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## Management of Small-Cell Lung Cancer: Incremental Changes but Hope for the Future

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### Abstract

Over 25,000 people are diagnosed with small-cell lung cancer (SCLC) in the United States annually. SCLC is a highly aggressive tumor with a propensity for early metastases and a high case-fatality rate. Systemic treatment with etoposide plus a platinum agent is recommended for all stages of this disease and has been a standard first-line therapy for SCLC since the 1980s. Three recently presented randomized clinical trials failed to show superiority of newer regimens over etoposide and cisplatin. Patients with limited-stage (LS) disease benefit from the addition of radiotherapy to systemic chemotherapy, a combination that affords high complete response rates and potential cures. Incremental improvements in radiotherapy delivery over the past decade include the use of accelerated hyperfractionated thoracic radiotherapy for LS disease. Prophylactic cranial irradiation, previously recommended for patients with LS disease, has recently been shown to benefit those with extensive-stage (ES) disease as well. Surgery, largely abandoned in the 1970s, is being reevaluated as primary local therapy inpatients with very early-stage SCLC. Topotecan remains the only US Food and Drug Administration–approved therapy for recurrent disease. Amrubicin has demonstrated single-agent activity in multiple phase II trials in both chemotherapy-sensitive and -refractory relapse. The past 2 decades have been marked by an improved understanding of SCLC biology, and these discoveries are reflected in the number and diversity of novel therapies entering early-phase testing in this disease.

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Small-cell lung cancer (SCLC) accounts for approximately 15% of the 215,000 new lung cancer diagnoses in the United States annually. With a case-fatality rate greater than 90%, SCLC will be the cause of over 25,000 deaths in 2008 alone. SCLC is seen almost exclusively in current or former smokers and is characterized by a rapid tumor doubling time, high growth fraction, and early development of metastases. At the time of diagnosis, SCLC is usually disseminated and, if left untreated, rapidly fatal with an average survival of less than 4 months. Essentially all patients are treated with chemotherapy, either alone or in combination with local therapy such as radiation therapy. EP (etoposide and cisplatin [Platinol]), a chemotherapy regimen established in the 1980s, remains a primary standard of

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care for first-line therapy today. Here we describe the clinical presentation, diagnosis, and staging of SCLC and discuss standard disease management in the context of recently presented trials.

## Clinical Presentation

SCLC typically arises in the central airways and can quickly metastasize to the lymph nodes and beyond. As such, many patients present with symptoms related to central airway disease, including cough, dyspnea, and chest discomfort.[1] SCLC displays the propensity for early metastases to sites including the liver, bones, adrenal glands, and brain. Reflecting the systemic nature of this disease, up to 50% of patients will present with weight loss, fatigue, and anorexia.

SCLC patients may also present with an endocrinologic or neurologic paraneoplastic syndrome. Hyponatremia, due to ectopic production of antidiuretic hormone or atrial natriuretic peptide, is observed in up to 15% of patients with SCLC, while Cushing's syndrome is seen in 2% to 5% of SCLC patients.[2] Clinically disabling paraneoplastic neurologic syndromes, thought to be mediated by antibodies directed against "on-coneural" antigens, are observed in 1% to 3% of SCLC patients. Anti-Hu antibodies are seen in multifocal encephalomyelitis/sensory neuronopathy and limbic encephalitis.[3] Lambert-Eaton myasthenic syndrome (LEMS) is associated with anti-voltage-gated calcium channel (VGCC) antibodies. Fifty percent of LEMS patients will eventually be diagnosed with SCLC; accordingly, a smoker diagnosed with LEMS should be closely followed and screened for SCLC.[4] In a minority of patients who present with neurologic paraneoplastic syndromes, symptoms may remit with treatment of the underlying cancer.

## Diagnosis

The diagnosis of SCLC is primarily made by light microscopy. With standard hematoxylin-and-eosin stain, the tumors appear as small blue cells with scant cytoplasm and a high mitotic index. Nuclear molding is considered characteristic, and the nuclei themselves have fine granular chromatin and absent nucleoli.[5] Keratin and epithelial membrane antigen are seen almost uniformly. At least one marker of neuroendocrine differentiation is observed in 75% of SCLC cases, including dopa decarboxylase, calcitonin, synaptophysin, chromogranin A, CD56 (nuclear cell adhesion molecule, or NCAM), and gastrin-releasing peptide.[6,7]

## Staging

Introduced by the Veterans' Administration Lung Study Group (VALSG) in the 1950s, the two-stage classification system is typically used clinically to stage SCLC.[8] The VALSG system defines patients as having either limited-stage (LS) or extensive-stage (ES) SCLC. Patients with LS SCLC have disease confined to the ipsilateral hemithorax that can be safely included in a tolerable radiation portal, and ES disease includes all remaining patients. Approximately 30% of all new SCLC diagnoses are classified as LS. Patients with LS disease have a median survival of 18 to 23 months, and up to 20% of patients can achieve

long-term remission with concurrent chemoradiotherapy. The median survival of patients with ES disease is 8 to 10 months despite aggressive chemotherapy.

In 1987 the International Association for the Study of Lung Cancer (IASLC) published a consensus report revising the VALSG classification in accordance with TNM staging for malignant tumors. By TNM criteria, limited-stage disease includes stages I–III, whereas ES disease is comprised of stage IV tumors only.[9] By convention, LS and ES descriptors are still predominantly used.

Staging evaluation for SCLC patients should include a routine history and physical exam, hematology and chemistry panels, and computed tomography (CT) scan of the chest to evaluate the extent of intrathoracic disease, including pleural effusion. Concurrent chemotherapy can offer cures in up to 20% of LS patients but at the cost of significant toxicity. Thus, accurate assessment of extrathoracic disease is imperative. Common sites of metastases include bone, liver, adrenal glands, and brain, and therefore, CT scan of the abdomen, magnetic resonance imaging (MRI) of the brain, and bone scan are recommended. A bone marrow biopsy may be performed as clinically indicated; however, it is rare that patients have bone marrow involvement as a sole site of metastasis.[10] Patients, who present with a pleural effusion in the absence of extrathoracic disease should have further studies of their pleural fluid—such as chemistry studies consistent with an exudate or, better yet, cytopathologic confirmation—to verify tumor involvement.

As SCLC is a highly metabolic tumor that avidly takes up fluorodeoxyglucose, positron-emission tomography (PET) scanning is an attractive modality for staging. In small prospective studies, PET scans have correctly upstaged patients to ES disease.[11,12] However, larger prospective studies are still needed, and reimbursement in the United States for this particular indication remains an issue.

## First-Line Treatment

If left untreated, patients with SCLC survive for a median of 2 to 4 months. SCLC is exquisitely sensitive to chemotherapy, producing an objective response rate of 60% to 80%. Early metastasis is common, and all patients, even those with LS disease, require systemic chemotherapy. For patients with LS SCLC, chemotherapy plus radiation is the standard of care, as the addition of radiation therapy has been shown to decrease intrathoracic failures and is potentially curative. Prospective studies are underway to evaluate the role of surgical resection in the earliest of LS disease, ie, stage I tumors. For patients with ES disease, combination chemotherapy can provide prolonged survival and symptomatic improvement.

## Chemotherapy

Various chemotherapeutic agents have demonstrated activity against SCLC, and randomized trials have established that combination chemotherapy provides a survival benefit over monotherapy in the first-line setting.[13] During the 1970s, cyclophosphamide, vincristine, plus an anthracycline (doxorubicin [Adriamycin] or epirubicin [Ellence], as in CAV or CEV) was the standard of care. Randomized trials demonstrated that EP (etoposide plus cisplatin) was at least as effective as CAV or CEV with less toxicity.[14,15] As neither

etoposide nor cisplatin cause significant mucosal or pulmonary toxicity, the combination also allowed for treatment with concurrent radiotherapy in LS patients.

EP has been the standard of care since the early 1980s. In 2008, the results of three randomized clinical trials combining cisplatin with irinotecan (Camptosar), topotecan (Hycamtin), or pemetrexed (Alimta) in the first-line setting were reported. All three studies were negative, reporting no advantage to newer regimens over standard EP.

In 2002, the Japanese Clinical Oncology Group (JCOG) reported that IP (irinotecan plus cisplatin) provided superior median survival (12.8 vs 9.4 months), as well as improved 1-year (58.4% vs 37.7%) and 2-year (19.5% vs 5.2%) survival rates relative to EP.[16] Two trials have sought to reproduce these promising results in North America. The North American/Australia Study found no difference in median, 1-year, or 2-year survival between patients treated with IP vs EP. Notably in this study, IP was delivered in a different dosing schedule.[17] In 2008, the results of the S0124 trial, which followed the dosing protocol of the JCOG trial, were presented. In this trial, 671 patients with newly diagnosed ES SCLC were randomized to receive IP vs EP.[18] There was no difference in median overall survival, progression-free survival, or response rates between the two arms.

Reasons for the disparity in efficacy between the JCOG and the two North American trials are not entirely clear. Correlative genomic studies from the S0124 found that differences in toxicities such as diarrhea and neutropenia, but not response, were associated with polymorphisms of UGT1A1 and ABCB1.[19]

Topotecan is US Food and Drug Administration (FDA)-approved for recurrent SCLC and has been evaluated in combination with cisplatin in the context of previously untreated disease. Oral topotecan plus cisplatin in the first-line setting failed to show significant differences in overall survival, response rate, or time to disease progression, compared with EP.[20] To evaluate the efficacy of intravenous (IV) topotecan in this setting, a more recent study randomized newly diagnosed ES SCLC patients into three treatment arms: EP, IV topotecan plus cisplatin (TP) or IV topotecan plus etoposide (TE).[21] The TE arm was closed early due to toxicity. Patients on the TP arm had an increased response rate (55.5% vs 45.5%) and time to progression (7 vs 6 months,  $P = .004$ ), and a significant but transient improvement in symptoms. Treatment with TP, however, did not confer a significant difference in overall survival (10.3 vs 9.4 months,  $P = .3$ ) and was associated with a higher incidence of hematologic toxicities, including those requiring transfusions and growth factor support, and an increase in deaths that were likely treatment-related (5.2 vs 2.7%).

Pemetrexed, an antifolate agent that is FDA-approved for the treatment of mesothelioma and non-small-cell lung cancer, plus carboplatin (Pem-Cb) was recently compared with EP in a randomized clinical trial of newly diagnosed ES disease.[22] At 16 months, a planned interim analysis of 733 patients revealed poorer progression-free, overall, and median survival for the Pem-Cb arm compared with EP, and the trial was closed early.

Based on these recent studies, EP remains the primary standard of care for the first-line treatment of ES SCLC and in combination with radiation therapy for patients with LS disease in the US. The recommended doses are etoposide at 80 to 120 mg/m<sup>2</sup> IV on days 1

to 3, and cisplatin at 60 to 80 mg/m<sup>2</sup> IV on day 1, repeated every 21 days for a total of four to six cycles for ES disease. Continuing therapy to six cycles has not demonstrated a survival benefit in LS SCLC, and four cycles of chemotherapy with radiation are recommended. For patients who cannot tolerate cisplatin, carboplatin can be substituted.[23] A recommended regimen is etoposide at 100 mg/m<sup>2</sup> IV on days 1 to 3 and carboplatin AUC 5 to 6 IV on day 1, repeated every 21 days for a total of four to six cycles.[24]

## Radiation

A large majority of patients with LS SCLC treated with chemotherapy alone will develop local tumor progression. Two meta-analyses demonstrated that the addition of thoracic radiotherapy reduces intrathoracic recurrence and provides a small, but statistically significant, improvement in overall survival.[25,26] Although LS disease still carries a poor prognosis, treatment with concurrent chemoradiation can provide complete response rates of greater than 80%, a median survival of 17 months and a 5-year disease-free survival of up to 15%–25%.[27]

Concurrent chemoradiotherapy is superior to sequential chemotherapy and radiation in terms of both median and overall survival.[28] Early initiation of radiation has also demonstrated clinical benefit over delayed radiation, particularly in studies utilizing EP regimens. Accelerated hyperfractionation is preferred over daily radiation dosing; Turrisi et al reported that 45 Gy, given concurrently with EP, administered twice-daily in fractions of 1.5 Gy over 3 weeks, was superior to daily fractions of 1.8 Gy over 5 weeks. In this study, accelerated hyperfractionation provided a 10% survival benefit at 5 years (26% vs 16%) at the cost of an increase in severe esophagitis.[27] Whether accelerated hyperfractionation to 45 Gy is superior to daily fractionation to 50.4–60 Gy is under investigation.

Patients with LS disease and an Eastern Cooperative Oncology Group performance status of 0–2 may be optimally treated with cisplatin plus etoposide for four cycles with concurrent accelerated hyperfractionated radiotherapy to 45 Gy initiated within the first or second cycle of chemotherapy. Patients who cannot tolerate aggressive therapy should receive chemotherapy followed by radiation therapy. All LS SCLC patients who respond to initial therapy should be considered for prophylactic cranial irradiation (PCI), which we discuss later in this review.

## Surgery

Prior to the 1970s, surgical resection was used to treat localized SCLC. However, resection was largely supplanted by radiation after the British Medical Research Council reported that radiotherapy provided better survival than did surgery as primary local therapy for patients with LS SCLC.[29] Surgical resection does not improve survival after induction chemotherapy, as demonstrated in a trial of 340 patients with stage I–IIIB disease.[30]

Recent retrospective studies have suggested a potential for benefit from surgical intervention in very early-stage (stage I/II) disease. A retrospective review of 82 patients with T1–2, N0 (stage I) lesions who underwent resection and adjuvant platinum chemotherapy reported an impressive 86% 5-year survival rate.[31] Another retrospective study demonstrated a 47-month median overall survival and a 47% 5-year survival rate for stage IA–IIB patients who

underwent resection followed by adjuvant chemotherapy with or without thoracic radiotherapy.[32] Prospective randomized trials are planned or currently underway to make definitive recommendations.

Less than 5% of SCLC patients present with stage I disease. For these patients, surgical resection may be considered and should be followed by adjuvant cisplatin-based chemotherapy. Patients who have undergone complete resection for a solitary pulmonary nodule and are found to have SCLC should similarly be referred for adjuvant chemotherapy. If final pathologic staging of resected SCLC reveals node-positive disease or positive surgical margins, patients should also receive adjuvant radiation therapy. These patients are recommended to receive PCI after adjuvant chemotherapy.

### Prophylactic Cranial Irradiation

Cerebral metastases are common in SCLC patients including those with complete responses to initial therapy. A meta-analysis of seven randomized clinical trials demonstrated a clinical benefit associated with PCI in LS patients who achieved a complete response to initial therapy with an overall decreased incidence of brain metastases at 3 years and increased survival at 5 years.[33]

Until recently, the role of PCI was not clear in patients with ES disease. In 2007, the European Organisation for Research and Treatment of Cancer (EORTC) reported the results of a phase III study randomizing ES SCLC patients with a partial or complete response after first-line systemic therapy to PCI (20–30 Gy) vs best supportive care. At 1 year, patients who received PCI had a significantly lower rate of symptomatic brain metastases (15% vs 40%;  $P < .001$ ), improved disease-free ( $P = .02$ ), 1 year (27% vs 13%), and overall (median 6.7 vs 5.4 months,  $P = .003$ ) survival compared with patients in the best supportive care arm.

In 2008, the PCI99 Intergroup presented results of a randomized phase III study of 720 LS SCLC patients with a complete response to first-line therapy, randomized to receive 25 or 36 Gy PCI.[34] Toxicities and treatment delivery were not different between the two arms. Patients who received 36 Gy had a nonsignificant decrease in brain metastases and, for unclear reasons, a worse overall survival ( $P = .03$ ). Thus, PCI at 25 Gy is recommended for LS and ES SCLC patients who respond to first-line therapy.

### Recurrent Disease

Approximately 80% of LS and nearly all ES patients will develop recurrent disease. Patients with recurrent SCLC have a median survival of 2 to 3 months if untreated. Recurrent SCLC is characterized as chemotherapy-sensitive (progression of disease 3 months after completing primary therapy), chemotherapy-resistant (progression within 3 months of primary therapy), or chemotherapy-refractory (progression during therapy), though the distinction between the latter two is not significant.

At least six large randomized clinical trials have been published concerning patients with recurrent SCLC, which include randomization of patients to chemotherapy vs best supportive care or to alternate second-line therapies.[35] The majority of studies of second-

line therapy for SCLC are single-arm phase II trials and have been summarized elsewhere. [36]

### **Chemotherapy-Sensitive Relapse**

Patients with chemotherapy-sensitive disease are most likely to benefit from currently available second-line therapy, with response rates of up to 25%. Reinduction therapy (ie, retreatment with the patient's original chemotherapy regimen) has been reported to have response rates as high as 50% to 67% in patients with remissions > 8 months after initial therapy.[37–39] Reinduction therapy should be considered for patients with remissions of 6 months or greater.

For patients with remissions between 3 and 6 months, reinduction therapy is not recommended, but several agents have demonstrated activity in this setting. Topotecan has demonstrated equivalent response rates, time to progression, and overall survival compared with CAV in patients previously treated with EP.[40] In patients unable to tolerate IV chemotherapy, oral topotecan (2.3 mg/m<sup>2</sup> on days 1–5 of a 21-day cycle) has demonstrated superiority over best supportive care for both median survival (25.9 vs 13.9 weeks) and quality of life. In phase II and III studies, oral topotecan has demonstrated equivalence to IV topotecan in terms of median survival (35.0 vs 33.0 weeks) and 1-year (32.6% vs 29.2%) and 2-year (12.4% vs 7.1%) survival rates, while providing a comparable toxicity profile. [41,42] Oral topotecan is associated with more grade 3/4 diarrhea, whereas IV topotecan is associated with more neutropenia.

In phase II clinical trials, several agents have demonstrated activity as monotherapy in chemotherapy-sensitive disease. Response rates ranging from 23% to 52% have been reported for amrubicin (discussed later), irinotecan, oral etoposide, paclitaxel, docetaxel (Taxotere), and ifosfamide.[33] Most of these agents have not been evaluated in phase III trials but may be considered as reasonable options for third-line therapy in this disease. High response rates have been reported for combination chemotherapy regimens in this setting, but they are typically associated with significant toxicities.[43]

Topotecan is FDA-approved for chemotherapy-sensitive disease after failure of first-line chemotherapy. Recommended doses are 1.5 mg/m<sup>2</sup> IV given on days 1 to 5 every 21 days or 2.3 mg/mg<sup>2</sup> po given on days 1 to 5 every 21 days. Many oncologists find these doses to be difficult for patients to tolerate, and topotecan at 1.0 to 1.2 mg/m<sup>2</sup> IV on days 1 to 5 every 21 days is frequently used.

### **Chemotherapy-Resistant or Chemotherapy-Refractory Relapse**

Compared with chemotherapy-sensitive disease, the designation of chemotherapy-resistant or -refractory disease portends a poorer prognosis and response to chemotherapy. Recommended regimens for this subset of patients are lacking. Several agents have demonstrated single-agent and combinatorial activity in phase II trials. In heavily pretreated patients, paclitaxel given every 21 days has been reported to provide a 29% response rate and 3-month survival.[44] A 40% response rate has been reported in a phase II study of paclitaxel plus gemcitabine (Gemzar) in chemotherapy-refractory patients.[45]

There are no recommended regimens for the treatment of chemotherapy-resistant or -refractory patients. In patients with a good performance status, it would be reasonable to try paclitaxel, topotecan, or paclitaxel plus gemcitabine.

## Ongoing Research Directions

For diseases such as SCLC, where standard therapeutic options are of limited utility, enrollment in clinical trials is an important facet of standard-of-care considerations. A few agents of particular interest are summarized here, and are described in detail in other recent reviews.[46,47]

### Amrubicin

Amrubicin, a fully synthetic anthracycline, is active in recurrent SCLC including chemotherapy-refractory disease. In two early studies from Japan, amrubicin demonstrated response rates of 37% to 52% and a median survival of up to 11.2 months.[48,49] In 2008, the results of three trials—two of which were conducted in North America—were presented. These studies reiterated the positive results observed previously and further supported the potential efficacy of amrubicin in chemotherapy-refractory patients.[50–52]

In a study of amrubicin vs topotecan in recurrent SCLC, amrubicin provided better response rates in chemotherapy-sensitive (53% vs 21%) and chemotherapy-refractory disease (17% vs 0%) compared with topotecan. Overall progression-free survival was also better in the amrubicin arm (3.5 vs 2.2 months).[50] In a second trial in patients with chemotherapy-sensitive disease only, amrubicin demonstrated a superior response rate (34% vs 3.8%) and progression-free survival (4.6 vs 3.5 months) compared with topotecan.[51] In this study, the rates of hematologic toxicities including neutropenia, anemia, and thrombocytopenia were comparable between the two arms. In a single-arm study of 75 chemotherapy-refractory patients, 39 of which were assessable at the time of presentation, treatment with amrubicin resulted in an 18% response rate and a progression-free survival of 3 months.[52]

These results are highly encouraging, and further studies are underway. The FDA has granted fast track status to amrubicin for the treatment of SCLC after first-line chemotherapy. The agent is currently approved as an orphan drug in this setting.

### Targeted Therapies

Current early-phase clinical trials reflect the numerous biologic pathways implicated in SCLC initiation, growth, and maintenance. Inhibitors of proteins involved in angiogenesis, apoptosis, and key intracellular signaling cascades have been borne out of decades of observation and study of basic SCLC biology. For laboratory researchers, new SCLC models based on the growth of patient-derived tumors may provide a better platform for preclinical analyses. Thus far, inhibitors of key angiogenic mediators such as the anti-vascular endothelial growth factor (VEGF) antibody bevacizumab (Avastin) and small-molecule inhibitors of VEGF receptors (vandetanib [Zactima], cediranib, and sorafenib [Nexavar]) have not demonstrated superiority over standard regimens in the first- or second-line settings.[53–55]



Numerous phase I/II evaluations of drugs with potential activity in SCLC are underway. These include inhibitors of proteins highly expressed in SCLC such as the antiapoptotic protein Bcl-2 and the receptor tyrosine kinases c-MET, c-src, and IGF-1R. Investigational agents based on unique approaches to targeting SCLC are also being evaluated in clinical trials. CD56, a cell surface protein expressed on the vast majority of SCLC cells is currently being exploited as a means of targeting the delivery of cytotoxic agents. A phase I clinical trial evaluating the efficacy of a humanized anti-CD56 antibody (BB-10901) conjugated to a cytotoxic drug, maytansinoid, is underway. The oncolytic picornavirus SVV-001, which demonstrates selective tropism for neuroendocrine cells, is currently undergoing phase I evaluation. The hedgehog pathway, an embryonic signaling pathway, has been implicated in normal and tumor stem cell maintenance. Inhibitors of this pathway are currently in phase I trials.

## Summary and Recommendations

SCLC continues to be almost universally fatal and carries the same poor prognosis as it did 25 to 30 years ago. In the 1980s, the introduction of platinum agents as primary therapy in SCLC resulted in improved response rates and survival duration and, together with improvements in radiation therapy, established the possibility of cure in a minority of patients. A summary of current therapy options is presented in Table 1. Changes in recommended therapy have been incremental at best over the past 3 decades. Topotecan was approved for the second-line treatment of SCLC in 1998. Adjustments in radiotherapy include the use of accelerated hyperfractionated thoracic radiotherapy and the demonstration of clinical benefit for PCI in both LS and ES disease.

Hope for the future of SCLC therapy can be found not only in improved general cytotoxics such as amrubicin, which has promising efficacy in both chemotherapy-sensitive and chemotherapy-refractory relapsed disease, but also in the multitude of clinical trials emerging from therapeutic targets identified through study of basic SCLC biology. Included among these investigational agents are inhibitors of well-defined signaling cascades such as the Bcl-2, c-MET, c-src, and IGF-1R pathways; drug delivery based on CD56 expression; and inhibitors of embryonic signaling cascades such as the hedgehog pathway. Testing of these and other novel approaches to SCLC will be the focus of clinical investigation over the next several years.

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**Table 1****Current Therapeutic Options for Small-Cell Lung Cancer<sup>a</sup>****FIRST-LINE THERAPY****Limited-Stage SCLC (Stage I–III)**

Concurrent chemoradiotherapy

Chemotherapy: total of 4 cycles

Cisplatin 60–80 mg/m<sup>2</sup> IV on d1 of a 21-day cycle +

Etoposide 100–120 mg/m<sup>2</sup> IV on d 1–3 of a 21-day cycle

Radiotherapy: to be started during cycle 1 or 2 of chemotherapy

Accelerated hyperfractionation (1.5 Gy bid) to a total dose of 45 Gy

For patients with a poor performance status consider

Sequential chemotherapy and radiation therapy

Patients with clinical stage I disease may also be considered for

Surgical resection and adjuvant chemotherapy

Surgery: lobectomy preferred

Chemotherapy: total of 4 cycles

Cisplatin 60–80 mg/m<sup>2</sup> IV on d1 of a 21-day cycle +

Etoposide 100–120 mg/m<sup>2</sup> IV on d1–3 of a 21-day cycle

**Extensive-Stage SCLC (Stage IV)**

Chemotherapy

Cisplatin 60–80 mg/m<sup>2</sup> IV on d1 of a 21-day cycle +

Etoposide 100–120 mg/m<sup>2</sup> IV on d1–3 of a 21-day cycle

Total: 4–6 cycles

For patients who cannot tolerate cisplatin

Carboplatin AUC 5–6 IV on d1 of a 21-day cycle +

Etoposide 100 mg/m<sup>2</sup> IV on d 1–3 of a 21-day cycle

Total: 4–6 cycles

**PROPHYLACTIC CRANIAL IRRADIATION**

Prophylactic cranial irradiation to 25 Gy is recommended for limited- and extensive-stage patients who have had a response to first-line therapy

**SECOND-LINE THERAPY****Chemotherapy-Sensitive Relapse**

Progression > 6 months after primary therapy:

Reinduction with primary chemotherapy regimen

Progression > 3 mo after primary therapy:

Topotecan 1.5 mg/m<sup>2</sup> IV on d1–5 of a 21-day cycle or

Topotecan 2.3 mg/m<sup>2</sup> po on d1–5 of a 21-day cycle

**Chemotherapy-Refractory Relapse or Progressive Disease**

No specific regimens are recommended

Consider: paclitaxel monotherapy or paclitaxel plus gemcitabine

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**FIRST-LINE THERAPY**

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**Other Agents/Regimens Available in the US With Activity in Recurrent SCLC**

Irinotecan, gemcitabine, oral etoposide, CAV

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<sup>a</sup>For all stages of disease, clinical trial enrollment is recommended.

AUC = area under the concentration-time curve; CAV = cyclophosphamide, doxorubicin, vincristine; SCLC = small-cell lung cancer.