CLINICAL INVESTIGATION

Emerging treatments for small-cell lung cancer: Phase II and III trials

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Small-cell lung cancer (SCLC) comprises up to 20% of lung cancers, and continues to have a long-term survival rate in limited disease of only approximately 15%. Advanced stage disease is often fatal in less than 1 year. Over the last 30 years, the treatment for extensive stage SCLC has remained relatively unchanged. Treatment with cisplatin or carboplatin plus etoposide leads to response rates over 70%, but patients inevitably recur with subsequent rapid progression. Newer chemotherapeutics such as irinotecan, amrubicin and picoplatin have shown some promising activity. Inhibitors of angiogenesis, such as bevacizumab and thalidomide, have shown minimal activity to date. Hope lies with ongoing clinical trials with novel targeted agents against various oncogenic signaling pathways in SCLC.

Keywords: angiogenesis • cisplatin • etoposide • limited stage small-cell lung cancer • refractory disease • resistant disease

Lung cancer is a leading cause of cancer-related death worldwide. Lung cancer was the eighth most frequent cause of death in 2004, killing an estimated 1.3 million people [1]. In the USA, approximately 222,000 cases of lung and bronchus cancers were anticipated to be diagnosed in 2010, and over 157,000 people will die of this disease [2]. Therefore, there exists an urgent need for safer and more effective therapies for lung cancer.

Small-cell lung cancer (SCLC) is a high grade neuroendocrine carcinoma of the lung (for recent perspectives, see [3,4]). SCLC has historically comprised as much as 20% of lung cancer, with non-small-cell lung cancer (NSCLC) comprising the remainder. The incidence of SCLC appears to be decreasing in the USA, perhaps due to corresponding declines in smoking prevalence as the development of SCLC is strongly associated with smoking [5]. Most patients present with symptoms related to the bulk or dissemination of disease, including cough, pain and weight loss. Occasionally, these tumors also cause a variety of paraneoplastic syndromes, such as hyponatremia from SIADH, Cushing's syndrome from adrenocorticotropic hormone production or neuromuscular disorders. SCLC is staged as either limited stage, when disease is localized within one radiotherapy portal (generally consisting of the ipsilateral hemithorax, plus mediastinum and supraclavicular nodes) or extensive stage (ES) when disease is widespread. Unfortunately, the prognosis for patients has changed minimally over the last 25 years. In limited-stage disease, the median overall survival (OS) is approximately 20 months, and 5-year survival is less than 15%. Extensive stage disease has a median survival of 8–12 months, with less than 2% of patients surviving past 5 years [5]. Therefore, there is an urgent need for improved treatments for this disease.

Standard treatment for SCLC

Limited stage SCLC is generally treated with a combination of chemotherapy, most commonly four cycles of cisplatin and etoposide, and concurrent thoracic radiation, with radiotherapy starting early in the course of treatment [6] (for a recent review,

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see [7]). The addition of surgery to treatment does not appear to improve survival. There is evidence that twice-daily thoracic radiation to 45 Gy of therapy is superior to daily treatment of the same total dose of 45 Gy [8]. However, a similar trial from Canada compared daily radiation with twice-daily radiation, including a midway treatment break in an attempt to make the biologic effective doses more similar, and did not demonstrate a survival difference between the groups [9]. As a result, this practice has not been uniformly adopted, but a large intergroup trial is ongoing to answer the question of whether twice-daily standard radiation to 45 Gy, daily radiation to 70 Gy, or a hybrid of the two techniques is superior [101]. For patients with controlled disease following initial treatment, prophylactic cranial irradiation (PCI) improves long term survival by 5% [10].

As no Phase III clinical trials in the past 10 years have demonstrated a survival advantage in limited-stage disease, further improvements in therapy are most likely to be based on initial advances in ES disease. Thus, the remainder of this article will focus on recent developments in metastatic SCLC.

The proportion of patients diagnosed with ES-SCLC has increased from 50% to approximately 75% over the past few decades, probably caused by upstaging from the increased use of CT and PET scanning. Standard treatment consists of chemotherapy alone, generally cisplatin or carboplatin plus etoposide for up to six cycles [11]. Response rates exceed 75% in previously untreated patients. As with limited-stage disease, PCI is recommended after initial therapy as it improves the 1-year survival rate by 15% [12], but also may reduce the quality of life for patients due to increased fatigue and hair loss and a small but real chance for some cognitive impairment [13]. As virtually all patients eventually relapse, second- and third-line chemotherapy consisting of topotecan, irinotecan or docetaxel, gemcitabine and others are used with diminishing response rates depending on the line of therapy and the duration of the initial response. Patients with an initial response to treatment lasting more than 3–6 months from the completion of chemotherapy are considered chemotherapy 'sensitive' and have a better prognosis than patients without an initial response or early relapse, who are considered 'refractory'. Retreatment with a second course of a platinum/etoposide regimen can also be considered in patients who are initially platinum-sensitive patients.

Recent trials involving chemotherapy

Since 1985, frontline chemotherapy for ES-SCLC has consisted of a platinum plus etoposide [11]. Many newer chemotherapeutic agents have been tested in the second-line treatment of SCLC to determine activity before moving them to the front-line setting, but generally these agents have not demonstrated sufficient promise. For example, gemcitabine has modest 5–15% response rates in relapsed, refractory and resistant SCLC [14,15], but carboplatin/gemcitabine demonstrated no additional efficacy over cisplatin/etoposide [16]. Therefore, newer Phase II and III trials involving chemotherapy of agents that demonstrated promise will be reviewed (Table 1).

Irinotecan

In 1997, second-line activity of the topoisomerase I inhibitor topotecan was suggested by a Phase II study, with response rates of 38% in sensitive patients and 6% in refractory patients [17]. When compared head-to-head with the standard combination regimen of cyclophosphamide, doxorubicin and vincristine (CAV), topotecan had an equivalent response and survival with less toxicity [18]. An oral version of topotecan has also been approved in this setting with similar efficacy, but is not widely utilized [19,20]. Based on this, the related agent irinotecan has been extensively tested in combination with platinum in the first-line setting. In 2002, the Phase III Japanese Clinical Oncology Group (JCOG) 9511 study compared cisplatin/etoposide (EP) treatment with cisplatin and irinotecan (IP) in 174 patients [21]. This study was terminated early due to an improvement in survival in patients receiving IP, from a median survival of 9.4 months to 12.8 months ($p = 0.002$). This regimen is now the standard of care in Japan as first-line therapy. Based on the concern that these results from a predominantly Japanese population may not be applicable to Western countries, two subsequent Phase III studies were conducted with similar regimens in patients from the USA. In the first, 331 patients were randomized in a 1:2 fashion to EP or a dose-reduced administration of IP, with irinotecan 65 mg/m^2 given on days 1 and 8 of a 3 week cycle [22]. This study failed to demonstrate a difference between the treatment arms, with median survival time 9.3 months for IP and 10.2 months for EP ($p = 0.74$). As a result, it was unclear whether the failure to demonstrate an improvement in survival was caused by a slight modification of the regimen from the Japanese trial. A third Phase III trial was conducted, utilizing the exact regimen from the Japanese study, Southwest Oncology Group (SWOG) 0124, in which 651 patients were randomized to EP or IP, with irinotecan 60 mg/m^2 given on days 1, 8 and 15 of a 3-week cycle. Unfortunately, this trial also demonstrated no difference in survival (9.9 months for IP and 9.1 months for EP, $p = 0.71$), with more hematologic toxicity on the EP arm, but more diarrhea on the IP arm [23]. Therefore, currently IP is a potential alternative to EP in the first-line treatment of ES-SCLC, but does not appear to be superior, and so, has not been widely incorporated into

Table 1. Comparison of recent Phase III clinical trials of chemotherapy in small-cell lung cancer.

Trial/population	Agents	Patients (n)	Response rate (%)	PFS (months)	OS (months)	Ref.
JCOG 9511	Cisplatin/irinotecan	75	84†	6.9†	12.8†	[21]
First line	Cisplatin/etoposide	77	68	4.8	9.4	
Hanna *et al.*	Cisplatin/irinotecan	221	48	4.1	9.3	[22]
First line	Cisplatin/etoposide	110	44	4.6	10.2	
SWOG S0124	Cisplatin/irinotecan	324	60	5.8	9.9	[23]
First line	Cisplatin/etoposide	327	57	5.2	9.1	
GALES	Carboplatin/pemetrexed	453	31	3.8	8.1	[43]
First line	Carboplatin/etoposide	455	52†	5.4†	10.6†	
SPEAR	Picoplatin	268	4	2.1†	4.8	[38]
Refractory or resistant second line	Best supportive care	133	0	1.5	4.6	

†Statistically superior value with $p < 0.05$.

GALES: Global Analysis of Pemetrexed in Small-Cell Lung Cancer Extensive Stage; JCOG: Japanese Clinical Oncology Group; OS: Overall survival; PFS: Progression-free survival; SPEAR: Study of Picoplatin Efficacy After Relapse; SWOG: Southwest Oncology Group.

clinical practice in the USA and Europe. However, irinotecan is still used in the second-line treatment of SCLC.

Amrubicin

Amrubicin is a new synthetic anthracycline that acts primarily as an inhibitor of DNA topoisomerase II [24] and unlike the related compound doxorubicin, has not been associated with that compound's cumulative cardiotoxicity in animal models [25] or in subsequent human studies. The dose-limiting toxicity is neutropenia [26], although management with growth factors can reduce the incidence of febrile neutropenia. Thus far, amrubicin has been most extensively tested in Japanese patients, and has been approved in Japan for use in SCLC and NSCLC since 2006 [27]. There have been promising results from the use of frontline amrubicin in patients with SCLC both as a single agent, with a 75% response rate among 35 patients [28], and in combination with carboplatin in an elderly population, with an 89% response rate among 36 patients [29]. Notably, a more recent Phase III study randomizing elderly patients to amrubicin alone versus carboplatin/etoposide was terminated early after there were three treatment-related deaths in the amrubicin arm out of 32 patients, although there were no statistically significant differences between the two arms with respect to response, progression, survival or quality of life [30]. However, the bulk of ongoing development has been as a second-line agent in relapsed or platinum-refractory disease. A Phase II study of second-line use of amrubicin by the Thoracic Oncology Research Group in Japan (Study 0301) observed a response rate of 52% (95% CI: 37–68) among 44 platinum-sensitive patients and 50% (25–75%) among 16 platinum-refractory patients [31]. The only published randomized Phase II study to date is the North Japan Lung Cancer Study Group 0402 Trial, in which 59 assessable patients (36 sensitive and 23 refractory) were randomized to amrubicin or topotecan as second-line treatment. Response was higher in the amrubicin arm, 38 versus 13% ($p = 0.039$) [32]. In a US and European population, a single-arm Phase II study evaluated second-line use of amrubicin in 75 patients with platinum-refractory SCLC, demonstrating a response rate of 21.3% (95% CI: 12.7–32.3%) and a median OS of 6.0 months (4.8–7.1 months) [33]. Among patients who had not responded to their first-line platinum-based chemotherapy, the response rate was 16.3%. Given these promising results, an international Phase III trial comparing amrubicin to topotecan was conducted in the second-line setting and has completed accrual, but results have yet to be reported [102].

Picoplatin

Although cisplatin is effective in the frontline treatment of SCLC, some patients are refractory from the outset, and the majority of others will develop resistance over time. Picoplatin is an analog of cisplatin that incorporates a large picoline ring. By increasing the steric bulk of the compound, the ring is intended to reduce the platinum DNA adduct's susceptibility to certain mechanisms of platinum resistance [34]. Unlike cisplatin, picoplatin causes minimal ototoxicity or nephrotoxicity, and myelosuppression is the dose-limiting toxicity, with thrombocytopenia more common than neutropenia [35]. In a Phase II study of 77 patients either refractory to first-line platinum or who had relapsed within 6 months,

treatment with picoplatin produced just a 4% response rate; although when stable disease was included, the disease control rate was 43%, with a median survival of 27.1 weeks (6.3 months) [36]. These results were consistent with an earlier Phase II study of 37 patients that had a higher response but similar survival (response rate of 15% among platinum-resistant patients and 8% among platinum-sensitive patients, and with survival of 6.3 and 8.2 months, respectively) [37]. More recently, results were reported from the Study of Picoplatin Efficacy After Relapse (SPEAR) trial, a Phase III study that randomized 401 relapsed or refractory patients on a 2:1 basis to picoplatin or best supportive care (Table 1) [38]. The study did not meet its primary end point of OS, with median survival time 4.8 months for picoplatin versus 4.6 months for best supportive care (hazard ratio 0.82, p = 0.090); although on subgroup analysis there was a modest survival advantage among patients who had initially been refractory to platinum with median survival time of 4.9 versus 4.3 months (hazard ratio 0.72, p = 0.017). The investigators suggested that failure to meet the survival end point may have been partly due to any picoplatin advantage being attenuated by differential use of poststudy chemotherapy between the two groups (28% in the picoplatin arm vs 41% in the best supportive care arm). The authors do note a significant difference in progression-free survival (PFS) favoring the picoplatin arm, 2.1 versus 1.5 months (hazard ratio: 0.78; p = 0.028), but given the small magnitude of this difference and the failure to show improvement in OS, the future of picoplatin in SCLC is uncertain.

■ Pemetrexed

Pemetrexed is a recently developed multitargeted antifolate chemotherapeutic that inhibits important enzymes for tumor nucleotide metabolism [39]. Given its efficacy in NSCLC both as monotherapy and in combination with cisplatin [40,41], pemetrexed was tested in the first-line setting in SCLC. In a Phase II study, pemetrexed in combination with either cisplatin or carboplatin appeared tolerable, with a median OS of 10.4 months [42]. Based on this, a randomized Phase III trial compared carboplatin and etoposide with carboplatin plus pemetrexed. While the initial accrual goal was over 1800 patients, enrollment was halted at 908 patients after an analysis demonstrated potential inferiority of the carboplatin/pemetrexed arm, with median OS of 8.1 months as compared with 10.6 months in the carboplatin/etoposide arm (p < 0.01) [43]. Additionally, the response rate was lower in the pemetrexed arm (31%) as compared with the etoposide arm (52%).

Pemetrexed also appears to have minimal activity in patients with relapsed sensitive or refractory SCLC, with a response rate across 116 patients of only 0.9%, even in patients treated with higher dose pemetrexed (900 mg/m^2) [44]. One proposed mechanism for the relative resistance of SCLC to pemetrexed therapy is that SCLC has a higher level of thymidylate synthase expression than the adenocarcinoma histologic subtype of NSCLC [45]. While molecular analysis of tissue from these trials may help the understanding of predictors of response, pemetrexed should not be used for SCLC outside the scope of a clinical trial due to its inferiority to other available agents.

Antiangiogenic therapies

■ Bevacizumab

Microscopic tumors are dependent on the growth of new blood vessels to overcome hypoxia [46]. Bevacizumab is a monoclonal antibody that targets VEGF and improves PFS when added to chemotherapy in NSCLC, with an OS benefit seen in one trial with carboplatin/paclitaxel as the chemotherapy backbone [47]. In the Eastern

Table 2. Comparison of recent randomized Phase II and III clinical trials of antiangiogenic therapy in small-cell lung cancer.

Trial/population	Agents	Patients (n)	Response rate (%)	PFS (months)	OS (months)	Ref.
SALUTE	Platinum/etoposide/bevacizumab	50	48	5.5†	9.4	[51]
First line	Platinum/etoposide/placebo	52	58	4.4	10.9	
FNCLCC cleo04-IFCT 00–01	Thalidomide	49	N/A	6.6	11.7	[58]
Responding patients postchemotherapy	Placebo	43	N/A	6.4	8.7	
Lee *et al.*	Carboplatin/etoposide/thalidomide	365	74	7.6	10.1	[59]
LS and ES-SCLC, first line	Carboplatin/etoposide/placebo	359	72	7.6	10.5	

†Statistically superior value with p < 0.05.

ES: Extensive stage; FNCLCC: Federation of the French Cancer Centre; LS: Limited stage; N/A: Not applicable; OS: Overall survival; PFS: Progression-free survival; SALUTE: Study of Bevacizumab in Previously Untreated Extensive-Stage Small-Cell Lung Cancer; SCLC: Small-cell lung cancer.

Cooperative Oncology Group (ECOG)-3501 Phase II trial, bevacizumab was added to the cisplatin and etoposide backbone in 63 patients with ES-SCLC. In this single-arm trial, the response rate was 63%, with a PFS of 4.7 months and median OS of 10.9 months [48]. One potentially life-threatening side effect of bevacizumab treatment is the development of pulmonary hemorrhage, and one patient did experience grade 3 pulmonary hemorrhage in this trial. Additional single-arm Phase II trials were also conducted with irinotecan-based chemotherapy plus bevacizumab. Among 51 patients treated with carboplatin, irinotecan and bevacizumab, the response rate was 84%, with median PFS of 9.1 months and OS of 12.1 months, without any grade 3 or higher bleeding complications [49]. In the Cancer and Leukemia Group B (CALGB) 30306 trial, patients received cisplatin, irinotecan and bevacizumab with a response rate of 75%, median PFS of 7.1 months and median OS of 11.7 months [50]. Based on these single-arm studies, the Study of Bevacizumab in Previously Untreated Extensive-Stage Small-Cell Lung Cancer (SALUTE) Phase II trial stratified and randomized 102 patients to four cycles of treatment with carboplatin or cisplatin and etoposide, either with or without bevacizumab followed by maintenance bevacizumab. In a preliminary report of this trial, patients that received bevacizumab had a significantly better PFS (5.5 vs 4.4 months; p = 0.01; HR: 0.53; 95% CI: 0.32–0.86) with subgroup analysis favoring patients that received carboplatin over cisplatin [51]. However, there was no significant difference in OS between patients that received bevacizumab (9.4 months) and patients that received placebo (10.9 months, HR: 1.16; 95% CI: 0.66–2.04). Based on this, there are no current plans for a Phase III randomized trial including bevacizumab in SCLC.

Sorafenib & sunitinib

Sorafenib is a small molecule inhibitor with activity against many tyrosine kinases, including B-raf and the VEGF receptors (VEGFR)-1, -2 and -3. This potentially results in both antiangiogenic and antiproliferate properties, and this drug is effective in both renal cell carcinoma and hepatocellular carcinoma [52,53]. In SCLC, a Phase II trial, SWOG 0435, was conducted in patients with relapsed or refractory disease using sorafenib 400 mg twice daily [54]. Among 38 patients with platinum-sensitive disease and 45 patients with platinum-refractory disease, the response rates were 11 and 25%, with PFS of 2.2 and 2.0 months and OS of 5.3 and 6.7 months, respectively. Toxicities of this agent typically include fatigue, rash, hand–foot syndrome and gastrointestinal disorders. Based on the lack of survival improvement as compared with historical controls, the authors of this study conclude that there is not sufficient signal to further pursue development of single-agent sorafenib in SCLC. However, a Phase I/II trial in combination with chemotherapy is ongoing [103].

Sunitinib is a related drug with an overlapping spectrum of activity against VEGFR, PDGFR and the KIT receptor. It is being tested both in the frontline setting in a randomized Phase II CALGB study [104] as well as in the maintenance setting after chemotherapy [105], with results eagerly anticipated.

Thalidomide

Inhibition of angiogenesis is one putative mechanism of action for the anti-tumor activity of the small molecule thalidomide [55]. In ES-SCLC, front-line treatment with thalidomide 100 mg orally daily, in combination with carboplatin and etoposide appeared to be safe in a Phase II trial of 25 patients, yielding a response rate of 68%, with PFS of 8.1 months and a median OS of 10.1 months [56]. A second Phase II trial used maintenance thalidomide at a dose of 200 mg daily following first-line chemotherapy and demonstrated a median OS of 12.8 months [57]. Based on these trials, two Phase III trials were conducted. In the smaller French trial, a chemotherapy backbone of cisplatin, etoposide, cyclophosphamide and 4′-epidoxorubicin was employed. After two cycles of therapy, patients received four more cycles of treatment plus either thalidomide 400 mg daily or placebo [58]. Among 92 randomized patients, median OS was 11.7 months in patients treated with thalidomide and 8.7 months for those treated with placebo (p = 0.16), with an exploratory subset analysis demonstrating a statistically significant benefit in patients with performance status of 1 or 2, but not 0. As this trial did not have sufficient power to demonstrate difference in survival, a larger randomized trial was also conducted in the UK. A total of 724 patients with both ES- and limited stage (LS)-SCLC in equal proportions were treated with carboplatin and etoposide, and randomized to thalidomide 200 mg daily or placebo [59]. In patients with LS disease, there was no survival difference between the treatment groups. However, among patients with ES-SCLC, the median OS was significantly worse in patients treated with thalidomide (8.0 months) compared with patients treated with placebo (9.1 months, HR for death: 1.36, 95% CI: 1.10–1.68). This may have been due to a 19% risk of thrombotic events, including deep venous thrombosis and pulmonary embolism, in the thalidomide-treated group, as compared with a 10% risk in the placebo group. Other grade 3/4 toxicities potentially related to thalidomide included neuropathy and somnolence in approximately 5% of patients. Given the lack of efficacy

and the possibility of harm in this large, definitive trial, thalidomide should be avoided in the treatment of SCLC.

Targeted therapies

Many targeted therapies are being tested in SCLC, but few reports of efficacy have been published to date (Table 2). Some of the newer agents undergoing evaluation include navitoclax (ABT-263), everolimus (RAD001), and the hedgehog (Hh) inhibitor GDC-0449.

The Bcl-2 protein is an inhibitor of chemotherapy-induced cell death that is overexpressed in many SCLCs [60]. Navitoclax (ABT-263) is a small molecule BH3 mimetic that inhibits Bcl-2, allowing a lower threshold for apoptosis. In a preliminary report of a Phase IIa trial of navitoclax, 39 patients were treated with this drug, with a median time of study of 49 days. Only adverse events have been reported, these included thrombocytopenia in 29% of patients, and diarrhea in 43% of patients [61]. A Phase I study is ongoing to test navitoclax in combination with cisplatin and etoposide [106]. Another strategy developed to target the Bcl-2 signaling pathway is the antisense oligonucleotide, oblimersen, which appeared safe in combination with chemotherapy in Phase I studies [62]. However, in a small randomized Phase II study of 56 patients, the survival was significantly worse in patients receiving carboplatin, etoposide and oblimersen, suggesting that this molecule will no longer be developed in SCLC [63].

Everolimus, an oral rapamycin analog, which works by inhibiting mTOR and the PI3K/AKT signaling pathway, was recently approved by the FDA for treatment of advanced kidney cancer. In a preliminary report of a Phase II trial, 40 patients with relapsed or refractory SCLC were given everolimus. Of 35 evaluable patients, one patient had a partial response and eight patients had stable disease, with a median PFS of 1.4 months and median OS of 5.5 months [64]. Everolimus was generally well tolerated, with grade 3 toxicities that included cytopenias, transaminitis, infection and renal failure. While the observed activity was minimal, everolimus is also being tested in combination with carboplatin and etoposide for treatment-naive patients with SCLC [107].

Ligand-dependent activation of the Hh signaling pathway appears to be important for the growth of many lung cancer cell lines [65]. There is also growing evidence that Hh signaling is critical for the survival of cancer stem cells, such that inhibitors of this pathway might kill a relatively small population of chemotherapy-resistant self-renewing cells within a tumor [66]. GDC-0449 is a cyclopamine derivative inhibitor of Hh signaling, which has elicited remarkable responses in patients with metastatic basal cell cancer and medulloblastoma [67,68]. In addition, the IGF-1 receptor also appears to be important in lung cancer, as inhibition of this pathway may potentiate chemotherapy, EGF receptor inhibitors, and even radiation effects in lung cancer cell lines [69–71]. The ongoing ECOG-1508 Phase II trial is enrolling up to 170 patients with SCLC for treatment with cisplatin and etoposide, in combination with either GDC-0449 or the IGF-1 receptor antibody cixutumumab, in order to determine whether either of these agents has activity [108].

Vaccine therapy

As SCLC can become rapidly resistant to chemotherapy, an alternative strategy has been to use cancer vaccines to harness the immune system to fight both LS- and ES-SCLC. Despite promising early results, a large study in patients with LS-SCLC using a vaccine against Bec2/BCG did not demonstrate a survival benefit [72]. More recent studies testing a dendritic cell-based vaccine targeting p53 [73, 109] and the anti-CTLA4 antibody ipilimumab to boost anti-tumor immunity [110] have not been formally reported; however, further investigation in this area of research is eagerly anticipated as it holds the potential to yield long-term remissions in patients with SCLC.

Future perspective

Despite the high response rates to chemotherapy, there have been few advances in the treatment of ES-SCLC since the introduction of platinum chemotherapeutics almost 30 years ago. Agents recently shown to be effective in NSCLC like pemetrexed and bevacizumab do not have appreciable activity in this disease, but amrubicin is a promising anthracycline that merits further study. More significant advances in the treatment of SCLC will probably come through a better understanding of the biology of this disease, which could lead to the development of effective targeted therapies. Therefore, consideration of clinical trials is still an important part of the treatment of patients initially diagnosed with SCLC, as well as patients with recurrent or refractory disease.

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Executive summary

- Standard first-line chemotherapy for extensive stage small-cell lung cancer consists of carboplatin or cisplatin plus etoposide.
- Irinotecan plus cisplatin yields equivalent overall survival times as cisplatin and etoposide, with slightly different side effects.
- Amrubicin is a promising second-line agent, with Phase III results eagerly awaited.
- Picoplatin is well tolerated but has not demonstrated a convincing survival benefit in the second line.
- The angiogenesis inhibitors bevacizumab and thalidomide have minimal activity in small-cell lung cancer.
- Targeted inhibitors of the hedgehog and IGF-1 receptor signaling pathways, as well as drugs that stimulate apoptosis and antitumor immunity, are currently being studied in this disease.

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