 24 and 18%, and median survival was 25.0 and 24.7 weeks for topotecan and cyclophosphamide, doxorubicin and vincristine, respectively. Topotecan, however, provided greater symptom improvement in terms of improved dyspnoea, anorexia, fatigue, insomnia and daily activity.

A randomised controlled trial published in 2006 demonstrated that chemotherapy with oral topotecan is associated with improved survival and quality of life in patients with relapsed SCLC compared to best supportive care [73]. Treatment with oral topotecan has obvious advantages over intravenous treatment, and has been shown to exhibit similar activity and tolerability to intravenous topotecan [74, 75]. Taken together, these data (summarised in table 2) have led to the official registration of topotecan (either intravenous or oral) as a second-line treatment for SCLC, with response rates of 10–40% and a median survival time of 6.0 months [71, 73].

Several other cytotoxic agents, including taxanes, gemcitabine, vinorelbine, irinotecan and pemetrexed, have been investigated as second-line treatment, in either single-agent or combination treatment (table 3) [41, 65, 76–90]. Some agents, such as paclitaxel and irinotecan, have shown some degree of activity in phase II trials. However, these trials have only included a relatively small number of patients and most often there was an uneven distribution of sensitive *versus* refractory disease. The lack of comparative phase III trials precludes any formal conclusions.

Several trials with amrubicin have shown impressive results for the second-line treatment of relapsed SCLC. High response rates (37–60%) have been reported for single-agent amrubicin in three Japanese phase II trials [86–88]. Interestingly, the response rate and median survival were similar in both sensitive and resistant patients. A phase II trial in the USA has investigated single-agent amrubicin in patients with refractory or resistant SCLC [89]. Activity was observed, and the most frequently observed toxicity was myelosuppression, but no anthracycline-induced cardiotoxicity was noted.

A randomised phase II trial has compared amrubicin and topotecan in previously treated SCLC. This study further supports the efficacy of amrubicin in both sensitive (overall response 53%) and resistant patients (overall response 17%). A higher response rate was achieved with amrubicin than with topotecan [90]. Further evaluation is currently ongoing within a phase III setting [34].

RADIOTHERAPY IN ES-SCLC

Thoracic radiotherapy is traditionally reserved for LS-SCLC, where the addition of chest irradiation to chemotherapy results in better local control and improved survival [91]. However, there is some preliminary evidence that adding thoracic radiotherapy to chemotherapy improves the survival of patients with ES-SCLC that respond to an initial three cycles of platinum/etoposide chemotherapy with a complete response outside the thorax and an at-least-partial response in the thorax [92]. These favourable results were obtained from a single-centre trial and require replication in a multicentric setting. A randomised trial addressing this issue is currently ongoing [93].

Although routine use of thoracic radiotherapy in ES-SCLC should not yet be integrated into the standard care of patients, there is more convincing evidence for offering PCI to patients with ES-SCLC. In 2007, the EORTC published a landmark trial that clearly demonstrated the usefulness of PCI in ES-SCLC [4]. They demonstrated that, in patients with ES-SCLC who responded to chemotherapy, PCI reduced the risk of brain metastases at 1 yr by 26% (40% brain metastases in control

TABLE 3 Drugs evaluated in relapsed small cell lung cancer (phase II trials)

	Patients n	OR %	OS	Conclusion	[Ref.]
Gemcitabine	27	0	6 months	Limited activity	[76]
	41	13	17 weeks	Modest activity	[77]
	46	12	7 months	Modest activity	[78]
Irinotecan	16	47	7 months	Active agent	[79]
Paclitaxel	24	29	100 days	Active agent	[41]
	44	20	4 months	Active agent	[80]
Vinorelbine	24	13		Modest activity	[81]
	26	16		Modest activity	[82]
Pemetrexed	43	S: n=1 PR; Rs: n=1 PR		Minimal activity	[83]
	34	3	18 weeks	Limited activity	[84]
	121	1 (n=1 PR in S)	2.5–6 months	Minimal activity	[85]
Amrubicin	60	S: 52; Rs: 50	S: 12 months; Rs: 10 months	Significant activity	[86]
	35	S: 50; Rs/Rf: 60	S: 10 months; Rs/Rf: 7 months	Significant activity	[87]
	19	37		Active agent	[88]
	75	PR n=13/39		Active agent	[89]
	60	38 *versus* 13		Amrubicin possibly superior to topotecan	[90]
Picoplatin	77		28 weeks	Compares favourably with other therapeutic options	[65]

OR: overall response; OS: overall survival; PR: partial response; S: sensitive (initially responded and then relapsed/progressed within 60–180 days); Rs: resistant (initially responded to first-line platinum-containing chemotherapy and then relapsed/progressed within 60–90 days); Rf: refractory (failed or progressed with first-line platinum-containing chemotherapy).

group *versus* 15% in PCI group). Moreover, the 1-yr survival rate was 27% in the irradiation group and 13% in the control group; in other words, PCI offers a 14% survival gain at 1 yr. In a recently published study of SLOTMAN *et al.* [94], the mean global health status score was 8 points higher in the PCI group, a difference that is below the cut-off of a 10-point difference for clinical significance. The most important side-effects of PCI were fatigue and hair loss, whereas the impact on other health-related quality-of-life aspects, such as cognitive and emotional functioning, was limited [94]. Hence it seems reasonable to offer PCI to all patients with ES-SCLC who respond to induction first-line chemotherapy.

TARGETED THERAPIES

Several targeted therapies have been evaluated in the treatment of SCLC (table 4), but, in contrast to advanced-stage NSCLC, none of these have yet made their way into daily clinical practice.

Epidermal growth factor receptor (EGFR) antagonists, such as erlotinib and gefitinib, have been proven to be effective in NSCLC, and were the first targeted agents to be used in the treatment of NSCLC. However, tumoural cells in SCLC either do not express the EGFR or express very small amounts [109], and clinical trials have not shown any benefit of treatment with EGFR inhibitors in SCLC [95].

Bevacizumab, a monoclonal antibody that binds vascular endothelial growth factor (VEGF), is currently being used in the treatment of advanced-stage NSCLC [110], and is now also being evaluated in SCLC [101–103]. Final results of two cooperative group phase II trials evaluating the use of bevacizumab in the treatment of ES-SCLC are pending [101, 102].

Vandetanib is an orally bioavailable inhibitor of VEGF receptor 2 (VEGFR-2 or kinase insert domain receptor (KDR)) and, to a lesser extent, EGFR [111]. Vandetanib was evaluated in a phase II trial, in which 107 patients who exhibited a partial or complete response to their induction therapy were randomly assigned to vandetanib or placebo [104]. Vandetanib failed to demonstrate efficacy as maintenance therapy for SCLC.

Sorafenib, a multikinase inhibitor affecting pathways involved in tumour progression and angiogenesis, has some promising activity in ES-SCLC [105], whereas the antiangiogenic agent cediranib (an inhibitor of the VEGFR-1, -2 and -3 tyrosine kinases) does not appear to be beneficial when added to standard chemotherapy [104].

Thalidomide, another antiangiogenic agent, has shown promising results as first-line chemotherapy and as maintenance therapy in phase II trials [107, 112]. However, two large randomised phase III trials failed to show a significant benefit of thalidomide in the treatment of SCLC [106, 113].

Temsirolimus, an inhibitor of the mammalian target of rapamycin, was evaluated as maintenance therapy in ES-SCLC in a phase II Eastern Cooperative Oncology Group trial. Patients with either stable or responding disease following induction chemotherapy were treated with temsirolimus, but this seemed not to increase progression-free survival in this patient population [114].

Stem cell factor is coexpressed with its tyrosine kinase receptor (c-kit) on SCLC tumoural cells [115]. Treatment of SCLC cell lines with imatinib, a small-molecule inhibitor of several receptor tyrosine kinases, including c-kit, inhibited tumoural cell growth [116]. Despite these promising *in vitro* results,

TABLE 4 Targeted therapies in small cell lung cancer

	Phase	Patients n	Combination regimen	Population	RR	OS/PFS	Conclusion	[Ref.]
TK inhibitors								
Gefitinib	II	18		Relapsed, Rs/S	No PR, SD 11%	OS: 55 days (Rs); 254 days (S)	No clinical activity	[95]
Imatinib	II	29		Relapsed, Rs/S (c-kit+)	No OR, no SD	OS: 4 months (Rs); 5 months (S)	No clinical activity	[96]
	II	12		Relapsed, Rs/S (c-kit+)	No OR, no SD	OS: 2 months	No clinical activity	[97]
	II	19		ES, UT, relapsed, S	No OR	OS: 9 months (UT); 7 months (S)	No clinical activity	[98]
	II	8		ES, no PD after first-line IP (c-kit+)	No OR	OS: 10 months; PFS: 6 months	Disease stability not maintained	[99]
	II	68	Carboplatin/ irinotecan	ES, UT	PR 66%	OS: 8 months; PFS: 5 months	No benefit compared to chemotherapy alone	[100]
Antiangiogenics								
Bevacizumab	II	64	EP	ES, UT	OR 69%	PFS at 6 months: 33%	Promising results	[101]
	II	72	IP	ES, UT	CR 3%; PR 59%	OS: 11 months; PFS: 7 months	Primary end-point (12-month overall survival rate) not reached	[102]
	II	34	Paclitaxel	Relapsed, S	PR 11%; SD 56%	OS: 21 weeks; PFS: 13 weeks	Active regimen	[103]
Vandetanib	II	107		ES/LS, CR/PR after first-line combination chemotherapy		OS: 11 (vandetanib) *vs* 12 months (placebo) (NS); PFS: 3 (vandetanib) *vs* 3 months (placebo) (NS)	No efficacy as maintenance therapy	[104]
Sorafenib	II	89		ES, relapsed, Rs/S	PR: 5% (S); 2% (Rs)	OS: 7 months (S); 5 months (Rs)	Clinical activity	[105]
Thalidomide	III	119	PCDE	ES, after response to 2 cycles of PCDE		OS: 12 (thalidomide) *vs* 9 months (placebo) (NS)	No significant improvement in survival	[106]
	III	724	Carboplatin/ etoposide	ES/LS, UT		OS: 10 (thalidomide) *vs* 11 months (placebo) (NS)	No significant improvement in survival	[107]
Cediranib	II	25		Relapsed	PR 1 patient (unconfirmed) SD 8 patients	PFS: 8 weeks	No clinical activity	[108]

RR: response rate; OS: overall survival; PFS: progression-free survival; TK: tyrosine kinase; EP: etoposide and cisplatin; IP: irinotecan and cisplatin; PCDE: cisplatin, cyclophosphamide, 4'-epidoxorubicin and etoposide; Rs: resistant; S: sensitive; c-kit: mast/stem cell growth factor receptor; ES: extensive stage; UT: untreated; PD: progressive disease; LS: limited stage; CR: complete response; PR: partial response; SD: stable disease; OR: overall response; NS: nonsignificant.

TABLE 5 Guidelines from international organisations on the treatment of extensive-stage small cell lung cancer

	ACCP	ESMO	NICE	NCCN
Publication year	2007	2008	2005	2009
First-line treatment	4–6 cycles of platinum-based chemotherapy Platin with etoposide or irinotecan	4–6 cycles of platinum-based chemotherapy Platin with etoposide	4–6 cycles of platinum-based chemotherapy Preferred combination not specified	4–6 cycles of EP, EC, IP, IC or CAV
PCI	Patients with CR	Patients with major response after chemotherapy	To be evaluated in clinical trials	Patients with CR or near-CR Not when multiple comorbid conditions, poor PS or impaired mental function
Thoracic radiotherapy	Patients with CR outside chest and CR or PR in chest	Not discussed	Patients with CR outside chest and CR or PR in chest	Patients with low-bulk metastatic disease and CR or near-CR
Second-line treatment	No drug regimen specified	No drug regimen specified	No drug regimen specified	Preferably in clinical trials Topotecan for relapse at 2–6 months Original regimen for relapse after >6 months

ACCP: American College of Chest Physicians; ESMO: European Society for Medical Oncology; NICE: UK National Institute for Clinical Excellence; NCCN: National Comprehensive Cancer Network; PCI: prophylactic cranial irradiation; EP: etoposide and cisplatin; EC: etoposide and carboplatin; IP: irinotecan and cisplatin; IC: irinotecan and carboplatin; CAV: cyclophosphamide, doxorubicin and vincristine; CR: complete response; PS: performance status; PR: partial response.

phase II trials failed to show any benefit from adding imatinib to chemotherapy [96–100].

Matrix metalloproteinases (MMPs) are proteolytic enzymes that are released by stromal and tumoural cells. MMPs are able to degrade the extracellular matrix, and thus permit the migration of tumoural cells through the extracellular matrix, leading to their dissemination and the development of metastatic disease. Increased expression of metalloproteinases is associated with poor prognosis in SCLC [117]. However, clinical trials with two different MMP inhibitors (marimastat and BAY 12-9566) demonstrated no improved survival, and even a detrimental effect on quality of life [118, 119].

SCLC cells express several antigens belonging to the ganglioside family (polysialic acid, fucosyl GM1, GM2, GD2 and GD3). These antigens are not expressed on normal tissue and are thus interesting targets for vaccine therapy. Once again, however, phase III trials in SCLC with vaccine therapy targeted against these gangliosides have failed to show any benefit from this approach [120].

Another kind of targeted therapy is the use of antisense oligonucleotides, which target specific RNA sequences of genes involved in tumoural cell growth. Oblimersen is an antisense oligonucleotide that targets Bcl-2, an inhibitor of apoptotic cell death that is highly expressed in SCLC. *In vitro* studies suggest that antisense oligonucleotides directed against Bcl-2 induce apoptosis and enhance the cytotoxicity of chemotherapeutic agents in SCLC cell lines [121, 122]. A multicentric randomised phase II trial found no evidence of improvement in response rate or overall survival when oblimersen was combined with carboplatin plus etoposide compared to chemotherapy alone [123]. Indeed, the proportion of patients alive at 1 yr was 24% with oblimersen and 47% without oblimersen, suggesting a worse outcome for patients receiving this drug.

GUIDELINES FROM INTERNATIONAL ORGANISATIONS

Several international cancer organisations have issued guidelines and recommendations for the treatment of ES-SCLC. The American College of Chest Physicians [124], European Society for Medical Oncology [125], UK National Institute for Clinical Excellence [126] and National Comprehensive Cancer Network [127], an alliance of 21 leading cancer centres in the USA, have all published new guidelines on the treatment of ES-SCLC. These guidelines are updated on a regular basis and are summarised in table 5.

HOPE FOR THE FUTURE?

Despite all of the efforts illustrated above, little advance has been made in the treatment of ES-SCLC (fig. 2). The standard treatment with platin/etoposide has been unbeaten for >20 yrs. Increasing dose intensity, adding a third or even a fourth drug, alternating drug regimens and maintenance chemotherapy fail to improve overall survival. For the moment, targeted therapies have not (yet) been as successful for SCLC as for NSCLC. Unexpectedly, the most important progress in the treatment of ES-SCLC results from the introduction of PCI, resulting in a 14% survival gain at 1 yr.

There is no room for despair, however. Decreased incidence of smoking will decrease the incidence of SCLC in Western countries. Moreover, numerous phase I/II evaluations of drugs with potential activity in SCLC are underway. These include inhibitors of proteins highly expressed in SCLC, such as the receptor tyrosine kinases hepatocyte growth factor receptor, c-src and insulin-like growth factor-I receptor. Picornavirus Seneca Valley Virus-001, an oncolytic virus with selective tropism for neuroendocrine cells, is currently undergoing phase I evaluation. Embryonic signalling pathways, such as the hedgehog pathway, are implicated in normal and tumour stem cell maintenance. Inhibitors of this pathway are currently in phase I trials. Epigenetic modulation through DNA

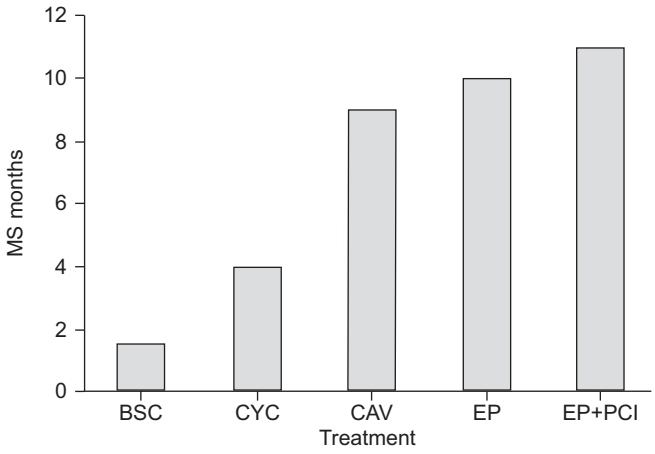

FIGURE 2. Median survival (MS) in extensive-stage small cell lung cancer with various treatments developed since the 1960s. BSC: best supportive care; CYC: cyclophosphamide; CAV: cyclophosphamide, doxorubicin and vincristine; EP: etoposide and platin; PCI: prophylactic cranial irradiation.

methylation and histone deacetylation may play a role in the progression of the disease. This observation has led investigators to initiate phase I/II trials with histone deacetylase inhibitors in combination with standard agents [128].

These are only a few examples of the trials currently running in SCLC. Inclusion of patients with SCLC in clinical trials should be encouraged, as this is the only means of improving the current standard of care. The virtual *status quo* since the early 1980s in the treatment of ES-SCLC (with the exception of PCI) must not lead to defeatism, but should rather be seen as a challenge for researchers and clinicians to join forces in developing new and better treatments for patients with SCLC. We owe it to our patients to continuously expand the borders of our knowledge.

STATEMENT OF INTEREST

None declared.

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