Drugs 2007; 67 (15): 2135-2152
0012-6667/07/0015-2135/$49.95/0

Modern Management of Small-Cell Lung Cancer

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Contents

Abstract

In this article, we review best standard practice for the management of small-cell lung cancer (SCLC) and indicate the likely areas of development over the next 5–10 years. A number of prognostic scores have been developed and these allow more rational decisions on treatment.

Treatment with cisplatin plus etoposide with early, concurrent radiotherapy is the standard of care for patients with limited-stage disease (LD) suitable for this approach. A 5-year survival rate of 25% has been reported for concurrent hyperfractionated radiotherapy; however, the applicability of this in most busy hospitals is uncertain and this treatment is currently being compared with a high-dose, once-daily regimen. Patients unsuitable for concurrent chemo-radiotherapy are treated with a sequential approach. Patients with LD responding to treatment should be offered prophylactic cranial irradiation (PCI). A variety of strategies for improving survival have been investigated. Intensification of chemotherapy has

not shown any clear survival advantage, but maintenance of dose intensity in patients with good prognosis is important. The evidence around maintenance therapy is conflicting and this is not routinely used.

Patients with extensive-stage disease but few other adverse prognostic factors should be treated with a platinum compound plus etoposide, and carboplatin is a reasonable choice. Responding patients should be offered PCI as this is associated with a survival benefit. The initial positive results for irinotecan have not been repeated in a larger study. Age is not a prognostic factor, but caution needs to be exercised as prognostic scores do not reflect co-morbidity.

Patients with relapsed disease have a poor prognosis, but there is evidence of a survival benefit for salvage chemotherapy in those fit for treatment. The choice of treatment will depend on a number of factors, including the disease-free interval. Topotecan is the only drug licensed in this indication, but myelosuppression is considerable.

A number of new drugs are under evaluation and showing promise in SCLC. One of the most promising of these is amrubicin. A large randomised study has failed to show any benefit from the addition of thalidomide to chemotherapy with carboplatin and etoposide in extensive-stage disease patients responding to chemotherapy. Studies of a number of targeted treatments are also ongoing. The challenge for the future is to identify new targets, overcome drug-resistance mechanisms and redundancy in biological systems, and incorporate these new treatments into concurrent chemo-radiotherapy schedules.

Lung cancer is the leading cause of cancer-related death in the world. Recent epidemiological data suggest that the incidence of small-cell lung cancer (SCLC) is falling and that the proportion of lung cancer patients with small-cell histology is now ≈13% (compared with 20–25% previously).[1] The last 20 years have seen considerable efforts to improve the outcome for these patients, although progress has been slow. We now have a far greater understanding of the optimum chemotherapy, the importance of appropriate and timely radiotherapy, the importance of prognostic factors and the impact of co-existing morbidity. As we move into the era of targeted therapy, there is hope that many of these new treatment modalities will be useful in SCLC. Here, we review what we consider to be the optimum management of patients with SCLC, taking into account the most current data, and provide an idea of direction for further improvements in the treatment of this difficult tumour type.

2. Staging and Prognostic Scores

Characterisation of patients with SCLC into limited-stage disease (LD) and extensive-stage disease (ED) has been the basis of treatment choice for a number of years. Patients are staged as LD or ED based on the anatomical extent of the disease as proposed originally by the Veterans Administration Lung Study Group (VALG).[2] In the VALG staging system, LD is defined as disease confined to one hemithorax, which can be safely encompassed within a tolerable radiation field. Patients with LD are currently treated with a combined modality approach. All other patients are considered to have ED. This system is generally accepted in clinical practice; however, it does not accurately segregate patients into homogenous prognostic groups and the appropriate classification of selected sites remains controversial. As a result, the consensus report of the International Association of Lung Cancer (IASLC) revised the VALG classification,[3] in accordance with the tumor, node, metastasis (TNM)

system.[4] In the IASLC system, LD is defined essentially as stages I–IIIB, and ED is limited to patients with distant metastasis. Micke et al.[5] compared the prognostic utility of the two systems in a retrospective analysis of 109 consecutive patients treated between 1989 and 1999. Twenty-seven patients (25%) were classified as LD according to the VALG classification, whereas 48% were classified as LD according to IASLC criteria. The IASLC criteria had greater discriminatory power in predicting survival.

Multivariate analysis studies have shown that a number of other factors have independent prognostic significance over and above anatomical staging. These include performance status (PS) and various biochemical factors. The Manchester Prognostic Score, initially published by Cerny et al.[6] in 1987, and subsequently validated by Rawson and Peto,[7] consists of five prognostic factors (tumour stage, PS, and serum sodium, serum alkaline phosphatase and serum lactate dehydrogenase levels). Other groups have reported similar results and these have been summarised by Sagman et al.[8] and Thatcher et al.[9] Using a cumulative risk score, patients fall into three main groups (Manchester Score 0–1, 2–3 or >4).[6] Over 50% of patients with a Manchester Prognostic Score of 0–1 will be alive at 1 year; no patients with a score of 4–5 will be alive at 1 year. The identification of groups of patients with better or worse prognosis has allowed rational development of treatment approaches. A number of other, similar prognostic scores have been devised, some of which include response to therapy.[10,11]

3. Patients with Good Prognosis Disease

3.1 Which Chemotherapy?

The gold standard chemotherapy for patients with good prognosis disease is a platinum-based regimen, typically cisplatin plus etoposide (PE). Many studies have reported median survival of 17–18 months with cisplatin combined with radiotherapy, which is significantly higher than that generally reported for anthracycline-based therapy.[12] A number of studies have compared PE with anthracycline-based therapy. Most failed to demonstrate superiority for PE, possibly because many of these studies were conducted almost exclusively in patients with ED.[13-15] A recent comparison of PE with cyclophosphamide plus epirubicin plus vincristine (CEV) showed that overall survival was significantly better for patients randomised to receive PE (10.2 vs 7.8 months, respectively; $p = 0.0004$).[16] In subset analysis, the advantage was confined to patients with LD (14.5 vs 9.7 months, respectively; $p = 0.001$), with no survival advantage seen in patients with ED (8.4 vs 6.5 months, respectively; $p > 0.05$). However, a recent overview of US National Cancer Institute-sponsored trials in ED-SCLC demonstrated that platinum-containing regimens do impart a relatively modest survival advantage compared with non-platinum regimens.[17] A further meta-analysis of 19 trials published between 1981 and 1999 showed a significant survival advantage for patients receiving platinum-based chemotherapy compared with those not receiving a platinum agent.[18] A randomised study from the UK Medical Research Council (MRC) that compared ifosfamide, carboplatin, etoposide plus vincristine (ICE-V) with standard chemotherapy (predominantly cyclophosphamide, doxorubicin plus etoposide [CDE]), showed better survival with acceptable toxicity with ICE-V.[19]

3.2 Cisplatin versus Carboplatin

Cisplatin is associated with significant toxicity and requires fluid hydration, which can be problematic in patients with cardiovascular disease. Carboplatin is active in SCLC, is dosed according to renal function and is associated with less non-haematological toxicity.[20] The Hellenic Oncology Group conducted a phase III trial comparing PE with carboplatin plus etoposide.[21] The median survival was 11.8 months in the cisplatin arm and 12.5 months in carboplatin-treated patients. Whilst this difference was not statistically significant, the trial was underpowered to prove equivalence of the two treatment regimens in either LD or ED. PE remains the gold standard for treatment, although carboplatin plus etoposide represents an acceptable alternative.

3.3 Other Approaches

A number of different approaches have been used, including addition of further agents to the existing regimen, dose intensification, use of maintenance treatment and alternation of non-cross resistant regimens. Most of these approaches failed to improve survival convincingly and their role remains uncertain.

There is no clear evidence that adding a third or forth drug to standard therapy is advantageous. The Hoosier Oncology Group evaluated the addition of ifosfamide to cisplatin plus etoposide in a phase III trial of 171 patients with ED.[22] The 2-year survival rate increased from 5% to 13% with the addition of ifosfamide, at the expense of increased toxicity.

Studies evaluating alternating, non-cross resistant treatment have shown no clear advantage and an increased toxicity with this approach.[13-15,23]

Maintenance chemotherapy in responding patients, either by continuing initial therapy or substituting a different drug, has been evaluated in a number of studies. These trials are heterogeneous in terms of their design and have employed different chemotherapy regimens, making it difficult to draw clear conclusions. When Sculier et al.[24] conducted a critical review of 13 trials published since 1980, they concluded that the overall quality of the publications was not good, with important methodological aspects missing, such as a clear definition of the primary objective or an *a priori* estimate of the sample size necessary to conduct the trial. Whilst the majority of published studies showed an improvement in progression-free survival (PFS), only one showed an improvement in overall survival. A recent meta-analysis of 14 published randomised clinical trials involving 2550 patients indicated that maintenance chemotherapy decreased the 1- and 2-year risk of death or disease progression in SCLC and improved 1- and 2-year overall survival by 9% and 4%, respectively.[25] New randomised clinical trials are needed to further refine this approach. Maintenance chemotherapy is associated with a significant risk of toxicity and is not recommended outside the context of a clinical trial.

The role of dose intensification in SCLC remains unclear. Early studies showed that under-treatment compromised outcome and suggested that early dose intensification may improve survival.[26,27] Other early studies that concentrated on increasing the amount of chemotherapy given by increasing the total number cycles of treatment did not show a survival advantage for prolonged or maintenance chemotherapy, but many showed a trend in this direction.[28-33] The introduction of haemopoietic growth factors facilitated maintenance of dose intensity, and reduction in the severity and duration of neutropenic infection.[34,35] More recently, a number of clinical trials have examined the use of colony-stimulating factors to support dose-intensified chemotherapy in SCLC.[36-44] These studies have yielded conflicting results (table I). Four studies have shown that a modest increase in dose intensity (≈25–34%) was associated with a significant improvement in survival with no compromise in quality of life (QOL).[36-39] Three studies have been reported that examined combinations of the variables of interval, dose per cycle and number of cycles.[40-42] Two were in patients with poorer prognosis or ED and showed no advantage.[40,41] The European Organization for Research and Treatment of Cancer (EORTC) reported a randomised comparison of standard-dose CDE given every 3 weeks for five cycles versus intensified treatment given at 125% of the dose every 2 weeks for four cycles with granulocyte colony-stimulating factor (GCSF) support.[42] The median dose intensity delivered was 70% higher in the experimental arm; the median cumulative dose was similar in both arms. There was no difference between treatment groups in median or 2-year survival. We have reported a randomised phase III trial comparing ICE given every 4 weeks with 2-weekly ICE with GCSF and autologous blood support.[43] Despite achieving a relative dose intensity of 1.84 in the dose-accelerated arm, there was no difference in response rate (88% vs 80%, respectively), median survival (14.4 vs 13.9 months, respectively) or 2-year survival (19% vs 22%, respectively) for dose-dense compared with standard treatment. Patients receiving dose-dense treatment spent less time on treatment and had fewer

Table I. Trials comparing dose intensified (DI) with standard dose chemotherapy in small-cell lung cancer

Study	No. of patients/ disease stage	Treatment	Interval (wk)	Relative dose intensity	Median survival (mo) [DI vs standard]	2yr OS (%) [DI vs standard]	p-Value
Fukuoka et al.[36]	63 ED	CODE ± GCSF		1.17	13.7 vs 7.4	31.3 vs 6.5	<0.01
Woll et al.[37]	65 LD/ED	ICE-V	Not fixed	1.25	15.9 vs 15.0	32 vs 15	<0.05
Steward et al.[38]	299 LD/ED	ICE-V	4 vs 3	1.26	14.2 vs 11.5	33 vs 18	0.001
Thatcher et al.[39]	403 LD/ED	ACE	3 vs 2	1.34	11.5 vs 10.9	13 vs 8	0.04
James et al.[40]	167 ED	CAV/PE alternating	Six cycles at 100% 3-weekly vs 12 cycle at 50% 1.5-weekly	1.0	5.8 vs 6.4	2.5 vs 4.3	NS
Pujol et al.[41]	125 ED	PECE	6 vs 4 at 150% DI + GCSF	NA	8.9 vs 10	13 vs 3	0.0005
Ardizzoni et al.[42]	244 LD/ED	ACE	Five cycles 3-weekly vs 4 cycles twice-weekly + GCSF	1.7	12.5 vs 12.0	15 vs 18	NS
Lorigan et al.[43]	311 LD/ED	ICE	4 vs 2 + autologous blood + GCSF	1.84	14.4 vs 13.9	19 vs 22	NS
Buchholz et al.[44]	70	ICE	4 vs 2 + autologous blood + GCSF	NA	29.8 vs 17.4	62 vs 36	0.05

ACE = doxorubicin, cyclophosphamide, etoposide; **CAV** = cyclophosphamide, doxorubicin, vincristine; **CODE** = cyclophosphamide, vincristine, doxorubicin, etoposide; **ED** = extensive-stage disease; **GCSF** = granulocyte colony-stimulating factor; **ICE** = ifosfamide, carboplatin, etoposide; **ICE-V** = ICE plus vincristine; **LD** = limited-stage disease; **NA** = not available; **NS** = non-significant; **OS** = overall survival; **PE** = cisplatin, etoposide; **PECE** = cisplatin, epirubicin, cyclophosphamide, etoposide.

episodes of infection. A randomised phase II study of identical design reported a significantly better median survival for the dose-dense arm (29.8 vs 17.4 months, respectively; p = 0.02) and 2-year survival (62% vs 36%, respectively; p = 0.05).[44] However, given the small study size (only 70 patients), these results should be viewed with caution.

High-dose chemotherapy with stem-cell support has been investigated mostly as consolidation treatment in responding patients after induction chemotherapy. Currently, there is no evidence to support this approach. A randomised phase III study of late intensification with high-dose chemotherapy followed by autologous bone marrow transplantation reported an increased complete remission and relapse-free survival rate with no increase in overall survival.[45] The number of patients studied were small and there was an 18% toxic death rate in the intensification arm. The interim analysis results of a European Group for Blood and Marrow Transplantation phase III study of sequential high-dose ICE chemotherapy supported by peripheral blood progenitor cells versus standard ICE showed no evidence of improvement resulting from increasing the dose-intensity.[46] The 3-year survival rates were 18% and 19% (p = 0.767) in the high-dose and standard-dose chemotherapy groups, respectively. Median survival, PFS and overall response rate were not statistically different between the arms. The toxicity of high-dose chemotherapy was significantly worse than that of the standard arm in terms of myelosuppression, infection rate, mucositis, gastrointestinal toxicity, nausea and vomiting.

3.4 Patients with Extensive-Stage Disease and Good Prognosis

A proportion of patients will have ED but no other adverse prognostic factors. The meta-analysis by Chute et al.[17] confirmed a small but significant advantage for platinum-based therapy in this group of patients. The management of these patients should essentially be the same as for LD, except for radiation therapy. A recent study of prophylactic cranial irradiation (PCI) in ED patients responding to chemotherapy showed this conferred a survival benefit.[47]

4. Patients with Advanced Age and/or Poor Performance Status

Age alone is an uncertain prognostic factor for the outcome of treatment of SCLC and has been the basis of a number of trials.[48-54] These have shown that, in general, older patients tend to receive fewer numbers of chemotherapy cycles, more dose reductions, less intense radiotherapy and are less likely than younger patients to be included in clinical trials. However, there is no evidence of a difference in response rate, disease-free survival or overall survival in elderly patients compared with younger patients. Despite this, there is clear evidence of differential referral of patients with lung cancer for chemotherapy based on age.[55]

Advancing age is an independent prognostic factor predicting septic complications of chemotherapy and increased prevalence of coexisting illness.[49,56,57] This is particularly the case in lung cancer, where elderly patients often have a long history of cigarette smoking with the associated increased risks of coronary artery disease, cerebrovascular disease, chronic obstructive lung disease etc. Currently used prognostic scores in SCLC utilise PS, but do not include an assessment of co-morbidity. A reliable assessment of co-morbidity is important for establishing the benefits and risks of anti-cancer treatment in the elderly population, although it is important to note that co-morbidity and PS are poorly correlated in older patients.[58-63] More robust prognostic scores, taking into account both tumour and host-related prognostic factors including assessment of co-morbidity, would allow standardisation of the management of this large group of patients.

5. Patients with Poor Prognosis Disease

Recognition of an identifiable group of patients with SCLC who have a universally poor prognosis has led to a variety of treatment approaches. One study using a low-dose, high-frequency regimen to maintain dose intensity reported similar response and more myelosuppression, but also a trend towards improved QOL compared with standard treatment.[40] Other approaches have included use of abbreviated chemotherapy followed by radiotherapy[64] or reduced-dose combination therapies.[65] A study comparing chemotherapy every 3 weeks with treatment given as required for symptom control showed an improvement in QOL in those receiving regular treatment.[66] Other studies have tested intensive one-drug or two-drug regimens (table II). A UK MRC study also demonstrated similar efficacy for an etoposide plus vincristine regimen and a four-drug regimen.[67] The latter regimen was associated with a greater risk of toxicity and early death, but was superior with respect to palliation of symptoms and psychological distress. Studies comparing a convenient oral treatment with single-agent oral etoposide versus combination therapy showed that the overall response rate and survival were significantly worse in the oral etoposide arm with a suggestion of an increased number of early deaths in patients receiving this treatment.[68,69] A randomised com-

Table II. Randomised trials of chemotherapy in poor-prognosis small-cell lung cancer

Study	Treatment	No. of patients	PS 2 (%)	ES (%)	Toxic death % (early death)	Median survival
James et al.[40]	ECMV EV	310	77	71	7 (25) 1 (12)	20wk 19wk
Girling[68]	Oral E CAV EV	302	100	57	Combination (10) Oral E (6)	Combination 26wk Oral E 18.5wk p = 0.03
Souhami et al.[69]	Oral E CAV/PE	155	52	89		Combination 5.9mo Oral E 4.8mo
White et al.[70]	Carbo CAV	119	97	71	3 (5.2) 0 (6.9)	16wk 17wk

Carbo = carboplatin; **CAV** = cyclophosphamide, doxorubicin, vincristine; **E** = etoposide; **ECMV** = etoposide, cyclophosphamide, methotrexate, vincristine; **ES** = extensive-stage disease; **EV** = etoposide, vincristine; **PE** = cisplatin, etoposide; **PS** = performance status.

parison of single-agent carboplatin (area under the concentration-time curve of 6) with cyclophosphamide, doxorubicin plus vincristine (CAV) in patients with Karnofsky performance score of ≤50 and a prognostic score indicator of 1-year survival ≤15% showed similar median and overall survivals.[70] The response rates were higher for combination therapy (38% vs 25% with single-agent carboplatin) but this was not statistically significant. Combination therapy was associated with improved symptom relief compared with single-agent carboplatin, albeit at the expense of increased non-haematological toxicity and increased risk of early treatment-related death.

At present, a standard therapy for patients with poor-prognosis SCLC is a combination of carboplatin plus etoposide. Single-agent carboplatin is acceptable for those with very poor prognosis (e.g. ≤20% survival at 1 year).

6. Relapsed/Refractory Disease

The majority of patients with SCLC will relapse after their initial chemotherapy. However, there is no standard treatment for relapsed SCLC. Further treatment will depend on a number of factors and many patients are not fit for further chemotherapy. The best predictor of future response to second-line therapy is the response seen to first-line treatment. In the vast majority of patients, this means previous response to platinum-based treatment. Patients who have not responded to initial chemotherapy are said to have refractory disease, and those who have had an initial response but have then progressed within 3 months of completion are said to have resistant disease. The prognosis for both of these groups of patients is poor, with an expected median survival of 2–3 months.[71] These patients are very unlikely to benefit from standard chemotherapy and consideration should be given to enrolling these patients in clinical trials of new agents. In patients who relapse beyond 6–12 months after initial therapy, consideration should be given to re-treatment with the same drug that had been given previously; a small percentage of these patients are long-term survivors.[72,73] For the remaining patients, in the absence of appropriate clinical trials, treatment plans will need to be individualised on a patient-by-patient basis and should involve a non-cross-resistant drug or combination. Because responses to standard chemotherapy regimens are usually brief and overall survival is low, there is an urgent need to identify new active treatments.

Topotecan, a topoisomerase-I inhibitor, is a semisynthetic derivate of camptothecin that has demonstrated anti-tumour activity in several phase II trials in both chemo-sensitive and chemo-resistant SCLC.[74-77] A recent phase III trial, the first randomised trial comparing chemotherapy with best supportive care (BSC) in relapsed SCLC, demonstrated that addition of oral topotecan to BSC significantly increased overall survival and resulted in better symptom control compared with BSC alone.[78] 141 patients with relapsed SCLC, chemosensitive or -resistant, who were unsuitable for further standard intravenous chemotherapy, were enrolled in the study. The median treatment-free interval after first-line therapy was 90 days with BSC and 84 days with topotecan. The median survival times for patients receiving topotecan plus BSC were 25.9 weeks versus 13.9 weeks for BSC alone ($p = 0.01$). The 6-month survival rates were 49% and 26% in the two groups, respectively (no p-value provided). Prolongation of survival in the topotecan group was preserved when analysed according to stratification factors of sex, time from prior therapy (<60 days or ≥60 days), PS (0–1 or 2) and presence of liver metastases. A randomised comparison of topotecan versus CAV in 211 patients with SCLC who had relapsed at least 60 days after completion of first-line therapy showed no difference in response rate or survival between treatment arms, but patients receiving topotecan had better symptom control.[79] Toxicity in both arms was considerable. An early randomised phase II trial and preliminary results from a phase III study confirm that oral topotecan has activity and tolerability similar to intravenous topotecan in chemo-sensitive SCLC and offers patients a convenient alternative to intravenous therapy.[80,81] Intravenous topotecan is the first agent to be approved in Europe and in the USA with the specific indication of treatment of relapsed SCLC

for which re-treatment with the first-line regimen is not considered appropriate.

7. Newer Drugs

Strategies used to evaluate new drugs in SCLC usually involve addition of an agent to an established regimen or substitution for an active drug. New drugs being evaluated include the topoisomerase-I inhibitors topotecan and irinotecan, the taxanes docetaxel and paclitaxel, vinorelbine, gemcitabine, pemetrexed and the synthetic 9-aminoanthracycline amrubicin.

7.1 Topotecan

The *in vitro* antitumour synergy of topotecan with taxanes, platinum agents and topoisomerase II inhibitors, in addition to its activity in relapsed SCLC (see section 6), has prompted investigators to study topotecan as first-line therapy for SCLC.[82-84] A recent randomised, multicentre, phase III study compared oral topotecan plus intravenous cisplatin (TC) with intravenous PE in 784 patients with untreated ED-SCLC.[85] At study initiation, the dose of topotecan was 2.0 mg/m^2/day; however, two patients died as a result of neutropenia associated with enterocolitis. Five other patients in the TC arm also died: two died as a result of neutropenia after therapy, one patient had empyema with sepsis, one had respiratory failure after a viral syndrome and one had a ruptured abdominal aortic aneurysm. After 75 patients were enrolled, the protocol was amended to reduce the starting dose of oral topotecan to 1.7 mg/m^2/day and measures were established to exclude patients of borderline PS 2–3 or rapidly worsening PS. All patients enrolled in the study before the dose reduction were excluded from the intent-to-treat population. There was no significant difference in overall survival and the study showed non-inferiority (<10% difference) of oral TC 1-year survival. In another study, maintenance chemotherapy with four cycles of topotecan in stable or responding patients after four cycles of PE demonstrated better PFS, but no difference in overall survival and QOL in patients with ED-SCLC.[86]

7.2 Irinotecan

The topoisomerase I inhibitor irinotecan has been studied as a single agent and in combination with other drugs for the treatment of SCLC. Based on the results of a WJTOG (West Japan Thoracic Oncology Group) phase II trial of irinotecan and cisplatin that yielded a complete response rate of 29% and an overall response rate of 86% (median survival, 13.2 months) in patients with ED-SCLC,[87] a randomised phase III trial was conducted by the Japanese Clinical Oncology Group (JCOG) comparing PE with cisplatin plus irinotecan in chemo-naive patients with ED-SCLC.[88] The planned size of the study population was 230 patients, but enrolment was halted early because an interim analysis found a significant survival benefit for the study arm, and only 154 patients were randomised. Cisplatin plus irinotecan was associated with a significantly better median (12.8 vs 9.4 months with PE) and 2-year (19.5 vs 5.2% with PE) survival. Toxicity was as expected for this new combination, with significant diarrhoea in 16% of patients. A larger confirmatory study reported by Hanna and colleagues[89] in 331 patients showed no difference in survival with significantly more grade 3/4 diarrhoea in the irinotecan-treated patients. However, in this study, a different dose and schedule of irinotecan and cisplatin were chosen and patients appeared to have more advanced disease at baseline compared with the JCOG trial. Patients with PS of 2 were subsequently excluded after the first 31 patients were enrolled because of high rates of neutropenic complications and treatment-related deaths. The lack of superiority of the irinotecan combination in this trial compared with the increased survival noted in the JCOG trial may possibly have been due to pharmacogenomic differences that may exist between North American and Japanese patient populations. A study from Norway that randomised 209 patients with ED to either carboplatin plus irinotecan or carboplatin plus etoposide reported a survival advantage at 1-year for the irinitecan-based regimen (34% vs 24%; $p = 0.02$), but has been criticised for the doses and route of administration used in the control arm.[90] The results of a SWOG (Southwest Oncology

Group) phase III trial using the same dose/schedule of the JCOG and evaluating pharmacogenomic differences as predictors for response and toxicity to irinotecan are awaited.

7.3 Paclitaxel

Paclitaxel showed considerable activity in phase II trials as a single-agent and in combination with other drugs in untreated ED-SCLC.[91-95] A multicentre randomised clinical trial compared paclitaxel, cisplatin plus etoposide (TEP) with PE as first-line treatment in patients with SCLC.[96] The study was terminated early because of a higher number of toxic deaths in the TEP arm (8 vs 0 in the PE arm). Despite a statistically significant improvement in time-to-progression for TEP compared with PE (11 vs 9 months, respectively; p = 0.02), the duration of response, 1-year survival and overall survival were similar in the two arms. The randomised phase III intergroup trial (CALGB [Cancer And Leukemia Group B] 9732) of etoposide and cisplatin with or without paclitaxel and GCSF support in patients with ED-SCLC reported similar results.[97] Despite a higher complete and overall response rate in the three-drug regimen arm, there was no improvement in failure-free survival, overall survival, or 1-, 2- and 3-year survivals, and the addition of paclitaxel was associated with unacceptable toxicity. Another randomised trial evaluated the combination of paclitaxel, etoposide plus carboplatin (TEC) versus a combination of carboplatin, etoposide plus vincristine (CEV) in 614 patients with SCLC.[98] The 3-year survival rate was 17% (95% CI 12, 21) in the TEC arm versus 9% (95% CI 6, 13) in the CEV arm. Comprehensive QOL analysis also showed that TEC significantly improved relevant QOL parameters, including global overall QOL and physical functioning.[99] Smit et al.[100] reported the results of a randomised phase III trial that compared CDE with carboplatin plus paclitaxel (CP) in 197 chemonaive patients with ED-SCLC. Preliminary results showed no difference in response rate or in PFS (141 vs 102 days, respectively; p = 0.89) between treatment arms, but haematological toxicity was significantly lower in patients treated with CP. A phase III randomised trial compared CP with CAV chemotherapy in LD or ED patients with a prognostic score in the intermediate or poor-prognosis range.[101] The 1-year survival rate in the CAV arm was 6% compared with 13% in the CP arm (p = 0.014), and the incidence of severe neutropenia and infections was higher in the CAV arm.

7.4 Pemetrexed

Pemetrexed is a novel, multi-targeted antifolate that inhibits several folate-dependent enzymes involved in purine and pyrimidine synthesis, and is active as a single-agent or in combination with a platinum in both non-SCLC and malignant pleural mesothelioma. Pemetrexed has shown minimal single-agent activity in patients with relapsed SCLC.[102] In a randomised phase II trial, pemetrexed plus platinum combinations appeared to be active and well tolerated in patients with previously untreated ED-SCLC, with a median survival and 1-year survival of 7.6 months and 33.4%, respectively, for cisplatin plus pemetrexed and 10.4 months and 39.0%, respectively, for carboplatin plus pemetrexed.[103] The GALES (Global Analysis of Pemetrexed in SCLC Extensive Stage) trial is a large international phase III study comparing carboplatin plus pemetrexed with carboplatin plus etoposide in 1820 patients.[104]

7.5 Amrubicin

Amrubicin is a totally synthetic 9-aminoanthracycline that has been investigated in Japan. Two recent phase II studies have reported response rates of 50–53% with amrubicin in patients with relapsed or refractory SCLC.[105,106] The main toxicity was haematological. Response rates of 75.8% for single-agent treatment and a response rate of 87.8% with a median survival of 13.6 months in combination with cisplatin, have been reported in patients with untreated ED-SCLC.[107,108] Further studies of this promising new agent are underway.

7.6 Other Agents

Other drugs examined for the treatment of SCLC include docetaxel, gemcitabine, vinorelbine and pe-

gylated liposomal doxorubicin. These are reviewed in detail elsewhere.[109] The London Lung Cancer Group compared PE with carboplatin plus gemcitabine (GC) in patients with both LD and ED with poor-prognosis disease in order to test the hypothesis that GC would produce equivalent survival but with better QOL and fewer hospital admissions.[110] Preliminary results suggested that GC produces more haematological but less non-haematological toxicity than PE. The overall response rates were 58% in the GC arm and 63% in the PE arm. Median survival was 8.1 and 8.2 months, respectively.

8. Targeted Molecules and Immunotherapies

Novel approaches employing targeted therapies are under evaluation for the treatment of SCLC. The role of these novel biological agents, including bcl-2 antisense oligonuclide, proteasome inhibitor bortezomib, inhibitors of matrix metalloproteinases (MMPs), tyrosine kinase inhibitors and anti-angiogenic strategies, has recently been reviewed in detail elsewhere.[111]

Immunotherapies and immunoconjugates have shown some promise and require further evaluation. A small pilot study demonstrated promising results after adjuvant treatment with the anti-idiotypic antibody to the ganglioside GD3 (BEC2; mitumomab) plus Bacillus Calmette-Guerin (BCG) in 15 SCLC patients who had completed standard therapy.[112] However, a larger phase III trial reported no impact on outcome from vaccination with mitumomab plus BCG in 515 patients with LD-SCLC responding to combined-modality treatment.[113] Thalidomide possesses both immunomodulatory and anti-angiogenic properties. In a placebo-controlled study, patients with ED-SCLC responding to two cycles of etoposide, cisplatin, cyclophosphamide plus epidoxorubicin chemotherapy were randomised to four additional cycles of chemotherapy plus thalidomide 400 mg/day or placebo.[114] The median survival was 11.7 months for thalidomide compared with 8.7 months for placebo ($p = 0.03$). However, only 92 of a planned 200 patients were randomised and 55.3% of patients withdrew from the thalidomide arm because of toxicity. However, a large, double-blind, placebo-controlled, phase III study that randomised 724 ED patients to carboplatin AUC 5 and etoposide +/− thalidomide 100mg/day, increased to 150mg/day then 200mg if tolerated, showed no difference in overall survival, with a median survival of 10.5 months for placebo and 10.2 months for thalidomide (hazard ratio [HR] = 1.10, 95% CI 0.94, 1.29; $p = 0.24$).[115]

Several inhibitors of MMPs have been developed and evaluated in SCLC. Of these, marimastat is the first to be used in clinical trials. A phase III trial was conducted in 532 SCLC patients randomised to receive either marimastat or placebo following complete or partial remission with first-line chemotherapy.[116] Treatment with marimastat did not result in improved survival and had a negative impact on QOL. Dose modifications because of musculoskeletal toxicity were required in almost one-third of patients.

9. Surgery

The role of surgical resection in the treatment SCLC is unclear. Large-scale, randomised confirmatory studies are lacking. At present, in the majority of patients that have had surgery for SCLC, the diagnosis is usually made after resection of a lung mass without prior histological diagnosis. Surgery as the primary treatment for SCLC was generally abandoned in the early 1970s after the UK MRC published the results of a study showing better survival for patients receiving radiotherapy compared with surgery.[117] Subsequently, a number of case series and institutional reviews of surgery followed by adjuvant chemotherapy suggested a 5-year survival rate of ≥50% for patients with pathologically proven stage I disease.[118-125] In a recent review of 82 patients who underwent surgery with curative intent, Brock et al.[126] reported a 5-year survival rate of 86% for those patients with completely resectable T1-2N0 disease who received postoperative platinum chemotherapy.

Prospective data on inclusion of surgery in combined-modality treatment of LD-SCLC are limited.

A small number of prospective trials of chemotherapy followed by surgery reported a resection rate of ≈50% with high local control rates.[124,127-130] One prospective randomised trial investigated the role of adjuvant surgical resection after chemotherapy in node-positive disease.[131] Patients demonstrating a response to five cycles of CAV were randomly assigned either to resection plus thoracic radiotherapy (TRT) and PCI or to TRT and PCI alone. Survival of patients in the two arms was equivalent, suggesting no benefit of surgery in this setting.

10. Radiotherapy for Limited-Stage Disease

Radiotherapy plays an important role in the management of LD-SCLC. Randomised trials have shown that TRT and PCI improve both tumour control and overall survival. Combination chemotherapy alone is associated with intrathoracic failure rates of 75–90%, and addition of thoracic irradiation reduces this risk to 30–60%.[132-134] Two meta-analyses published in 1992 found a statistically significant advantage for addition of TRT to chemotherapy.[135,136] However, essential questions related to the optimisation of TRT remain unanswered. In particular, the optimal radiotherapy dose, fractionation and timing of chemo-radiation have not been well defined.

Historically, SCLC was treated with lower doses of radiation than non-SCLC because patients receive initial chemotherapy and SCLC is considered to be a radiosensitive disease. However, whilst improved chemotherapy increases the control of distant metastases, low-dose schedules, such as 30Gy in 10 fractions, are associated with a high frequency of local failure.[137] Retrospective studies[137-139] suggest that TRT doses of ≥50Gy can translate into improved PFS, but an impact on overall survival has yet to be demonstrated. Doses similar to those given to non-SCLC may be necessary to improve both local control and overall survival.

Conventional radiotherapy fractionation can be modified by hyperfractionation (radiotherapy more than once a day) and/or acceleration (shortening of the overall treatment time). Studies on SCLC cell lines showed a lack of shoulder on radiation survival curves and low-surviving fractions at 2Gy.[140] These observations suggest that SCLC may be sensitive to, and thus benefit from, the lower doses used in hyperfractionated radiotherapy. Five-year survival rates >20% have been reported in patients receiving twice-daily radiotherapy with concurrent chemotherapy. A landmark study by Turrisi et al.[141] compared 45Gy administered either twice daily (1.5Gy per fraction) over 3 weeks or once daily (1.8Gy per fraction) over 5 weeks. Radiation was given concurrently, starting with the first cycle of chemotherapy. Twice-daily radiotherapy improved overall 5-year survival (26% versus 16% in the once-daily arm [p = 0.04]) but increased the rate of grade 3/4 radiation oesophagitis (32% vs 16% in the once-daily arm [p , 0.001]). In contrast, the North Central Cancer Treatment Group (NCCTG) conducted a similar study that did not result in improvement in local control or survival with use of the twice-daily radiation.[142] However, there were many differences between the two regimens. In the NCCTG trial, radiotherapy was delayed until the start of the fourth cycle of PE and patients randomly assigned to hyperfractionated radiation were given a midcourse break of 2.5 weeks, resulting in no overall acceleration in the hyperfractionated arm.

Chemotherapy and radiotherapy can be delivered concurrently, sequentially or as alternating treatment. When the results of randomised controlled trials are compared, it appears that the best results have been obtained with early concurrent TRT (table III).[143-151] The 20% 5-year survival milestone has generally been achieved with early TRT. A Japanese study comparing sequential with concurrent TRT has demonstrated the superiority of concurrent chemo-radiotherapy.[143] In 2004, two meta-analyses evaluated the timing of TRT in combined modality therapy. Fried at al.[152] showed that studies using platinum-based chemotherapy had a 2-year overall survival benefit of 9.8% for early (defined as prior to 9 weeks after the initiation of chemotherapy) compared with late TRT (95% CI 3.8, 15.9; p = 0.002) favouring early TRT.[152] However, results from the London Lung Cancer Group

Table III. Timing and sequencing of radiotherapy (RT) for small-cell lung cancer

Author (year)	No. of patients	Timing of thoracic RT	PCI	Survival (%)	Median survival (months)
Takada et al.[143] (2002)	228	Day 2 (C)	If CR or near CR	23.7 (5y)	27.2
		After cycle 4 (S)		18.3 (5y)	19.7
Jeremic et al.[144] (1997)	103	Day 1 (C)	Yes	30.0 (5y)	34.0
		Day 43 (C)	Yes	15.0 (5y)	26.0
Murray et al.[145] (1993)	308	Day 22 (C)	Yes	20.0 (5y)	21.2
		Day 106 (C)	Yes	11.0 (5y)	16.0
Work et al.[146] (1997)	199	Day 1 (A)	Yes	10.8 (5y)	10.5
		Day 120 (A)	Yes	12.0 (5y)	12.0
Skarlos et al.[147] (2001)	81	Day 1 (C)	If CR only	22.0 (3y)	17.5
		Day 64 (C)		13.0 (3y)	17.0
Lebeau et al.[148] (1999)	156	Day 30 (C)	Yes	6.0 (3y)	13.5
		Day 36 (A)	Yes	11.0 (3y)	14.0
Perry et al.[149] (1998)	270	Day 1 (C)	Yes	6.6 (5y)	13.0
		Day 64 (C)	Yes	12.8 (5y)	14.5
Gregor et al.[150] (1997)	334	Day 43 (A)	Not mandatory	12.0 (3y)	14.0
		Day 99 (S)		15.0 (3y)	15.0
Spiro et al.[151] (2006)	325	Day 22 (C)	Yes	16.0 (3y)	13.7
		Day 106 (C)	Yes	22.0 (3y)	15.1

A = alternating; **C** = concurrent; **CR** = complete response; **PCI** = prophylactic cranial irradiation; **S** = sequential.

study,[151] which showed no difference in outcome between early and late TRT, were not included in this meta-analysis. More patients in the late TRT arm of this study received six cycles of chemotherapy and PCI, which may in part have explained the results.

In the Cochrane review that included the London Lung Cancer Group study, there was no significant 2- or 3-year overall survival benefit in favour of early (defined as starting within 30 days of initiation of chemotherapy) versus late TRT with either cisplatin (odds ratio [OR] 0.73; 95% CI 0.5, 1.03; p = 0.07) or non-cisplatin-based chemotherapy (OR 1.97; 95% CI 1.10, 3.53; p = 0.42).[153] There was a 5-year survival benefit in favour of early TRT and cisplatin-based chemotherapy (OR 0.64; 95% CI 0.44, 0.92; p = 0.02). There were three trials in which the proportion of patients who completed their planned chemotherapy was similar between the TRT arms (HR = 0.73; 95% CI 0.62, 0.86) and five in which proportionally fewer patients in the early TRT arm completed their planned chemotherapy (HR = 1.06; 95% CI 0.97, 1.17). However, these results should be interpreted with caution because the largest trial has follow-up data at 3 years, but no later.[151] The new concept of SER (Start of any treatment to End of Radiotherapy) also supports early TRT.[154] This systematic overview included four trials and showed that SER is the most important predictor of outcome. There was a significantly higher 5-year survival rate in the shorter SER arms, with 5-year survival increasing to >20% when the SER was ≤30 days. In the absence of randomised controlled trials designed to evaluate the SER, this concept should be interpreted with caution.

PCI also plays an important role in the management of SCLC. Patients whose cancer can be controlled have a 60% actuarial risk of developing brain metastasis within 2–3 years after starting treatment. This risk can be decreased by 50% with administration of PCI.[155] A meta-analysis of seven randomised controlled trials evaluating the role of PCI in SCLC patients in complete remission after chemotherapy reported improvements in brain recurrence, disease-free survival and overall survival with addition of PCI.[155] Prospective studies have shown that patients treated with PCI do not have significantly worse neuropsychological function than patients not treated with PCI.[156,157] The EULINT (EUropean Lung INTergroup) PCI trial randomised 700 patients to either high-dose (36Gy in 18 fractions) or standard dose (25Gy in 10 fractions) radiotherapy to

the whole brain (Le Péchoux C, personal communication). A recent study[47] randomised 286 patients with ED responding to chemotherapy to observation or PCI. PCI significantly decreased the risk of symptomatic brain metastases (p = 0.0001), from 40.4% in the control arm (95% CI 32.1, 48.6) at 1 year, to 14.6% in the PCI group (95% CI 8.3, 20.9). Furthermore, PCI significantly prolonged disease-free survival (p = 0.0218) with a HR of 0.76 (95% CI 0.59, 0.96) in favour of PCI, and significantly prolonged overall survival (p = 0.0033) with a mortality HR of 0.68 (95% CI 0.52, 0.88) in favour of PCI. The 1-year survival rate was 27.1% (95% CI 19.4, 35.5) for the PCI arm versus 13.3% (95% CI 8.1, 19.9) for controls.

11. Conclusion

The last 10 years have seen a significant improvement in our understanding in how best to manage patients with SCLC. Further improvements in conventional chemotherapy are likely to be modest. Real progress is most likely to come with identifying newer, novel drugs, based on a greater understanding of the molecular biology of SCLC and the importance of events outside the nucleus. Although identification of the role of targeted therapies for SCLC has lagged behind that for non-SCLC and other more common cancers, early phase studies with new targeted therapies have given some cause for optimism. Efforts over the next 5–10 years will be concentrated on defining the roles of these new drugs, and how best to combine them with standard chemotherapy and radiotherapy. A number of critically important questions remain concerning optimal radiotherapy treatment for patients with LD. These include dose, fractionation, timing and treatment volume. CONVERT (Concurrent ONce-daily VERsus Radiotherapy Twice-daily), a large international study addressing these issues, will be launched in late 2007.[158] After a period of time consolidating and refining our understanding of standard chemotherapy and radiotherapy for SCLC, it is time to move forward to the next phase of development.

Acknowledgements

No sources of funding were used to assist in the preparation of this review. Dr Nick Thatcher has acted as a consultant to and received honoraria from Bristol-Myers Squibb, Lilly, Roche and Amgen, and has been the recipient of a grant from Lilly. The other authors have no conflicts of interest that are directly relevant to the content of this review.

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