Current Management of Small Cell Lung Cancer

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KEYWORDS

• Small cell lung cancer • Limited stage • Advanced stage • Chemotherapy

In 2010, approximately 222,000 cases of lung and bronchus cancers were anticipated to be diagnosed in the United States,[1] and worldwide, lung cancer is the eighth most common cause of death, killing an estimated 1.3 million people in 2004.[2] Small cell lung cancer (SCLC) is a high-grade, neuroendocrine carcinoma of the lung, named for its histologically distinct features, including small cells with sparse cytoplasm, fine chromatin, nuclear molding, and the presence of markers of neuroendocrine differentiation such as synaptophysin and chromogranin A. In the United States, SCLC accounts for a shrinking percentage of lung cancers, from 17% in 1986 to 13% in 2002, with non–small cell lung cancer (NSCLC) making up most of the remaining fraction.[3] This decreasing incidence may be a result of recent advances in public health measures, such as antismoking campaigns and bans on smoking in the workplace and other public places.[4] Because improvements in survival among patients with SCLC have been only modest over the last 30 years, the best way to eliminate morbidity from this disease may be through prevention.[3]

CLINICAL PRESENTATION AND STAGING

Presenting symptoms of SCLC are usually related to the tumor burden or effects of metastatic disease burden. Most disease presents in the central airways and mediastinum, leading to cough, shortness of breath, chest pain, hemoptysis, and compression of the superior vena cava. Common manifestations of metastatic disease include fatigue, anorexia, weight loss, headaches, and neurologic symptoms, with less than 10% of patients being asymptomatic at the time of presentation.[5] SCLC also has a propensity to cause paraneoplastic syndromes in up to 40% of patients as a result of release of peptide hormones. These syndromes include hyponatremia from inappropriate antidiuretic hormone secretion and Cushing syndrome from tumor-derived adrenocorticotropic hormone production. Less frequently, antigenic similarity to nervous system proteins triggers inappropriate autoimmune reactions, leading to neuromuscular disorders such as proximal motor weakness from Lambert-Eaton myasthenic syndrome, encephalomyelitis from anti-Hu antibodies, or cerebellar degeneration from anti-Purkinje cell antibodies.[6] Although the hormone-mediated paraneoplastic syndromes often respond to effective anticancer therapy, the antibody-mediated neurologic disorders often persist even despite disease response.

Although the *American Joint Commission on Cancer, Seventh Edition* staging criteria include both NSCLC and SCLC,[7] in clinical practice few SCLCs are diagnosed as small, peripheral solitary nodules with lymph nodes isolated to the lung

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(stage I–IIB). In contrast, the 2-stage Veterans Administration Lung Study Group staging system is a useful and simple staging system. Limited stage (LS) is disease contained within 1 hemithorax, including the primary tumor, mediastinal nodes, and ipsilateral supraclavicular disease. Extensive stage (ES) is disease that cannot be contained in a single radiotherapy portal, including overtly metastatic disease. Historically the staging workup included computed tomography (CT) scan of the torso, bone scan, brain magnetic resonance imaging or CT with contrast, and occasionally a bone marrow biopsy. [^{18}F]fluorodeoxyglucose positron emission tomography/CT scans are sufficiently sensitive to replace the bone scan and biopsy, but cannot substitute for dedicated brain imaging. With modern staging tools, the proportion of patients diagnosed with ES-SCLC has increased from 50% to 75% over the last 30 years, but the prognosis of patients has changed minimally. The median overall survival (OS) in LS disease is approximately 20 months, with expected 5-year survival less than 15%. In ES disease the expected median survival is only 8 to 12 months, and less than 2% of patients survive past 5 years.[4] Therefore, it is hoped that ongoing clinical research will yield important advances in the treatment of SCLC.

STANDARD TREATMENT OF SCLC

The treatment of LS-SCLC involves multimodality therapy with concurrent thoracic radiotherapy and chemotherapy with cisplatin and etoposide,[8] based on a meta-analysis that showed a 14% reduction in the mortality of LS patients treated with radiotherapy in addition to chemotherapy.[9] Some treatment paradigms that have incrementally improved on this backbone of concurrent chemoradiation include the commencement of radiotherapy early in the course of treatment, consideration of twice-daily thoracic radiation over a shorter total course, and the use of prophylactic cranial irradiation (PCI) in selected patients. Addressing the optimal timing of initiation of radiation, a meta-analysis published in 2007 reported a significant OS benefit when radiotherapy started within 9 weeks of chemotherapy or before the third cycle of chemotherapy, particularly in patients who received hypofractionated (twice-daily) courses of radiation.[10] One commonly used schedule is twice-daily thoracic radiation given in 1.5-Gy fractions to 45 Gy over 3 weeks, based on a study among 419 patients that showed an improvement in median survival from 19 months to 23 months among patients receiving the accelerated course.[11] However, 1 criticism is that 45 Gy may be an inadequate dose of radiation, compared with the more typical 60 to 70 Gy. To help address this question, another trial used a treatment break midway through in the hypofractionated arm to try to make the biologic effective doses more similar, and did not report a survival difference between the groups.[12] Therefore, the adoption of twice-daily radiotherapy in LS-SCLC has been limited. To provide more conclusive evidence regarding the best radiotherapy approach, an ongoing 3-arm intergroup trial randomizes patients to twice-daily standard radiation to 45 Gy, daily radiation to 70 Gy, or a hybrid of the 2 techniques (NCT00632853).

After completion of chemoradiotherapy, PCI should be considered in patients with systemic disease control and no evidence of metastases on repeat cranial imaging. A meta-analysis included 987 patients and reported a 5% absolute increase in the rate of 3-year survival in patients who received PCI as well as a decrease in the risk of brain metastases.[13] Doses of radiation used for PCI are generally lower than full treatment doses in patients with known brain metastases.

Although the single prospective randomized clinical trial that evaluated the role of surgery in SCLC reported no benefit for resection in patients who achieved a response to chemotherapy,[14] a recent retrospective review showed impressive 1-year and 5-year survival times of 75% and 50% among 59 patients who had undergone complete surgical resection.[15] Surgery seems to be most appropriately restricted to patients presenting with extremely limited disease (ie, clinical stage I by the American Joint Commission on Cancer criteria). Adjuvant chemotherapy and PCI should be considered in all patients who undergo surgical resection.

The standard treatment of ES-SCLC consists of chemotherapy alone, generally cisplatin or carboplatin plus etoposide for up to 6 cycles, followed by watchful waiting.[16] Even patients with an Eastern Cooperative Oncology Group (ECOG) performance status of 3 or 4 as a result of disease should be considered for treatment with chemotherapy, because response rates to chemotherapy exceed 75% and clinical improvement can be observed within a few days. After initial chemotherapy, PCI is recommended, as in LS disease, as a result of an improvement in 1-year OS of 15%.[17] However, mounting evidence suggests that PCI increases the chances of hair loss, fatigue, and cognitive impairment, and therefore may hinder quality of life in patients.[18] Despite rapid and impressive responses to initial chemotherapy, virtually all patients eventually relapse. The choice of subsequent treatment depends on the duration and magnitude of response to platinum-based chemotherapy. Patients with an initial response to