Chemotherapy for small cell lung cancer: a comprehensive review

Syed Mustafa Karim, Jamal Zekri

King Faisal Specialist Hospital and Research Center, Saudi Arabia

Abstract

Combination chemotherapy is the current strategy of choice for treatment of small cell lung cancer (SCLC). Platinum containing combination regimens are superior to non-platinum regimens in limited stage-SCLC and possibly also in extensive stage-SCLC as first and second-line treatments. The addition of ifosfamide to platinum containing regimens may improve the outcome but at the price of increased toxicity. Suboptimal doses of chemotherapy result in inferior survival. Early intensified, accelerated and high-dose chemotherapy gave conflicting results and is not considered a standard option outside of clinical trials. A number of newer agents have provided promising results when used in combination regimens, for example, gemcitabine, irinotecan and topotecan. However, more studies are required to appropriately evaluate them. There is a definitive role for radiotherapy in LD-SCLC. However, timing and schedule are subject to further research. Novel approaches are currently being investigated in the hope of improving outcome.

Introduction

Lung cancer is the leading cause of cancer death in the developed world. In the UK and many European countries small cell lung cancer (SCLC) accounts for approximately 10-20% of histological types.[1,2]

Until the 1970s, radiotherapy was the standard treatment for SCLC, but this had little effect on survival. The awareness that most patients present with advanced stage disease[3] has led to the use of chemotherapy as the main treatment. In the early 1970s, systemic treatment consisted initially of single agent therapy but in the mid-1970s, a number of studies investigated the efficacy of combination regimens. In the late 1970s, cisplatin emerged as an active agent in SCLC alone and in combination with other chemotherapeutic agents.[4] In the 1980s, attention moved to the use of alternating non-cross resistant regimens and studies testing the role of maintenance chemotherapy.[5] The next decade saw much research into the role of dose intensification for SCLC[6-9] (Table 1). Together with chemotherapy, radiotherapy plays an important role in the radical management of SCLC. The results available so far have not yet answered the questions concerning optimum timing, schedule and dose of radiotherapy. Despite the known chemosensitivity of SCLC (response rates of 70-80% with up to 50% complete responses with combination chemotherapy in patients with limited disease),[10] the majority of patients die from recurrent cancer.

The fact that SCLC demonstrates an exquisite sensitivity to chemotherapy and radiotherapy means that studies should be carried out into how best to deliver these types of therapy in order to improve the outcome of patients with this disease. This report presents a review on the use of chemotherapy in the management of SCLC.

Correspondence: Syed Mustafa Karim, Consultant, Medical Oncology, MBC-J64, PO Box 40047, King Faisal Specialist Hospital and Research Center, Jeddah 21499, Saudi Arabia.
Tel. +966.2.667.7777, Ext 61360 - Fax: +966.2.667.7777, Ext 66030.
E-mail: skarim@kfshrc.edu.sa

Key words: small cell lung cancer, SCLC, chemotherapy, cisplatin, carboplatin, etoposide, taxanes, ifosfamide, high-dose chemotherapy, amrubicin, picoplatin, novel agents.

Conflict of interests: the authors declare no potential conflict of interests.

Received for publication: 17 December 2011.
Revision received: 18 March 2012.
Accepted for publication: 27 March 2012.

Oncology Reviews 2012; 6:e4
doi:10.4081/oncol.2012.e4

Prognostic factors

After a diagnosis of SCLC has been established, careful staging and identification of prognostic factors are necessary to plan treatment. With the therapeutic options currently available, it is important to define the objective of treatment. In frail patients and in those with an adverse prognosis, palliation may be the most realistic option whereas in other patients, aggressive chemotherapy regimens with radiotherapy are justified to aim for long-term survival. A number of multivariate analyses of adverse prognostic factors have been performed in SCLC. In several studies, the parameters identified as having independent prognostic significance included poor performance status, extensive disease, elevated lactate dehydrogenase, high alkaline phophatase, low sodium, low serum albumin, high aspartate aminotransferase and low bicarbonate.[11,12] The widely used Manchester prognostic score is shown in Table 2.

The role of combination chemotherapy

Theoretically, combination chemotherapy provides maximum cell kill and provides a broader range of coverage to resistant cell lines in a heterogeneous tumor population preventing or slowing the development of resistant clones.[13]

Results of studies comparing single and combination chemotherapy are shown in Table 3. These confirm superior outcome with a combination chemotherapy approach.

Lowenbraun *et al.*[14] compared cyclophosphamide with the combina-

tion of cyclophosphamide, doxorubicin and dacarbazine (DTIC). Responding patients and those who did not progress were then randomized to receive their initial regimen alone or their initial regimen with added cycle-active therapy (vincristine, hydroxyurea and methotrexate). Response rates were 12% and 57%, respectively, (P=0.005). Survival for combination-treated patients was significantly better than for those treated with cyclophosphamide alone (P=0.012). Combination treated patients had more treatment related leukopoenia and gastrointestinal toxicity. No quality of life data were available. Two important studies compared single agent with combination chemotherapy in patients with poor prognosis SCLC.[15,16] Both compared oral etoposide to intravenous combination chemotherapy. In the first study, the Medical Research Council randomized 339 patients to four cycles of 50 mg oral etoposide twice daily for ten days or a standard intravenous regimen of etoposide

Table 1. Studies of high-dose chemotherapy and stem cell support.

Reference	Number	Regimen (dose mg/m^2)	RR	Median survival	Survival (at year)
Humblet[6]	22	BCE (60, 750, 600)		55 w	NR
	23	BCE (300, 6000, 500)	CR 39% and 79% (< and > HDC)	68 w	NR (curve only)
	P value			0.13	0.001
Elias[7]	36	BCP (480, 5625, 165)	PR to CR conversion 69%	30 m	53% (2y) 41% (5y)
Rizzo[8]	103	BCP and ICE	79% ORR	23.5 m (LD) ED NR	(3y) LD 43% ED 10%
Bessho[9]	8	ICE (1500, 1200, 1500)	CR 6/8 (75%)		

BCE, carmustine, cyclophosphamide, etoposide; BCP, carmustine, cyclophosphamide, cisplatin.

Table 2. Manchester prognostic score for small cell lung cancer.

	Definition (each positive factor scores 1)
Factor	
Serum sodium	<lower limit of normal range
Performance status	>2 (WHO) or <60 (Karnofsky)
LDH	>upper limit of normal range
Serum alkaline phosphatase	>1.5 × normal
Extensive stage disease	
Serum bicarbonate	<24 mmol/L

Score	Prognostic group	Median survival
0-1	Good	11.5 months
2-3	Intermediate	8 months
4-5	Poor	5 months

WHO, world health organization; LDH, lactate dehydrogenase.

Table 3. Results of studies comparing single and combination chemotherapy.

Reference	Number	Regimen	Response rate	Median survival	Survival (at year)
Lowenbraun *et al.*[14]	39	Cyclophosphamide	12%	17.8 weeks	NR
	249	Cyclophosphamide Doxorubicin Dacarbazine	57%	31.2 weeks	NR
	P value		0.005	0.012	
Girling[15]	171	Etoposide (oral)	45%	130 days	11% (1y)
	168	Etoposide Vincristine or CAV	51%	183 days	13% (1y)
	P value		NR	0.03	0.03
Souhami[16]	75	Etoposide (oral)	32.9%	4.8 months	9.8% (1y)
	80	PE/CAV	46.3%	5.9 months	19.3 (1y)
	P value		<0.01	NR	<0.05
Ettinger[17]	43	Ifosfamide	49%	43 weeks	NR
	46	CAV	56%	42 weeks	NR
	46	Teniposide	43%	38 weeks	NR
	P value			0.76	

CAV, cyclophosphamide, adriamycin, vincristine; PE, cisplatin, etoposide.

and vincristine (EV), or cyclophosphamide, doxorubicin, and vincristine (CAV). Patients on the combination arm had higher overall response rate than etoposide-treated patients (51% *vs* 45%). There was a small disadvantage in survival associated with oral etoposide (hazard ratio 1.35, 95% CI 1.03-1.79, P=0.03). Median survival was longer for the combination arm. The palliative effects of treatment were similar in the etoposide group and control group (41% *vs* 46%). Grade 2 or worse hematologic toxicity occurred in 35 (29%) etoposide-treated patients and 26 (21%) controls. The study was stopped prematurely before the planned 450 patients had been recruited due to the clear superiority of combination chemotherapy.[15] In the second study, 155 patients were randomly assigned to receive oral etoposide (100 mg given twice daily for 5 days) *versus* intravenous chemotherapy consisting of alternating cycles of cisplatin and etoposide (PE) and CAV. Six cycles of chemotherapy were administered every 21 days in both regimens. This confirmed better outcome with combination chemotherapy. With the exception of acute nausea and vomiting associated with intravenous chemotherapy, all aspects of symptom control and quality of life were either the same or worse in the oral etoposide group.[16] Combination chemotherapy is, therefore, accepted as the best first-line approach even in relatively frail patients with multiple adverse features. A large number of combination regimens have been used. A survey was conducted in the UK among 266 clinicians treating SCLC. In all, 34 regimens were reported with 151 different combinations of dose and schedule. In 2311 good prognosis patients, 23 regimens were used, the commonest being ACE (doxorubicin, cyclophosphamide, etoposide), ICbE (ifosfamide, carboplatin, etoposide), CAV (cyclophosphamide, doxorubicin, vincristine), CbE (carboplatin, etoposide), and PE (cisplatin, etoposide). In 1517 poor prognosis patients, 21 regimens were used, the most common being CAV, EV (etoposide, vincristine), CbE, CAV alternating with PE, and oral etoposide. The main reasons affecting choice of regimen were local routine practice, patients' convenience, quality of life considerations, trial results and cost.[18] In the second-line setting, combination chemotherapy was initially found to be more effective than single agent treatment. The response rates obtained by combination of PE or reinduction therapy were 45% and 64%, respectively. With P and E not given in combination, the response rates were less than 20%.[19]

Platinum containing regimens

In the late 1970s, cisplatin emerged as an active agent in SCLC alone and in combination with other chemotherapeutic agents.[20-22] Cisplatin had good antitumor activity and was easy to combine with other agents because of mild myelotoxicity but was unpleasantly emetogenic and required hospitalization for complex pre- and post-treatment hydration to avoid nephrotoxicity. Early studies comparing platinum based and anthracyclin based regimens showed that while overall response rates can be higher in the anthracycline based regimens, there was little effect on survival.[23,24] Subsequent studies consistently showed higher response rates with platinum containing regimens and longer survival as compared to non-platinum containing regimens (Table 4).[4,33] In a review of 21 published phase III trials for patients with extensive-stage (ED) SCLC identified through a search of the National Cancer Institute Cancer Therapy Evaluation Program database from 1972 to 1993, median survival times of patients treated on the control arms of the trials initiated from 1972 to 1981 was seven months and was 8.9 months for patients treated on trials from 1982 to 1990 (P=0.001). There has also been a significant trend toward prolonged survival time in patients treated on the control arms initiated over the entire period of the analysis (1972 to 1993, P=0.0001). The improvement in survival could be partly due to improvement in supportive care. However, the median survival time of patients treated with platinum based regimens (n=14) was 9.5 months compared to 7.1 months for patients treated with non-platinum based regimens (n=40) (P=0.04). Squares regression analysis showed that cisplatin based therapy and the year of study initiation were significantly related to median survival (P=0.04 and P=0.002, respectively).[25] A systemic review of 36 published randomized clinical trials (from 1980 to 1998) was conducted comparing regimens containing cisplatin (CDDP) and/or etoposide (VP-16) with others omitting the same drug(s) given as first-line therapy in SCLC patients. One trial tested a CDDP based regimen (without VP16) against another arm that did not include either CDDP or VP16. Survival hazard ratio with 95% confidence intervals was 0.70 (range 0.41-1.21). Nine of the trials in the review compared a regimen including CDDP and VP16 with a regimen using neither drug. Survival hazard ratio was 0.57 (range 0.51-0.64). Nine other trials included in the analysis compared a regimen based on both drugs with a regimen based on VP16 only. Survival hazard ratio was 0.74 (range 0.66-0.83). Overall survival benefits could also be shown for regimens including CDDP (HR=0.61, confidence interval (CI), 0.57-0.66).[31] A meta-analysis of 19 clinical trials (4,054 patients) randomizing a cisplatin-containing regimen *versus* a regimen without cisplatin was conducted. Patients randomized in a cisplatin-containing regimen had an increase in probability of being responders with an OR of 1.35, 95% confidence interval (CI) of 1.18-1.55, corresponding to an increase of objective (partial plus complete) response rate from 0.62 to 0.69. Patients treated with a cisplatin containing regimen benefited from a significant reduction in risk of death at six months and one year (OR 0.87, 95% CI 0.75-0.98, P=0.03 and OR 0.80, 95% CI 0.69-0.93, P=0.002, respectively). This corresponded to a significant increase in the probability of survival of 2.6% and 4.4% at six months and one year, respectively.[26] Another meta-analysis of 29 clinical trials (5530 patients) comparing results of platinum based chemotherapy *versus* non-platinum based chemotherapy showed no significant difference in overall tumor response or overall survival. However, a significant difference was seen in complete response rate in favor of platinum containing regimens. Results were not stratified according to extent of disease.[34] There is growing evidence showing an advantage for concurrent chemo-radiotherapy over sequential treatment (*see below*). To our knowledge, there have been no studies directly comparing platinum against non-platinum containing regimens in patients treated with concurrent chemo-radiotherapy. However, in a multi-institutional phase III study including 386 patients with LD-SCLC, the South-Eastern Cancer Study Group showed that the concurrent use of radiotherapy and CAV failed to improve the survival of LD-SCLC patients compared with CAV alone. The survival in patients treated with CAV (with or without RT) was improved with two cycles of cisplatin and etoposide consolidation therapy, resulting in superior median (21.1 *vs* 13.2 months, P=0.028) and 2-year survival (44% *vs* 26%, P=0.028) rates).[29] In another study, consolidation CAV after initial PE-based concurrent chemo-radiotherapy was not associated with increased survival but significant toxicity was observed.[30] PE combination therapy is also an effective second-line regimen. In platinum-naive patients the response rate is 40%.[35] The PE combination appears to be of benefit in patients who respond to primary treatment with CAV (RR=23%) whereas second-line therapy with CAV has less benefit after PE (RR=8%).[24] In 29 patients who received CAV after their tumors failed to respond or who relapsed after PE or carboplatin and etoposide, RR was 27.5% and the median survival was 15 weeks.[17] The response rates obtained by combination PE therapy or reinduction therapy were 45% and 64%, respectively. With P and E not given in combination the response rates were less than 20%.[19] Carboplatin, an analog of cisplatin, is a widely used platinum agent with less renal and neurological side effects as compared to cisplatin but more myelosuppression (especially thrombocytopenia). In studies in which patients were previously untreated, the overall response rate to single agent carboplatin was 59% and CR rate was 11%. In previously treated patients, overall response rate was 17% and CR rate was 4%.[36] Single agent carboplatin produces response

rates, relief of tumor related symptoms, and survival similar to that seen in patients who receive CAV chemotherapy. This was shown in a randomized study comparing single agent carboplatin with CAV in patients with poor prognosis, poor performance status SCLC (n=119). Symptom relief occurred in 48% and 41% of patients in the CAV and carboplatin treatment arms, respectively. Dyspnoea was improved in 66% and 41% of patients and cough was improved in 21% and 7% of patients in the CAV and carboplatin treatment arms, respectively. CAV therapy produced a higher response rate than carboplatin (38% *vs* 25%), but this was not statistically significant (P=0.15). The median overall survival for patients in the CAV and carboplatin treatment arms was 17 weeks and 15.9 weeks, respectively. Grade 3-4 neutropenia and intravenous antibiotic use were significantly more common with the CAV regimen (P<0.005). Conversely, Grade 3-4 thrombocytopenia was more common (P<0.0009) and platelet transfusion was more frequent (P<0.05) with carboplatin therapy. Non-hematologic toxicity was similar in both treatment arms, except for alopecia with CAV therapy (P<0.0007).[32] The efficacy and toxicity of PE and carboplatin and etoposide (CaE) combinations along with thoracic irradiation have been prospectively assessed in only one study in 147 patients with SCLC. Both combinations were equally effective. The CR rates were 57% and 58% for PE and CaE, respectively. Median survival for all patients was 12.5 and 11.8 months, respectively. However, the CaE regimen caused significantly less nausea, vomiting, nephrotoxicity, and neurotoxicity, and it was easier to administer. Dose intensity and treatment delays were similar in both groups.[10] In the absence of other comparative data, cisplatin must be regarded as the standard option in limited stage disease, and consideration should be given to carboplatin based regimen in extensive stage disease due to favorable toxicity profile. Picoplatin is a novel platinum agent that showed modest activity in platinum refractory/resistant SCLC with a partial response rate of 4% and stable disease in 43%. Median overall survival was 26.9 weeks and toxicity was mainly hematologic.[37]

Addition of ifosfamide to platinum-containing regimens

Ifosfamide is an alkylating agent closely related structurally to cyclophosphamide by transposition of one of the side chain chloroethyl groups to the ring nitrogen. This minor structural change may account for the different pharmacological behavior of these two compounds as

Table 4. Results of phase III studies comparing platinum and non-platinum containing regimens.

Reference	Number	Regimen	Response rate	Median survival	Survival (at year)
Roth *et al.*[23]	159	PE	61%	8.6 m	NR
	156	CAV	51%	8.3 m	NR
	162	CAV/PE	59%	8.1 m	NR
	P value		0.175	0.425	
Fukuoka[24]	97	PE	78%	9.9 m	11.5 (2y)
	97	CAV	55%	9.9 m	10.4 (2y)*
	94	CAV/PE	76%	11.8 m	21.4 (2y)*
	P value	<0.01		0.027	
Evans[4]		CAV	63%		Longer for CAV/PE
		CAV/PE	80%		
	P value		0.002		0.03
Chut[25]		Platinum regimens	NR	9.5 m	NR
(Meta-analysis of 21 studies)		Non-platinum regimens	NR	7.1 m	
	P value			0.04	
Pujol[26]	1814	Platinum	OR=1.35	NR	0.8 (1y)
(Meta-analysis of 19 studies)	2240	Non-platinum		NR	Death OR
	P value		<0.0001		0.002
Sundstrom *et al.*[27]	218	PE	NR	14.5 m	14% (2y)
	218	CEV	NR	9.7 m	6% (2y)
	P value			(Limited disease) 0.001	0.0004
Thatcher[28]	203	ICE-V	83%	15.6 m	20% (2y)
	199	CDE or PE	80%	11.6 m	11% (2y)
	P value		NR	0.026	NR
Johnson[29]	72	CAV+(PE×2)	NR	21.1 m	44% (2y)
	79	CAV	NR	13.2 m	26% (2y)
	P value			0.028	0.028
Beith[30]	50	PE	76%	52 w	NR
	54	PE+(CAV)	NR	54 w	NR
	P value			0.636	
Mascaux[31]		Platinum			NR
Meta-analysis of 31 studies		Non-platinum		HR=0.61	NR
	P value			95% CI (0.57-0.66)	
White[32]	59	CAV	38%	17 w	12% (1y)
	60	Carboplatin	25%	15.9 w	6% (1y)
	P value		0.15	NS	0.8

ICE-V, ifosfamide, cisplatin, etoposide, vincristine; CDE, cyclophosphamide, doxorubicin, etoposide; CAV, cyclophosphamide, adriamycin, vincristine; PE, cisplatin, etoposide; *P value=0.059.

well as for their different spectrums of clinical activity and toxicity. Ifosfamide has activity in a variety of disseminated refractory solid tumors that do not traditionally respond to conventional alkylating agent therapy, specifically refractory germ cell tumors, soft tissue sarcomas, NSCLC and malignant lymphomas. This has encouraged investigators to test the activity of ifosfamide in SCLC. Available data indicate that single agent ifosfamide can produce 50% objective response rate in SCLC.[38,39] Ifosfamide, platinum (cisplatin or carboplatin) and etoposide (ICE) yielded 71-87% over all response rates and a median survival of 36-42 weeks in patients with ED-SCLC.[40-43]

Ifosfamide has been included in platinum based regimens in phase II studies and has shown activity and lack of crossresistance.[44]

Phase III studies investigating the role of adding ifosfamide to platinum based chemotherapy yielded conflicting results. In 92 SCLC patients randomized to receive PE or ICE (cisplatin) combination chemotherapy, there was no statistical difference in response rates, duration of response, median survival or 2-year survival. Severe leukopenia occurred more often after ICE (73%) than after PE (44%).[45] VIC (vincristine, ifosfamide and carboplatin) alternating with ACE did not improve survival or time to progression when compared to ACE in a phase III EORTC study.[46] On the other hand, the Hoosier Oncology Group randomized 171 patients with ED-SCLC to receive PE or IPE. There was a statistical difference in the median time to progression (P=0.039). The median survival times on PE and IPE were 7.3 months and 9.0 months, respectively (P=0.045) with 2-year survival rates of 5% *versus* 13%, respectively. Hematologic toxicity was more severe in the patients in the IPE arm, but both arms had a 6-7% treatment-related mortality rate.[47] The same group showed that ICE (oral etoposide) is an effective second-line treatment with 55% response rate in 46 patients with recurrent disease of whom 36 of 42 patients had received prior PE.[49]

The MRC LU21 study compared vincristine, ifosfamide, carboplatin and etoposide (VICE) with *standard treatment* (78% ACE, 13% PE) in 402 patients. The median survival was 15.1 months for VICE and 11.6 months for standard treatment (P=0.026) with significantly more patients surviving at 12 and 24 months.[48] Overall, when added to platinum based regimens, ifosfamide may result in a modest improvement in outcome but at the expense of increased side effects, mainly myelotoxicity and nephro-urothelial toxicity (Table 5).

Dose-intense chemotherapy

Theoretically, dose escalation can increase cell kill and overcome drug resistance. A variety of methods have been used to achieve increased cytotoxic dose intensity including the use of increased doses, shorter treatment intervals, hematopoietic growth factor support and hematopoietic progenitor cell support.

Suboptimal chemotherapy doses result in inferior survival, but it is not certain how far survival in SCLC patients can be improved by increasing dose intensity. An early study showed significantly higher response rates, median survival and long-term survival when the cyclophosphamide dose was increased from 0.5 to 1 g/m^2 body-surface area, lomustine from 50 to 100 mg/m^2, and methotrexate increased from 10 to 15 mg/m^2 (Table 6).[50] Many now consider the standard arm of this study to have been under-dosed.

A number of phase II studies investigated the effect of higher chemotherapy doses in the first 1-4 cycles (Table 7), although no survival advantage was seen for this approach. Only one study showed a survival advantage for early dose intensification. In this study, 105 patients with LD-SCLC were randomly assigned to receive higher or lower initial doses of cisplatin (100 or 80 mg/^{2}) and cyclophosphamide (300 or 225 mg/m^2 daily for four days) in the first cycle. All patients received the lower doses from the 2nd through the 6th cycle of chemotherapy. The 2-year survival rate for the 55 patients who received the higher doses of chemotherapy was 43%, as compared with 26% for the 50 patients who received the lower doses (P=0.02). Disease-free survival at two years was 28% in the higher-dose group, as compared with 8% in the lower-dose group (P=0.02). There was no increase in

Table 5. Studies of ifosfamide containing regimens in the first-line setting.

Reference	Number	Regimen	RR	Median survival	Survival (at year)
Lohrer[40]	40	ICE	71%	42 w	NR
Evans[41]	37	ICE	87%	41 w	NR
Ettinger[42]	43	Ifosfamide	49%	43 w	NR
	46	CAV	56%	42 w	NR
	46	Teniposide	43%	38 w	NR
	P value			0.76	
Wolff[43]	35	ICE	83%	8.3 m	37% (1y)
		(Oral VP16)			14% (2y)
Le Chevalier[44]	30	Ifosfamide & Carboplatin	63%	8 m	17% (1y)
Miyamoto[45]	Total 92	PE	78%	55 w	15% (2y)
		ICE	74%	54 w	17% (2y)
	P value		NS	NS	NS
Postmus[46]	73	CDE	68%	7.6 m	NR
	70	CDE/VIMP	70%	8.7 m	NR
	P value		NS	0.243	
Lohrer[47]	Total 171	PE	67%	7.3 m	5% (2y)
		ICE	73%	9 m	13% (2y)
	P value		NS	0.045	
Thatcher[48]	200	ACE or PE	81%	11.6 m	45% (1y)
	202	VICE	83%	15.1 m	54% (1y)
	P value		NS	0.026	0.026

CDE, cyclophosphamide, adriamycin, etoposide; VIMP, vincristine, ifosfamide, mesna, carboplatin; VICE, vincristine, ifosfamide, cisplatin, etoposide.

Table 6. Phase II studies investigating dose intense chemotherapy.

Reference	Number	Regimen (dose mg/m^2)	RR	Median survival	Survival (at year)
Cohen[50]	9	(500, 10, 50) Cyclo,MTX,CCNU	45%	13+months for 7 CR pts	
	23	(1000, 15, 100)			
	P value		96%		
Figueredo[51]	51	(1000, 50, 1) CAV (+/-PE)	61% (66%)	NR	NR
	52	(>=1500, 60, 1)	63% (73%)	NR	NR
	P value		NS		
Johnson[52]	146	(1000, 40, 1) CAV	53%	29.3 w	NR
	124	(1200, 70, 1)	63%	34.7 w	NR
	P value		0.12 (CR 0.045)	NS	NS
Ihde[53]	125	(80 d1, 80 d1-3) PE	22%	11.4 m	
		(27 d1-5, 80 d1-5)	23%	10.7 m	
	P value		0.99	0.68	
Arriagada[54]	50	(40, 225, 75-80) ACE-P	CR=54%	NR	26% (2y)
	55	(40, 300, 75-100) first cycle only	CR=67%	NR	43% (2y)
	P value		0.16	0.02	0.02

MTX, methotrexate; CAV, cisplatin, adriamycin, vincristine; PE, cisplatin, etoposide; ACE-P, adriamycin, cyclophosphamide, etoposide, cisplatin.

Table 7. Phase III studies investigating accelerated chemotherapy.

Reference	Number	Regimen	RR	Median survival	Survival (at year)
Furuse[55]	113	CAV/PE	77%	10.9 m	39% (1y) 8.5% (2y)
	114	CODE	84%	11.6 m	46% (1y) 12% (2y)
	P value		NS	0.1034	
Murray[56]	109	CAV/PE	70%	0.91 y	52% (1y) 15% (2y)
	110	CODE	87%	0.98 y	47% (1y) 15% (2y)
	P value		0.006	NS	NS
Steward[57]	153	VICE (q4w)	77%	351 d	18% (2y)
	147	VICE (q3w)	90%	443 d	33% (2y)
	P value		NS	0.0014	NR
Thatcher[58]	202	ACE (q3w)	79% (CR 28%)	NR	39% (1y) 8% (2y)
	201	ACE (q2w)	78% (CR 40%)	NR	47% (1y) 13% (2y)
	P value		NS (0.02)		NS
Ardizzoni[59]	119	ACE (q3w)	79%	54 w	24.4% (1y) 8.9% (2y)
	125	ACE (q2w)	84%	52 w	21.8% (1y) 11.8% (2y)
	P value		NR	0.885	NS
Sculier[60]	78	EVI (q3w)	59%	286 d	5% (2y)
	78	EVI (q2w) +GMCSF	76%*	264 d	6% (2y)
	77	EVI (q2w) +Antibiotics	70%	264 d	6% (2y)
	P value			NS	NS
Woll[61]	25	ICE (q4w)	76%	355 d	NR
	25	ICE (q2w)	80%	371 d	NR
	P value		NS	0.89	
Lorigan[62]	Total 318	ICE (q4w)	80%	13.8 m	22% (2y)
		ICE (q2w)	88%	14.4 m	19% (2y)
	P value		0.09	0.76	NS

CODE, cisplatin, vincristine, doxorubicin, etoposide; EVI, epirubicin, vindesine, ifosfamide, *P value = 0.04.

side effects from treatment in the higher-dose group.[54] Phase III studies investigating dose intensity are summarized in Table 6.

Another approach to improve the dose intensity of chemotherapy is to reduce the interval between the cycles of chemotherapy with the use of hematopoietic growth factors with or without autologous peripheral blood progenitor cell rescue.

The combination of cisplatin, vincristine, doxorubicin, and etoposide (CODE) was designed to double the dose intensity of these drugs in comparison with a standard regimen (alternating CAV/PE) for ED-SCLC. Dose intensity was increased by more frequent treatment administration rather than by increasing the size of the dose. CODE was investigated in 48 patients with ED-SCLC in a phase II study with encouraging results.[63] Ninety-four percent responded to chemotherapy, with 40% attaining CR. After consolidative thoracic irradiation, the CR rate was 56%. The median time to progression was 43 weeks, and the median survival was 61 weeks. The 2-year survival rate was 30%. Grade IV granulocytopenia occurred in 56% of patients. There were 2 treatment related deaths. However, a phase III study conducted in Japan failed to confirm any advantage with CODE over CAV/PE in patients with ED-SCLC. There was no difference in the incidence of leukopenia between the two arms, but there was a significantly higher incidence of anemia and thrombocytopenia in the CODE arm. Four treatment-related deaths from neutropenic fever occurred in the CODE arm.[55] In addition, a NCIC/SWOG phase III study was discontinued early because of excessive treatment related mortality in the CODE arm as compared to CAV/PE (8.2% *vs* 0.9%) with a non-statistically different median survival (0.98 *vs* 0.91 years).[56]

Steward *et al.* randomized 300 patients with good or intermediate prognosis LD and ED-SCLC to six cycles of chemotherapy with ifosfamide 5 g/m^2, carboplatin 300 mg/m^2, etoposide 120 mg/m^2 intravenously on Days 1 and 2 and 240 mg/m^2 orally on Day 3, and vincristine 0.5 mg/m^2 i.v. on Day 15 (VICE) every three weeks (intensified arm) or every four weeks (standard arm). The planned RDI of the intensified arm was 1.33 and the overall actual delivered DI was 1.26. Survival was significantly increased in the intensified compared with the standard arm (P=0.0014). Myelosuppression was the main toxicity, with no significant difference in the incidence or grade between treatment groups.[57] This survival benefit was confirmed in another study in which 403 patients with LD and ED-SCLC were randomized to receive 6 cycles of ACE either every three weeks or every two weeks with G-CSF support. The received dose intensity was 34% higher in the accelerated arm. CR and survival were statistically better in the accelerated arm. In the accelerated arm, there was less neutropenia but more thrombocytopenia and more frequent blood and platelet transfusions.[58] Other trials failed to show survival benefit from accelerated chemotherapy. In a similarly designed study, 244 previously untreated SCLC patients were randomized to standard ACE (doxorubicin 45 mg/m^2 on Day 1, cyclophosphamide 1000 mg/m^2 and etoposide 100 mg/m^2 on Days 1-3 every three weeks, for 5 cycles) or intensified (higher dose and more frequent) ACE (doxorubicin 55 mg/m^2 on Day 1, cyclophosphamide 1250 mg/m^2 and etoposide 125 mg/m^2 on Days 1-3 with granulocyte colony-stimulating factor (G-CSF) 5 g/kg/d on Days 4 to 13 every two weeks, for 4 cycles). Delivered DI on the intensified arm was 70% higher than on the standard arm. Intensified ACE was associated with more grade 4 leukopenia (79% *vs* 50%), grade 4 thrombocytopenia (44% *vs* 11%), anorexia, nausea, and mucositis. Febrile neutropenia and number of toxic deaths were similar on the two arms. There was no statistical difference in response and survival rates.[59] This study failed to show survival benefit despite delivery of higher DI of 70% over the standard arm as compared to the study by Thatcher *et al.* that delivered 34% higher DI compared to the standard arm.

The European Lung Cancer Working Party (ELCWP) designed a 3-arm phase III randomized trial of 233 patients with ED-SCLC to: arm A, standard chemotherapy with 6 courses of EVI (epirubicin, vindesine, ifosfamide), all drugs given on Day 1 repeated every three weeks; arm B, accelerated chemotherapy with EVI administered every two weeks and GM-CSF support; arm C, accelerated chemotherapy with EVI and oral antibiotics (cotrimoxazole). There was, however, no difference in 2-year survival (5% for arm A, 6% for arm B and 6% for arm C).[60]

Sixty published studies in LD and ED SCLC were retrospectively analyzed for any relationship between intended dose intensity (DI) and response or median survival. For CAV, increasing RDI of the regimen showed no correlation with outcome. For the individual drugs, C RDI correlated positively, while A RDI correlated negatively with achievement of CR in limited disease, but both only after unduly influential observations were eliminated. In extensive-stage disease, A RDI correlated positively with CR and PR but only in randomized trials, and this correlation lost statistical significance after unduly influential observations were eliminated. For CAE and CAVE, the RDI of the regimens correlated positively with median survival in extensive-stage disease as did the C RDI. In limited disease, the C RDI correlated negatively with median survival. For EP, no significant correlations were seen. The authors concluded that DI-outcome correlations are not consistent for these chemotherapy regimens in SCCL.[64]

Hematologic growth factors with the support of autologous peripheral blood progenitor cell rescue may allow further acceleration of chemotherapy delivery. In a feasibility study, Woll *et al.* confirmed this hypothesis when they randomized 50 consecutive SCLC patients with a favorable prognosis to receive 6 cycles of ifosfamide, carboplatin, and etoposide (ICE), at 4-week (standard treatment) or 2-week (intensified treatment) intervals. Intensified treatment was supported by daily subcutaneous filgrastim injections and reinfusion of autologous blood collected immediately before each cycle. Over all 6 cycles, the median received DI was 0.95 for the standard treatment arm and 1.60 for the intensified treatment arm (P<0.001). Febrile neutropenia was more common on the standard treatment arm (84% *vs* 56%) resulting in more days of intravenous antibiotics (median 10 *vs* 3 days, P=0.035). Transfusion requirements were similar in the two groups.[61] This study was extended to a phase III trial using the support of hematologic growth factors and autologous peripheral blood progenitor cells rescue, Lorigan *et al.* confirmed the ability to deliver 1.82 of ICE dose intensity in 2-weekly intervals as compared to 0.99 DI in the standard arm (4-weekly) in 318 patients with adverse prognostic SCLC and PS 1-2. However, median survival was similar in both groups.[62]

To date, there has been only one randomized phase III trial (Table 8) completed in patients with SCLC investigating the role of high-dose chemotherapy and hematologic stem cell transplantation.[6] In this study, 101 patients with LD or ED-SCLC receive induction chemotherapy consisting of methotrexate, vincristine, cyclophosphamide and doxorubicin followed by prophylactic cranial irradiation followed by 2 cycles of cisplatin and etoposide. Forty-five patients, selected for their sensitivity to this induction treatment, were randomized to a last cycle of chemotherapy that combined cyclophosphamide, BCNU, and VP-16-213 either at a conventional dosage of 750 mg/m^2 i.v., 60 mg/m^2 i.v., and 600 mg/m^2 orally or alternatively at a very high dosage of 6 g/m^2 i.v., 300 mg/m^2 i.v., and 500 mg/m^2 i.v., respectively. In the late intensification group, the CR rate increased from 39% before randomization to 79% after high-dose chemotherapy. Median relapse-free survivals after randomization for intensified and control chemotherapy groups were 28 and 10 weeks, respectively (P=0.002). However, median survival after induction therapy was 68 weeks for the intensified group compared with 55 weeks for the conventional therapy group (P=0.13). Four patients died from treatment related complications in the high-dose chemotherapy arm.

Two retrospective reviews are worth mentioning in this context. The first included 36 patients with only LD-SCLC selected on the basis of

their continued response to first-line therapy, their relative lack of significant co-morbidity, and their ability to obtain financial clearance. The 2- and 5-year survival rates after dose intensification were 53% and 41%, respectively. Of 29 patients who were in or near CR before undergoing high-dose therapy, 14 (48%) remain continuously progression free at a median of 61 months (40-139 months) after high-dose therapy. Overall 2- and 5-year PFS rates were 57% and 53%, respectively. The procedure-related mortality was 8%.[7] The second review by Rizzo *et al.* included 103 patients receiving high-dose chemotherapy with autologous hematopoietic stem cell transplantation for LD and ED-SCLC in the years 1989-1997 at 22 centers participating in the Autologous Blood and Marrow Transplant Registry. Most patients underwent transplantation after partial response (66%) or complete response (27%) to combination therapy. The procedure related mortality was 11%. Three-year probabilities of survival and progression free survival were 33% and 26%, respectively, for all patients. Three-year survival and PFS rates were higher in patients with limited *versus* extensive disease, 43% *versus* 10% (P<0.001) and 35% *versus* 4% (P<0.001), respectively.[8] In a feasibility study, 8 of 11 patients (4 LD and 4 ED) with adequate organ function were treated with HD-ICE (15 g/m^2 ifosfamide, 1200 mg/m^2 carboplatin and 1500 mg/m^2 etoposide) followed by ABPCT. Hematologic recovery was rapid and non-hematologic toxicities were acceptable without treatment-related mortality. In ED-SCLC, all of the 4 patients achieved CR or near CR but developed a relapse of the disease. In LD-SCLC, 2 of 4 patients are alive in continuous CR for 18 and 21 months after the beginning of induction therapy.[9]

Overall, there is some evidence for improved survival with dose intensity through treatment acceleration and hematologic growth factor support. However, further dose intensification requiring autologous peripheral blood progenitor cells or stem cell rescue has not yet been proved to improve survival and further randomized studies are required.

Table 8. Phase II and III studies of irinotecan (single agent and combination).

Reference	N	Regimen	ORR	Median survival	Survival (at year)	Disease/line of treatment
Masuda[65]	16	100 mg/w	47%	6 m (187 d)	NR	Relapsed/refractory 2nd
Le Chevalier[66]	32	350 mg/3w	16%	4.1 m (125 d)	NR	Ref/Rel
Ando[67]	25	I 60 mg/m^2/w and P 30 mg/m^2 d1, 8, 15 (all every 4w)	80%	7.9 m	44% (1y) 20% (2y)	Ref/Rel 2nd
Kudoh[68]	75	I 60 mg/w d1, 8, 15 P 60 mg/m^2 d1 (all every 3w)	84%	13.2 m	19.3% (2y)	First
Nakanishiy[69]	21	I 60 mg/m^2 d1, 8, 15 P 30 mg/m^2 d1, 8, 15 (all every 4w)	29%	7.5 m (32w)	43% (1y) 11% (2y)	Ref
Noda[70]	63	I 60 mg/m^2 d1, 8, 15 and P 60 mg/m^2 d1 (all every 4w)	84%	12.8 m	58.4% (1y) 19.5% (2y)	First
		P 80 mg/m^2 d1 and E 100 mg/m^2 d1, 2, 3 (all every 3w)	67.5%	9.4 m	37.7% (1y) 5.2% (2y)	
	P value			0.002	NR	
Hanna[71]	200	I 60 mg/m^2 and P 30 mg/m^2 d1, 8 (all every 3w)	52%	9.3 m	35.4% (1y) 8% (2y)	First D
	100	P 60 mg/m^2 d1 and E 120 mg/m^2 d1-3 (all every 3w)	51%	10.2 m	36.7% (1y) 7.9% (2y)	
	P value		NS	NS	Not Rep	
Kudoh[72]	50	I 60 mg/w d1, 8, 15 E 80 mg/m^2 d2-4	66%	11.5 m	43.2% (1y) 14.4% (2y)	First
Hirose[73]	22	I 50 mg/m^2 d1, 8 and Carbo 5AUC d1 (all every 3w)	68.2% (194d)	6.5 m	NR	Ref Rel
Masuda[74]	25	I 70 mg/m^2 d1, 8, 15 and E 80 mg/m^2 d1, 2, 3 (all every 4w)	71%	9 m (271d)	28% (1y)	Ref Rel
Ichiki[75]	44	I 80 mg/m^2 d1, 8, 15 and ifosfamide 1.5 g/m^2 d1-3 (all every 4w)	29.5%	12.5 m	52.3% (1y) 11.3% (2y)	Second
Agelaki[76]	31	I 300 mg/m^2 d8 and G 1 g/m^2 d1, 8, 15 (all every 4 w)	10%	6 m	17% (1y)	Ref Rel
Goto[77]	40	I 90 mg/m^2 w2, 4, 6, 8 and P 25 mg/m^2/w (for 9 w) and E 60 mg/m^2 d1-3 (w 1, 3, 5, 7, 9)	78%	11.8 m	49% (1y)	Rel
Lara[78]	651	I 60 mg/m^2 d1, 8, 15 and P 60 mg/m^2 d1 (all every 4w)	60%	9.9 mo		First-line
		P 80 mg/m^2 d1 and E 100 mg/m^2 d1, 2, 3 (all every 3w)	57% NS	9.1 mo NS		

I, irinotecan; P, cisplatin; G, gemcitabine; AUC, area under the curve; mg/w, milligrams per week; mg/m^2/w, milligrams per square meter per week; mg/3w, milligrams every 3 weeks; d, day; w, week.

Newer agents

Although improvements have been made in the treatment of SCLC, the overall results remain disappointing with only a small percentage of patients achieving long-term survival. Active newer agents are clearly needed. Several new agents have been studied and have demonstrated significant activity.

Irinotecan (CPT-11)

Irinotecan (CPT-11) is a topoisomerase I inhibitor (Table 8). Single agent irinotecan in 2 phase II studies shows overall response rates of approximately 16% and 47% in previously treated patients.[65,66] Adding cisplatin to irinotecan yields higher RRs.[67-69] Based on these results, a multicenter phase III trial was conducted comparing irinotecan/cisplatin (IP) and PE in ED-SCLC. At the interim analysis, 154 patients had been enrolled. Enrolment was closed early because interim analysis showed significantly superior survival in patients assigned to receive IP.[70] However, results of other randomized trials conducted outside Japan failed to confirm these findings. A multicenter, open-label, randomized trial in chemo-naïve patients with ED-SCLC using a modified weekly regimen of IP *versus* PE to improve tolerability and achieve greater dose intensity showed no significant differences in RRs and OS in this patient population. Patients receiving IP had less myelosuppression but more diarrhea than those receiving PE.[71] The Southwest Oncology Group (SWOG S0124) trial showed no difference in response rates, progression free survival or overall survival in 651 patients randomized to received PE or IP in arms identical to those in the Japanese JCOG 9511 trial.[78] When studied in combination in a first-line setting, irinotecan and etoposide yielded response rates of 60-66% and median survival of 9.9-11.5 months.[71,78]

Other phase II studies investigated irinotecan in combination with other agents (gemcitabine, ifosfamide, carboplatin or etoposide) in previously treated patients with RRs of 10-71% (Table 9). Irinotecan was added to the standard combination (cisplatin and etoposide). This 3-drug combination was evaluated in 40 patients who responded to first-line chemotherapy but relapsed more than eight weeks after the completion of first-line therapy. The overall response rate was 78% (95% CI 61.5-89.2%). The median survival time was 11.8 months, and the estimated one-year survival rate was 49%. Grade 3-4 leukocytopenia, neutropenia, and thrombocytopenia were observed in 55%, 73%, and 33% of the patients, respectively.[77]

Topotecan

Topotecan is another topoisomerase I inhibitor (Table 9). Single agent topotecan yields an overall response rate of 39%, median survival of 10.0 months and a one-year survival rate of 39% in previously untreated ED-SCLC.[79] Studies evaluating single agent topotecan in refractory and relapsed patients report 3-11% and 15-37.8% response rates, respectively.[80-83,90]

In the EORTC 08957 phase II study, combined topotecan and cisplatin (TP) yielded overall response rates of 29.4% and 23.8% and median survival of 6.4% and 6.1% months in chemo-sensitive and chemo-refractory previously treated patients, respectively.[80] Christodoulou *et al.* reported 7.8 and 6.2 months median survival with this combination in relapsed and refractory patients.[84] Topotecan in combination with either cisplatin or etoposide in patients with untreated ED-SCLC showed similar RRs (63% and 61%) and median survival (10.1 and 9.6

Table 9. Phase II and III of topotecan.

Reference	N	Regimen	RR	Median survival	Survival (at year)	Disease/line of treatment
Schiller[79]	48	2 mg/m^2 d1-5 q3w	39%	10 m	39% (1y)	First
Ardizzoni[80]	47	1.5 mg/m^2 d1-5 q3w	6.4%	4.7 m	6.4% (1y)	Ref
	45		37.8%	6.9 m	33% (1y)	Rel
	P value			0.002		
Eckardt[81]	38	1.5 mg/m^2 d1-5 q3w	3%	4.8 m	NR	Ref
	36		19%	6 m	NR	Rel
Von Pawel[82]	52	Oral	23%	7.4 m	NR	Rel
	54	IV	15%	5.8 m	NR	Rel
Perez-Soler[83]	32	1.25 mg/m^2 d1-5 q3w	11%	4.6 m	NR	Ref
Christodo[84]	34	T 0.9 mg/m^2 and P 20 mg/m^2 (all d1-3 all/3w)	18%	6.5 m	NR	Ref Rel
Quoix[85]	41	T 1.25 mg/m^2 d1-5 and P 50 mg/m^2 d5	63%	9.6 m	NR	First
	41	T 0.75 mg/m^2 and E 60 mg/m^2 (all d1-5) (all/3w)	61%	10.1 m		
	P value		NS	NS		
Eckardt[86]	389	T 1.7 mg/m^2 (oral) and P 60 mg/m^2 d5	63%	9.2 m	31% (1y)	First
	395	P 80 mg/m^2 d1 and E100 mg/m^2 d1-3	68.9%	9.4 m	31% (1y)	ED
			NS	NS	NS	
Hobdy[87]	42	T 1mg/m^2 d1-5 and Cyclo 0.6 g/m^2 d1 (all/3w)	40.5%	9 m	21% (2y)	Rel
Ramalingam[88]	32	T 1mg/m^2 d1-5 and Taxol 135 mg/m^2 d1 (all/3w)	69%	12.7 m	50% (1y) 10% (2y)	First
Von Pawel[89]	107	T 1.5 mg/m^2 d1-5	24.3%	5.8 m	14.2% (1y)	Rel
	104	CAV	18.3%	5.8 m	14.4% (1y)	
	P value		0.285		NS	

IV, intravenous; T, topotecan; P, cisplatin; E, etoposide; q, every; d, day; w, week.

months), respectively.[85] In a large phase III study, topotecan/cisplatin (TP) and PE showed comparable activity in previously untreated patients with ED-SCLC. There were less incidences of grade 4 neutropenia (26% *vs* 56.8%) and associated fever (3.9% *vs* 8.9%) with TP as compared to PE.[86]

The combinations (topotecan and cyclophosphamide) in relapsed patients and (topotecan and paclitaxel) in chemo-naïve ED patients yields RRs and median survival of 40.5% and 9 months and 69% and 12.7 months, respectively.[87,88] Topotecan and CAV were evaluated in a randomized, multicenter study of 211 patients with SCLC who had relapsed at least 60 days after completion of first-line therapy. There was no statistical difference in RRS, PFS and median survival. Greater symptomatic improvement was seen in patients who received topotecan for symptoms of dyspnea (P=0.002), anorexia (P=0.042), hoarseness (P=0.043), and fatigue (P=0.032), and for interference with daily activities (P=0.023). Grade 4 neutropenia occurred in 37.8% of topotecan courses *versus* 51.4% of CAV courses (P<0.001). There were more frequent incidences of grade 4 thrombocytopenia and grade 3-4 anemia with topotecan.[89] Based on these findings, topotecan was approved by the Food and Drug Administration for treatment of recurrent disease.

Overall, topotecan demonstrates antitumor activity in both chemosensitive and refractory disease. Furthermore, topotecan therapy is associated with significant symptom palliation in this patient population. Since topotecan has a predictable toxicity profile (toxicity is generally manageable and non-cumulative), the agent is also potentially useful in patients with a poor prognosis and/or a poor performance status. Alternative dosing regimens (lower dose, weekly) and the introduction of an oral formulation may expand the use of topotecan both as a single agent and in combination therapy in the second- and first-line treatment of this disease.

Paclitaxel

Paclitaxel is an antimicrotubule agent that interferes with cell division (Table 10). It has well documented broad spectrum cytotoxic activity and is now licensed for use in many solid tumors including breast, ovary and non-small cell lung cancer. Overall response rate was 34% and 53% when single agent paclitaxel was investigated in previously untreated patients with ED-SCLC and 29% in patients with refractory disease.[91-93] Doublets of paclitaxel and carboplatin or etoposide yield RRs of 38% and 63.6% in first-line treatment of patients with ED-SCLC.[94,95]

The triplet PET (cisplatin, etoposide and paclitaxel) achieved a RR of 90% including CR of 16% and median survival of 11 months in chemo-naïve ED patients.[96] Lower RRs (57%) were seen with a similar regimen treating similar group of patients.[98] When cisplatin was replaced by car-

Table 10. Phase II and III studies of paclitaxel.

Reference	N	Regimen	RR	Median survival	Survival (at year)	Disease/line of treatment
Ettinger[91]	36	T 250 mg/m^2 q3w, if NR/PD change to PE	34% (T + PE=53%)	10 m	37% (1y)	First ED
Kirschling[92]	43	T 250 mg/m^2 q3w	53%	9 m	24% (1y)	First ED
Smit[93]	24	T 175 mg/m^2 q3w	29%	3.3 m	NR	Ref
Neubauer[94]	77	T 80 mg/m^2 and Carbo 2AUC d1, 8, 15 (all/4w)	38%	7.2 m	30% (1y)	First ED
Perez[95]	57	T 150 mg/m^2 and E 50 mg BD PO d1-10	63.6%		41.8% (1y)	First ED
Glisson[96]	41	P 175 mg/m^2 d1 and E 80 mg/m^2 d1-3 and T 130 mg/m^2 d1	90% (CR=16%)	11 m	10% (2y)	First ED
Hainsworth[97]		Carbo 5-6 AUC d1 and E 50/100 mg d1-19 and T 135-200 mg/m^2 d1 (all/3w)	LD 98% ED 84%	10 m	NR	First LD ED
Kelly[98]	88	P 80 mg/m^2 d1 and E 80 (d1) 160 (d2, 3) mg/m^2 and T 175 mg/m^2 d1 (all/3w)	57%	11 m	43% (1y)	First ED
Mavroudis[99]	71	P 80 mg/m^2 d1 and E 120 mg/m^2 d1-3	48%	9.5m	28.2% (1y)	First LD
	62	P 80 mg/m^2 d2 and E 80 mg/m^2 d2-4 and T 175 mg/m^2 d1 (all/4w)	50%	10.5	37% (1y)	ED
	P value		0.08	NS	NS	
Niell[100]	282	P 80 mg/m^2 d1 and E 80 mg/m^2 d1-3	68%	9.9 m	37% (1y) 8% (2y)	
		As PE plus T 175 mg/m^2 d1 (all/3w)	75%	10.6 m	38% (1y) 11% (2y)	
	P value	283	NR	0.169	NS	
Reck[101]	309	Carbo 5 AUC d1 and E 125/159 mg/m^2 d1-3 and V 2 mg d1, 8	69.4%	11.7 m	48% (1y) 16% (2y)	First LD
	305	T173 mg/m^2 d4 and E102/125 mg/ m^2 d1-5 and Cardo 5AUC d1	63.9%	12.7 m	51% (1y) 20% (2y)	ED
	P value		NS	NS	HR for death 1.22 0.024	
Hainsworth[102]	105	T 135 mg/m^2 d.75 mg/m^2 d1-3 (All/3w)	ED 88%	ED 8.3 m	ED 8% (2y)	LD ED

T, paclitaxel; P, cisplatin; E, etoposide; d, day; w, week.

boplatin, the RR was 84% and 98% in ED and LD patients, respectively.[97] PET was not statistically superior to PE and imposed more hematologic and non-hematologic toxicity.[99,100] However, a randomized phase III multicenter showed better outcome with carboplatin, etoposide and paclitaxel (CET) when compared to carboplatin, etoposide, and vincristine (CEV) in patients with previously untreated LD and ED-SCLC. The hazard ratio of death and PFS were statistically significantly better in patients on CET. There were no differences in CEV: (69.4%) and CET (72.1%). Rates of severe grade of anemia, leukocytopenia, neutropenia, and thrombocytopenia were lower in the CET arm than in the CEV arm. Rates of leukocytopenia, neutropenia, and febrile neutropenia were similar among patients in both arms.[101] It is possible that the use of carboplatin in this study improved the toxicity profile in CET when compared to studies using cisplatin (PET). The triplet carboplatin, paclitaxel and topotecan provided no apparent improvement in efficacy.[102]

Docetaxel

Docetaxel is another antimicrotubule agent with broad spectrum cytotoxic activity[103-108] (Table 11). Phase II studies showed only limited activity in SCLC. In previously treated patients, the response rate was 25%.[103] In previously untreated patients, the response rates (all PR) in 2 studies were 8.3% and 23%.[104,105] In previously treated patients, the combination of docetaxel and gemcitabine showed disappointing results with no response seen in 22 patients.[106] In previously untreated patients, docetaxel in combination with gemcitabine was assessed in ED-SCLC. Only 6 patients showed a partial response and the trial ended prematurely since at least seven responses were required among the first 19 patients.[107] In similar patients, the combination showed some activity (RR 23%).[108]

Over all, early studies with docetaxel did not show promising results. This may explain why available data are scarce. It should not be considered in treatment of SCLC outside clinical trials.

Vinorelbine

Vinorelbine is a semisynthetic vinca alkaloid (Table 12). In small phase II studies, single agent vinorelbine yielded only modest response rates of 0-16% in previously treated and untreated patients.[109-113] Higher responses (55%) were shown in 2 studies combining vinorelbine and carboplatin. However, this combination was found to be extremly toxic, including toxic deaths. The authors concluded that this

Table 11. Studies of docetaxel.

Reference	N	Regimen	ORR	Median survival	Survival (at year)	Disease/line of treatment
Smyth[103]	34	Tax 100 mg/m^2	25%	NR	NR	2
Latreille[104]	14	Tax 75 mg/m^2	8.3%	10.4m	NR	1 ED
Hesketh[105]	47	Tax 100 mg/m^2	23%	9 m	28% (1y)	1 ED
Agelaki[106]	22	Tax 75 mg/m^2 d8 and Gem 1g/m^2 d1, 8 (all/3w)	0%	3.2 m	28% at (6 m)	2 LD/ED
Skarlos[107]	20	Tax 50 mg/m^2 d1, 8 and Gem 1g/m^2 d1, 8 (all/3w)	30%	9.6 m	NR	1 ED
Hainsworth[108]	40	Tax 30 mg/m^2 d1, 8, 15 and Gem 0.8 g/m^2 d1, 8, 15 (all/3w)	23%	4m	14% (1y)	1 ED

Tax, docetaxel; Gem, gemcitabine; d, day; w, week.

Table 12. Studies of vinorelbine.

Reference	N	Regimen	RR	Median survival	Survival (at year)	Disease/line of treatment
Higano[109]	22	Vin 30 mg/m^2	5%	8 m	NR	First
Tummarello[110]	7	Vin 25 mg/m^2	0%	Not Rep	Not Rep	First
Jassem[111]	26	Vin 30 mg/m^2	16%	Not Rep	Not Rep	Previously treated
Furuse[112]	25	Vin 25 mg/m^2	13%	Not Rep	Not Rep	Previously treated
Johnson[113]	34	Vin 30 mg/m^2	15%	5 m	Not Rep	Second
Gridelli[114]	28	Vin 25 mg/m^2 d1, 8 and Carbo 5AUC d1 (q/3w)	55%	7.9 m	27%	First
Mackay[115]	58	Vin 30 mg/m^2 d1, 8 and Carbo 5AUC d1 (q/4w)	55%	6 m	NR	First
Johnson[116]	NR	Vin 25 mg/m^2 d1, 8 and Doxorubicin 50 mg/m^2 (q/3w)	26.7%	NR Stopped early due to toxicity	NR	Second
Hainsworth[117]	28	Vin 20 mg/m^2 and Gem 1g/m^2 d1, 8, 15 (q4/w)	10%	5 m	17% (1y)	Rel Ref
Rapti[118]	35	Vin 25 mg/m^2 and Gem 1.1g/m^2 d1, 8 (q3/w)	6%	4.5 m	42.6% at 6 m	Pre-treated
Dudek[119]	16	Vin 25 mg/m^2 and Gem 1g/m^2 d1, 8 (q3/w)	6%	5.4 m	NR	Pre-treated

Vin, vinorelbine; Gem, gemcitabine; d, day; w, week.

combination is active but the toxicity profile is such that further evaluation is not considered appropriate.[114,115] Combining vinorelbine with doxorubicin was also found to be very toxic. Johnson *et al.* reported a 26.7% response rate. Toxicities included grade 4 neutropenia in 73% and febrile neutropenia and/or sepsis in 60%. Three patients died from sepsis during the first cycle of treatment.[116] A combination of the 2 new agents, vinorelbine and gemcitabine, has shown only modest activity with RRs of 6-10% in previously treated patients.[117-119]

From the evidence available, single agent vinorelbine provided only modest results but using it in combination with other cytotoxic agents yields moderate activity; however, the toxicity profile is unacceptable.

Gemcitabine

Gemcitabine is a pyrimidine nucleoside antimetabolite that, through incorporation into the DNA, leads to inhibition of DNA synthesis and cytotoxicity (Table 13). Response rates to single agent are at best 13% in refractory and relapsed patients and 27% in previously untreated patients.[120-123] In 42 previously untreated ED-SCLC, combination gemcitabine and etoposide yielded an overall response rate of 46% and median survival of 10.5 months.[124] Doublets of gemcitabine and other agents, for example, irinotecan, vinorelbine and cocetaxel yield poor response rates of no more than 17% in pre-treated patients.[125-130] In the first-line setting in poor performance elderly patients with ED, gemcitabine and docetaxel resulted in an unimpressive RR of 23% and median survival of four months.[131]

The London Lung Cancer Group is conducting a multicenter, open-label, randomized, phase III trial in patients with ED, locally advanced LD, or LD with poor prognostic factors. Chemotherapy consists of 21-day cycles of GC (gemcitabine 1200 mg/m^2 on Days 1 and 8, plus carboplatin area under the curve of 5 on Day 1) or PE (cisplatin 60 mg/m^2 on Day 1 plus etoposide 120 mg/m^2 i.v. on Day 1 and 100 mg orally on Days 2 and 3). Between January 1999 and September 2001, 241 patients were recruited. Collective grade 3-4 anemia, neutropenia and thrombocytopenia were 19% and 12% in the GC and PE arms, respectively. PE-treated patients experienced more alopecia, nausea and vomiting. Overall response rates were 58% and 63% (NS), and median survival

Table 13. Phase II and III studies of gemcitabine.

Reference	N	Regimen	RR	Median survival	Survival (at year)	Disease/ line of treatment
Masters[120]	46	G 1g/m^2 d1, 8, 15 (q4/w)	11.9%	7.1 m	Not Rep	Ref Rel
Hoang[121]	27	G 1.25 g/m^2 d1, 8 (q3/w)	0%	6.4 m	25.4 at 1y	Ref Rel
Van der Lee[122]	38	G 1g/m^2 d1, 8, 15 (q4/w)	13%	4 m	3% (1y)	Ref
Cormier[123]	29	G 1.25 g/m^2 d1, 8, 15 (q4/w)	27%	12 m	50%	First ED
Vansteenkiste[124]	42	G 1g/m^2 d1, 8, 15 E 80 mg/m^2 d8, 9, 10 (4/w)	46%	10.5 m	37% (1y)	First ED
Agelaki[125]	31	G 1g/m^2 d1, 8 and I 300 mg/m^2 d8 (q3/w)	10%	6 m	17% (1y)	Ref Rel LD and ED
Schuette[126]	35	G 1g/m^2 and I 100 mg/m^2 d1, 8 (q3/w)	17%	5.8 m	34% (1y)	Ref Rel
Hainsworth[127]	28	Vin 20 mg/m^2 and Gem 1g/m^2 d1, 8, 15 (q4/w)	10%	5 m	17% (1y)	Rel Ref
Rapti[128]	35	Vin 25 mg/m^2 and Gem 1.1g/m^2 d1, 8 (q3/w)	6%	4.5 m	42.6% at 6 m	Pre-treated
Dudek[129]	16	Vin 25 mg/m^2 and Gem 1g/m^2 d1, 8 (q3/w)	6%	5.4 m	NR	Pre-treated
Agelaki[130]	22	G 1g/m^2 d1, 8 and D 75 mg/m^2 d8 (q3/w)	0%	3.3 m	28% at 6 m	Ref Rel
Hainsworth[131]	40	G 8 g/m^2 and D 30 mg/m^2 d1, 8, 15 (q4/w)	23%	4 m	14% (1y)	First Poor PS Elderly ED
Lee[132]	241	GC G 1.2 g/m^2 d1, 8 and Carbo 5AUC d1	58%	8.1 m	Not Rep	First ED and locally advanced
		PE P 60 mg/m^2 d1 and E 120 mg/m^2 d1, E 100 mg d2, 3	63%	8.2 m	Not Rep	
De Marinis[133]	56	P 70 mg/m^2 d2 and E escalating and G 1 g/m^2 d1, 8	72.2%	10 m	37.5 at 1y	First
De Marinis[134]	70	PEG P 70 mg/m^2 d2 and E 50 mg/m^2 d1,8 and G 1 g/m^2 d1, 8	63% CR=18.6%	9.5 m	50% (1y) 9% (2y)	First ED and poor prognosis LD
	70	PG P 70 mg/m^2 d1 and G 1.25 g/m^2 d1, 8 (3/w)	57% CR=4.3%	10 m	48% (1y) 7% (2y)	

G, gemcitabine; E, etoposide; Vin, vinorelbine; GC, gemcitabine, cisplatin; PE, cisplatin, etoposide; PEG, cisplatin, etoposide, gemcitabine; PG, cisplatin, gemcitabine; d, day; w, week.

was 8.1 and 8.2 months for GC and PE, respectively.[132] Complete results of this study are still awaited.

In a phase I/II study, the triplet combination of cisplatin, etoposide, and gemcitabine (PEG) was investigated. In the phase I section of the study, etoposide dose of 50 mg/m^2 was defined as the maximum tolerated dose (MTD). In the subsequent phase II evaluation, 48 additional patients were enrolled. PEG showed an overall response rate of 72.2% and one-year survival of 37.5% in 56 previously untreated patients with LD or ED SCLC.[133] This study was followed by a randomized phase II study by the same group comparing PEG and PG. The objective response rate was 63% for PEG and 57% for PG, with the suggestion of a higher complete response rate in the PEG arm (18.6% and 4.3%, respectively). A similar time to disease progression (6 months in the PEG arm and 7 months in the PG arm) and a similar median survival (9.5 months in the PEG arm and 10 months in the PG arm) were observed in both arms. The PEG regimen was associated with more severe hematologic toxicity in terms of neutropenia, febrile neutropenia, and a higher rate of treatment delays and dose reductions, whereas there was no difference in non-hematologic toxicities between the two arms.[134]

From the available evidence, gemcitabine has shown promising results when combined with platinum derivatives as a doublet or with platinum derivatives and etoposide as a triplet. However, this evidence is reported in ED and poor prognosis patients. It would be interesting to investigate these regimens in a group of patients with better prognosis.

Amrubicin

Amrubicin is a synthetic anthracycline that has shown significant activity in SCLC and has minimal cardiac toxicity. It is approved in Japan for treatment of SLCL. Phase II studies showed significant response rates when used as single agent or in combination with platinum agents (Table 14) in the upfront setting. In the relapsed setting, phase II studies also showed promising results, with a hint of superiority over topotecan.[140-143] The dose of amrubicin is 35mg/m^2 daily for three days. A recently presented phase III trial randomized 637 platinum pre-treated patients to receive either topotecan or amrubicin. Preliminary results of this study showed non-inferiority of amrubicin, but there was no significant improvement in primary end point of overall survival. However, progression free survival (4.1 *vs* 3.5 months, P=0.02) and response rates (31% *vs* 17%, P=0.0001) improved significantly with amrubicin. The overall incidence of febrile neutropenia was higher in the amrubicin group (9.3% *vs* 6.3%) but there was no incidence of cardiotoxicity.[146]

Combined modality treatment

Despite the improvement in survival with the widespread use of chemotherapy for SCLC, 30-80% of patients will develop local recurrence. The use of radiotherapy in addition to chemotherapy has, therefore, been

Table 14. Phase II trials of amrubicin.

Reference	N	Regimen	RR	Median survival	Survival (at year)	Disease/line of treatment
Yana[135]	35	Amrubicin	75.8%	11.7 months	48.5% 1 y 20.2% 2 y	First ED
Kobayashi[136]	45	Cisplatin/Irinotecan, followed by Amrubicin	79%	15.4 months	NR	First
O'Brien[137]	28 30	Amrubicin Cisplatin/amrubicin	61% 77%	NR	NR	First
Ohe[138]	44	Amrubicin/cisplatin	87.8%	13.6 months	56% 1 y	First ED
Onoda[139]	16 refractory 44 sensitive	Amrubicin	50% (refractory group) 52% (sensitive group)	10.3 months 11.6 months	40% 1 y 46% 1 y	Refractory/relapsed
Inoue[140]	36 sensitive 23 refractory	Amrubicin	53% sensitive group 17% refractory group	PFS 3.5 m	NR	Relapsed
			21% sensitive group 0% refractory group			
		Topotecan		PFS 2.2 months		
Inoue[141]	36	Amrubicin/carboplatin	89%	18.6 m	NR	First-line, elderly
Ettinger[142]	69	Amrubicin	21.3%	6 m	NR	Platinum refractory
Jotte[143]	50	Amrubicin	44%	9.2 m	NR	Relapsed platinum-sensitive
	26	Topotecan	15% P=0.021	7.6 m		
Hirose[144]	25	Amrubicin/carboplatin	58% in sensitive relapse 15% in refractory relapse P=0.03	10 months sensitive relapse 5 months refractory relapse P=0.004	NR	Relapsed platinum-sensitive or refractory
Nogami[145]	59	Amrubicin/topotecan	74% First-line 43% Relapsed	14.9 months 10.2 months	NR	Relapsed or ED

ED, Extensive Stage Disease.

investigated. The role of radiotherapy in the management of SCLC is outside the scope of this review. However, this section briefly presents some of the landmark findings in this treatment method when used in conjunction with chemotherapy.

A meta-analysis of 13 randomized trials clearly demonstrated a significant survival advantage of 5.4% at three years for combined modality in LD-SCLC.[147] Pooling data from 8 randomized controlled trials enrolling over 1,500 patients showed that early integration of chest radiotherapy with systemic chemotherapy increases OS by 34-216%, depending on the end point of interest. Etoposide plus cisplatin in conjunction with chest irradiation appears to offer the greatest increase in survival *versus* delayed or split-course radiation therapy and non-PE containing drug schedules.[148]

The optimal dose and fractionation schedule of radiotherapy is still uncertain. Turrisi *et al.* demonstrated a longer survival in favor of twice daily as compared to once daily concurrent chemo-radiotherapy.[149] This is confirmed by the meta-analysis of 7 RCTs which showed 2-year overall survival relative risks compared with late radiotherapy as follows: RR 1.17, 95% CI 1.02-1.35 in favor of early radiotherapy; RR 1.44, 95% CI 1.17-1.83 in favor of hyperfractionation; RR 1.30, 95% CI 1.10-1.53 in favor of early radiotherapy added to platinum based chemotherapy.[150] Use of concurrent radiotherapy with chemotherapy as opposed to sequential was compared in a Japanese Clinical Oncology Group study.[151] There was a marked improvement in median and overall survival in favor of the concurrent chemo-radiotherapy group, but this did not reach statistical significance. In the UK, sequential treatment is the current standard management of patients with LD-SCLC. However, some centers are starting to recommend concomitant treatment. Further research is required to investigate the role and the best scheduling of sequential chemotherapy.

Prophylactic cranial irradiation (PCI) is used in patients with LD-SCLC who had CR to initial treatment. This intervention reduces the risk of brain metastases by about 45% and may improve OS. Larger doses of radiation have led to greater decreases in the risk of brain metastasis.[152,153] An ongoing international phase III study is investigating the effect of radiotherapy dose. The study randomizes patients with LD-SCLC in CR to 25 Gy in 10 fractions *versus* 36 Gy in 18 fractions or hyperfractionation regimen.

A phase III EORTC trial investigated the role of PCI in ED-SCLC in CR or PR. PCI resulted in a significant decrease in incidence of new brain metastases and appeared to increase overall survival. One-year survival was significantly increased from 13% to 27%.[154]

PCI is offered routinely to LD-SCLC patients in CR or very good PR. Further trials are needed in patients with ED-SCLC to determine optimal dose of radiation and to determine which patients would derive most benefit.

Novel biological approaches

Innovative applications of conventional chemotherapy agents have not improved long-term outcome to any great extent despite a modest increase in response rates. Clearly innovative approaches are needed to significantly improve the prognosis. It has been recognized that tumor vascularization is a vital process for the progression of solid tumors from a small, localized focus to a large tumor with the capability of metastasizing. Such observations have resulted in a large number of drugs being developed intentionally, or positioned as angiogenesis inhibitors and these have been evaluated in pre-clinical and clinical trials.[155]

High pre-treatment serum VEGF is associated with poor response to treatment and unfavorable survival in patients with SCLC treated with combination chemotherapy.[156] Thalidomide is an inhibitor of angiogenesis induced by basic fibroblast growth factor in a rabbit cornea micropocket assay and inhibits vascular endothelial growth factor (VEGF)-induced corneal neovascularization.[157-159]

Anti-tumor activity of thalidomide has been demonstrated against glioma, renal cell carcinoma, multiple myeloma and prostate cancer. A phase II study of maintenance thalidomide undertaken in patients who responded to conventional chemotherapy showed median survival from time of initiation of induction chemotherapy of 12.8 months and one-year survival of 51.7%. Thalidomide was well tolerated with median duration of treatment of 79 days.[160] In a phase II study, the London Lung Cancer group investigated thalidomide in patients with SCLC in combination with chemotherapy and as a maintenance therapy in an attempt to improve the outcome. Preliminary data appeared to show promising clinical activity. Thalidomide was well tolerated without adding to the expected toxicity of chemotherapy or radiotherapy.[161] Based on these findings the investigators extended the study into a randomized double blind phase III trial to test whether the addition of thalidomide to chemotherapy improves survival, time to tumor progression, performance status and quality of life as compared to chemotherapy alone (carboplatin and etoposide). The study recruited a total of 724 patients (51% with limited and 49% with extensive stage disease) with randomization to placebo or oral thalidomide 100 to 200 mg daily. There was no difference in survival mong patients with limited stage disease, but survival was worse in the thalidomide arm in patients with extensive stage disease. Thalidomide was also associated with increased risk of thromboembolism (19% with thalidomide *vs* 10% with placebo, P<0.001), as well as more rash, constipation and neuropathy. There was no difference in median overall survival between the two arms (10.5 months in placebo and 10.1 months in the thalidomide arm, P=0.28).[162] Bevacizumab, which is a novel anti-angiogenic agent with activity against circulating VEGF has also been studied in SCLC. A phase II study combining paclitaxel and bevacizumab in relapsed chemosensitive SCLC showed median progression free survival of 14.7 weeks (equivalent to historic controls), an overall response rate of 18.1% and median survival time of 30 weeks. No unexpected toxicities were noted.[163] In the first-line setting, 3 phase II trials have evaluated the addition of bevacizumab to platinum based chemotherapy. Response rates ranged from 63.5% to 84%, and median survival of 10.9 to 12.1 months was achieved. No significant toxicities from addition of bevacizumab were noted.[164-166] A phase III trial randomizing untreated ES-SCLC to chemotherapy alone *versus* addition of bevacizumab is underway (*ClinicalTrials.gov identifier NCT00930891*). Sorafenib is an oral small molecule tyrosine kinase inhibitor affecting multiple pathways involved in progression and angiogenesis. A phase II study of single agent sorafenib in platinum treated patients, however, failed to show adequate disease control,[167] and combination trials of sorafenib and chemotherapy are underway.

CD56 is a neural cell adhesion molecule (NCAM) expressed on the cells of tumors of neuroendocrine origin including SCLC, carcinoid tumors, neuroblastomas and on neuroectodermal tumors such as astrocytomas. It is expressed in almost all cases of SCLC.[168] BB-10901 is an immunoconjugate created by the conjunction of the cytotoxic maytansinoid drug DM1 to a humanized version of the murine antibody N901. BB10901 binds with high affinity to CD56, the conjugate is internalized and releases DM1. Released DM1 inhibits tubulin polymerization and microtubule assembly causing cell death. Four centers in the UK are conducting a phase II study which started in April 2003 to evaluate the safety, tolerability, pharmacokinetics and efficacy of BB-10901 in patients with relapsed or refractory SCLC or other CD56 expressing tumors.

Various novel targeted agents have been investigated in SCLC. About 80% of SCLC cells express c-Kit. However, imatinib, a c-Kit inhibitor, has

shown has shown disappointing results in SCLC.[169-170] These studies recruited 19 and 29 patients, respectively. There were no responders.

Increased expression of metalloproteinases (MMP) is associated with poor prognosis. In a phase III NCI/EORTC study, 532 SCLC patients in complete or partial remission were randomized to receive marimastat (MMP inhibitor) 10 mg or placebo orally for up to two years. The median time to progression for marimastat patients was 4.3 months compared with 4.4 months for placebo patients (P=0.81). Median survival for marimastat and placebo patients were 9.3 months and 9.7 months, respectively, (P=0.90). Toxicity was generally limited to musculoskeletal symptoms (18% grade 3/4 for marimastat). Patients on marimastat had significantly poorer quality of life at three and six months.[171]

R115777 is an oral, non-peptidomimetic farnesyl transferase inhibitor which blocks the activity of farnesylated proteins (*e.g.* ras or rhoB) involved in signal transduction pathways critical for cell proliferation and survival. There were no responders in 22 patients.[172]

The phosphatidylinositol 3' kinase/AKT pathway may play an important role in the proliferation of SCLC. The mammaliam target of rapamycin (mTOR) is a downstream target in this pathway. In a phase II study, 87 patients with ED-SCLC in CR, PR or SD were randomized to 2 dose levels of temsirolimus (an inhibitor of mTOR). The median survival for all patients is 19.8 months.[173] These are considered to be favorable survival figures. However, they need to be confirmed in a phase III setting. A newer mTOR inhibitor everolimus (RAD001) was evaluated as a single agent in a phase II study in 40 previously treated SCLC patients. Everolimus was well tolerated but had limited single agent anti-tumor activity.[174] Further evaluation of everolimus in combination with chemotherapy is a subject of ongoing trials.

The proteasome inhibitor PS-341 inhibits growth of SCLC cell lines through decreased bcl-2 via NFk-B. In a phase II study, previously platinum-treated patients with ED-SCLC were treated with PS-341; 57 were evaluable for response. Seven patients discontinued treatment due to adverse events or side effects from therapy. There was only one responder to PS-341.[175]

One novel approach to the treatment of lethal residual disease relies on the induction of a host-immune response to attack chemoresistant tumor cells. Because of its neuroectodermal origin, SCLC has a number of specific antigens that could be used as immune targets.

Interferon may have immune-modulating properties. It failed to show any positive impact on the survival outcome of patients with LD-SCLC. If anything, it may increase the deleterious effects of radiation on normal lung tissue.[176]

Immunotherapy with immunological adjuvants such as MER-BCG did not prolong the time to disease progression or improve survival.[177] Immunization of patients with SCLC after standard therapy using anti-idiotypic antibody such as BEC2, which mimics the ganglioside GD3 expressed on the surface of most SCLC tumors is another approach.[178] However, a randomized phase III EORTC study showed that vaccination with BEC2/BCG has no impact on the outcome of patients with LD-SCLC.[179] Further studies using vaccines that produce a better immunological response may be warranted.

The anti-apoptotic Bcl-2 proteins have been associated with a more aggressive malignant phenotype and chemoresistance in various cancer types including small cell lung cancer.[180] Oblimersen, an anti-sense oligonucleotide agent with activity against Bcl-2, was evaluated in a phase II clinical trial in SCLC but failed to show additional activity in combination with chemotherapy.[181] More recently, a Bcl-2 antagonist, obatoclax mesylate, was evaluated in combination with topotecan in relapsed SCLC. The combination also failed to improve on historic response rates seen with topotecan alone in relapsed SCLC.[182]

Overall, it seems that it is going to be a long time before we can achieve impressive results with these novel approaches.

Conclusions

Combination chemotherapy is the current strategy of choice for treatment of SCLC. Platinum containing combination regimens are superior to non-platinum regimens in LS-SCLC and possibly also in ED-SCLC as first and second-line treatments. The addition of ifosfamide to platinum containing regimens may improve the outcome but this may be achieved with increased toxicity. Suboptimal chemotherapy doses result in inferior survival. Early intensified, accelerated and high-dose chemotherapy gave conflicting results and are not considered to be standard options outside clinical trials. A number of newer agents have shown promising results when used in combination regimens, *e.g.* gemcitabine, irinotecan and topotecan. However, more studies are needed to evaluate these agents. The role for radiotherapy in LD-SCLC has now been definitively confirmed. However, timing and schedule are subject to further research. Novel approaches are currently being investigated in the hope of improving outcome.

References

1. Riaz SP, Lüchtenborg M, Coupland VH, et al. Trends in incidence of small cell lung cancer and all lung cancer. Lung Cancer 2012;75:280-4.
2. Andrea B, Massimo B, Luca M, Alessandra S. Impact of histopathological diagnosis with ancillary immunohistochemical studies on lung cancer subtypes incidence and survival: a population-based study. J Cancer Epidemiol 2011;2011:275758.
3. Govindan R, Page N, Morgensztern D, et al. Changing Epidemiology of Small-Cell Lung Cancer in the United States Over the Last 30 Years: Analysis of the Surveillance, Epidemiologic, and End Results Database. J Clin Oncol 24:4539-44.
4. Evans WK, Feld R, Murray N, et al. Superiority of alternating non-cross-resistant chemotherapy in extensive small cell lung cancer. A multicenter, randomized clinical trial by the National Cancer Institute of Canada. Ann Intern Med 1987;107:451-8.
5. Maurer LH, Tulloh M, Weiss RB, et al. A randomized combined modality trial in small cell carcinoma of the lung: comparison of combination chemotherapy-radiation therapy versus cyclophosphamide-radiation therapy effects of maintenance chemotherapy and prophylactic whole brain irradiation. Cancer 1980;45:30-9.
6. Humblet Y, Symann M, Bosly A, et al. Late intensification chemotherapy with autologous bone marrow transplantation in selected small-cell carcinoma of the lung: a randomized study. J Clin Oncol 1987;5:1864-73
7. Elias A, Ibrahim J, Skarin AT, et al. Dose-intensive therapy for limited-stage small-cell lung cancer: long-term outcome. J Clin Oncol 1999;17:1175.
8. Rizzo JD, Elias AD, Stiff PJ, et al. Autologous stem cell transplantation for small cell lung cancer. Biol Blood Marrow Transplant 2002;8:273-80.
9. Bessho A, Ueoka H, Kiura K, et al. High-dose ifosfamide, carboplatin and etoposide with autologous peripheral blood progenitor cell transplantation for small-cell lung cancer. Anticancer Res 1999;19:693-8.
10. Skarlos DV, Samantas E, Kosmidis P, et al. Randomized comparison of etoposide-cisplatin vs. etoposide-carboplatin and irradiation in small-cell lung cancer. A Hellenic Co-operative Oncology Group study. Ann Oncol 1994;5:601-7.
11. Cerny T, Blair V, Anderson H, et al. Pretreatment prognostic fac-

tors and scoring system in 407 small-cell lung cancer patients. Int J Cancer 1987;39:146-9.
12. Rawson NS, Peto J. An overview of prognostic factors in small cell lung cancer. A report from the Subcommittee for the Management of Lung Cancer of the United Kingdom Coordinating Committee on Cancer Research. Br J Cancer 1990;61:597-604.
13. Douple EB, Cate CC, Curphey TJ, et al. Evaluation of drug efficacy in vitro using human small cell carcinoma of the lung spheroids. Cancer 1985;56:1918-25.
14. Lowenbraun S, Bartolucci A, Smalley RV, et al. The superiority of combination chemotherapy over single agent chemotherapy in small cell lung carcinoma. Cancer 1979;44:406-13.
15. Girling DJ. Comparison of oral etoposide and standard intravenous multidrug chemotherapy for small-cell lung cancer: a stopped multicentre randomised trial. Medical Research Council Lung Cancer Working Party. Lancet 1996;348563-6.
16. Souhami RL, Spiro SG, Rudd RM, et al. Five-day oral etoposide treatment for advanced small-cell lung cancer: randomized comparison with intravenous chemotherapy. J Natl Cancer Inst 1997;89:577-80.
17. Shepherd FA, Evans WK, MacCormick R, et al. Cyclophosphamide, doxorubicin, and vincristine in etoposide- and cisplatin-resistant small cell lung cancer. Cancer Treat Rep 1987;71:941-4.
18. Sambrook RJ, Girling DJ. A national survey of the chemotherapy regimens used to treat small cell lung cancer (SCLC) in the United Kingdom. Br J Cancer 2001;84:1447-52.
19. Andersen M, Kristjansen PE, Hansen HH. Second-line chemotherapy in small cell lung cancer. Cancer Treat Rev 1990;17:427-36.
20. Cioccari L, Goldhirsch A, Cavalli F. Preliminary results of a phase-II study with DDP (cis-diaminedichloro-platinum) in the small cell bronchogenic carcinoma. Schweiz Med Wochenschr 1979;109:845-7.
21. Cavalli F, Jungi WF, Sonntag RW, et al. Phase II trial of cis-dichlorodiammineplatinum(II) in advanced malignant lymphoma and small cell lung cancer: preliminary results. Cancer Treat Rep 1979;63:1599-603.
22. Sierocki JS, Hilaris BS, Hopfan S, et al. cis-Dichlorodiammineplatinum(II) and VP-16-213: an active induction regimen for small cell carcinoma of the lung. Cancer Treat Rep 1979;63:1593-7.
23. Roth BJ, Johnson DH, Einhorn LH, et al. Randomized study of cyclophosphamide, doxorubicin, and vincristine versus etoposide and cisplatin versus alternation of these two regimens in extensive small-cell lung cancer: a phase III trial of the Southeastern Cancer Study Group. J Clin Oncol 1992;10:282-91.
24. Fukuoka M, Furuse K, Saijo N, et al. Randomized trial of cyclophosphamide, doxorubicin, and vincristine versus cisplatin and etoposide versus alternation of these regimens in small-cell lung cancer. J Natl Cancer Inst 1991;83:855-61.
25. Chute JP, Chen T, Feigal E, et al. Twenty years of phase III trials for patients with extensive-stage small-cell lung cancer: perceptible progress. J Clin Oncol 1999;17:1794-801.
26. Pujol JL, Carestia L, Daures JP. Is there a case for cisplatin in the treatment of small-cell lung cancer? A meta-analysis of randomized trials of a cisplatin-containing regimen versus a regimen without this alkylating agent. Br J Cancer 2000;83:8-15.
27. Sundstrøm S, Bremnes RM, Kaasa S, et al. Cisplatin and etoposide regimen is superior to cyclophosphamide, epirubicin, and vincristine regimen in small-cell lung cancer: results from a randomized phase III trial with 5 years' follow-up. J Clin Oncol 2002;20:4665-72.
28. Thatcher N, Qian W, Clark PI, et al. Ifosfamide, carboplatin, and etoposide with midcycle vincristine versus standard chemotherapy in patients with small-cell lung cancer and good performance status: clinical and quality-of-life results of the British Medical Research Council multicenter randomized LU21 trial. J Clin Oncol 2005;23:8371-9.
29. Johnson DH, Bass D, Einhorn LH, et al. Combination chemotherapy with or without thoracic radiotherapy in limited-stage small-cell lung cancer: a randomized trial of the Southeastern Cancer Study Group. J Clin Oncol 1993;11:1223-9.
30. Beith JM, Clarke SJ, Woods RL, et al. Long-term follow-up of a randomised trial of combined chemoradiotherapy induction treatment, with and without maintenance chemotherapy in patients with small cell carcinoma of the lung. Eur J Cancer 1996;32A:438-43.
31. Mascaux C, Paesmans M, Berghmans T, et al. A systematic review of the role of etoposide and cisplatin in the chemotherapy of small cell lung cancer with methodology assessment and meta-analysis. Lung Cancer 2000;30:23-36.
32. White SC, Lorigan P, Middleton MR, et al. Randomized phase II study of cyclophosphamide, doxorubicin, and vincristine compared with single-agent carboplatin in patients with poor prognosis small cell lung carcinoma. Cancer 2001;92:601-8.
33. Feld R, Evans WK, Coy P, et al. Canadian multicenter randomized trial comparing sequential and alternating administration of two non-cross-resistant chemotherapy combinations in patients with limited small-cell carcinoma of the lung. J Clin Oncol 1987;5:1401-9.
34. Amarasena IU, Walters JA, Wood-Baker R, et al. Platinum versus non-platinum chemotherapy regimens for small cell lung cancer. Cochrane Database Syst Rev 2008;4:CD006849.
35. Figoli F, Veronesi A, Ardizzoni A, et al. Cisplatin and etoposide as second-line chemotherapy in patients with small cell lung cancer. Cancer Invest 1988;6:1-5.
36. Bunn PA Jr. Review of therapeutic trials of carboplatin in lung cancer. Semin Oncol 1989;16:27-33.
37. Eckardt JR, Bentsion DL, Lipatov ON, et al. Phase II study of picoplatin as second-line therapy for patients with small-cell lung cancer. J Clin Oncol 2009;27:2046-51.
38. Johnson DH. Overview of ifosfamide in small cell and non-small cell lung cancer. Semin Oncol 1990;17:24-30.
39. Ettinger DS. The place of ifosfamide in chemotherapy of small cell lung cancer: the Eastern Cooperative Oncology Group experience and a selected literature update. Semin Oncol 1995;22:23-7.
40. Loehrer PJ Sr, Rynard S, Ansari R, et al. Etoposide, ifosfamide, and cisplatin in extensive small cell lung cancer. Cancer 1992;69:669-73.
41. Evans WK, Stewart DJ, Shepherd FA, et al. VP-16, ifosfamide and cisplatin (VIP) for extensive small cell lung cancer. Eur J Cancer 1994;30A:299-303.
42. Ettinger DS, Finkelstein DM, Ritch PS, et al. Study of either ifosfamide or teniposide compared to a standard chemotherapy for extensive disease small cell lung cancer: an Eastern Cooperative Oncology Group randomized study (E1588). Lung Cancer 2002;37:311-8.
43. Wolff AC, Ettinger DS, Neuberg D, et al. Phase II study of ifosfamide, carboplatin, and oral etoposide chemotherapy for extensive-disease small-cell lung cancer: an Eastern Cooperative Oncology Group pilot study. J Clin Oncol 199;1:1615-22.
44. Le Chevalier T, Thomas F, Subirana R, et al. A phase II study of the combination of carboplatin and ifosfamide in previously untreated metastatic small cell lung carcinoma. Cancer 1991;67:2980-3.

45. Miyamoto H, Nakabayashi T, Isobe H, et al. A phase III comparison of etoposide/cisplatin with or without added ifosfamide in small-cell lung cancer. Oncology 1992;49:431-5.
46. Postmus PE, Scagliotti G, Groen HJ, et al. Standard versus alternating non-cross-resistant chemotherapy in extensive small cell lung cancer: an EORTC Phase III trial. Eur J Cancer 1996;32A: 1498-503.
47. Loehrer PJ Sr, Ansari R, Gonin R, et al. Cisplatin plus etoposide with and without ifosfamide in extensive small-cell lung cancer: a Hoosier Oncology Group study. J Clin Oncol 1995;13:2594-9.
48. Thatcher N, Qian W, Girling DJ, et al. Ifosfamide, carboplatin, and etoposide with midcycle vincristine versus standard chemotherapy in patients with small-cell lung cancer and good performance status: clinical and quality-of-life results of the British Medical Research Council multicenter randomized LU21 trial. J Clin Oncol 2005;23:8371-9.
49. Faylona EA, Loehrer PJ, Ansari R, et al. Phase II study of daily oral etoposide plus ifosfamide plus cisplatin for previously treated recurrent small-cell lung cancer: a Hoosier Oncology Group Trial. J Clin Oncol 1995;13:1209-14.
50. Cohen MH, Creaven PJ, Fossieck BE Jr, et al. Intensive chemotherapy of small cell bronchogenic carcinoma. Cancer Treat Rep 1977;61:349-54.
51. Figueredo AT, Hryniuk WM, Strautmanis I, et al. Co-trimoxazole prophylaxis during high-dose chemotherapy of small-cell lung cancer. J Clin Oncol 1985;3:54-64.
52. Johnson DH, Einhorn LH, Birch R, et al. A randomized comparison of high-dose versus conventional-dose cyclophosphamide, doxorubicin, and vincristine for extensive-stage small-cell lung cancer: a phase III trial of the Southeastern Cancer Study Group. J Clin Oncol 1987;5:1731-8.
53. Ihde DC, Mulshine JL, Kramer BS, et al. Prospective randomized comparison of high-dose and standard-dose etoposide and cisplatin chemotherapy in patients with extensive-stage small-cell lung cancer. J Clin Oncol 1994;12:2022-34.
54. Arriagada R, Le Chevalier T, Pignon JP, et al. Initial chemotherapeutic doses and survival in patients with limited small-cell lung cancer. N Engl J Med 1993;329:1848-52.
55. Furuse K, Fukuoka M, Nishiwaki Y, et al. Phase III study of intensive weekly chemotherapy with recombinant human granulocyte colony-stimulating factor versus standard chemotherapy in extensive-disease small-cell lung cancer. The Japan Clinical Oncology Group. J Clin Oncol 1998;16:2126-32.
56. Murray N, Livingston RB, Shepherd FA, et al. Randomized study of CODE versus alternating CAV/EP for extensive-stage small-cell lung cancer: an Intergroup Study of the National Cancer Institute of Canada Clinical Trials Group and the Southwest Oncology Group. J Clin Oncol 1999;17:2300-8.
57. Steward WP, von Pawel J, Gatzemeier U, et al. Effects of granulocyte-macrophage colony-stimulating factor and dose intensification of V-ICE chemotherapy in small-cell lung cancer: a prospective randomized study of 300 patients. J Clin Oncol 1998;16:642-50.
58. Thatcher N, Girling DJ, Hopwood P, et al. Improving survival without reducing quality of life in small-cell lung cancer patients by increasing the dose-intensity of chemotherapy with granulocyte colony-stimulating factor support: results of a British Medical Research Council Multicenter Randomized Trial. Medical Research Council Lung Cancer Working Party. J Clin Oncol 2000;18:395-404.
59. Ardizzoni A, Tjan-Heijnen VC, Postmus PE, et al. Standard versus intensified chemotherapy with granulocyte colony-stimulating factor support in small-cell lung cancer: a prospective European Organization for Research and Treatment of Cancer-Lung Cancer Group Phase III Trial-08923. J Clin Oncol 2002;20:3947-55.
60. Sculier JP, Paesmans M, Lecomte J, et al. A three-arm phase III randomised trial assessing, in patients with extensive-disease small-cell lung cancer, accelerated chemotherapy with support of haematological growth factor or oral antibiotics. Br J Cancer 2001;85:1444-51.
61. Woll PJ, Thatcher N, Lomax L, et al. Use of hematopoietic progenitors in whole blood to support dose-dense chemotherapy: a randomized phase II trial in small-cell lung cancer patients. J Clin Oncol 2001;19:712-9.
62. Lorigan P, Woll PJ, O'Brien ME, et al. Randomized phase III trial of dose-dense chemotherapy supported by whole-blood hematopoietic progenitors in better-prognosis small-cell lung cancer. J Natl Cancer Inst 2005;97:666-74.
63. Murray N, Shah A, Osoba D, et al. Intensive weekly chemotherapy for the treatment of extensive-stage small-cell lung cancer. J Clin Oncol 1991;9:1632-8.
64. Klasa RJ, Murray N, Coldman AJ. Dose-intensity meta-analysis of chemotherapy regimens in small-cell carcinoma of the lung. J Clin Oncol 1991;9:499-508.
65. Masuda N, Fukuoka M, Kusunoki Y, et al. CPT-11: a new derivative of camptothecin for the treatment of refractory or relapsed small-cell lung cancer. J Clin Oncol 1992;10:1225-9.
66. Le Chevalier T, Ibrahim N, Chomy P, et al. A phase II study of irinotecan (CPT-11) in patients with small cell lung cancer (SCLC) progressing after initial response to first-line chemotherapy (Meeting abstract). 1997 ASCO Annual Meeting.
67. Ando M, Kobayashi K, Yoshimura A, et al. Weekly administration of irinotecan (CPT-11) plus cisplatin for refractory or relapsed small cell lung cancer. Lung Cancer 2004;44:121-7.
68. Kudoh S, Fujiwara Y, Takada Y, et al. Phase II study of irinotecan combined with cisplatin in patients with previously untreated small-cell lung cancer. West Japan Lung Cancer Group. J Clin Oncol 1998;16:1068-74.
69. Nakanishi Y, Takayama K, Takano K, et al. Second-line chemotherapy with weekly cisplatin and irinotecan in patients with refractory lung cancer. Am J Clin Oncol 1999;22:399-402.
70. Noda K, Nishiwaki Y, Kawahara M, et al. Irinotecan plus cisplatin compared with etoposide plus cisplatin for extensive small-cell lung cancer. N Engl J Med 2002;346:85-91.
71. Hanna NH, Einhorn L, Sandler A, et al. Randomized phase III trial comparing irinotecan/cisplatin with etoposide/cisplatin in patients with previously untreated extensive-stage disease small-cell lung cancer. J Clin Oncol 2006;24:2038-43.
72. Kudoh S, Nakamura S, Nakano T, et al. Irinotecan and etoposide for previously untreated extensive-disease small cell lung cancer: a phase II trial of West Japan Thoracic Oncology Group. Lung Cancer 2005;49:263-9.
73. Hirose T, Horichi N, Ohmori T, et al. Phase II study of irinotecan and carboplatin in patients with the refractory or relapsed small cell lung cancer. Lung Cancer 2003;40:333-8.
74. Masuda N, Matsui K, Negoro S, et al. Combination of irinotecan and etoposide for treatment of refractory or relapsed small-cell lung cancer. J Clin Oncol 1998;16:3329-34.
75. Ichiki M, Rikimaru T, Gohara, et al. Phase II study of irinotecan and ifosfamide in patients with advanced non-small cell lung cancer. Oncology 2003;64:306-11.
76. Agelaki S, Syrigos K, Christophylakis C, et al. A multicenter phase II study of the combination of irinotecan and gemcitabine in previously treated patients with small-cell lung cancer. Oncology 2004;66:192-6.
77. Goto K, Sekine I, Nishiwaki Y, et al. Multi-institutional phase II trial of irinotecan, cisplatin, and etoposide for sensitive relapsed

small-cell lung cancer. Br J Cancer 2004;91:659-65.
78. Lara PN Jr, Natale R, Crowley J, et al. Phase III trial of irinotecan/cisplatin compared with etoposide/cisplatin in extensive-stage small-cell lung cancer: clinical and pharmacogenomic results from SWOG S0124. J Clin Oncol 2009;27:2530.
79. Schiller JH, Kim K, Hutson P, et al. Phase II study of topotecan in patients with extensive-stage small-cell carcinoma of the lung: an Eastern Cooperative Oncology Group Trial. J Clin Oncol 1996;14: 2345-52.
80. Ardizzoni A, Manegold C, Debruyne C, et al. European organization for research and treatment of cancer (EORTC) 08957 phase II study of topotecan in combination with cisplatin as second-line treatment of refractory and sensitive small cell lung cancer. Clin Cancer Res 2003;9:143-50.
81. Eckardt J, Gralla R, Palmer MC, et al. Topotecan (T) as Second-Line Therapy In Patients (Pts) with Small Cell Lung Cancer (SCLC): A Phase II Study. Ann of Oncol 1996;7. Abstract 513P.
82. von Pawel J, Gatzemeier U, Pujol JL, et al. Phase II comparator study of oral versus intravenous topotecan in patients with chemosensitive small-cell lung cancer. J Clin Oncol 2001;19:1743-9.
83. Perez-Soler R, Glisson BS, Lee JS, et al. Treatment of patients with small-cell lung cancer refractory to etoposide and cisplatin with the topoisomerase I poison topotecan. J Clin Oncol 1996;14:2785-90.
84. Christodoulou C, Kalofonos HP, Briasoulis E, et al. Combination of topotecan and cisplatin in relapsed patients with small cell lung cancer: a phase II study of the hellenic cooperative oncology group (HeCOG). Cancer Chemother Pharmacol 2006;57:207-12.
85. Quoix E, Breton JL, Gervais R, et al. A randomised phase II study of the efficacy and safety of intravenous topotecan in combination with either cisplatin or etoposide in patients with untreated extensive disease small-cell lung cancer. Lung Cancer 2005;49:253-61.
86. Eckardt JR, von Pawel J, Papai Z, et al. Open-label, multicenter, randomized, phase III study comparing oral topotecan/cisplatin versus etoposide/cisplatin as treatment for chemotherapy-naive patients with extensive-disease small-cell lung cancer. J Clin Oncol 2006;24:2044-51.
87. Hobdy EM, Kraut E, Masters G, et al. A phase II study of topotecan and cyclophosphamide with G-CSF in patients with advanced small cell lung cancer. Cancer Biol Ther 2004;3:89-93.
88. Ramalingam S, Belani CP, Day R, et al. Phase II study of topotecan and paclitaxel for patients with previously untreated extensive stage small-cell lung cancer. Ann Oncol 2004;15:247-51.
89. von Pawel J, Schiller JH, Shepherd FA, et al. Topotecan versus cyclophosphamide, doxorubicin, and vincristine for the treatment of recurrent small-cell lung cancer. J Clin Oncol 1999;17:658-67.
90. Ardizzoni A, Hansen H, Dombernowsky P, et al. Topotecan, a new active drug in the second-line treatment of small-cell lung cancer: a phase II study in patients with refractory and sensitive disease. The European Organization for Research and Treatment of Cancer Early Clinical Studies Group and New Drug Development Office, and the Lung Cancer Cooperative Group. J Clin Oncol 1997;15:2090-6.
91. Ettinger DS, Finkelstein DM, Sarma RP, Johnson DH. Phase II study of paclitaxel in patients with extensive-disease small-cell lung cancer: an Eastern Cooperative Oncology Group study. J Clin Oncol 1995;13:1430-5.
92. Kirschling RJ, Grill JP, Marks RS, et al. Paclitaxel and G-CSF in previously untreated patients with extensive stage small-cell lung cancer: a phase II study of the North Central Cancer Treatment Group. Am J Clin Oncol 1999;22:517-22.
93. Smit EF, Fokkema E, Biesma B, et al. A phase II study of paclitaxel in heavily pretreated patients with small-cell lung cancer. Br J Cancer 1998;77:347-51.
94. Neubauer M, Schwartz J, Caracandas J, et al. Results of a phase II study of weekly paclitaxel plus carboplatin in patients with extensive small-cell lung cancer with Eastern Cooperative Oncology Group Performance Status of 2, or age > or = 70 years. J Clin Oncol 2004;22:1872-7.
95. Perez EA, Geoffroy FJ, Hillman S, et al. Phase II study of oral etoposide and intravenous paclitaxel in extensive-stage small cell lung cancer. Lung Cancer 2004;44:347-53.
96. Glisson BS, Kurie JM, Perez-Soler R, et al. Cisplatin, etoposide, and paclitaxel in the treatment of patients with extensive small-cell lung carcinoma. J Clin Oncol 1999;17:2309-15.
97. Hainsworth JD, Gray JR, Stroup SL, et al. Paclitaxel, carboplatin, and extended-schedule etoposide in the treatment of small-cell lung cancer: comparison of sequential phase II trials using different dose-intensities. Clin Oncol 1997;15:3464-70.
98. Kelly K, Lovato L, Bunn PA Jr, et al. Cisplatin, etoposide, and paclitaxel with granulocyte colony-stimulating factor in untreated patients with extensive-stage small cell lung cancer: a phase II trial of the Southwest Oncology Group. Clin Cancer Res 2001;7: 2325-9.
99. Mavroudis D, Papadakis E, Veslemes M, et al. A multicenter randomized clinical trial comparing paclitaxel-cisplatin-etoposide versus cisplatin-etoposide as first-line treatment in patients with small-cell lung cancer. Ann Oncol 2001;12:463-70.
100. Niell HB, Herndon JE 2nd, Miller AA, et al. Randomized phase III intergroup trial of etoposide and cisplatin with or without paclitaxel and granulocyte colony-stimulating factor in patients with extensive-stage small-cell lung cancer: Cancer and Leukemia Group B Trial 9732. J Clin Oncol 2005;23:3752-9.
101. Reck M, von Pawel J, Macha HN, et al. Randomized phase III trial of paclitaxel, etoposide, and carboplatin versus carboplatin, etoposide, and vincristine in patients with small-cell lung cancer. J Natl Cancer Inst 2003;95:1118-27.
102. Hainsworth JD, Morrissey LH, Scullin DC Jr, et al. Paclitaxel, carboplatin, and topotecan in the treatment of patients with small cell lung cancer: a phase II trial of the Minnie Pearl Cancer Research Network. Cancer 2002;94:2426-33.
103. Smyth JF, Smith IE, Sessa C, et al. Activity of docetaxel (Taxotere) in small cell lung cancer. The Early Clinical Trials Group of the EORTC. Eur J Cancer 1994;30A:1058-60.
104. Latreille J, Cormier Y, Martins H, et al. Phase II study of docetaxel (taxotere) in patients with previously untreated extensive small cell lung cancer. Invest New Drugs 1996;13:343-5.
105. Hesketh PJ, Crowley JJ, Burris HA 3rd, et al. Evaluation of docetaxel in previously untreated extensive-stage small cell lung cancer: a Southwest Oncology Group phase II trial. Cancer J Sci Am 1999;5:237-41.
106. Agelaki S, Veslemes M, Syrigos K, et al. A multicenter phase II study of the combination of gemcitabine and docetaxel in previously treated patients with small cell lung cancer. Lung Cancer 2004;43:329-33.
107. Skarlos DV, Dimopoulos AM, Kosmidis P, et al. Docetaxel and gemcitabine combination, as first-line treatment, in patients with extensive disease small-cell lung cancer. A phase II study of the Hellenic Cooperative Oncology Group. Lung Cancer 2003;41:107-11.
108. Hainsworth JD, Carrell D, Drengler RL, et al. Weekly combination chemotherapy with docetaxel and gemcitabine as first-line treatment for elderly patients and patients with poor performance status who have extensive-stage small cell lung carcinoma:

a Minnie Pearl Cancer Research Network phase II trial. Cancer 2004;100:2437-41.
109. Higano CS, Crowley JJ, Veith RV, Livingston RB. A phase II trial of intravenous vinorelbine in previously untreated patients with extensive small cell lung cancer, a Southwest Oncology Group study. Invest New Drugs 1997;15:153-6.
110. Tummarello D, Graziano F, Giordani P. Phase II study of vinorelbine (VNB) in small cell lung cancer (SCLC) patients (pts) unsuitable for standard chemotherapy (CHT) (Meeting abstract). 1995 ASCO Meeting. Abstract 1137.
111. Jassem J, Karnicka-Młodkowska H, van Pottelsberghe C, et al. Phase II study of vinorelbine (Navelbine) in previously treated small cell lung cancer patients. EORTC Lung Cancer Cooperative Group. Eur J Cancer 1993;29A:1720-2.
112. Furuse K, Kubota K, Kawahara M, et al. Phase II study of vinorelbine in heavily previously treated small cell lung cancer. Japan Lung Cancer Vinorelbine Study Group. Early Phase II study of vinorelbine (VRB) in small cell lung cancer. Oncology 1996;53:169-72.
113. Johnson E, Lake D, Herndon JE 2nd, et al. Phase II trial of vinorelbine plus doxorubicin in relapsed small-cell lung cancer: CALGB 9332. Am J Clin Oncol 2004;27:19-23.
114. Gridelli C, Rossi A, Barletta E, et al. Carboplatin plus vinorelbine plus G-CSF in elderly patients with extensive-stage small-cell lung cancer: a poorly tolerated regimen. Results of a multicentre phase II study. Lung Cancer 2002;36:327-32.
115. Mackay HJ, O'Brien M, Hill S, et al. A phase II study of carboplatin and vinorelbine in patients with poor prognosis small cell lung cancer. Clin Oncol 2003;15:181-5.
116. Johnson E, Lake D, Herndon JE 2nd, et al. Phase II trial of vinorelbine plus doxorubicin in relapsed small-cell lung cancer: CALGB 9332. Am J Clin Oncol 2004;27:19-23.
117. Hainsworth JD, Burris HA 3rd, Erland JB, et al. Combination chemotherapy with gemcitabine and vinorelbine in the treatment of patients with relapsed or refractory small cell lung cancer: a phase II trial of the Minnie Pearl Cancer Research Network. Cancer Invest 2003;21:193-9.
118. Rapti A, Agelidou A, Stergiou I, et al. Combination of vinorelbine plus gemcitabine in previously treated patients with small cell lung cancer: a multicentre phase II study. Lung Cancer 2005;49: 241-4.
119. Dudek AZ, Le niewski-Kmak K, Bliss RL, et al. Pilot phase II study of gemcitabine and vinorelbine in patients with recurrent or refractory small cell lung cancer. Lung 2005;183:43-52.
120. Masters GA, Declerck L, Blanke C, et al. Phase II trial of gemcitabine in refractory or relapsed small-cell lung cancer: Eastern Cooperative Oncology Group Trial 1597. J Clin Oncol 2003;21:1550-5.
121. Hoang T, Kim K, Jaslowski A, et al. Phase II study of second-line gemcitabine in sensitive or refractory small cell lung cancer. Lung Cancer 2003;42:97-102.
122. van der Lee I, Smit EF, van Putten JW, et al. Single-agent gemcitabine in patients with resistant small-cell lung cancer. Ann Oncol 2001;12:557-61.
123. Cormier Y, Eisenhauer E, Muldal A, et al. Gemcitabine is an active new agent in previously untreated extensive small cell lung cancer (SCLC). A study of the National Cancer Institute of Canada Clinical Trials Group. Ann Oncol 1994;5:283-5.
124. Vansteenkiste J, Gatzemeier U, Manegold C, et al. Gemcitabine plus etoposide in chemonaive extensive disease small-cell lung cancer: a multi-centre phase II study. Ann Oncol 2001;12:835-40.
125. Agelaki S, Syrigos K, Christophylakis C, et al. A multicenter phase II study of the combination of irinotecan and gemcitabine in previously treated patients with small-cell lung cancer. Oncology 2004;66:192-6.
126. Schuette W, Nagel S, Juergens S, et al. Phase II trial of gemcitabine/irinotecan in refractory or relapsed small-cell lung cancer. Clin Lung Cancer 2005;7:133-7.
127. Hainsworth JD, Burris HA 3rd, Erland JB, et al. Combination chemotherapy with gemcitabine and vinorelbine in the treatment of patients with relapsed or refractory small cell lung cancer: a phase II trial of the Minnie Pearl Cancer Research Network. Cancer Invest 2003;21:193-9.
128. Rapti A, Agelidou A, Stergiou I, et al. Combination of vinorelbine plus gemcitabine in previously treated patients with small cell lung cancer: a multicentre phase II study. Lung Cancer 2005;49: 241-4.
129. Dudek AZ, Le niewski-Kmak K, Bliss RL, et al. Pilot phase II study of gemcitabine and vinorelbine in patients with recurrent or refractory small cell lung cancer. Lung 2005;183:43-52.
130. Agelaki S, Veslemes M, Syrigos K, et al. A multicenter phase II study of the combination of gemcitabine and docetaxel in previously treated patients with small cell lung cancer. Lung Cancer 2004;43:329-33.
131. Hainsworth JD, Carrell D, Drengler RL, et al. Weekly combination chemotherapy with docetaxel and gemcitabine as first-line treatment for elderly patients and patients with poor performance status who have extensive-stage small cell lung carcinoma: a Minnie Pearl Cancer Research Network phase II trial. Cancer 2004;100: 2437-41.
132. Lee SM, James LE, Qian W, et al. Comparison of gemcitabine and carboplatin versus cisplatin and etoposide for patients with poor-prognosis small cell lung cancer. Thorax 2009;64:75-80.
133. De Marinis F, Migliorino MR, Paoluzzi L, et al. Phase I/II trial of gemcitabine plus cisplatin and etoposide in patients with small-cell lung cancer. Lung Cancer 2003;39:331-8.
134. De Marinis F, Nelli F, Lombardo M, et al. A multicenter, randomized, Phase II study of cisplatin, etoposide, and gemcitabine or cisplatin plus gemcitabine as first-line treatment in patients with poor-prognosis small cell lung carcinoma. Cancer 2005;103:772-9.
135. Yana T, Negoro S, Takada M, et al. Phase II study of amrubicin in previously untreated patients with extensive-disease small cell lung cancer: West Japan Thoracic Oncology Group (WJTOG) study. Invest New Drugs 2007;25:253-8.
136. Kobayashi M, Matsui K, Iwamoto Y, et al. Phase II study of sequential triplet chemotherapy, irinotecan and cisplatin followed by amrubicin, in patients with extensive-stage small cell lung cancer: West Japan Thoracic Oncology Group Study 0301. J Thorac Oncol 2010;5:1075-80.
137. O'Brien ME, Konopa K, Lorigan P, et al. Randomised phase II study of amrubicin as single agent or in combination with cisplatin versus cisplatin etoposide as first-line treatment in patients with extensive stage small cell lung cancer - EORTC 08062. Eur J Cancer 2011;47:2322-30.
138. Ohe Y, Negoro S, Matsui K, et al. Phase I-II study of amrubicin and cisplatin in previously untreated patients with extensive-stage small-cell lung cancer. Ann Oncol 2005;16:430-6.
139. Onoda S, Masuda N, Seto T, et al. Phase II trial of amrubicin for treatment of refractory or relapsed small-cell lung cancer: Thoracic Oncology Research Group Study 0301. J Clin Oncol 2006;24:5448-53.
140. Inoue A, Sugawara S, Yamazaki K, et al. Randomized phase II trial comparing amrubicin with topotecan in patients with previously treated small-cell lung cancer: North Japan Lung Cancer Study Group Trial 0402. J Clin Oncol 2008;26:5401-6.
141. Inoue A, Ishimoto O, Fukumoto S, et al. A phase II study of amrubicin combined with carboplatin for elderly patients with small-

cell lung cancer: North Japan Lung Cancer Study Group Trial 0405. Ann Oncol 2010;21:800-3.
142. Ettinger DS, Jotte R, Lorigan P, et al. Phase II study of amrubicin as second-line therapy in patients with platinum-refractory small-cell lung cancer. J Clin Oncol 2010;28:2598-603.
143. Jotte R, Conkling P, Reynolds C, et al. Randomized phase II trial of single-agent amrubicin or topotecan as second-line treatment in patients with small-cell lung cancer sensitive to first-line platinum-based chemotherapy. J Clin Oncol 2011;29:287-93.
144. Hirose T, Nakashima M, Shirai T, et al. Phase II trial of amrubicin and carboplatin in patients with sensitive or refractory relapsed small-cell lung cancer. Lung Cancer 2011;73:345-50.
145. Nogami N, Hotta K, Kuyama S, et al. A phase II study of amrubicin and topotecan combination therapy in patients with relapsed or extensive-disease small-cell lung cancer: Okayama Lung Cancer Study Group Trial 0401. Lung Cancer 2011;74:80-4.
146. Jotte R, et al. Randomized phase III trial of amrubicin versus topotecan as second-line treatment for small cell lung cancer. J Clin Oncol 2011;29:453s.
147. Pignon JP, Arriagada R, Ihde DC, et al. A meta-analysis of thoracic radiotherapy for small-cell lung cancer. N Engl J Med 1992;327: 1618-24.
148. Huncharek M, McGarry R. A meta-analysis of the timing of chest irradiation in the combined modality treatment of limited-stage small cell lung cancer. Oncologist 2004;9:665-72.
149. Turrisi AT 3rd, Kim K, Blum R, et al. Twice-daily compared with once-daily thoracic radiotherapy in limited small-cell lung cancer treated concurrently with cisplatin and etoposide. N Engl J Med 1999;340:265-71.
150. Fried DB, Morris DE, Poole C, et al. Systematic review evaluating the timing of thoracic radiation therapy in combined modality therapy for limited-stage small-cell lung cancer. J Clin Oncol 2004;22:4837-45.
151. Takada M, Fukuoka M, Kawahara M, et al. Phase III study of concurrent versus sequential thoracic radiotherapy in combination with cisplatin and etoposide for limited-stage small-cell lung cancer: results of the Japan Clinical Oncology Group Study 9104. J Clin Oncol 2002;20:3054.
152. Auperin A, Arriagada R, Pignon JP, et al. Prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission. Prophylactic Cranial Irradiation Overview Collaborative Group. N Engl J Med 1999;341:476-84.
153. Gregor A, Cull A, Stephens RJ, et al. Prophylactic cranial irradiation is indicated following complete response to induction therapy in small cell lung cancer: results of a multicentre randomised trial. United Kingdom Coordinating Committee for Cancer Research (UKCCCR) and the European Organization for Research and Treatment of Cancer (EORTC). Eur J Cancer 1997;33:1752-8.
154. Slotman BJ, Moyer ME, Bottomley A, et al. Prophylactic cranial irradiation in extensive disease small-cell lung cancer: short-term health-related quality of life and patient reported symptoms: results of an international Phase III randomized controlled trial by the EORTC Radiation Oncology and Lung Cancer Groups. J Clin Oncol 2009;27:78.
155. Kerbel RS. Clinical trials of antiangiogenic drugs: opportunities, problems, and assessment of initial results. J Clin Oncol 2001;19:45S-51S.
156. Salven P, Ruotsalainen T, Mattson K, Joensuu H. High pre-treatment serum level of vascular endothelial growth factor (VEGF) is associated with poor outcome in small-cell lung cancer. Int J Cancer 1998;79:144-6.
157. D'Amato RJ, Loughnan MS, Flynn E, Folkman J. Thalidomide is an inhibitor of angiogenesis. Proc Natl Acad Sci USA. 1994;91:4082-5.
158. Kenyon BM, Browne F, D'Amato RJ. Effects of thalidomide and related metabolites in a mouse corneal model of neovascularization. Exp Eye Res 1997;64:971-8.
159. Brock CS, Lee SM. Anti-angiogenic strategies and vascular targeting in the treatment of lung cancer. Eur Respir J 2002;19:557-70.
160. Dowlati A, Subbiah S, Cooney M, et al. Phase II trial of thalidomide as maintenance therapy for extensive stage small cell lung cancer after response to chemotherapy. Lung Cancer 2007;56:377-81.
161. Lee SM, James LE, Mohamed-Ali V, et al. A phase II study of carboplatin/etoposide with thalidomide in small cell lung cancer. ASCO Annual meeting 2002. Abstract 1251.
162. Lee SM, Woll PJ, Rudd R, et al. Anti-angiogenic therapy using thalidomide combined with chemotherapy in small cell lung cancer: a randomized, double-blind, placebo-controlled trial. J Natl Cancer Inst 2009;101:1049-57.
163. Jalal S, Bedano P, Einhorn L, et al. Paclitaxel plus bevacizumab in patients with chemosensitive relapsed small cell lung cancer: a safety, feasibility, and efficacy study from the Hoosier Oncology Group. J Thorac Oncol 2010;5:2008-11.
164. Horn L, Dahlberg SE, Sandler AB, et al. Phase II study of cisplatin plus etoposide and bevacizumab for previously untreated, extensive-stage small-cell lung cancer: Eastern Cooperative Oncology Group Study E3501. J Clin Oncol 2009;27:6006-11.
165. Spigel DR, Greco FA, Zubkus JD, et al. Phase II trial of irinotecan, carboplatin, and bevacizumab in the treatment of patients with extensive-stage small-cell lung cancer. J Thorac Oncol 2009;4:1555-60.
166. Ready NE, Dudek AZ, Pang HH, et al. Cisplatin, Irinotecan, and Bevacizumab for Untreated Extensive-Stage Small-Cell Lung Cancer: CALGB 30306, a Phase II Study. J Clin Oncol 2011. Epub ahead of print.
167. Gitlitz BJ, Moon J, Gandara DR, et al. Sorafenib in platinum-treated patients with extensive stage small cell lung cancer: a Southwest Oncology Group (SWOG 0435) phase II trial. J Thorac Oncol 2010;5:1835-40.
168. Huang YG, Xu YY, Zheng ZH. Significance of MOC-31 and CD56 detection in human lung carcinoma tissues. Ai Zheng 2002;21: 1235-7.
169. Johnson BE, Fischer T, Fischer B, et al. Phase II study of imatinib in patients with small cell lung cancer. Clin Cancer Res 2003;9:5880-7.
170. Dy GK, Miller AA, Mandrekar SJ, et al. A phase II trial of imatinib (ST1571) in patients with c-kit expressing relapsed small-cell lung cancer: a CALGB and NCCTG study. Ann Oncol 2005;16:1811-6.
171. Shepherd FA, Giaccone G, Seymour L, et al. Prospective, randomized, double-blind, placebo-controlled trial of marimastat after response to first-line chemotherapy in patients with small-cell lung cancer: a trial of the National Cancer Institute of Canada-Clinical Trials Group and the European Organization for Research and Treatment of Cancer. J Clin Oncol 2002;20:4434-9.
172. Heymach JV, De Porre PM, Russell F, et al. ASCO Annual meeting 2002. Abstract 1275.
173. Pandya KJ, Levy DE, Hidalgo M, et al. A randomized, phase II ECOG trial of two dose levels of temsirolimus (CCI-779) in patients with extensive stage small cell lung cancer in remission after induction chemotherapy. A preliminary report. ASCO Annual Meeting 2005. Abstract 7005.
174. Tarhini A, Kotsakis A, Gooding W, et al. Phase II study of everolimus (RAD001) in previously treated small cell lung cancer. Clin Cancer Res 2010;16:5900-7.

175. Johl J, Chansky K, Lara PN, et al. The proteasome inhibitor PS-341 (Bortezomib) in platinum (plat)-treated extensive-stage small cell lung cancer (E-SCLC): A SWOG (0327) phase II trial. ASCO Annual meeting 2005. Abstract 7047.
176. van Zandwijk N, Groen HJ, Postmus PE, et al. Role of recombinant interferon-gamma maintenance in responding patients with small cell lung cancer. A randomised phase III study of the EORTC Lung Cancer Cooperative Group. Eur J Cancer 1997;33:1759-66.
177. Maurer LH, Pajak T, Eaton W, et al. Combined modality therapy with radiotherapy, chemotherapy, and immunotherapy in limited small-cell carcinoma of the lung: a Phase III cancer and Leukemia Group B Study. J Clin Oncol 1985;3:969-76.
178. Grant SC, Kris MG, Houghton AN, Chapman PB. Long survival of patients with small cell lung cancer after adjuvant treatment with the anti-idiotypic antibody BEC2 plus Bacillus Calmette-Guérin. Clin Cancer Res 1999;5:1319-23.
179. Giaccone G, Debruyne C, Felip E, et al. Phase III study of adjuvant vaccination with Bec2/bacille Calmette-Guerin in responding patients with limited-disease small-cell lung cancer (European Organisation for Research and Treatment of Cancer 08971-08971B; Silva Study). J Clin Oncol 2005;23:6854-64.
180. Hurwitz JL, McCoy F, Scullin P, Fennell DA. New advances in the second-line treatment of small cell lung cancer. Oncologist 2009;14:986-94.
181. Rudin CM, Salgia R, Wang X, et al. Randomized phase II study of carboplatin and etoposide with or without the Bcl-2 antisense oligonucleotide oblimersen for extensive-stage small-cell lung cancer: CALGB 30103. J Clin Oncol 2008;26:870-876.
182. Paik PK, Rudin CM, Pietanza MC, et al. A phase II study of obatoclax mesylate, a Bcl-2 antagonist, plus topotecan in relapsed small cell lung cancer. Lung Cancer 2011. Epub ahead of print.