Chemotherapy strategies in the treatment of small cell lung cancer

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Lung cancer is the most prevalent, yet most preventable malignancy worldwide. Given the tendency of small cell lung cancer (SCLC) to early relapse and its subsequent resistance to treatment, there is an urgent need to optimize standard treatment strategies and develop new treatments. Over the last decade, several strategies have been adopted and advances in the molecular biology of lung cancer have identified a number of targets for future therapy. In this article, we review chemotherapy strategies that have been evaluated in the management of patients with SCLC.
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Introduction

Small cell lung cancer (SCLC) represents around 20% of all lung carcinomas and has the strongest association with smoking. It is rarely observed in non-smokers [1]. The mainstay of treatment for most patients with SCLC remains chemotherapy, achieving major responses in most patients, including those with extensive stage (ES) disease at presentation. In those with limited stage (LS) disease, achieving a complete remission, prophylactic cranial irradiation and mediastinal radiotherapy can reduce the risk of metastases and improve survival [2].

Standard drugs available for the treatment of SCLC include cyclophosphamide, doxorubicin, methotrexate, etoposide, vincristine, cisplatin and carboplatin. Using these in combination, response rates of 70% or more have been reported, with complete responses (CR) of up to 50% in LS-SCLC patients. Despite its marked sensitivity to induction chemotherapy, SCLC is characterized by high relapse rates and a subsequent poor prognosis. Delineating the molecular mechanisms of lung carcinogenesis coupled with advances in drug rationale and design will allow development of new drugs for clinical trials. In this article, we review chemotherapy strategies that have been evaluated in the management of patients with SCLC.

Scheduling with established agents

Combination chemotherapy for SCLC is superior to single-agent treatment [3,4]. The precise drug combination and scheduling have been the focus of considerable investigation over the past 30 years. Anthracycline-based combination treatment with cyclophosphamide, doxorubicin and vincristine (CAV) became standard therapy during the 1970s [5], and was followed by etoposide-containing regimes [6–8]. Combination regimes with cisplatin for first-line treatment were introduced in the 1980s, and reported response rates of around 40% and median survivals of around 14 months [9]. The superiority of cisplatin over anthracycline-based regimes was demonstrated by a recent randomized study of 436 patients in Norway [10]. Patients with either LS/ES-SCLC received either PE chemotherapy (cisplatin 75 mg/m^2, etoposide 100 mg/m^2 i.v. day 1, oral etoposide 200 mg/m^2 days 2–4) or CEV (epirubicin 50 mg/m^2, cyclophosphamide 1000 mg/m^2, vincristine 2 mg, i.v. day 1) 3-weekly. With a minimum of 5 years follow-up, a significant benefit for PE chemotherapy was observed (median survival 10.2 versus 7.8 months, $p < 0.001$). Although this was primarily seen in the LS-SCLC cohort (median survival 14.5 versus 9.7 months), a non-significant trend to an improved survival for PE was also seen in ES-SCLC patients (median survival 8.4 versus 6.5 months).

Given the impact of platinum-based regimes, a number of additional strategies have been investigated to consolidate this benefit. These include extending treatment cycle number, maintenance chemotherapy, non-cross-resistant regimes, intensive weekly therapy, dose intensification, dose-dense treatments and high-dose chemotherapy. Whilst there may be considerable overlap between these strategies, the key studies reported to date are discussed below.

Number of chemotherapy cycles has been assessed by few randomized studies [11–13]. Spiro *et al.* [11] randomized a heterogeneous-staged cohort of 610

0959-4973

patients to either four or eight cycles of cyclophosphamide, etoposide and vincristine chemotherapy, with a second randomization at relapse of either symptomatic treatment, or methotrexate and doxorubicin. Patients receiving four cycles of chemotherapy and treated symptomatically on relapse had the poorest median survival (30 weeks), whilst median survival in those initially receiving four chemotherapy cycles followed by further chemotherapy on relapse was not significantly different to those receiving longer chemotherapy on induction. The UK Medical Research Council (MRC) randomized 458 patients to epirubicin, cyclophosphamide, methotrexate and vincristine (ECMV) for three cycles, ECMV for six cycles or etoposide and ifosfamide for six cycles [12,13]. Although no statistically significant difference in survival between patients receiving three cycles compared to six cycles was observed, this study was under-powered to exclude a small survival advantage.

Studies investigating number of chemotherapy cycles overlap those assessing maintenance therapy. Several randomized trials have assessed the role of additional cycles of chemotherapy over standard treatment schedules (Table 1) [14–23]. The majority of these studies compared four to six cycles, with or without maintenance therapy in patients initially responding to treatment. Two studies demonstrated a survival benefit in patients randomized to receive maintenance chemotherapy [14,15]. Mauer *et al.* [14] showed an improved survival of around 10 months in the subcohort of 46 patients with LS-SCLC randomized to receive maintenance therapy (median survivals 16.8 versus 6.8 months), whilst a survival advantage was demonstrated in 61 patients with ES-SCLC in complete remission randomized to receive eight additional cycles of CAV by Cullen *et al.* [15]. A more recent study by Hanna *et al.* investigated the role of 3 months of oral etoposide maintenance therapy in non-progressing patients with ES-SCLC [24]. A total of 144 patients were randomized to either maintenance etoposide or observation. A significant improvement in progression-free survival (PFS) in favor of the maintenance arm (8.23 versus 6.5 months, $p = 0.002$), but only a trend to an improved survival (median 12.2 versus 11.2 months), was observed. The other studies showed no survival advantage for additional cycles of treatment (total 4054 patients with 2008 in maintenance phases). The role of topotecan maintenance after cisplatin-based induction has been investigated by the Eastern Cooperative Oncology Group (ECOG) and is discussed in the section on new drugs. Given that most studies of maintenance treatment have been negative, prolonged therapies are generally not used and early diagnosis of relapse with prompt introduction of active drugs remains the optimal treatment strategy. However, revisiting maintenance therapy for patients in remission following cisplatin-based induction with new agents remains attractive.

On a similar theme, several randomized phase III studies have assessed the role of non-cross-resistant regimes using anthracycline- or cisplatin-based regimes [25–28] (Table 2), with three showing a benefit [25–27]. Einhorn *et al.* [26] randomized 160 LS-SCLC patients in remission following six cycles of CAV induction therapy to either PE consolidation or no further treatment. Patients randomized to consolidation PE had significantly longer remission duration (49 versus 28 weeks) and survival (98 versus 68 weeks). Evans *et al.* randomized 289 ES-SCLC patients to either CAV or CAV alternating with PE [25]. Both response rates (80 versus 63%) and overall survival (OS) (9.6 versus 8.0 months) favored the alternating regime. Subsequently, Fukuoka *et al.* [27]

Table 1 Studies investigating treatment duration

Study	Staging	Study size	Maintenance arm	Induction		Maintenance		No. cycles	OS benefit
				Anthracycline based	Platinum based	Anthracycline based	Platinum based		
Maurer [14]	LD, ED	258	57	–	–	–[a]	–[a]	6 versus –[c]	yes
Cullen [15]	LD, ED	309	93	+	–	+[b]	–[b]	6 versus 14	yes (ED cohort only)
Byrne [16]	LD	66	66	–	+	–	–	3 versus 9	no
Lung Cancer Working Party [17]	LD, ED	497	265	–	–	–[b]	–[b]	6 versus 12	No
Party [17]									
Ettinger [18]	ED	577	86	+	–	+[b]	–[b]	6 versus –[c]	No
Lebeau [19]	LD, ED	320	79	+	–	+[b]	–[b]	6 versus 12	No
Giaccone [20]	LD, ED	687	585	+	–	+[b]	–[b]	5 versus 12	No
Beith [21]	LD, ED	202	129	–	+	+	–	4 versus 14	No
Sculier [22]	LD, ED	235	91	+	–	–	–	6 versus 18	No
Schiller [23]	ED	402	112	–	+	–	–	4 versus 8	No
Hanna [24]	LD, ED	233	72	–	+	–	–	4 versus 7	Yes
Spiro [11]	LD, ED	610	294	–	–	–	–	4 versus 8	No
Bleehen [12]	LD, ED	458	301	–	–	–	–	3 versus 6	No

[a]CR patients only.
[b]Same drugs as induction.
[c]Until relapse for PRs or two additional cycles for CRs.

Table 2 Phase III studies of alternating non-cross-resistant regimes

Study	Staging	Sample size	Standard regime	Study regime (alternating regime)	Outcome
Einhorn *et al.* [26]	LD	160	CAV	CAV/PE	improved OS for alternating regime ($p=0.009$)
Evans *et al.* [25]	ED	289	CAV	CAV/PE	improved OS for alternating regime ($p=0.03$)
Fukuoka *et al.* [27]	LD, ED	288	CAV PE	CAV/PE	improved OS for alternating regime in LD ($p=0.023$)
Roth *et al.* [28]	ED	437	CAV PE	CAV/PE	OS NS difference

A, doxorubicin; C, cyclophosphamide; E, etoposide; ED, extensive stage disease; LD, limited stage disease; P, cisplatin; OS, overall survival; NS non-significant; V, vincristine.

randomized 288 patients to CAV, PE or CAV alternating with PE. Although a survival advantage was associated with the alternating regime compared to PE or CAV alone (12, 10 and 10 months, respectively), stratified analysis showed the benefit restricted to LS-SCLC patients only. Roth *et al.* [28] published the largest study of ES-SCLC randomizing patients to either six cycles of CAV, four cycles of PE or CAV alternating with PE (three cycles each). No differences in response rates or median survival (8.3, 8.6 and 8.1 months, respectively) were observed, implying that four cycles of PE and six cycles of CAV are equivalent. Thus, given the conflicting data, the use of alternating regimes should not currently be considered standard practice, but is the rationale for the treatment of relapsed disease.

Advancing from the strategy of non-cross-resistant regimes, another approach has been the rapid sequencing of active agents over short treatment periods. One such regime is CODE (weekly cisplatin, vincristine, doxorubicin, i.v. etoposide), alternating myelosuppressive agents with non-myelosuppressive agents. This regime was designed to double the dose intensity of these drugs in comparison to CAV alternating with PE. However, recent larger studies have failed to confirm an improved survival initially reported by a small pilot study and confirmed the greater toxicities associated with CODE [29,30].

Another similar approach has been dose intensification (Table 3). Several randomized trials with relatively small numbers and different patient groups have assessed this treatment strategy [31–39]. Five of these studies [31–35] were doxorubicin- or alkylating agent-based, and only one [33] (the largest) demonstrated a survival advantage for the dose-intense arm. In this ECOG study, 349 patients with LS/ES-SCLC were randomized to receive either standard therapy [cyclophosphamide (700 mg/m^2), CCNU and methotrexate 3 weekly] or a dose-intense regime of the same chemotherapy, but with an increased cyclophosphamide dose (1500 mg/m^2). A survival advantage was shown for the dose-intense arm (41 versus 36 weeks, $p = 0.04$), most pronounced in patients with LS-SCLC (56 versus 42 weeks). However, given the extra toxicity observed and a complicated study design, this approach has not been followed up.

Two subsequent randomized trials were based on cisplatin regimes and results were conflicting [36,37,39]. Arriagada *et al.* [36,39] randomized 105 LS-SCLC patients to doxorubicin, etoposide, cisplatin (80 mg/m^2) and cyclophosphamide (900 mg/m^2) or a dose-intense regime with higher doses of cisplatin (100 mg/m^2) and cyclophosphamide (1200 mg/m^2). The higher chemotherapy doses were given for cycle 1 only and all patients subsequently received identical treatment doses. A clear survival advantage was observed for the dose-intense arm (5-year survival 26 versus 8%). By contrast, a National Cancer Institute (NCI) study [37] randomized 90 ES-SCLC patients to either standard-dose PE (cisplatin 80 mg/m^2, etoposide 80 mg/m^2 days 1–3) or high-dose PE (cisplatin 135 mg/m^2, etoposide 80 mg/m^2 days 1–5) for cycles 1 and 2 only. No survival advantage, but more toxicity for the dose-intense arm was observed.

The London Lung Group investigated a dose-intense alternating CAV/PE regime [38]. ES-SCLC patients ($n = 167$) were randomized to receive either alternating PE/CAV or treatment with the same drugs, but with each course consisting of half the 3-weekly dose given every 10 or 11 days. Again, no survival advantage but more toxicity for the dose-intense arm was observed.

Moving on from dose-intense regimes, using hematopoietic growth factors to maintain dose intensity (dose dense chemotherapy) is another strategy previously investigated, and has been reported by four randomized studies over the past 5 years (Table 4) [40–43], with two demonstrating a survival benefit in the supported arm [40,41]. Steward *et al.* [40] randomized 300 LS/ES-SCLC in a 2×2 design to receive either 3-weekly (intensified) or 4-weekly (standard) ifosfamide, etoposide, carboplatin and vincristine (V-ICE). An improved survival was observed in the dose-dense arm (433 versus 351 days, $p = 0.001$), which also had an over-representation of patients with good prognostic factors, making these results difficult to interpret. Thatcher *et al.* on behalf of the MRC [41] randomized 403 LS/ES-SCLC patients to either a 2- or 3-weekly combination of doxorubicin, cyclophosphamide and etoposide (ACE), with granulocyte colony stimulating factor (G-CSF) support. Most patients had LS-SCLC and good performance status

Table 3 Randomized studies investigating dose intensification

Study	Staging	Sample size	Standard regime (mg/m^2)	Study regime (mg/m^2)	Outcome
Cohen *et al.* [31]	LD, ED	32	C 500 M 10 Cc 50	C 1000 M 15 Cc 100	↑OS in dose-intense arm (p=NR)
Dinwoodie *et al.* [32]	NR	45	C 750 A 50 V 1.4 weekly	C 1200 A 70 V 1.4 weekly	OS NS difference
Mehta *et al.* [33]	LD, ED	349	C 700 M 15 Cc 70	C 1500 M 15 Cc 70	↑OS in dose-intense arm (p=0.04)
Figueredo *et al.* [34]	LD, ED	103	C 1000 A 50 V 1 cycles 1–4	C 1500 A 60 V 1 cycles 1–4	OS NS difference
Johnson *et al.* [35]	ED	298	C 1000 A 40 V 1 cycles 1–3	C 1200 A 70 V 1 cycles 1–3	OS NS difference
Arriagada *et al.* [36,39]	LD	105	C 225 d1–4 A 40 P 80 E 75 d1–3 cycle 1 only	C 300 d1–4 A 40 P 100 E 75 d1–3 cycle 1 only	↑OS in dose-intense arm (p=0.02)
Ihde *et al.* [37]	ED	90	E 80 d1–3 P 80 d1 cycles 1–2	E 80 d1–5 P 27 d1–5 cycles 1–2	OS NS difference
James *et al.* [38]	ED	167	P 60 E 120 d1, 100 b.d. d2–3 C 600 A 50 V 2 3-weekly alternating CAV/PE	P 30 E 60 d1, 50 b.d. d2–3 C 300 A 25 V 1 every 10/11 days alternating CAV/PE	OS NS difference

A, doxorubicin; C, cyclophosphamide; Cc, CCNU; E, etoposide; ED, extensive stage disease; LD, limited stage disease; M, methotrexate; NR not reported; NS non-significant; OS, overall survival; P, cisplatin; V, vincristine.

Table 4 Randomized studies of dose-dense chemotherapy regimes

Study	Staging	Sample size	Chemotherapy regime	Outcome
Steward *et al.* [40]	LD, ED	300	V-ICE q4 versus q3 (± GM-CSF)	↑OS in dose-dense arm (p=0.0014)
Thatcher *et al.* [41]	LD, ED	403	ACE q3 versus q2 + G-CSF	↑OS in dose-dense arm (p=0.04)
Sculier *et al.* [42]	ED	233	EVdI q3 versus EVdI q2 + G-CSF versus EVdI q2 + cotrimoxazole	OS NS difference
Ardizzoni *et al.* [43]	LD, ED	119	ACE q3 versus q2 + G-CSF	OS NS difference

A, doxorubicin; C, cyclophosphamide; E, etoposide; ED, extensive stage disease; G(M)-CSF, granulocyte (monocyte) colony stimulating factor; I, ifosfamide; LD, limited stage disease; NS non-significant; OS, overall survival; P, cisplatin; V, vincristine; Vd, vindesine.

(PS). A survival advantage was observed with the dose-dense arm at 12 months (47 versus 39%, $p = 0.04$) in patients with either stage, which started at approximately 1 year post-randomization and was maintained at 2 years (13% versus 8%).

By contrast, Sculier *et al.* [42] failed to detect a survival advantage with dose-dense therapy in their three-arm randomized study of ES-SCLC patients. Similarly, the European Organization for Research and Treatment of Cancer (EORTC) [43] reported a study of comparative design to the MRC study, in which SCLC patients were randomized to either standard dose ACE or a dose-intense regime (125% dose fortnightly, with G-CSF support). In contrast to the MRC study, survival did not differ between the two groups.

Thatcher *et al.* [44] have recently reported another dose-dense regime, on behalf of the MRC (LU21 study), based on ifosfamide in combination with carboplatin and etoposide with mid-cycle vincristine (ICE-V). By contrast to the above dose-dense regimes, no cytokine support was used. Four-hundred and two patients were randomized to receive either six cycles of ICE-V 4-weekly or six cycles of 'standard' chemotherapy 3-weekly. A survival advantage for patients receiving ICE-V was observed (median 15.1 versus 11.6 months). Again, the published data for dose-dense regimes is difficult to summarize, but in general maintaining dose intensity in limited stage SCLC probably makes a small contribution to improved outcome.

A logical progression to investigating dose-intense and dose-dense chemotherapy regimes with growth factor

support is high-dose chemotherapy with antilogous bone marrow transplantation (ABMT). Smith *et al.* [45] initially investigated the role of high-dose cyclophosphamide ($7\,g/m^2$) with ABMT in 17 patients pre-treated with chemotherapy. However, the median duration of response was only 4 months.

Only one randomized trial of high-dose chemotherapy with ABMT support has been published in SCLC patients [46]. In this study, 101 patients with either LS/ES-SCLC initially received conventional therapy with three cycles of a doxorubicin combination followed by two cycles of PE chemotherapy. LS-SCLC patients in complete or partial remission, or ES-SCLC patients in CR were then randomized to a final cycle of either low or myeloablative doses of BCNU, cyclophosphamide and etoposide. Forty-five patients were randomized. Although a significant relapse-free survival advantage was observed for patients in the high-dose arm (28 versus 10 weeks, $p = 0.002$), this did not translate to an improved median OS (68 versus 55 weeks, $p = 0.13$). In addition, four high-dose treatment-associated deaths were observed. A recent study of dose-dense chemotherapy, supported by G-CSF and antilogous stem cell support, echoed this result [47]. In this study, 318 patients were randomized to receive either 4- or 2-weekly ICE chemotherapy. Patients receiving 2-weekly treatment received G-CSF support, with autologous stem cells with each cycle. No survival benefit was observed in the 2-weekly group.

Overall, these delivery and dosing strategies have proved disappointing, and suggest we have gone as far as we can with current drugs and schedules.

New agents

Gemcitabine

Gemcitabine is a pyrimidine antimetabolite and functions as an analog of deoxycytidine. Cormier *et al.* [48] investigated 29 previously untreated SCLC patients with 1000 or $1250\,mg/m^2$ gemcitabine weekly every 4 weeks. Although an overall response rate of 27% was observed, subsequent studies of gemcitabine monotherapy have demonstrated only modest activity. A Dutch study of 41 patients with resistant SCLC demonstrated an overall response rate of 13% [49], which was again observed in a more recent ECOG phase II study of 46 relapsed patients [50].

In view of this modest efficacy for monotherapy, gemcitabine combination therapy has been investigated. In an Italian study of 56 chemonaive patients receiving gemcitabine, cisplatin and etoposide (PEG), an overall response rate of 72% [10 CRs and 29 partial responses (PRs)] was observed [51]. However, two patients died of neutropenic sepsis. Combination docetaxel and gemcitabine in extensive stage SCLC was investigated in 20 chemonaive patients by the Hellenic Cooperative Group [52]. Although the response rate was low, toxicity was acceptable and median survival was 9.6 months.

The London Lung Group has reported a randomized phase III study of gemcitabine and carboplatin (GC) versus standard PE as first line treatment [53]. Two-hundred and forty-one poor prognosis patients were randomized. Although no difference in median survival was observed between GC and PE (8.1 versus 8.2 months), GC was associated with more hematological toxicity, and less alopecia and nausea.

Topotecan

Topotecan is a semi-synthetic camptothecin analog functioning as a topoisomerase I inhibitor. Pooled analysis of 168 SCLC patients in sensitive relapse, from three early multicenter phase II studies, receiving topotecan i.v. ($1.5\,mg/m^2$/day, days 1–5, 3-weekly), demonstrated a role for the drug in SCLC with an overall response rate of 18% and OS of 30 weeks [54].

A subsequent large multicenter study randomized 211 patients in sensitive relapse to CAV or topotecan monotherapy [55]. Response rates were similar between the two (18 and 24%, respectively), as well as PFS and OS, although more patients receiving topotecan reported symptom improvement.

Topotecan is now available orally as well as i.v. as second-line therapy for sensitive relapsed SCLC [56] and the role of oral topotecan maintenance therapy has been investigated by the ECOG [23]. In this randomized phase III study, previously untreated ES-SCLC patients had improved PFS with oral topotecan maintenance compared to observation alone after four cycles of PE chemotherapy (3.6 versus 2.3 months, $p < 0.001$), but OS was not significantly different.

Vinorelbine

Vinorelbine is a semisynthetic vinca alkaloid selected for its high affinity in preventing tubulin polymerization. It has been assessed both as monotherapy and in combination. Phase II data have indicated response rates of around 17% in patients in sensitive relapse and a favorable toxicity profile [57,58]. This has prompted a number of studies designed to assess it in combination.

Vinorelbine is tolerated well in combination with gemcitabine and has moderate efficacy. Hainsworth *et al.* [59] investigated this combination in 30 patients with refractory or relapsed SCLC. The combination was well tolerated with three PRs (28%), all from the relapsed cohort. Several groups have assessed carboplatin and vinorelbine combination therapy [60,61]. Although this regime is active in SCLC, the toxicity profile suggests that doses need

refinement. The role of vinorelbine in the treatment of SCLC may therefore be worth revisiting, particularly in view of the development of an oral formulation [62].

Amrubicin

Amrubicin is a completely synthetic 9-aminoanthracycline derivative, similar in structure to doxorubicin, and has previously been shown to have potent antitumor activities against a variety of human tumor xenografts [63]. Developed and investigated primarily in Japan, phase I/II data of combination amrubicin and cisplatin in previously untreated ES-SCLC patients showed that the combination was generally tolerated well and response rates were around 90% in a cohort of 38 patients [64]. The major toxicity noted was hematological with a grade 3/4 neutropenia occurring in most patients. Further developments on this drug in Europe are awaited.

Irinotecan

Based on the results of a randomized phase II study of cisplatin and irinotecan (PI) [65], the Japan Clinical Oncology Group (JCOG) performed a randomized phase III trial (JCOG-9511) comparing PI to standard PE chemotherapy in a homogeneous cohort of previously untreated ES-SCLC patients. Patients were all aged 70 years or younger, of good PS and received either PI (irinotecan 60 mg/m^2 days 1, 8 and 15, and cisplatin 60 mg/m^2 day 1, 4-weekly for four cycles) or PE (cisplatin 80 mg/m^2 day 1 and etoposide 100 mg/m^2 days 1–3, 3-weekly for four cycles). The planned study size was 230 patients, but enrolment was terminated after an unscheduled interim analysis at an accrual of only 77 patients in each arm demonstrated a significant survival advantage for those receiving PI (median survival 12.8 versus 9.4 months, $p = 0.002$). Although grade 3/4 myelosuppression was more common in the PE group, grade 3/4 diarrhea was more common in the PI group. Indeed, only 29% of patients randomized to PI received their assigned treatment schedule without dose modification.

As a result of this study, PI is the current standard of care for ES-SCLC patients in Japan. However, this study was based on analysis of a small number of patients (154 in total), a second randomization of patients into radiotherapy or no-radiotherapy arms was planned, but not completed, and a planned quality of life analysis was not completed due to poor compliance. In addition, an arbitrary age cut-off of 70 years was applied and, as with most SCLC trials the study population may not be truly representative of most SCLC patients. Finally, Japanese patients may not be representative of non-Japanese SCLC patients. Further larger randomized studies are therefore required to confirm these findings.

A North American randomized phase III trial has been initiated to investigate these promising results [66]. Based on pilot data, this study used modified doses of the original JCOG PI regimen (cisplatin 30 mg/m^2 day 1 and irinotecan 65 mg/m^2 days 1 and 8, 3-weekly) for ES-SCLC patients. Although PS 2 patients were initially accrued, they were later excluded because of excessive toxicity. Preliminary safety data has been reported. A median of four cycles per patient was administered. The incidence of grade 3/4 hematologic and grade 3/4 non-hematologic toxicities was considerably reduced with this modified dosing. The median dose intensity (actual dose delivered mg/m^2/week) was cisplatin 17.8 and irinotecan 38.5 (compared to 14.3 and 36.2, respectively, from the JCOG study). Overall, these results demonstrate that modified PI is well tolerated, inducing no grade 4 diarrhea and delivering higher dose intensity than the JCOG study. Primary efficacy data is awaited.

Taxanes

Both docetaxel and paclitaxel have been evaluated in SCLC. Smyth *et al.* [67] investigated docetaxel 100 mg/m^2 3-weekly in 28 previously treated patients. An overall response rate of 25% was observed. In another small phase II study of 12 patients, the observed response rate was 8% [68].

In contrast, response rates with paclitaxel monotherapy seem to be better than with docetaxel [69,70]. In an ECOG study [69], 36 patients with previously untreated SCLC received paclitaxel (250 mg/m^2, 24-h i.v. infusion, 3-weekly). Although 11 PRs were observed, most (56%) patients developed grade 4 leucopenia. In a North Central Cancer Treatment Group (NCCTG) phase II study, 43 patients with previously untreated SCLC received paclitaxel in a similar regime to that above, but with G-CSF support [70]. Responses were seen in 53% and although grade 4 neutropenia occurred in 56%, only two patients experienced grade 3 or higher infection, with no septic deaths. Response duration was, however, short (median 3.4 months).

A number of paclitaxel combination regimes have been evaluated. The most promising of these are paclitaxel, etoposide and cisplatin (TEP) or carboplatin (TEC). In a recent USA Intergroup study approximately 600 patients with ES-SCLC were randomized to receive TEP [paclitaxel 175 mg/m^2 (3 h) day 1, etoposide 80 mg/m^2 i.v. days 1–3 and cisplatin 80 mg/m^2 day 1 with G-CSF support days 4–14, every 21 days) or PE (identical cisplatin and etoposide doses) [71,72]. Patients with PS 2 were excluded after observing excessive toxicity. Toxicities were more frequent in the TEP versus PE arms (grade 3/4 neutropenia 63 versus 44% and thrombocytopenia 21 versus 11%, respectively). However, no difference in median survival between the two arms was observed (10.4 versus 9.9 months, $p = 0.27$), findings reiterated in the final report [72]. These results were confirmed by a smaller study by the Greek Lung Cancer

Cooperative Group in which 133 heterogeneously staged patients received modified TEP or PE [73]. The trial was closed before meeting the intended accrual goal because of excessive toxicity and mortality in the TEP arm (eight toxic deaths on TEP compared to none with PE) and there were no efficacy differences between the two arms.

Reck *et al.* [74] reported a randomized phase III multicenter trial of paclitaxel (175 mg/m^2, day 4), etoposide (125 mg/m^2 and 102.2 mg/m^2 for patients with stage I–IIIB and IV disease, respectively, days 1–3), and carboplatin (AUC 5, day 4) (TEC) versus vincristine (2 mg days 1 and 8), etoposide (159 mg/m^2 and 125 mg/m^2 for patients with stages I–IIIB and IV disease, respectively, days 1–3), and carboplatin (AUC 5, day 1) (CEV). Patients ($n = 608$) with LS/ES-SCLC were evaluable for all endpoints. Both an OS and PFS advantage for TEC was observed over CEV, with a median OS benefit of 2 months (12.7 versus 10.9 months, $p = 0.24$). However, when analyzed by stage, this OS advantage was only confined to the LS-SCLC cohort. Toxicities were reported at significantly lower levels than previous studies due to the use of carboplatin over cisplatin, with myelosuppression the principal toxicity in both arms, and grade 3/4 neurotoxicity and thrombocytopenia more common with CEV.

Although Reck *et al.* [74] conclude that TEC is a preferable regime over CEV for LS-SCLC, efficacy data from other studies does not demonstrate an unequivocal benefit for paclitaxel-including regimes over standard PE chemotherapy. Overall, the use of the taxanes has proved a great disappointment in the treatment of SCLC and at present should not be considered standard in any stage of the disease.

Targeted therapies

Anti-CD56 targeted therapy

Almost all SCLCs express CD56 [75]. Molecular analyses have shown that CD56 is a neural cell adhesion molecule (NCAM) isoform. NCAM plays a major role in neurite development, and is expressed on peripheral nerves, neuroendocrine tissue, myocardium as well as natural killer cells.

Conjugated monoclonal antibodies (mAbs) have been raised specifically against epitopes on CD56. The first of these was N901-bR, a ricin immunoconjugate of the anti-CD56 murine monoclonal N901 [76]. A phase I study of 21 patients with recurrent SCLC treated by continuous infusion for 7 days reported a dose-limiting toxicity of a capillary leak syndrome in two patients [77]. One patient had a PR to treatment lasting 3 months. Unfortunately, accrual to a subsequent phase II study was discontinued after the ninth patient died from a capillary leak syndrome [78].

Subsequently, another chimeric humanized anti-CD56 mAb (BB-10901; British Biotech) conjugated to a maytansinoid toxin (DM1) is currently undergoing phase I testing. Once bound to CD56, the immunoconjugate is internalized and releases DM1. This toxin inhibits tubulin polymerization and microtubule assembly, and causes cell death. DM1 is thought to be less likely to result in capillary leakage and therefore better tolerated.

Thalidomide

The growth of solid tumors is dependent on neoangiogenesis, and several pro-angiogenic factors have been identified, including vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF). In view of the critical role of neoangiogenesis in establishing tumor development, a number of anti-angiogenic strategies have been pursued in SCLC.

Thalidomide was first marketed as a non-barbiturate hypnotic for insomnia, but later withdrawn because of teratogenicity. The precise mechanism for its anti-angiogenic effect remains unknown. However, it has been shown to inhibit vascularization induced by bFGF [79], and inhibit bFGF- and VEGF-mediated neovascularization [80]. In a phase II feasibility study, 26 chemo-naive SCLC patients were treated with standard PE chemotherapy for six cycles with concurrent and maintenance thalidomide (100 mg daily) for up to 2 years [81]. Toxicity was acceptable (2% grade 2 neuropathy) and thalidomide compliance was good. No vascular toxicities were reported. Of the 23 patients evaluable, two CRs, 13 PRs, five cases of disease stabilization (SD) and three cases of progressive disease were observed. The median OS was 10 months and 1-year survival was 42%. In view of these promising results a phase III study is underway.

Matrix metalloproteinase inhibitors (MMPI)

Metalloproteinases are important enzymes in neoangiogenesis, playing a major role in tissue remodeling and tumor growth into the surrounding extracellular matrix. Tumor invasion as well metastasis formation is dependent on production and release of MMPs by tumor cells. MMPs are a family of at least 20 zinc-containing endoproteinases capable of degrading collagen and proteoglycan. A number of inhibitors of MMPs (MMPIs) have recently been developed and tested in SCLC. These include Marimastat (British Biotech) and BAY12-9566 (Bayer). The toxicities observed with most MMPIs are similar, and include proximal musculoskeletal pain, arthralgia and stiffness.

In a large study of Marimastat, over 500 patients with LS/ES-SCLC responding to initial chemo/chemoradiotherapy were randomized to either Marimastat (10 mg twice-daily) or placebo for 2 years [82]. However, no survival advantage was seen in the study arm and

only a preponderance of MMPI-associated toxicity was observed.

The Bayer compound BAY12-9566 is, however, structurally distinct from other MMPIs and this is reflected by its toxicity profile, which does not include musculoskeletal toxicities, but does include asymptomatic elevated transaminases and thrombocytopenia [83]. Efficacy data is, however, not encouraging. An initial phase III study of BAY12-9566 in combination with chemotherapy was terminated prematurely when interim analysis demonstrated inferior survival in the study arm (unpublished data). In a subsequent phase III study, 327 LS/ES-SCLCs, of which 28% were in CR, were randomized to BAY12-9566 or placebo alone [84]. At the time of a prospectively planned interim analysis, time to disease progression was significantly shorter in the BAY12-9566 group (3.2 versus 5.3 months, $p = 0.05$), with a significant increase in adverse events in the treatment arm. In light of these findings it is unlikely that this compound will be developed further for SCLC.

Tyrosine kinase receptor inhibitors

Gefitinib (Iressa, ZD1839)

Unlike non-SCLC, SCLCs either do not express the epidermal growth factor receptor (EGFR) or do so in small amounts [85]. Recent data on the relationship between genotype and phenotype has demonstrated no EGFR mutants in a small number of SCLC cell lines screened [86]. These agents will therefore probably not have activity in SCLC unless by individual or unrelated mechanisms, as yet unpredictable.

Imatinib (Gleevec, STI-571)

Imatinib has been investigated in SCLC, following on from its success in other tumor types. The rationale for this is the co-expression of c-*kit* and its natural ligand, stem cell factor, in 70% or less of SCLC tumors and cell lines [87]. Although promising *in vitro* [88], imatinib has not proven effective *in vivo* after a phase II study of 19 SCLC patients demonstrated no responses, but only one prolonged case of SD (90 days) [89]. However, prevalence of c-*kit* expression was only 30% in this series. A recent phase II study of 10 relapsed SCLCs that received imatinib on the basis of c-*kit* expression, demonstrated that although the drug was well tolerated, no responses were observed [90]. It is therefore unlikely that imatinib will be useful for SCLC patients.

Antisense bcl-2

Bcl-2 family members are important regulators of apoptosis. Bcl-2 is a negative regulator of cell death, prolonging survival of non-cycling cells and inhibiting apoptosis [91]. A bcl-2 antisense oligonucleotide has therefore been developed (Genasense, G3139, oblimersen). Initial data show that SD was maintained in two of 12 patients with recurrent SCLC treated with a combination of oblimseren (3 mg/kg/day, continuous infusion days 1–8) and paclitaxel (150–175 mg/m^2 on day 6). A phase I study evaluating oblimersen, carboplatin and etoposide in patients with previously untreated ES-SCLC has recently reported [92]. A total of 16 patients were enrolled and in the 14 patients evaluable for response, 12 PRs were observed (86%) and two SDs. Following on from these results, a randomized trial to assess the efficacy of adding oblimersen to standard carboplatin and etoposide chemotherapy will be conducted by the Cancer and Leukemia Group B (CALGB).

Vaccines

GD3 is a ganglioside expressed on tumors of neuroectodermal origin including melanoma and SCLC, and represents an attractive vaccine target. However, it is poorly immunogenic. In order to improve its antigenicity, several strategies designed to immunize patients against GD3 have been pursued, including the use of anti-idiotypes such as BEC2, an anti-idiotypic mAb that mimics GD3 [93]. Pilot trials in melanoma and SCLC indicated that BEC2 induces an anti-GD3 antibody response in a subset of patients. In a phase II study, 15 patients in CR after completing standard therapy for SCLC received a series of five intradermal immunizations of 2.5 mg of BEC2 plus BCG as an immune adjuvant over a 10-week period. Survival was improved in comparison to historical controls. Unfortunately, these initially promising results were not maintained in an EORTC phase III trial of BEC2/BCG as consolidation of CR in LS-SCLC [94].

SRL172 is a suspension of heat-killed *Mycobacterium vaccae*. It has been found to be a potent immunological adjuvant when used with autologous cells in animal models and is a potential alternative to BCG with less cutaneous toxicity. A phase II study of SRL172 in combination with chemotherapy for SCLC patients has been reported, with encouraging results [95]. This led to a randomized multicenter phase III, in which 76 patients with LS/ES-SCLC were randomized as per the phase II study [96]. Despite the encouraging phase II results, no response difference or survival advantage was observed in the vaccine arm. However, an increased symptomatic response rate was observed. Although SRL172 was non-toxic, future development will require the inclusion of a placebo.

Future aspects

Lung cancer is the most preventable of all common cancers. The WHO has predicted that over the next 30 years, tobacco will kill more people than the combined mortality from malaria, tuberculosis, and maternal and childhood diseases combined. Despite advances in treatment strategies with established drugs and the promise of newer agents, the elimination of cigarette

smoking remains still the best hope for reducing mortality from SCLC. Modern molecular analyses have enabled a greater understanding in not only the pathological processes required for SCLC carcinogenesis, but also the biological properties of individual lung cancers. This will undoubtedly lead to the development and widespread use of drugs targeted to key processes in SCLC carcinogenesis, as has been seen in the case of other cancers [86,97]. The role of screening for lung cancer of both the population in general and the targeted screening of at-risk individuals will play a more important role as the health economics of screening methodologies become more feasible [98]. Unfortunately, these strategies may only have minimal global impact if rates of new tobacco smokers in the Western and developing worlds continue to rise at current levels.

Conclusion

A number of novel strategies have been assessed for the treatment of SCLC, both in terms of the scheduling of established cytotoxics and the use of newer agents. These have aimed at improving survival by reducing the characteristically high relapse rates. Unfortunately, few unequivocal improvements have been noted, although some are encouraging and may prove to become standard given further data. Currently, the use of platinum-based regimes (e.g. PE) remains standard first-line strategy, with the option of anthracycline-based treatment (e.g. CAV or ACE) on relapse. There is no unequivocal evidence for the use of modified dosing/cycling schedules or newer cytotoxic drugs outside clinical trials.

It is unlikely that SCLC represents a clinically homogenous disease state and current treatment paradigms are based on data from which outcomes may have been confounded by heterogeneous SCLC cohorts. Such heterogeneity may be defined using either radiological or clinical criteria as LS/ES-SCLC or those with sensitive and resistant relapse.

Patients included in clinical trials may not necessarily be representative of the patient population as a whole. Although this general point should always be borne in mind when interpreting clinical trial data, this is particularly the case for SCLC, where due to the late presentation, poor PS, advanced age and associated co-morbidity in the majority of patients application of many clinical trial regimens may only be of limited value.

Despite the efficacy of a number of drugs discussed here, overall results still remain disappointing, with brief remissions and poor survival still characterizing the management of SCLC patients. Advances in the molecular biology of SCLC have demonstrated a number of potential new targets, and specific inhibitors of these are only now under development and assessment. It is likely, however, that the greatest impact from newer targeted drugs will be seen either in combination with, or in sequence with, standard chemotherapeutic strategies. It is hoped that either refinement of the strategies reviewed above or others yet to follow will prove successful and enhance our ability to treat this highly preventable disease.

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