

Treatment for small cell lung cancer, where are we now?—a review

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Abstract: Small cell lung cancer (SCLC) represents between 13% and 15% of all diagnosed lung cancers worldwide. It is an aggressive neoplasia, with a 5-year mortality of 90% or more. It has historically been classified as limited disease (LD) and extensive disease (ED) in most study protocols. The cornerstone of treatment for any stage of SCLC is etoposide-platinum based chemotherapy; in limited stage (LS), concomitant radiotherapy to thorax and mediastinum. Prophylactic radiotherapy to the central nervous system (CNS) [prophylactic cerebral irradiation (PCI)] has diminished the incidence of brain metastasis as the site for relapse in LD and ED patients, therefore it should be offered to patients with complete response to induction first-line treatment. Regarding second-line treatment, results are more modest and topotecan is accepted as treatment for this scenario offering a modest benefit.

Keywords: Small cell lung cancer (SCLC); treatment; limited disease (LD); extended disease; chemotherapy; radiation therapy

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Introduction

Lung cancer is the main cause of cancer-related death worldwide, and the second in incidence in both genders; nevertheless, the small cell lung cancer (SCLC) subtype covers only 13% to 15% of total lung cancer diagnoses. A decrease in its incidence has been seen in the last 20 years, probably related to the decrease in tobacco use in occidental countries (1), as well as to the recognition of other subtype: large cell neuroendocrine carcinoma, which before 1990 was considered to be SCLC. The worldwide estimate of SCLC for 2015 is 260,000 new cases, with over 11,000 in Europe (2). The 5-year mortality is expected to be about 90%.

SCLC is a highly aggressive, undifferentiated neoplasia that originates from the precursors of neuroendocrine cells. It is characterized by a high proliferation rate and early

metastasis. Although it is very sensitive to cytotoxic therapy and ionizing radiation, it has been observed to develop early resistance to conventional treatments, therefore showing early progression and lack of sensitivity to further pharmacological treatment.

The main cause of SCLC is tobacco use [at least 95% of patients have positive smoking history (3)]. Quitting smoking has been related not only to a reduction in the incidence of the disease, but also to a significant reduction in the risk of mortality—about 50% in early stages (4). Other environmental and occupational carcinogens have been related to SCLC, but the strongest evidence of the increase of SCLC is exposure to chloromethyl ether (used in the chemical manufacturer industry) and high radon levels, to which uranium miners are exposed (5).

The Veterans' Affairs Administration Lung Cancer

Study Group (VALG) proposed in 1957 a classification system based on extension of the disease rather than on the traditional TNM system used for most malignant diseases. This classification recognizes only two stages, limited disease (LD)—defined as tumor confined to one hemithorax with or without loco-regional adenopathies that could be included in a single radiation field—and extensive disease (ED), described as having escaped from the previous stage parameters, including the presence of hematogenous metastasis and malignant pleural effusion (6).

A retrospective survival analysis of 8,088 SCLC patients by the International Association for the Study of Lung Cancer (IASLC) demonstrated that patients classified as ED due to the presence of malignant pleural effusion had an intermediate prognosis between LD and ED. Therefore, it was concluded that this classification was not adequate for all patients. Nowadays it is considered that the TNM classification proposed by AJCC's 7th edition for non-small cell lung cancer (NSCLC) (7) should be used for SCLC, since it is more descriptive and precise. Another point that stands out of this analysis is the need to prove the malignant nature of pleural effusions by cytology (8). The former term LD now corresponds to tumors T1–3N0–3M0, while ED refers to patients with metastatic disease. It is also accepted that there is a group with better prognosis compared to LD, known as “very limited stage (LS)” that includes T1–2N0–1M0 tumors. At initial diagnosis, only 30% of SCLC patients present with LD, and the rest with metastatic disease.

Median and overall survival (OS) at 2 years in patients with localized disease varies from 15 to 20 months and 20% to 40% respectively (9). Patients with advanced disease have on average disease free survival (DFS) of 5.5 months and median survival of less than 10 months, although ranges of response to different treatments approach 70% (10).

Treatment overview

The treatment of patients with SCLC is complicated, since they usually present with multiple important comorbidities secondary to tobacco use such as chronic obstructive pulmonary disease, ischemic cardiopathy and hypertension, thus deteriorating their functional status. In addition, SCLC is highly aggressive and is accompanied in general by significant weight loss, fatigue and symptoms related to bulky intrathoracic disease and/or metastasis that contribute to the patients' frailty and obstruct optimal oncologic treatment.

In general, patients with LD should be offered

concomitant chemo-radiation and those with ED, palliative chemotherapy. Nevertheless, patients with very LS may benefit from surgical treatment sometimes.

Chemotherapy is based on cisplatin, as for NSCLC. Patients receiving platinum-based treatment may be empirically divided into refractory, resistant and sensitive to platinum based on their response to first-line chemotherapy as well as their progression free interval (PFI). Refractory patients are those with progressive disease during first-line treatment. Those showing an initial response but progressing within the first 3 months after treatment completion is defined as resistant. Finally, those patients with a PFI longer than 3 months after the end of the first-line treatment are considered as sensitive. When this last group of patients relapses, it is globally accepted to receive the same chemotherapy as for first-line treatment. For the former two groups, who have worse prognosis, treatment with anthracyclines or topotecan is recommended (11).

Treatment of very LS (stage I disease)

Approximately only 5% of SCLC patients present as T1–2N0–1M0; these have shown to have a more favorable long term prognosis, with a 5-year OS of 50% (12).

LS SCLC is a potentially curable disease when it is aggressively and rapidly treated with concomitant chemo-radiation. Surgery is rarely indicated, since most patients present in advanced stages or with extensive ganglionic involvement. Nevertheless, it has been seen in retrospective studies that in patients with very LS or stage I (T1–2N0M0) that undergo lobectomy, and with confirmed lack of mediastinal and supraclavicular involvement, long-term OS is 40–60% (13,14). NCCN guidelines consider that segmentary or wedge excisions are not adequate and that lobectomy with mediastinal node resection should be performed in order to obtain maximum benefit of the surgical treatment approach. On the other hand, it was demonstrated that patients with node involvement do not benefit from excisional treatment, and therefore this modality should not be offered to patients with N1–3 disease (15).

In cases where pathologic analysis of mediastinal nodes sampling is positive for malignant diseases (N1 or N2) and a complete lymphadenectomy has not been performed, post-operative mediastinal radiotherapy should be considered. It is also mandatory to offer four cycles of adjuvant chemotherapy in patients with successfully treated stage I disease (N0) (16,17).

Treatment of LS (stages I, II and III)

The combination of chemotherapy and thoracic irradiation is preferred to unimodal chemotherapy in the management of limited SCLC (18,19). Two meta-analyses have demonstrated that combining chemotherapy with thoracic irradiation significantly diminishes local relapse and improves OS (20,21). The first meta-analysis published by Pignon *et al.* (20), reviewed data of 2,140 patients from 13 studies and found a better 3-year OS for patients treated with chemo-radiotherapy when compared to chemotherapy only [14.3% *vs.* 8.9%, respectively; HR 0.86, 95% confidence interval (CI): 0.78–0.94, $P=0.001$]. In the second meta-analysis, Warde and Payne (21) combined the data of 11 randomized studies with or without chemo-radiotherapy and found that bimodal treatment offered a better local control at 2 years when compared to chemotherapy alone (34.1% *vs.* 16.5%, respectively). A significant improvement in tumor control in the thorax in patients receiving thoracic radiation therapy (+25.3%, 95% CI: 16.5–34.1%). The OS at 2 years was 5.4% greater in patients treated with chemo-radiation ($P<0.05$). However, the best order and modality to combine these treatments remains to be established.

Multiple studies have demonstrated that concurrent chemo-radiation, as well as early starting of radiotherapy (after the first or second cycles), produce better disease control than the sequential modality. Murray *et al.* (22) studied patients treated with cyclophosphamide, doxorubicin and vincristine, alternating with etoposide and cisplatin. Patients were distributed in two groups, those starting radiotherapy on the third week of treatment and those receiving it on week 15. Patients from the early radiation group had a significant improvement in progression-free survival (PFS) ($P=0.036$) and OS ($P=0.008$). The phase III study of the Japan Clinical Oncology Group (JCOG 9104) (23), compared concurrent chemo-radiotherapy to sequential treatment (chemotherapy followed by radiotherapy) in patients treated with LD SCLC. All patients received cisplatin and etoposide. Those receiving concurrent treatment had better OS at 2, 3 and 5 years *vs.* those in the sequential group (OS at 2 years 54.4% *vs.* 35.1%; at 3 years 29.8% *vs.* 20.2%; at 5 years 23.7% *vs.* 18.3%) but these differences were not statistically significant ($P=0.097$). Another meta-analysis collected data from 1985 to 2002 (24) and demonstrated a slight but significant difference in OS at 2 years with the use of early-start radiotherapy. This improvement was more evident with hyper-fractionation and platinum-based chemotherapy schemes. A meta-analysis (25) evaluated seven randomized

studies where radiotherapy was started early with platinum-based chemotherapy and found a better OS at 2 and 5 years when started within the first 30 days after chemotherapy.

The inferiority of sequential treatment compared to concurrent bimodal treatment proves the development of chemo-resistant clones, which are also radiation-resistant and produce a quick repopulation of the tumor (26). Additionally, another study by the Gyeongsang National University of Korea (27) reported in 2013 that concurrent chemo-radiation was superior to sequential treatment in terms of OS, with an acceptable toxicity profile. Based on the results of all the studies, concurrent treatment is currently the standard modality for LD SCLC (28).

The radiobiology argument in favor of this recommendation is that radiation can effectively remove chemo-resistant cells before they spread outside the chest. The simultaneous start of radiotherapy and chemotherapy has several disadvantages. First, chemosensitivity of the tumor cannot be verified *in vivo*, on the other hand, a higher volume has to be radiated, which can generate increased toxicity and complications, especially in patients with risk of poor pulmonary reserve. Complications include radiation pneumonitis, bone marrow suppression and radioepithelitis. It has also been documented that tolerance to chemotherapy decreases if initiated simultaneously with radiotherapy, so slow administration of cytotoxics reduces the long-term gain in relapse-free survival and distant relapse decrease. Because of these results, in general, early onset of radiation therapy is preferred after cycle 1 or 2 of chemotherapy (22,24). Nevertheless, a phase III trial addressing temporality (early *vs.* late radiation) showed that late radiation-chemotherapy (started at the third cycle) was no inferior to early start (with the first cycle of chemotherapy) in terms of complete response (36% *vs.* 38%). Regarding toxicity, the late radiation group had less grade 3–4 neutropenia (29).

There are still important questions without a definite answer, such as what is the optimal radiation dose, fractionation and the ideal starting time. It is accepted with reasonable evidence that the standard of care involves the concurrent administration of radiotherapy with chemotherapy scheme PE (cisplatin 60 mg/m² IV on day 1 and etoposide 120 mg/m² IV days 1 to 3) in a total of 4–6 cycles (30,31), with a maximum benefit when started early (after the first or second cycle of chemotherapy) and a manageable toxicity in the concurrent scheme. Some studies suggest that the best form of radiotherapy is hyperfractionation, such as the study from the Intergroup, which directly compared a group with a single fraction of

radiation a day versus. Two fractions (hyperfractionation), i.e., 45 Gy/25 fractions/5 weeks *vs.* 45 Gy/30 fractions/3 weeks with concurrent administration of cisplatin and etoposide. Initial analysis showed excellent results with median survival of 20 months and 40% 2-year OS, with a short follow, 5 years. A significant gain in survival for the hyperfractionation mode compared with the group who received conventional fractionation group once a day (26% *vs.* 16%) was achieved. The main difference appears to be in temporary acute toxicity, with an increase in grade 3 esophagitis in the group treated twice daily (27% *vs.* 11%, $P < 0.001$) (32).

The RTOG 0239 study (33) reported in phase I and II the concurrent chemo-radiotherapy with a “boost” approach. This scheme initially consisted of larger radiation field covering the primary tumor in daily fractions of 1.8 Gy, with a total of 61.2 Gy in 5 weeks and a second fraction of 1.8 Gy at a smaller field during the last 9 days of treatment, standard chemotherapy with cisplatin and etoposide. The locoregional tumor control at 2 years was 80%, although survival achieved in the same time range was only 37%, a non-significant gain when compared with other forms of radiation. However, presentation of grade 3 esophagitis was significantly improved and occurred only in 18% of patients *vs.* 27% in Intergroup 0096 study.

A phase III trial (CALGB 30610/RTOG 0538) (34) evaluating three different radiotherapy approaches in patients with LD SCLC is currently ongoing. The patients enrolled in this study received either 70 Gy (2 Gy once daily over 7 weeks) or 61.2 Gy (1.8 Gy once daily for 16 days followed by 1.8 Gy twice daily for 9 days). The aim is to improve median and 2-year OS compared to that from patients receiving 45 Gy (1.5 Gy twice daily over 3 weeks). The results are highly awaited.

Prophylactic radiotherapy to the central nervous system (CNS) [prophylactic cerebral irradiation (PCI)]

The CNS is a common site of metastasis in patients with SCLC. About 25% present at initial diagnosis with brain metastases (35). Of the patients who achieve a complete response to initial treatment, approximately 45% will present with CNS metastases as the only site of recurrence at 2 years (36,37). The presence of CNS disease significantly impairs functional status of patients and increases the need for hospitalizations (38). Therefore, prevention of relapse to CNS is an important component of treatment of patients

with SCLC.

After finishing chemo-radiotherapy in patients with adequate systemic control without evidence of metastatic disease to the CNS, PCI should be considered. Multiple studies have been done trying to assess the role of PCI. Unfortunately, most are small, heterogeneous studies with, not surprisingly, wide variability in their findings (39). Despite this, all show a significant decrease in the incidence of brain metastases. Two separate meta-analyses concluded that PCI reduces the incidence of CNS metastases between 52–54% and improves survival from 16% to 18% in those patients who achieved a complete response (40,41). A meta-analysis published in 1999 (41), involving 987 patients in remission reported a 5.4% increase in overall 3-year survival; as well as an increased rate of DFS (95% CI: 0.65–0.86; $P < 0.001$) in patients who received PCI. As expected, a decreased incidence of brain metastasis was observed (relative risk of 0.46; 95% CI: 0.38–0.57; $P < 0.001$).

The optimal dose of each fraction of radiation is still unclear. A randomized trial comparing standard dose of radiotherapy 25 Gy in 10 fractions to the PCI against high dose (36 Gy in 18 fractions once a day or 36 Gy in 24 fractions using 1.5 Gy twice daily) in 720 patients with LD SCLC who had complete response to treatment with chemo-radiotherapy showed no significant reduction in the incidence of brain metastases in the high dose group, but did find a significant increase in mortality (42). Currently the accepted standard is 25 Gy in 10 fractions to the PCI.

One of the biggest issues with PCI is long-term neurotoxicity. The frequency and severity of chronic toxicities associated with PCI are still unclear. Because patients undergoing PCI have an improvement in OS, they are more likely to develop chronic neurotoxicity. In a retrospective study of 98 patients who received PCI a significant improvement in mean quality time without symptoms and toxicity (Q-TWiST) (43) was observed. In a similar analysis, qualitatively life expectancy adjusted quality-adjusted life expectancy (QALE) was evaluated. PCI offers a benefit over no-PCI (QALE =4.31 and 3.7 for mild toxicity, 4.09 and 3.70 respectively for severe toxicity) (44). The results of these analyses suggested benefit of PCI despite chronic toxicity. However, it is necessary to design clinical trials with the specific aim to adequately answer the question of benefit *vs.* neurotoxicity and quality of life in patients receiving PCI.

Nowadays, the recommendation is to offer PCI to all LD-SCLC patients with good PS due to the evidence of the benefit of this therapy.

Table 1 Results of studies performed in first-line using combination treatment *vs.* monotherapy in patients with small cell lung cancer

Author [year]	Number of patients	Scheme	Results					
			ORR (%)	P value	Median OS (weeks)	P value	1-year survival (%)	P value
Lowenbraun <i>et al.</i> (56) [1979]	39	Cyclophosphamide	12.0	0.005	17.8	0.012	NR	–
	249	CAD	57.0		31.2		NR	
Girling <i>et al.</i> (57) [1996]	171	Etoposide (oral)	45.0	NR	18.5	0.03	11.0	0.03
	168	CAV	51.0		26.1		13.0	
Souhami <i>et al.</i> (58) [1997]	75	Etoposide (oral)	32.9	<0.01	19.2	NR	9.8	<0.05
	80	EP/CAV	46.3		23.6		19.3	
Ettinger <i>et al.</i> (59) [2002]	43	Ifosfamide	49.0	–	43	0.76	NR	–
	46	CAV	56.0		42		NR	
	46	Teniposide	43.0		38		NR	

CAD, cyclophosphamide, doxorubicin, dacarbazine; CAV, cyclophosphamide, doxorubicin, vincristine; EP, etoposide, cisplatin; ORR, overall response rate; NR, non-reported; OS, overall survival.

Treatment of ED (stage IV)

Advanced stages constitute an incurable form of disease and platinum-based chemotherapy remains the cornerstone of treatment with the aim of palliation of symptoms and increase survival. In general, treatment has an objective response of 60–75%, achieving up to 10% of radiological complete response. Although chemotherapy meets the objective of prolonging survival, relapse is the rule and only 5% of patients are alive 2 years after diagnosis.

The standard treatment of ED is chemotherapy as the only treatment modality, usually with cisplatin or carboplatin plus etoposide for up to six cycles, followed by active surveillance (45). Even patients with impaired functional status, Eastern Cooperative Oncology Group (ECOG) 3 or 4, should be considered for systemic chemotherapy because of potential responses of up to 75% and clinical improvement of symptoms secondary to the disease within a few days.

OS in patients with SCLC has changed little since the late 70s (46). Between 1973 and 2002, the 2-year survival for patients with LD improved from 15% to 22%, but the improvement in ED in the same period has been marginal, from 3.4% to 5.6% (47).

Historically SCLC patients not receiving therapy had a very poor prognosis with a median survival of seven weeks for those with ED and 14 weeks for patients with LD (48). The initial clinical studies with chemotherapy with one drug showed surprisingly that it was a very chemosensitive tumor, resulting in a long list of active drugs

including platinum compounds (cisplatin and carboplatin), camptothecins (topotecan, irinotecan), podophyllotoxins (etoposide, teniposide), anthracyclines (doxorubicin, epirubicin), alkylating agents (cyclophosphamide, ifosfamide), taxanes (paclitaxel, docetaxel) and vincristine, however responses to monodrug-based therapy were short-lived with low complete response rates, so the next step was to test effective combinations against SCLC.

Interestingly, intrathoracic control remains as one of the main sites of progression [about 90% of the patients at one year of diagnosis (49)] and some studies suggesting it may be beneficial for the patients in terms of local control and OS (50–52). The findings of a recent phase III trial by Slotman showed that patients with ED-SCLC have and improved OS at 2 years (13% *vs.* 3%, $P=0.04$) added to the PFS benefit at 6 months (24% *vs.* 7%, $P=0.001$) with an acceptable toxicity profile (53).

Schemes with alkylating agents

Studies performed in the 70s found that combined chemotherapy based on cyclophosphamide, doxorubicin/epirubicin and vincristine [CA(E)V] was effective in SCLC (54,55). This multidrug therapy based on alkylating agents significantly improved OS when compared with single drug-based treatments. In the patients with response ranges between 60% to 80% complete response rate of 15–25% and median survival time of 7–10 months were obtained. Unfortunately all ED patients eventually relapse with refractory disease (Table 1).

Etoposide and cisplatin (EP) regimen

In the 80s, combinations of regimens containing EP without alkylating agents were evaluated in patients with SCLC. The combination of EP obtained similar to that of the old schemes with alkylating results, but with a more favorable toxicity profile (45). More recently, a phase III study compared CEV EP (cyclophosphamide, epirubicin, and vincristine) and reported a significant improvement in OS in patients receiving EP (10.2 *vs.* 7.8 months, $P=0.0004$), which was most evident in the LS group of patients with SCLC (30). As a result of this study the EP scheme became the standard treatment for patients with SCLC. These results for EP have been confirmed in two meta-analyses, which show a modest but significant improvement in OS and a better toxicity profile, especially in patients receiving concurrent radiotherapy (31,60). The meta-analysis published by Pujol *et al.* (31) analyzed 19 randomized studies with a total of 4,054 patients, demonstrating a reduction in risk of death at 6 months and 1 year of 13% and 20%, respectively (OR 0.87, 95% CI: 0.75–0.98, $P=0.03$, and 0.80, 95% CI: 0.69–0.93, $P=0.002$) in patients who received a treatment regimen based on platinum. The second meta-analysis by Mascaux *et al.* (60), divided its analysis into four groups: group I, studies that included cisplatin-based regimens without etoposide; group II, 17 studies that included schemes without cisplatin etoposide; group III, 9 studies comparing a regimen including the combination of EP against other drug regimens; and group IV which compared 9 studies with monodrug EP against etoposide. Ninety five percent HRs were: 0.70 (0.41–1.21) for group I, 0.72 (0.67–0.78) in group II, 0.57 (0.51–0.64) group III, and finally 0.74 (0.66–0.83) for group IV. The benefit was seen in the groups that included the main agent cisplatin (HR =0.61; 95% CI: 0.57–0.66), as well as those involving etoposide (HR =0.65; 95% CI: 0.61–0.69).

Carboplatin

Carboplatin has been tried as a substitute for cisplatin in combination with etoposide and generally no difference was found in the ranges of response, though carboplatin is associated with less toxicity (61). Nevertheless, the COCIS meta-analysis showing no differences between cisplatin and carboplatin in terms of efficacy; the toxicity profile was quite different. Myelosuppression had a higher incidence in the Carboplatin group (mainly neutropenia, anemia and thrombocytopenia); whilst patients treated with cisplatin had significantly more non-hematologic toxicity (i.e.,

nausea, neurotoxicity and renal toxicity) (62). A second study evaluated long-term survival with carboplatin and concurrent radiotherapy in LD: patients had a median survival of 17.4 months and OS at 5 years of 20%, comparable to those of cisplatin (63).

Irinotecan

In Japan, in 2002 a phase III study, 9511 JCOG (64), comparing EP against irinotecan/cisplatin (irinotecan at a dose of 60 mg/m² on days 1, 8 and 15 cycles every 3 weeks) was conducted. This study was closed early because of the significant improvement in OS for patients receiving irinotecan for 12.8 months compared with the group of patients who received etoposide for 9.4 months, with a significant increase in response of 84% *vs.* 68%. Although this scheme was adopted as a standard treatment in Japan, these results have not been corroborated in Western populations. There have been three phase III studies using irinotecan and cisplatin, with small modifications. In the first, the irinotecan dose was 65 mg/m² on days 1 and 8 every 3 weeks. The 331 patients were randomized 1:2 to etoposide: irinotecan, resulting in a median survival of 10.2 months and 9.3 months etoposide to irinotecan (65). Another phase III study conducted with the same scheme as the Japanese study (66) with 651 patients showed no difference in survival (9.9 months for irinotecan and 9.1 months for etoposide $P=0.71$), with higher gastrointestinal toxicity with irinotecan (diarrhea) and hematologic toxicity for the etoposide arm. A third study compared carboplatin (AUC 5) combined with irinotecan at 50 mg/m² on days 1, 8 and 15 with carboplatin/etoposide. Two hundred and sixteen patients were evaluated, with survival of 10 months in the irinotecan group and 9 months for those who received etoposide (67).

A reasonable alternative is the combination of platinum plus irinotecan in first-line ED SCLC instead of the EP regime, according to the profile of individual patient toxicity. However, evidence from three Western studies did not corroborate the impressive survival average over 12 months in the Japanese study. These conflicting results may be due to pharmacogenomic differences between Japanese and Western populations in the metabolism of irinotecan, so EP remains the standard first-line treatment for extensive stage (ES) SCLC.

Treatment duration

Two randomized studies sought to evaluate the addition

of 2 more cycles of chemotherapy followed by 4 cycles of standard EP in patients with ED SCLC (46,68). Both showed that extending therapy can improve PFS but not OS. A meta-analysis evaluated 14 studies and 2,550 patients, suggesting that maintenance chemotherapy/consolidation is associated with increased survival at 1 and 2 years of 33% (69). However, only one study used what is now considered to be modern regime of chemotherapy, both induction and consolidation phase. Today maintenance cannot be recommended outside of clinical protocols.

Prophylactic cerebral irradiation (PCI)

In 2007, the pivotal study published by EORTC clearly demonstrated the utility of PCI in ED SCLC (49). This group showed that PCI reduced risk of CNS metastases at 1 year by 25% (40% of brain metastases in the control group *vs.* 15% in the PCI group) in patients who responded to chemotherapy. Besides the 1-year survival in the PCI group was 27% *vs.* only 13% in the control group. In other words, the experimental group showed a gain of 14% in 1-year survival. Recently, in another publication by Slotman (70) the average in global health (overall health status score) was 8 points higher in patients in the PCI group, on a scale from 0 to 100, at 6 weeks of treatment ($P=0.018$) and 3 months ($P=0.055$). The expected side effects of major PCI were fatigue and alopecia. Other quality of life aspects, such as emotional and cognitive function, appear to have a limited impact. From this information it is now accepted that PCI should be offered to patients with adequate response to chemotherapy in the context of ED.

Treatment of progressive disease, second-line

Although SCLC remarkably responds to initial treatment, most patients will relapse with relatively resistant disease. These patients have a median survival of only 4 or 5 months if treated with a second- or third-line chemotherapy (71,72). Patients with progressive disease are classified based on the response they had with the primary induction therapy and its duration. Subsequent chemotherapy provides significant palliation of symptoms in many patients, but success at this point depends on the time of relapse or progression. If the interval is less than 3 months (resistant or refractory disease), most agents or regimens yield very poor response (<10%). If the time to relapse is greater than 3 months (sensitive disease) the expected response will be around

25% (15).

In particular cases which had an excellent response to first-line platinum-based and relapse that occurs after 2 months of completed induction therapy, it is recommended to retry patients with the original chemotherapy regimen (73). A meta-analysis by Owonikoko showed that patients with sensitive disease have a higher RR when compared to refractory patients (27.7% *vs.* 14.8%, 95% CI: 1.51–3.29; $P=0.001$), as well as longer OS (74).

With regard to strategies using cytotoxic second-line therapy, there is no established consensus about the best and most effective regimen but there is a tendency to use single drug agents rather than the combinations. However, there is one agent approved by the FDA specifically for this group of patients, topotecan, camptothecin. However, there are multiple phase II studies with other drugs including paclitaxel, docetaxel, irinotecan, vinorelbine, gemcitabine, ifosfamide, temozolomide and oral etoposide.

Topotecan

In a phase III study comparing intravenous topotecan with CAV regimen, both arms had similar response and survival but, as expected, the arm with the single drug was less toxic than the combination (75). In another phase III study, oral topotecan obtained better survival when compared with BSC, 26 *vs.* 14 weeks ($P=0.014$) and survival at 6 months 49% *vs.* 26% and the benefit was observed in all subgroups analyzed, including the refractory and platinum group with ECOG 2 (76). Topotecan has been approved by the FDA since 2007 for recurrent, resistant and sensitive platinum disease, either oral or intravenous administration because efficacy and toxicity are similar regardless of the method of administration employed (77).

There are limited data on similar effectiveness between irinotecan and topotecan but this has never been evaluated in randomized studies in the context of relapse.

Amrubicin

Amrubicin, a synthetic anthracycline, has been evaluated extensively in Japan as an alternative treatment in patients in relapse. Initial studies in North America showed promising responses, especially for platinum and topotecan-refractory patients. The first of these studies to give rise to a possible alternative to topotecan in second-line was by Onoda *et al.* in 2006 (78), a multicenter phase II study, which managed to recruit 60 patients with relapsed

Table 2 Picoplatin: second-line studies in patients with small cell lung cancer

Author [year]	Treatment free interval	Scheme	Number of patients	ORR (%)	TTP or PFS (weeks/months)	Median overall survival (weeks/months)	Survival (%)
Treat <i>et al.</i> (80) [2002]	8 weeks	PIC	37 (13 resistant, 24 sensitive sensibles)	Resistant: 15.4; sensitive: 8.3	NR	Resistant: 27.3 weeks; sensitive: 36.7 weeks	NR
Eckardt <i>et al.</i> (77) [2009]	Included refractory, resistant and sensitive patients	PIC	77 (44 refractory, 27 resistant, 6 sensitive)	4	PFS: 9.1 weeks	26.9 weeks	6-month survival: 50.6; 1-year survival: 16.9
Ciuleanu <i>et al.</i> (81) [2010]	<6 months	PIC + BSC vs. BSC	401 (268 PIC + BSC vs. 133 BSC)	NR	PFS of refractory patients without treatment after study: PIC + BSC: 9 weeks; BSC: 7 weeks; P=0.003	PIC + BSC: 21 weeks; BSC: 20 weeks; NS	NR

PIC, picoplatin; BSC, best supportive care; ORR, overall response rate; NR, non-reported; TTP, time to progression; PFS, progression-free survival; NS, non-significant.

SCLC; 16 and 44 refractory patients sensitive to platinum. Amrubicin was administered on days 1–3 every 21 days and 40 mg/m². The most surprising information with this treatment regimen was the equivalent response in both groups of patients, sensitive and refractory, 50% and 52% respectively. However, they had a higher PFS (2.6 *vs.* 4.2 months), OS (10.3 *vs.* 11.6 months) and 1-year survival (40% *vs.* 46%), favoring all results in the platinum-sensitive group. Hematologic toxicity with amrubicin is considerable, with grade 3 or 4 neutropenia. However, the information from several small phase II study was not conclusive of the utility of amrubicin in second-line, with a tendency to have better results than topotecan in the group of patients refractory to platinum. A phase III study recently published explored this point (79), recruiting 637 patients and reporting that amrubicin did not improve OS as second-line therapy in SCLC when compared with topotecan, with median survival of 7.5 months for the amrubicin group and 7.8 months for those receiving topotecan. The behavior of patients with refractory disease was different: amrubicin had an average survival of 6.2 months and 5.7 months for topotecan (HR =0.77, P=0.047). Amrubicin had significant results regarding the progression-free period, 4.1 *vs.* 3.5 months (HR, 0.802; P=0.018) and ORR 31.1% *vs.* 16.9% (P<0.001). The conclusion of this study is that amrubicin did not significantly improve survival of patients treated in second-line since, despite good results in the refractory population, these are not clinically significant.

Other drugs

There are several small randomized trials with drugs that have been tested in second-line, however, further evidence is only available for two of them in this context: firstly picoplatin, an organic platinum analogue specially designed for the group of patients resistant to this treatment (Table 2). The second is belotecan, a new topoisomerase I inhibitor (Table 3). Both have a very modest improvement in overall response and progression-free periods which is not been reflected in OS. Therefore, additional studies to prove or disprove its usefulness are required (11,85).

Treatment duration

Unlike first-line treatment, the optimal duration of second-line treatment has not been clearly determined but an important point to consider is the cumulative toxicity of treatment, as well as the clinical benefit and quality of life. It is globally accepted to continue treatment for two more cycles after obtaining the maximum response or until disease progression or unacceptable toxicity. Additional chemotherapy after second-line progression should only be proposed in patients who continue to have adequate performance status (15).

Conclusions

Progress in the management of patients with SCLC has

Table 3 Belotecan: second-line studies in patients with small cell lung cancer

Author [year]	Treatment-free interval	Scheme	Number of patients	ORR (%)	PFS (months)	Median survival (months)	Survival (%)
Rhee <i>et al.</i> (82) [2011]	All patients on relapse (platinum sensitivity was not defined)	B	25	24	PFS: 2.2	9.9	1 year: 38.3
Jeong <i>et al.</i> (83) [2010]	≥3 months	B	27	22	PFS: 4.7	13.1	NR
Kim <i>et al.</i> (84) [2012]	All patients on relapse (platinum sensitivity was not defined)	B	50 (30 refractory, 20 sensitive)	14 (10 refractory, 20 sensitive)	PFS: 1.6; refractory: 1.5; sensitive: 2.8	4.5; refractory: 4.0; sensitive: 6.5	NR

B, belotecan; ORR, overall response rate; PFS, progression-free survival; NR, non-reported.

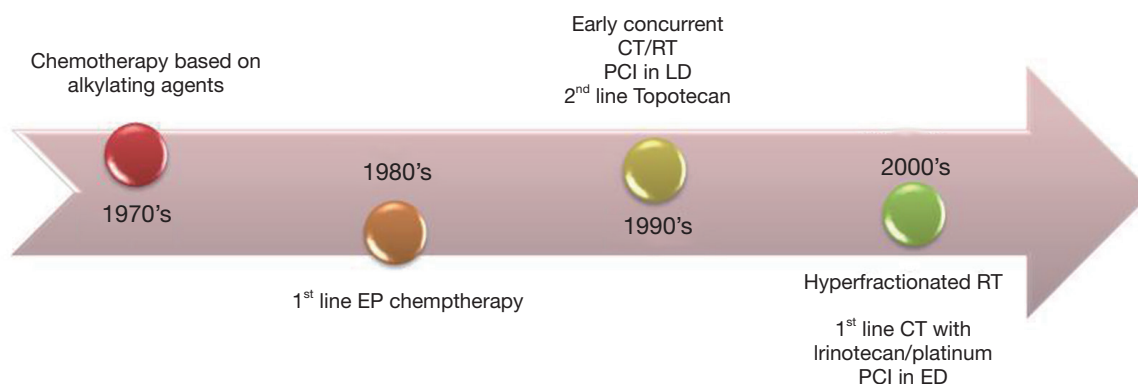


Figure 1 Timeline of the advances in the management of patients with SCLC. EP, etoposide + cisplatin; CT/RT, chemo-radiotherapy; PCI, prophylactic cerebral irradiation; LD, limited disease; ED, extended disease.

been modest in the past 20 years, the main contribution to improving patient survival has been provided by concurrent radiotherapy to the chest and management PCI (*Figure 1*) (86). Chemotherapy with etoposide and platinum remains the standard treatment for patients in Western countries, however, it is well accepted that the Eastern countries use the couplet of irinotecan and cisplatin which has been demonstrated to be superior in the Japanese population. Although patients usually have an excellent response to chemotherapy with or without initial radiotherapy, nearly all will relapse with local or distant disease and eventually die. Tumor cells at progression are less sensitive to treatment with cytotoxics, therefore treatment selection will depend on the time of relapse or progression. Clinical and basic research should continue to identify better treatment strategies that help increase the duration and effectiveness of treatment of patients with SCLC.

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Footnote

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