Systemic Therapy for Small Cell Lung Cancer

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Abstract
Small cell lung cancer is an aggressive tumor characterized by genetic complexity, rapid doubling time, and early development of disseminated disease. Unfortunately, few chemotherapeutic advances have been made in the treatment of extensive-stage disease, and cisplatin/etoposide has remained the standard of care for more than 30 years. Other regimens with comparable efficacy include cisplatin/irinotecan and carboplatin/etoposide. Each of these combinations is associated with a different toxicity profile that must be considered when selecting an initial regimen. Several strategies, including maintenance chemotherapy, 3-drug combinations, alternating combination chemotherapy regimens, and high-dose chemotherapy, have consistently failed to demonstrate improvements in survival when compared with 4 to 6 cycles of platinum doublets. Several options are available for patients who experience progression during or relapse after induction therapy, although topotecan is the only FDA-approved agent for second-line treatment. Recently, scientific efforts have identified potentially actionable genetic alterations in small cell tumors that may lead to the development of effective, targeted therapies. (JNCCN 2013;11:780–787)

Platinum Versus Non–Platinum-Based Regimens

Initial clinical trials evaluating chemotherapy for SCLC used single-agent therapy, including cyclophosphamide, methotrexate, and vincristine.\textsuperscript{2,3} Alkylator-based combination chemotherapy regimens, such as cyclophosphamide, doxorubicin, and vincristine (CAV), were the first to show improvement in overall survival (OS) compared with single-agent therapy, yielding response rates of 60% to 80% and median survival times of 7 to 10 months.\textsuperscript{4,5} These results led to the evaluation of many combination therapies, most notably cisplatin/etoposide (EP). Two phase III studies suggested improved clinical benefit with EP over nonplatinum regimens. Sundstrom et al\textsuperscript{6} randomized 436 patients with both
Systemic Therapy for Small Cell Lung Cancer

limited (n=214) and extensive disease (n=222) to 
EP or cyclophosphamide, epirubicin, and vincristine (CEV). Although this study reported an improvement in median OS with EP (10.2 vs 7.8 mo; \(P=0.004\)), this benefit was restricted to patients with limited-stage disease. A nonsignificant improvement in median OS for patients with ES-SCLC was identified (8.4 vs 6.5 
mo; \(P=0.21\)). Quality-of-life analysis revealed no significant differences between the treatment arms. The Manchester Lung Cancer Group\(^7\) randomized 280 patients with limited-stage (n=165) and extensive-stage disease (n=112) to either EP or ACE (doxorubicin, cyclophosphamide, and etoposide). In contrast to the study by Sundstrom et al,\(^6\) no difference was seen in response rate (77% vs 72%) or 1-year survival (34% vs 38%; \(P=0.497\)) between EP and ACE, respectively. Additionally, no difference in the 1-year survival rate was seen in the subset of patients with ES-SCLC (17% and 15%; \(P=0.9\)). More grade 3/4 adverse events occurred in the ACE arm, including anemia (27% vs 18%; \(P=0.03\)), neutropenia (90% vs 57%; \(P<0.005\)), and infection (73% vs 29%; \(P<0.0005\)), leading to more days of hospitalization and greater intravenous antibiotic use. This trial and several others suggested that EP may be the optimal choice for the initial treatment of ES-SCLC given the comparable clinical benefit and favorable toxicity profile compared with multidrug, nonplatinum therapy.

Because of conflicting results of randomized studies, several meta-analyses have evaluated platinum versus nonplatinum regimens to identify a superior treatment approach.\(^8\)–\(^11\) Pujol et al\(^8\) evaluated 4054 patients from 19 studies and found a significant reduction in risk of death at 1 year (hazard ratio [HR], 0.8; 95% CI, 0.69–0.93; \(P=0.002\)) for patients randomized to platinum-based regimens. Importantly, the benefit was not associated with increased risk of treatment-related mortality. Similarly, in a metaanalysis of 7173 patients from 36 trials, the European Lung Cancer Working Party showed improved outcomes with platinum-based treatment. Specifically, a survival advantage was demonstrated with the use of regimens containing either etoposide without cisplatin (HR, 0.72; CI, 0.67–0.78; \(P<0.001\)) or EP (HR, 0.57; CI, 0.51–0.64; \(P<0.001\)) compared with nonplatinum, non-etoposide regimens.\(^9\)

In contrast to these results, a recent meta-analysis of 5530 patients from 29 trials by the Cochrane Collaboration failed to show a significant benefit with platinum-based regimens compared with non-platinum-based therapies.\(^11\) Although platinum-based therapy did show a significantly higher rate of complete response, no differences in overall tumor response (relative risk [RR], 1.09; 95% CI, 0.97–1.21) or 1-year survival (RR, 1.08; 95% CI, 0.68–1.71) were seen in patients with ES-SCLC. In addition, platinum-based treatment was associated with higher rates of anemia (RR, 1.6; 95% CI, 1.22–2.08), thrombocytopenia (RR, 2.10; 95% CI, 1.54–2.86), and nausea and vomiting (RR, 1.51; 95% CI, 1.20–1.90). Despite the Cochrane review, EP remains the most accepted initial treatment of ES-SCLC in the United States. This is supported by an acceptable and more easily managed toxicity profile compared with multidrug nonplatinum regimens, and the survival advantage shown in the 2 aforementioned meta-analyses.

Etoposide Versus Irinotecan

The combination of irinotecan with cisplatin (IP) is also an effective regimen for untreated ES-SCLC. A median OS of 13 months was demonstrated in a small phase II study,\(^12\) and the Japanese Clinical Oncology Group (JCOG) subsequently compared IP with EP in a randomized phase III study of 154 chemotherapy-naive patients with ES-SCLC. However, this study was stopped prematurely when an interim analysis revealed a longer median OS with the IP regimen (12.8 vs 9.4 mo; \(P=0.02\)).\(^13\) Although more grade 3/4 neutropenia was seen in the IP group (92.2% vs 65.3%; \(P<0.001\)), more grade 3/4 diarrhea was identified in the IP group (16% vs 0%; \(P<0.001\)). This study generated significant interest in irinotecan as the preferred agent in the front-line setting. However, 3 subsequent phase III studies involving Western patients failed to confirm a survival advantage of IP over EP\(^14\)–\(^16\) (Table 1).

Hanna et al\(^14\) randomized 331 patients with ES-SCLC to IP or EP and found no statistically significant difference in the response rate (48% vs 43.6%) or median OS (9.3 vs 10.2 mo; \(P=0.74\)). This trial has been criticized for using different chemotherapy doses and schedules than the JCOG trial. However, similar findings were identified in a phase III SWOG study that randomized 651 patients to the identical doses and schedules of IP and EP used in the JCOG study. Again, no difference was seen between IP and EP in tumor response rate (60% vs 57%; \(P=0.56\)) or
median OS (9.9 vs 9.1 mo; \( P = .71 \)). Similar to the JCOG study, more grade 3/4 neutropenia in the EP arm (68% vs 33%) and more grade 3/4 diarrhea in the IP arm (19% vs 3%) was observed. In an effort to reconcile the discrepant outcomes and toxicities shown in patients treated with irinotecan in these studies, the SWOG trial assayed patient DNA for genetic polymorphisms involved in irinotecan metabolism. Although single polymorphisms in the \( ABCB1 \) and \( UGT1A1 \) genes were associated with increased risk of diarrhea and neutropenia, respectively, neither genotype correlated with efficacy outcomes (progression-free survival [PFS], OS).

In summary, although IP was found to be superior to EP in one Japanese study, larger phase III studies failed to show similar results in Western patients. Although EP is associated with more myelosuppression, this toxicity is typically less distressing for patients when compared with the diarrhea associated with irinotecan. Finally, the SWOG trial suggested that specific genetic polymorphisms correlated with specific toxicities, but whether pharmacogenomic differences can explain population-related differences in outcome or toxicity with irinotecan remains unclear. Both regimens are acceptable for initial treatment of ES-SCLC, and the toxicity profile of each should guide the clinician’s choice.

### Cisplatin Versus Carboplatin

Although EP has become a preferred initial regimen for ES-SCLC in the United States, the undesirable toxicity profile of cisplatin (including severe nausea, nephrotoxicity, ototoxicity, and peripheral neuropathy) has led to greater use of carboplatin. Recently, a meta-analysis of 663 patients from 4 trials compared cisplatin-based therapy (n=328) and carboplatin-based therapy (n=325) for first-line treatment of SCLC. This meta-analysis found no difference between cisplatin and carboplatin in response rate (67.1% vs 66%; \( P = .83 \)), median PFS (5.5 and 5.3 mo; \( P = .25 \)) or median OS (9.6 and 9.4 mo; \( P = .37 \)), respectively. Although carboplatin-based regimens were associated with more grade 3/4 myelosuppression, a higher incidence of any-grade nausea/vomiting, neurotoxicity, and renal toxicity was seen in patients treated with cisplatin-based regimens. Results of this meta-analysis suggest that carboplatin-based therapy is at least as effective as cisplatin-based regimens, with a more manageable toxicity profile. Therefore, EP should be considered an acceptable front-line therapy for ES-SCLC, especially for patients with contraindications to cisplatin.
Further Chemotherapeutic Strategies

Because of a plateau in survival rates with standard chemotherapy regimens, additional strategies have been investigated for ES-SCLC. These include adding a third agent to a standard 2-drug regimen, maintenance chemotherapy, alternating combination chemotherapy regimens, and high-dose chemotherapy with growth factor support and/or hematopoietic stem cell rescue.18 Although a handful of studies incorporating these strategies have shown a modest survival advantage, most have failed to show a consistent benefit. The 2 strategies that have garnered the most attention are high-dose chemotherapy and maintenance therapy.

In attempts to exploit the inherent chemosensitivity of ES-SCLC, several investigators have evaluated the role of higher-dose chemotherapy (administering up to 2 times the conventional doses) with and without growth factor or stem cell support. A phase II study using high-dose cyclophosphamide, methotrexate, and lomustine initially reported a response rate of 96% (complete response rate 30%).19 However, this strategy has failed to demonstrate a consistent survival advantage in phase III studies. Ihde et al20 randomized 90 patients with ES-SCLC to 2 cycles of high-dose EP (cisplatin, 27 mg/m² day 1–5; etoposide, 80 mg/m² day 1–5 every 3 weeks) or standard-dose EP (cisplatin, 80 mg/m² day 1; etoposide, 80 mg/m² day 1–3 every 3 weeks) followed by standard-dose EP for cycle 3 and 4 in both arms. No difference in complete response rate (23% vs 22%; P=.99) or median OS (10.7 and 11.4 months; P=.68) was identified, and more hematologic toxicity was reported in the high-dose arm. Growth factors (granulocyte colony-stimulating factor, granulocyte-macrophage colony-stimulating factor) have been evaluated in combination with high-dose chemotherapy in 3 phase III studies. Although one showed a modest improvement in survival (HR, 0.8; 95% CI, 0.65–0.99; P<.04),21 the other 2 showed no significant benefit in tumor response rate or median OS, with more hematologic and nonhematologic toxicities noted in the high-dose arms.22,23 Similar outcomes showing higher rates of toxicity with no improvement in survival have been noted in 2 phase III studies comparing high-dose ICE (ifosfamide, carboplatin, etoposide) followed by autologous stem cell rescue versus standard-dose ICE.24,25

Maintenance strategies have repeatedly failed to show a survival advantage in ES-SCLC.26–29 Continuation of the induction chemotherapy beyond 4 to 6 cycles,30–32 induction chemotherapy followed by switch maintenance etoposide or topotecan,33,34 and induction cytotoxic therapy followed by switch maintenance vandetanib, thalidomide, or interferon-based therapy35–42 have not improved survival in a meaningful way compared with standard chemotherapy for 4 to 6 cycles. Supporting these results is a recent meta-analysis of 3688 patients from 21 randomized controlled trials of maintenance therapy that showed no statistical advantage in median PFS (HR, 0.98; 95% CI, 0.91–1.06; P=.63) or OS (HR, 0.93; 95% CI, 0.87–1.00; P=.05).43 Currently, maintenance therapy for ES-SCLC should not be considered outside of a clinical trial.

Treatment of Relapsed/Resistant Disease

A durable response to initial platinum-based chemotherapy beyond 3 months of the last cycle is deemed chemosensitive disease. Progression during front-line therapy or within 3 months of completion is considered chemoresistant disease.44 Patients with the latter typically derive less benefit from second-line therapies and, in the absence of any further therapy, have a median OS of approximately 3 months.45 Unfortunately, few phase III clinical trials have been performed for relapsed/resistant ES-SCLC. Patients who experience recurrence beyond 6 months after completing first-line therapy are generally retreated with the initial regimen. This strategy has shown response rates of 50% to 67% and a median survival of 5 to 6 months.46

Several options are available for patients who relapse 3 to 6 months after completing initial chemotherapy. Currently, topotecan is the only FDA-approved agent for second-line treatment of SCLC. A phase III trial of intravenous topotecan versus CAV enrolled 200 patients with relapsed SCLC, but excluded patients with a progression-free interval of less than 2 months after initial therapy.47 The rates of response (24.3% vs 18.3%) and 1-year survival (14.2% vs 14.4%) were similar for topotecan and CAV, respectively. Topotecan provided better control of dyspnea, anorexia, and fatigue. In retrospective analyses, topotecan has shown clinical benefit in patients older than 65 years and patients with a Zubrod performance status of 2.48,49 A phase III study compared oral topotecan with best supportive care and found a median OS of 6.0 versus 3.2 months,
respectively.30 This was the first trial to clearly show a survival benefit for second-line chemotherapy in ES-SCLC. Another phase III trial compared second-line oral topotecan with intravenous topotecan in patients with chemosensitive ES-SCLC and showed similar response rates and median OS with comparable tolerability.51 Statistically, the study was unable to prove noninferiority of oral versus intravenous topotecan.

Commonly used agents in relapsed/resistant SCLC include irinotecan, oral etoposide, paclitaxel, and docetaxel. Weekly irinotecan has shown a response rate of 50% and a median survival of 6.1 months in a small phase II study.52 Oral etoposide has shown response rates of 23% to 45% and median survivals of 3.5 to 4.1 months.53,54 Patients who had not responded to front-line therapy did not respond to oral etoposide, suggesting its lack of clinical benefit for chemoresistant disease. Paclitaxel showed a response rate of 29% with a median survival of 3.3 months in patients who had received at least 2 prior lines of treatment.55 Because of its activity in this heavily pretreated population, paclitaxel is a reasonable option for chemoresistant disease. Two small phase II trials with docetaxel have shown response rates of 13% and 25%; however, no survival data were reported.56,57

Gemcitabine and vinorelbine have also shown modest clinical benefit as monotherapy for SCLC in the second-line setting.58,59 Ifosfamide has shown activity in chemoresistant disease, although it is not often used in the palliative setting because of the inconvenience of prolonged infusions and its undesirable toxicities.60 A small phase II study of CAV that included 29 patients previously treated with platinum-based chemotherapy showed a response rate of 28% and a median survival of 3.5 months.61 Recently, a phase II trial evaluated temozolomide in relapsed/resistant SCLC.62 Sixty-four patients who had received 1 to 2 prior chemotherapy regimens received temozolomide at 75 mg/m² for 21 days of a 28-day cycle. The overall response rate was 20%, which did not meet the study’s prespecified criteria for sufficient activity. However, the response rate in patients with chemoresistant disease and in those receiving the drug as third-line therapy were 13% and 19%, respectively. A 38% response rate for brain metastases was also noted. Finally, amrubicin, an anthracycline-class topoisomerase II inhibitor, is approved for the treatment of SCLC in Japan.63 A phase III trial in the United States of amrubicin versus topotecan showed response rates of 31% and 17%, respectively.64 However, OS was similar in both arms and thus far there are no plans to obtain FDA approval for the drug in the United States.

Emerging Therapies

Recently, a greater understanding of the molecular pathways driving carcinogenesis has led to the development of effective, novel agents in multiple tumor types, including non–small cell lung cancer. Unfortunately, SCLC has not shared these advances, because targeted agents have repeatedly failed to show improvements in survival, including antiangiogenesis drugs (bevacizumab, thalidomide, sorafenib, sunitinib, vandetanib), inhibitors of cell-signaling pathways (imatinib, dasatinib, gefitinib, everolimus, tipifarnib), and vaccine therapy (BEC-2 vaccine, BB-10901). In addition to these failed agents, very little insight has been gained into predictive biomarkers that may help define patients most likely to benefit from a targeted approach.

Despite these well-conceived but disappointing approaches, a significant effort remains to better characterize SCLC tumor biology in an attempt to develop more effective therapies (Table 2). For example, the antiapoptotic protein bcl-2 and a key transcription factor of the hedgehog pathway GLI1 are overexpressed in SCLC. Defining these 2 pathways has led to the clinical development and current testing of obatoclax and vismodegib, 2 small molecular inhibitors of apoptotic and hedgehog pathways, respectively. The insulin-like growth factor 1 receptor (IGF-1R) pathway may be deregulated in SCLC, and studies with the monoclonal antibody cixutumumab (IGF-1R antagonist) are underway.65 The anti–CTLA-4 antibody ipilimumab has shown promise in a phase II study when combined with carboplatin/paclitaxel.66 A median OS of 12.9 versus 9.9 months with chemotherapy alone was reported (HR, 0.75; P=.13), and a phase III study is currently accruing.

Most recently, 2 groups of investigators have used high-throughput sequencing technologies to allow the rapid identification of potential actionable mutations in SCLC tumor samples.67,68 Relevant genetic alterations include PTEN, TP53, and PI3K
mutations and fibroblast growth factor receptor 1 amplification. In addition, SOX 2, a transcription factor necessary for maintaining self-renewal of undifferentiated stem cells, was found to be amplified in 27% of SCLC tumor samples. Although it is too early to know whether these aberrant biological pathways are both drivers of the oncogenic phenotype and actionable with targeted agents, their discovery has created a new framework in which to develop innovative therapies that will hopefully translate into clinically meaningful improvements in survival. To optimally evaluate these new strategies, more patients with SCLC need to be referred to ongoing clinical trials (Table 2), preferably early in the course of their disease when their performance status and organ function are still preserved.

References

Levy et al


