Current Guidelines for the Management of Small Cell Lung Cancer

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Small cell lung cancer (SCLC) accounts for 20% to 25% of cases of bronchogenic carcinoma and results in pronounced morbidity and mortality in the United States. More than 90% of cases of SCLC are caused by cigarette smoking. Common pulmonary manifestations are dyspnea, persistent cough, hemoptysis, and postobstructive pneumonia. At the time of diagnosis, patients usually have extensive disease. To date, therapeutic approaches have made only modest advances in outcome. Combined modality approaches, such as radiotherapy administered concomitantly with the initiation of chemotherapy, induction chemotherapy followed by radiotherapy administered during the subsequent courses of chemotherapy, sequential chemotherapy and radiotherapy, and courses of radiotherapy split between cycles of chemotherapy, are important for improving survival in patients with SCLC.


Lung cancer is the second most common type of cancer in the United States. It accounts for only 15% of all cancers but is the most lethal, causing approximately 28% of cancer deaths. Small cell lung cancer (SCLC) constitutes 20% to 25% of the 177,000 new cases of lung cancer diagnosed annually in the United States and 40,000 of the 160,000 lung cancer deaths each year. Historically, lung cancer had been diagnosed predominantly in men, but with the increase in smoking among women, the estimated male-to-female lung cancer prevalence ratio is now 1.2:1.0. Currently, lung cancer is the leading cause of cancer death in women.

Patients with SCLC usually have widespread disease at the time of diagnosis. Without treatment, survival is about 6 to 12 weeks for those with extensive-stage disease and about 3 to 6 months for those with limited-stage disease.

Small cell lung cancer is sensitive to chemotherapy, with major responses in 70% to 90% of cases at initial treatment. However, most patients experience tumor relapse and die within 2 years. Thus, although survival with current therapies is superior to no treatment, the 5-year survival rate for patients receiving combined modality therapy ranges from 7% to 19%. The most important factor that predicts response to treatment and survival of patients with SCLC is the stage of disease. For a given disease state, the next most important prognostic factors are the patient’s performance status and extent of weight loss. Patients who have lost 5% or more of body weight in the preceding 2 to 6 months have a poor prognosis, as do nonambulatory patients. Biochemical and hematologic abnormalities are also important prognostic factors and reflect the extent and distribution of tumor metastasis. This review outlines the current management of SCLC.

ETIOLISTIC FACTORS

The most important cause of SCLC is cigarette smoking, which accounts for more than 90% of cases. Chromosomal and oncogene abnormalities associated with SCLC have been identified in ex vivo and in vitro studies. Allelic loss on the short arm of chromosome 3 has been observed in more than 90% of cases of SCLC. Several tumor suppressor genes from this site may contribute to the pathogenesis of SCLC. Putative candidates are the raf-1 proto-oncogene, the protein-tyrosine phosphatase-γ gene, the fhit (fragile histidine triad) gene, and the β-retinoic acid receptor gene. Amplification of the myc gene involved in nuclear transcription has been found in 25% to 40% of cases of SCLC. Loss of expression of the Rb tumor suppressor gene and mutations of the p53 tumor suppressor gene have also been discovered in SCLC.
CLINICAL MANIFESTATIONS

At diagnosis, SCLC usually is disseminated; only one third of patients have limited-stage disease. Pulmonary symptoms such as dyspnea, persistent cough, hemoptysis, and postobstructive pneumonia are common initial manifestations. Other signs and symptoms, such as pain, liver function test abnormalities, headache, seizures, malaise, fatigue, anorexia, and weight loss, are attributable to metastatic disease. Bone (35% of cases) is the most common metastatic site, followed by the liver (25%) and the central nervous system, lymph nodes, subcutaneous tissue, or pleura (10%).

Small cell lung cancer is often associated with endocrinologic or neurologic paraneoplastic syndromes. The commonest endocrinologic syndrome is inappropriate secretion of antidiuretic hormone, which occurs in up to 40% of patients. Secretion of atrial natriuretic peptide may also lead to hyponatremia and hypotension. Increased serum and tissue levels of immunoreactive corticotropin can cause the Cushing syndrome. Hypercalcemia, which is not noted in non-small cell lung cancer, is rare in SCLC. Neurologic syndromes include the Lambert-Eaton myasthenic syndrome, caused by immunologic cross-reactivity between tumor-associated antigens and calcium-gated ion channels. Paraneoplastic cerebellar degeneration is causally related to the production of anti-Purkinje cell autoantibodies. Encephalomyelitis and sensory neuropathy also occur. Cancer-associated retinopathy is recognized clinically by rapid bilateral loss of vision. All these neurologic syndromes are believed to have an autoimmune basis and generally continue on a clinical course unrelated to that of the underlying cancer. The endocrinologic syndromes related to peptide production by tumor usually abate after effective treatment of the cancer.

STAGING

Small cell lung cancer is typically classified according to the 2-stage system developed by the Veterans Administration Lung Cancer Study Group. In this classification, limited disease is defined as tumor confined to 1 hemithorax and its regional lymph nodes (hilar or mediastinal), with or without ipsilateral supravacular node involvement. Extensive disease is defined as disease beyond the confines of limited disease that cannot be encompassed safely in 1 radiation portal. Contralateral hilar, mediastinal, or supravacular node (or some combination) involvement usually is included in the limited-disease category if all the disease can be encompassed safely in 1 radiation portal. The presence of an ipsilateral malignant pleural effusion generally is considered extensive-stage disease.

The role of routine bone marrow aspiration and biopsy in the initial evaluation of SCLC is controversial. In patients who have normal findings on bone scans and normal values of lactate dehydrogenase, isolated bone marrow involvement with disease is found in less than 5%. In several large retrospective studies, increased concentrations of lactate dehydrogenase have correlated with the finding of bone marrow involvement by SCLC. In the absence of an increased level of lactate dehydrogenase or cytopeinia, routine bone marrow examination cannot be recommended at this time as part of initial staging outside a clinical trial. When bone marrow aspiration and biopsies are performed, whether to perform unilateral or bilateral procedures is debatable. In a study of patients who underwent bilateral bone marrow aspirate and biopsies, a higher incidence of bone marrow involvement was found than in studies in which unilateral procedures were performed. Thus, in the small proportion of cases in which bone marrow studies are thought to be indicated, performance of bilateral procedures may be reasonable. The suggested components of a complete initial evaluation are shown in Figure 1.

TREATMENT

Limited-Stage Disease

Bimodality therapy with chemotherapy and concurrent radiotherapy is generally recommended for the treatment of limited-stage SCLC. Surgery may be a part of therapy in a few selected patients.

Surgery.—Surgery is not a standard modality of treatment because SCLC is a systemic disease. However, in some patients with early-stage disease (T1-T2 N0 M0), surgical treatment and postoperative chemotherapy have been successful. Retrospective and phase 2 studies have shown that combined modality therapy with surgery either before or after chemotherapy is feasible in patients with SCLC. In the only prospective randomized phase 3 study, Lad et al found similar survival rates for patients receiving induction chemotherapy and radiation followed by surgery or observation. Thus, surgery cannot be recommended as a standard treatment option for this disease. In a select group of patients with T1-T2 N0 M0 disease, such as those found to have SCLC at thoracotomy, surgical resection is reasonable. These patients should receive postoperative chemotherapy.

Radiotherapy.—For many years, chemotherapy had been considered the principal treatment for limited-stage SCLC. A study conducted more than a decade ago showed that, in a series of 213 patients with limited-stage SCLC who received chemotherapy alone, 82% of those with recurrent disease had evidence of thoracic treatment failure. This study demonstrated the inadequacy of chemotherapy alone to achieve local disease control. However, results of several randomized studies of chemotherapy vs chemo-
History, physical examination, chest radiography, hematology group, chemistry group (AST, bilirubin, alkaline phosphatase, Na/K, creatinine, calcium, LDH), CT chest and upper abdomen, bone scan, CT brain

Protocol treatment if available

Chemotherapy + concomitant chest radiotherapy
Continue chemotherapy until maximal response + 2 cycles (4-6 cycles)

Progression
Partial remission/stable
Complete remission ± PCI

Follow-up
Every 3 mo 1st year
Every 4 mo 2nd year
Every 6 mo 3rd and 4th years
Yearly thereafter

Figure 1. Management of limited-stage small cell lung cancer (SCLC). AST = aspartate aminotransferase; CT = computed tomography; LDH = lactate dehydrogenase; PCI = prophylactic cranial irradiation.

therapy and radiation have been equivocal because of the small number of patients (<200 patients per arm). In recent years, combined modality therapy has been shown to produce a modest but significant improvement in survival compared with chemotherapy alone. Two recent meta-analyses demonstrated a 5% improvement in 3-year survival for patients receiving combination chemotherapy and radiotherapy compared with those receiving chemotherapy alone. Most of the benefit occurred in patients who received thoracic irradiation early during the course of treatment. Combined modality treatment can be associated with pronounced morbidity and mortality due to pulmonary, mucosal, and hematologic toxicity, especially in patients older than 65 years. Therefore, close collaboration between medical and radiation oncologists and close attention to detail are necessary.

Methods of combining radiotherapy with chemotherapy are (1) radiotherapy administered concomitantly with the commencement of chemotherapy, (2) induction chemotherapy followed by radiotherapy administered during the subsequent courses of chemotherapy, (3) sequential chemotherapy and radiotherapy, and (4) courses of radiotherapy split between cycles of chemotherapy.

Available data comparing chemotherapy plus radiotherapy with chemotherapy alone indicate that, regardless of the schedule of administration, radiation improves the local control rate by about 10% to 50%. However, in a Canadian randomized trial, median survival was greatest in the group receiving radiotherapy early (cycle 2) and concurrently with chemotherapy instead of late (with cycle 6 of chemotherapy) during the course of treatment. The investigators hypothesized that the early use of radiotherapy with chemotherapy helped to decrease the dissemination of chemoresistant clones and thus improved cure rates. However, this hypothesis needs further confirmation. The Cancer and Leukemia Group B trial of 399 patients evaluated CAV (cyclophosphamide, doxorubicin [Adriamycin], vincristine) chemotherapy alone or radiation given with either the first or the fourth cycle of chemotherapy. There was no difference in survival in the 2 radiation treatment arms; however, there was a trend toward decreased toxic effects and increased survival among the patients who received radiotherapy at cycle 4 instead of cycle 1. A potential advantage of delivering thoracic radiotherapy after 1 to 3 cycles of chemotherapy is that it may reduce the radiation field size and minimize toxic effects. Taken together, these 2 studies suggest that overlap between radiotherapy and chemotherapy is beneficial.

The optimal dose of radiation in combined modality therapy is unknown, although doses of at least 50 Gy have
been suggested for effective control of tumor in the thorax. Johnson et al are testing preclinical findings by comparing twice-daily radiotherapy with daily radiotherapy. Although the difference in survival thus far has not been significant, further follow-up is necessary. The North Central Cancer Treatment Group recently completed a phase 3 trial comparing once-daily radiotherapy with twice-daily radiotherapy. Interim results indicate that the incidence of grade 3 or greater esophagitis was more common on the twice-daily radiotherapy arm, with no difference in survival at 18 months.

The actuarial risk of central nervous system metastasis developing 2 years after successful treatment of SCLC is approximately 35% to 60%. Therefore, prophylactic cranial irradiation (PCI) has been used by many oncologists. Several randomized studies have shown that PCI reduces the frequency of brain metastases, particularly in patients with a complete response to therapy, although improvement in overall survival has not been demonstrated. In trials performed before the era of computed tomography and magnetic resonance imaging, some patients may have had occult brain metastases. In a recently published trial, 300 patients with limited- or extensive-stage disease who had achieved a complete response after chemotherapy were randomized to PCI or observation. The 2-year overall survival rate for the PCI group was 29% vs 21.5% for the observation group (P = .14). This trial lacked the power to detect the type of survival advantage that might be expected with the use of PCI (7% at 2 years), and larger studies are needed. However, the use of PCI is controversial because neurologic, mental, and psychometric deficits in long-term survivors may be related to earlier administration of PCI. Cranial imaging studies have shown white matter changes in some patients.

Neurologic toxic effects seem to be most frequent and severe when radiation is given concurrently with chemotherapy or before chemotherapy, when radiation fractions are higher than 2.5 Gy, and when the total dose of radiation exceeds 30 Gy. Until future studies show a definite survival benefit, PCI should be considered optional treatment in patients with limited-stage SCLC who had a complete response. Patients should be informed of the potential risks and benefits of PCI. Cranial radiation commencing after completion of chemotherapy or between cycles of chemotherapy seems preferable even though the issue of the ideal timing of cranial irradiation in relationship to chemotherapy remains unclear. Dose per fraction should not exceed 2.5 Gy.

Chemotherapy.—Several chemotherapeutic agents, including doxorubicin, methotrexate, vincristine, cyclophosphamide, etoposide, cisplatin, and carboplatin, produce a response rate of 30% or greater in patients with SCLC. However, combination regimens yield higher response rates and superior survival compared with these single agents. In limited-stage disease, active combination regimens, including thoracic radiation, produce complete responses in 50% to 60% of patients, with an overall response rate of 80% to 90%, a median survival of 14 to 20 months, and a 2-year survival rate of 20% to 40%. The commonly used regimens are (1) etoposide and cisplatin (Platinol) (EP); (2) CAV; (3) cyclophosphamide, doxorubicin, and etoposide (CAE); and (4) CAV alternating with EP.

Randomized studies have shown either no advantage or improved response rates with no survival benefit for EP or EP alternating with CAV vs CAV alone. All these studies allowed crossover at progression; thus, discerning any survival benefit was impossible. However, the EP regimen has been shown to be effective in patients with relapse who were treated initially with CAV, with response rates approaching 50%, whereas CAV is relatively ineffective as a second-line regimen.

Currently, EP is the regimen of choice for the treatment of limited-stage SCLC, partly because it has the more favorable toxicity profile. In combined modality therapy with radiation, EP causes fewer mucosal toxic effects, hematologic toxic effects, and interstitial pneumonitis compared with cyclophosphamide and doxorubicin-containing regimens. In extensive-stage disease, carboplatin can be substituted for cisplatin in the EP regimen. This combination seems to have equivalent activity, few mucosal toxic effects, but increased myelosuppression. In the absence of a prospectively randomized comparison of carboplatin and cisplatin in patients with limited-stage disease that is potentially curable, the routine substitution of carboplatin for cisplatin cannot be recommended.

Chemotherapy should be given until maximal response plus 2 cycles (4 cycles minimum) or 6 cycles, whichever is greater. Additional chemotherapy beyond this point has shown no survival benefit. In the single randomized trial that investigated the optimal duration of induction therapy, the median survival of patients receiving 4 cycles of chemotherapy, followed by additional chemotherapy at relapse, was similar to that of patients receiving 8 cycles of therapy initially.

Because of the responsiveness of SCLC to chemotherapy, the concept of increasing the dose intensity of chemotherapeutic regimens to improve treatment outcome has been studied extensively. In a meta-analysis of 60 published studies of SCLC, no significant correlation was found between dose intensity and either response rates or median survival in patients with limited- or extensive-stage disease. Subsequent randomized prospective trials have yielded conflicting results. Thus, the concept of increasing the dose intensity of chemotherapeutic agents...
Management of Small Cell Lung Cancer

**History, physical examination, chest radiography, hematology group, chemistry group (AST, bilirubin, alkaline phosphatase, Na/K, creatinine, calcium, LDH), CT chest and upper abdomen, bone scan, CT brain**

- **Protocol treatment if available**
- **Chemotherapy. Continue until maximal response + 2 cycles (4-6 cycles)**

**Progression**
- **Partial remission/stable**

**Follow-up 1-2-mo intervals**

**Complete remission**
- **Consider thoracic irradiation**

**Follow-up**
- Every 3 mo 1st year
- Every 4 mo 2nd year
- Every 6 mo 3rd and 4th years
- Yearly thereafter

Figure 2. Management of extensive-stage small cell lung cancer. AST = aspartate aminotransferase; CT = computed tomography; LDH = lactate dehydrogenase.

In the treatment of SCLC to improve outcome remains unproved.

High-dose chemotherapy (HDT) with autologous bone marrow transplantation (ABMT) for the treatment of SCLC has been under investigation for several years. In the only reported randomized trial, 45 patients who had a response to 5 cycles of standard chemotherapy were randomized to HDT with ABMT or to conventional treatment. No significant difference in overall survival was noted between the 2 arms, but a statistically significant difference in relapse-free survival was evident with the HDT/ABMT arm. However, the small sample size of this study precludes any meaningful interpretation of the results. Therefore, this approach to the treatment of SCLC remains investigational.

The taxanes (paclitaxel, docetaxel), topoisomerase I inhibitors (topotecan, irinotecan), vinorelbine, and gemcitabine are new agents with activity in SCLC. Their integration into current combinations may yield new regimens for the treatment of SCLC in the future.

A suggested algorithm for the management of limited-stage SCLC is outlined in Figure 1.

**Extensive Disease**

Chemotherapy, with regimens similar to those used in limited-stage disease, is the mainstay of treatment of extensive-stage SCLC. Because of metastatic disease, thoracic irradiation is seldom used. With the current combination regimens, complete responses are produced in about 20% to 30% of patients with extensive disease, with overall response rates of 50% to 70%, a median survival of 7 to 11 months, and a 2-year survival rate of 5% to 10%. Because of the poor performance status of a large number of these patients, less aggressive treatments are sometimes used. For such patients, single-agent etoposide has been considered appropriate and effective therapy. However, in 2 randomized trials that compared oral etoposide with intravenous multiagent chemotherapy, palliation of symptoms was equivalent or slightly worse for oral etoposide vs multiagent chemotherapy. In addition, in both studies, a small but significant survival benefit was associated with multiagent chemotherapy. Therefore, single-agent etoposide is inferior to intravenous multiagent chemotherapy for SCLC. In elderly patients and patients with pronounced auditory, renal, or neurologic impairment, carboplatin can be substituted for cisplatin. Radiotherapy is directed predominantly at symptomatic sites not controlled by chemotherapy. A suggested algorithm for the management of extensive-stage SCLC is outlined in Figure 2.

**Recurrent Disease**

Progressive or recurrent SCLC after initial therapy has an extremely poor prognosis. The overall median survival
of patients with recurrent disease is 2 to 3 months. Patients who have a relapse more than 4 months after the initial treatment have a 20% to 30% response to chemotherapy, and those with relapse less than 4 months after therapy have a 10% to 15% response to additional chemotherapy. In patients with a late relapse (more than 8 months after initial therapy), long-term survival may be possible after second-line therapy.54

Patients who do not receive treatment with a platinum-containing regimen as first-line therapy should receive a platinum agent as part of their second-line therapy. Substantial activity has been seen with some newer agents in the second-line setting. Response rates ranging from 11% to 29% have been obtained in phase 2 studies evaluating single-agent paclitaxel and topotecan as second-line therapy for patients with early and late relapses.55-67

Treatment of patients with recurrent SCLC is mostly palliative and consists of supportive care, second-line chemotherapy, or experimental therapy (chemotherapy, immunotherapy, or biologic therapy).

Besides analgesics and supplemental oxygen therapy, supportive care frequently includes palliative radiotherapy. This treatment modality is effective in symptomatic control of central nervous system metastases and in short-term local control of thoracic or bony disease. In addition, bronchoscopic laser therapy, brachytherapy, or both can provide good symptomatic control for some patients with endobronchial-obstructing lesions.

Follow-up Evaluation

The efficacy of routine follow-up testing in the detection of relapse in patients treated for SCLC has not been well studied. In a study of 115 patients in the SCLC trials of the North Central Cancer Treatment Group who had a complete response to treatment with subsequent relapse, recurrences occurred in 49% of patients in the first follow-up year, 44% in the second year, and 7% after 2 years. These recurrences were indicated by the medical history in 71% of cases, physical examination in 10%, chest radiography in 12%, and abnormal chemistry test results in 6%. In 59% of patients, disease recurrence was signaled by symptoms between scheduled appointments.68 A follow-up schedule of once every 3 months during the first year after therapy, once every 4 months during the second year, once every 6 months during the third and fourth years, and annually thereafter is reasonable. A history and physical examination, chest radiography, hematology group, and liver enzyme studies (aspartate aminotransferase, alkaline phosphatase, bilirubin, lactate dehydrogenase) are reasonable tests to perform. Although laboratory tests may not detect relapse early, they may enable health workers to recognize and follow up any toxic effects of therapy.

Smoking cessation in responding patients is imperative because the incidence of second malignancies is high in patients who continue to smoke.69 In addition to smoking-related second malignancies, patients surviving SCLC treatments may be at risk for the development of second primary malignancies as a consequence of therapy.70

The prognosis is poor for patients who do not have a complete response, and the follow-up schedule should be based on their clinical situation. In general, history and physical examination monthly or bimonthly should be considered basic for follow-up. Other testing should be dictated by signs or symptoms of the disease.

REFERENCES


