Small-Cell Lung Cancer: Treatment Progress and Prospects

ABSTRACT: Although small-cell lung cancer (SCLC) represents only 20% of all lung cancer cases in the United States, it is the most lethal subtype. Combination chemotherapy unequivocally offers the best chance for improved survival in SCLC. Either PE (platinum plus etoposide) or CAV (cyclophosphamide, Adriamycin, and vincristine) is a reasonable first-line therapy. Alternating PE with CAV does not appear to be significantly superior to PE or CAV alone. Increasing dose intensity, although sometimes associated with higher response rates, does not appear to significantly improve survival and should not be used outside of a clinical study. Several new agents with novel mechanisms of action show promise in treating SCLC. These include: gemcitabine (Gemzar), paclitaxel (Taxol), docetaxel (Taxotere), topotecan (Hycamtin), and irinotecan (Camptosar). Given the poor survival and response rates in relapsed patients and the chemoresponsiveness of SCLC, patients with newly diagnosed extensive disease should be encouraged to enroll in phase I or II trials. Thoracic radiotherapy confers a small survival advantage in limited-stage SCLC patients. Although prophylactic cranial irradiation does not significantly improve survival, it does reduce central nervous system (CNS) recurrences with minimal long-term sequelae. Surgery should be considered only for: (1) resection of a solitary pulmonary nodule, which must be followed by adjuvant chemotherapy; and (2) resection of an unresponsive chest tumor, which may harbor a non-small-cell lung cancer component.[ONCOLOGY 12(5): 647-662, 1998]

Lung cancer is the most common lethal malignancy. In 1997, there were 178,000 new cases of lung cancer in the United States and 160,400 deaths attributable to this cancer.[1] Lung cancer is the third most commonly diagnosed malignancy in American adults but is the number one cause of cancer-related death in both men and women. Fortunately, both incidence and mortality have plateaued overall and are decreasing in American men. Unfortunately, no such trend has been observed in American women.[1]

Although incidence and mortality of lung cancer are higher in African-American men than in white American men, mortality in the former group appears to be declining, as is occurring in the American male population as a whole. Lung cancer incidence and mortality are similar in white American and African American females and are increasing. This presumably reflects the American woman’s relatively late initiation to cigarette smoking and her greater reluctance to discontinue this deadly habit.[2]

Lung cancer is separated histologically into small-cell and non-small-cell variants. Non-small-cell lung cancer (NSCLC) is responsible for 80% of all lung cancers diagnosed in the United States, while small-cell lung cancer (SCLC) accounts for only 20%. In a recent analysis of lung cancer incidence trends for 1974 to 1991, Travis and associates found that rates for both SCLC and NSCLC peaked around 1984 and subsequently declined for white American and African-American men.[3] However, lung cancer rates among women continued to increase for all histologic subtypes, independent of race. Moreover, these authors noted a slightly increased rate of SCLC in white women and an increased rate of squamous cell lung cancer in African-American women.[3]

This article will review SCLC, with a particular emphasis on recent developments in treatment.

Epidemiology, Risk Factors, and Etiology

In a worldwide overview of the epidemiology of SCLC, Parkin and Sankaranarayanan noted a decline in overall lung cancer incidence in males that was associated with an increase in the incidence of adenocarcinoma.[4] They observed not only an increasing rate of lung cancer in women but also a
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rapid rise in SCLC incidence.[4] Cultural trends in tobacco consumption best explain these data.[4,5] Clearly, tobacco exposure is the primary risk factor for SCLC. In fact, it is associated with small-cell cancer more than with any other form of lung cancer.[4] Other risk factors include exposure to asbestos, second-hand smoke, radon-222, and bischloromethyl ether.[6]
The exact role of such exposures in the development of SCLC is presently an area of active research. However, it is known that tobacco smoke contains procarcinogens and carcinogens, such as acetaldehyde, formaldehyde, benzene, and polycyclic aromatic hydrocarbons, which can induce a variety of genetic mutations that may ultimately lead to neoplasia.[7]
For example, nearly all cases of SCLC show a deletion of the short arm of chromosome 3. It is believed that currently unidentified tumor-suppressor genes reside in the deleted region.[7] Essentially all cases of SCLC have abnormalities of the retinoblastoma gene. The absence of its functional protein results in uncontrolled cellular proliferation.[7] Also, somatic mutations of the p53 gene are found in 80% of SCLC cases.[7] Finally, overexpression of the myc family of oncogenes is a common event in SCLC and connotes a poor prognosis.[7]

“Differential Susceptibility”

In addition to environmental insults, host factors play a still poorly defined role in the development of SCLC. It is noteworthy that: (1) fewer than 10% to 15% of smokers develop lung cancer; (2) African-American men are more prone to the development of lung cancer than are white American men; and (3) some evidence shows that women are more likely to develop lung cancer than are men, after adjusting for the number of pack-years of cigarettes smoked.[5]
These observations lend credibility to the notion of “differential susceptibility” to lung cancer. One source of differential susceptibility may be related to host metabolism of carcinogens. For example, Bouchard and colleagues recently found that high levels of activity of the cytochrome P-450 CYP2D6 were associated with a significantly increased risk of lung cancer, but only in heavy smokers.[8] More recently, Wiencke and associates demonstrated ethnic variations in the expression of the gene coding for nicotinamide adenine dinucleotide phosphate oxidoreductase, a cytosolic reducing enzyme thought to be important in the metabolism of certain lung carcinogens.[9] These researchers found that polymorphisms of this gene were two times more common in Hispanic Americans, who develop lung cancer at significantly lower rates than white Americans and African-Americans; this finding still held even after the researchers corrected for variations in tobacco consumption.[9]
Moreover, differences in the frequencies of isozyme expression of glutathione transferase-mu, which metabolizes aromatic hydrocarbons, have been correlated with lung cancer susceptibility.[10]

Classification

There are two well-known classification systems for SCLC. The 1981 World Health Organization (WHO) classification recognizes three subtypes: (1) the classic “oat cell” type, characterized by small oval or round cells with hyperchromatic nuclei, indistinct nucleoli, and scant cytoplasm; (2) the intermediate type, characterized by larger cells, pleomorphic nuclei, and more abundant cytoplasm; and (3) the combined type, characterized by the presence of features of squamous cell carcinoma or adenocarcinoma.[11] TABLE 1

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<th>Evolution of Nomenclature for Small-Cell Lung Cancer Subtyping</th>
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Because of similarities in the clinical behavior and biochemical and growth characteristics of the subtypes, researchers for the International Association for the Study of Lung Cancer (IASLC) proposed a new classification system in 1988 (Table 1).[11] In this system, small-cell carcinoma denotes those cancers without a non-small-cell component. This entity comprises more than 90% of SCLC cases. The IASLC system also acknowledges two other subtypes of SCLC: (1) small-cell/large-cell cancer, characterized by a population of larger cells with an open chromatin pattern and prominent nucleoli; and (2) combined small-cell carcinoma, characterized by the presence of neoplastic squamous or glandular elements.[11]

Presentation
Although the interval from the development of symptoms to diagnosis is shorter for SCLC than for NSCLC patients, the presentation of the two histologic types is generally similar (Table 2).[12] Symptoms and signs stem primarily from tumor location and bulk. In a retrospective review of lung cancer presentation and cell type, Chute and colleagues found that the most common symptoms in patients with limited-stage disease were cough (41%), weight loss (35%), dyspnea (33%), and chest pain (33%). Only patients with stage I squamous cell lung cancer reported weight loss with such a high frequency (36%).[13] Due to the great frequency of mediastinal nodal disease in patients with SCLC, hoarseness, dysphagia, and superior vena cava syndrome also occur frequently.

Paraneoplastic Syndromes

Paraneoplastic syndromes, although a relatively uncommon occurrence in SCLC, are usually endocrinologic or neurologic in nature.[14,15] The most common endocrinologic syndrome is inappropriate secretion of antidiuretic hormone (SIADH), which is clinically apparent in 11% to 46% of SCLC patients.[14,15] This syndrome usually improves with successful treatment of the underlying malignancy and does not appear to adversely affect survival. Atrial natriuretic peptide (ANP), which promotes natriuresis and hypotension, may also contribute to hyponatremia in approximately 15% of SCLC patients. Its effects are ameliorated by cancer treatment.[14] Ectopic adrenocorticotropic hormone (ACTH) production, seen in < 5% of SCLC patients, presents with peripheral edema, proximal myopathy, hypertension, glucose intolerance, and metabolic alkalosis. Cushingoid stigmata are frequently absent, perhaps due to the rapidity with which the syndrome occurs.[14,15] Tumors with ectopic ACTH production are associated with a dismal prognosis, perhaps because of their poor response to therapy.[14]

The neurologic paraneoplastic syndromes of SCLC include Lambert-Eaton myasthenic syndrome, cerebellar degeneration, encephalomyelitis, sensory neuropathy, and cancer-associated retinopathy.[14] Seen in ≤ 5% of SCLC patients, Lambert-Eaton myasthenic syndrome develops because of the production of autoantibodies that interfere with voltage-gated calcium channels important to the release of acetylcholine from presynaptic neurons.[14] Patients present with proximal myopathy, “waddling gait,” hyporeflexia, and autonomic dysfunction. Ocular and bulbar symptoms are much less common than in myasthenia gravis.

Like other paraneoplastic syndromes, treatment of Lambert-Eaton myasthenic syndrome is directed at the underlying cancer. However, guanidine hydrochloride, aminopyridine, plasma exchange, and immunosuppression have all been given with occasional success. It is noteworthy that the use of aminoglycosides, beta-blockers, calcium-channel blockers, and class la antiarrhythmics (such as quinidine, procainamide, and disopyramide) should be avoided in these patients to avoid acute myasthenic crisis.[14]

Paraneoplastic cerebellar degeneration appears to be related to autoantibodies directed at Purkinje cells, although other antineuronal antibodies have been described as well. Cerebellar degeneration
responds poorly to cancer therapy; this is due presumably to the rapid and permanent destruction of cerebellar cells.[14] Like cerebellar degeneration, encephalomyelitis, sensory neuropathy, and cancer-associated retinopathy are suspected to represent autoimmune phenomena. These syndromes are minimally ameliorated by cancer treatment.[14]

**Prognostic Factors**

Various prognostic factors have been identified in SCLC patients.[16,17] These can be divided into three categories: host factors, tumor factors, and serum test abnormalities.

As is true of all malignancies, performance status at the time of SCLC diagnosis is by far the most important prognostic host factor.[16,17] Female patients also fare better than do males.[16,17] Extent of disease independently predicts outcome, with more extensive disease portending a worse outcome. This observation holds true even within each stage category. For example, for patients with limited-stage disease, the absence of mediastinal or supraclavicular nodes and pleural effusion confers a somewhat better prognosis. For patients with extensive-stage disease, the absence of central nervous system (CNS) or liver metastasis and a single site of metastasis have been associated with a better prognosis.[16,17]

Finally, although a variety of serum test abnormalities have been reported in patients with SCLC, hyponatremia and elevations of lactic dehydrogenase (LDH) and alkaline phosphatase are most often associated with a poor prognosis.[16,17]

**Diagnosis**

Lung cancer can be diagnosed histologically or cytologically. Cytologic specimens can be obtained via patient expectoration, bronchoscopic techniques (washings and brushings), and fine-needle aspiration.

In 1985, Truong and associates reported that the overall sensitivity of brush cytology was superior to that of sputum and washing cytology.[18] The sensitivity rates of bronchial sputum, washing, and brush cytology for SCLC were 69%, 64%, and 50%, respectively. Truong et al also noted a good correlation between histologic and cytologic diagnosis.[18] Arroliga and Matthay reported a similar accuracy for bronchoscopic specimens in 1993. They also noted excellent agreement between cytologic and histologic diagnosis of SCLC.[19] Expert pathology review is highly recommended, as crush artifact may sometimes be mistaken for SCLC.

Transthoracic needle aspiration is a safe, cost-effective diagnostic technique that may be performed in the outpatient setting. Pneumothorax occurs in approximately one-third of cases but requires chest tube decompression in ≤ 10% of patients; intrapulmonary hemorrhage also occurs frequently but rarely requires specific intervention.[20] Transthoracic needle aspiration has a diagnostic yield of at least 95% under fluoroscopic guidance and a 80% yield under computed tomographic (CT) guidance.[20] The ability to distinguish SCLC from NSCLC is not compromised by this technique. Moreover, in 40% to 75% of patients, a sample adequate enough for histologic confirmation of the cytologic impression can be safely obtained.[21]

For cases in which the aforementioned studies are nondiagnostic but the clinical suspicion for lung cancer remains high, diagnostic surgical procedures, such as mediastinoscopy, video-assisted thoracoscopy, and thoracotomy, are recommended.[20]

**Staging**

The international staging system for NSCLC reflects the important role of surgery in its management. In contrast, SCLC is rarely considered a surgical disease. Rather, as recommended by the Veterans Administration Lung Cancer Study Group in 1973, SCLC is usually staged as “limited” or “extensive” disease.[22]

Limited disease is defined as disease that can be encompassed within a tolerable radiation port. This definition introduces physician judgment about the patient’s ability to tolerate radiation into disease staging. Extensive disease refers to metastatic disease outside of the chest.[22] Patients with mediastinal or contralateral adenopathy or ipsilateral pleural effusion are included in the limited-stage category.

Two reviews of the Southwest Oncology Group (SWOG) SCLC databases have shown that patients with extensive intrathoracic adenopathy or ipsilateral pleural effusion have a prognosis similar to those with “true” limited-stage disease. However, due to the technical difficulties that arise with
pleural radiation, limited-disease SCLC with pleural effusion is treated as extensive-stage disease (ie, without chest radiation).[23,24] Thus, members of the International Association for the Study of Lung Cancer extended the Veterans Administration Lung Study Group’s definition of limited-disease SCLC to include those patients with ipsilateral pleural effusion or with mediastinal, or contralateral adenopathy.[22]

Approximately two-thirds of SCLC patients have extensive disease at the time of diagnosis.[25] Chest radiotherapy confers a small but significant survival advantage only in patients with limited disease. Thus, the primary role of the staging evaluation is to identify those patients who could benefit from chest radiotherapy in addition to chemotherapy.[25]

NCI Staging Algorithm

The proposed algorithm for staging small-cell lung cancer (SCLC), corresponding to the least expensive staging sequence examined (the numbers represent the patients involved in each step of the algorithm). CNS = Central nervous system

For better or worse, we are living in an era of increasing demands for cost-effective patient management. Researchers at the National Cancer Institute (NCI) have proposed a sequence of staging procedures that can decrease the cost of staging by approximately one-third (Figure 1).[25] In this algorithm, the staging evaluation halts once a metastatic site is identified. No further studies are necessary, as the patient will be treated with chemotherapy alone, except for radiation given for palliation of symptoms.

Of special interest, routine CT imaging of the chest is not performed in this algorithmic approach, as the presence or absence of mediastinal or hilar disease does not alter therapy for either limited or extensive disease. If limited-disease SCLC is confirmed, the treating radiotherapist will use CT of the chest to determine the treatment volume.

Role of New Imaging Studies

New imaging techniques may eventually make the above algorithm obsolete. Positron emission tomography (PET) uses radiolabeled glucose to measure metabolic rates in normal and malignant tissue; malignant tissue takes up the radiolabeled glucose at a more rapid rate.[26] Positron emission tomography has been shown to have a mean sensitivity of 96% and a mean specificity of 52% for malignant mediastinal disease.[26]

Technetium-labeled murine monoclonal antibody scanning is another diagnostic technique that shows promise. Balaban and associates reported the overall accuracy of this technique in staging SCLC patients to be 88%.[27] The ability of technetium-labeled murine monoclonal antibody scanning to detect liver lesions and lesions < 2 cm is somewhat disappointing; this may be related to hepatobiliary and renal excretion of the radiotracer.[27]

Somatostatin receptor scintigraphy uses radiolabeled somatostatin analogs to assess the whole body for sites of metastatic neuroendocrine malignancies.[28,29] O’Byrne and colleagues reported that although this technique localized 100% of primary SCLC sites, it detected only 50% of known...
metastatic sites.[29] These disappointing results may reflect the fact that only 50% to 75% of SCLCs express somatostatin receptors. Moreover, it may be that receptors at metastatic sites have different binding affinities or somatostatin receptors.[29] Other investigators have also noted the low sensitivity of somatostatin receptor imaging in SCLC.[28]

**Combination Chemotherapy**

Until the mid-1960s, surgery was the standard of care for patients with SCLC despite the extremely low number of long-term survivors.[16] A landmark study published in 1973 demonstrated that patients with “operable” SCLC cancer enjoyed longer survival when managed with thoracic radiation rather than surgical resection, although only 3 of 73 irradiated patients survived to the 10-year mark.[30] In an autopsy study of lung cancer patients dying within 30 days of presumed “curative” surgery,³ 50% of SCLC patients had widely metastatic disease and ³ 70% had persistent disease at the operative site.[31]

With the realization of the frequently disseminated nature of SCLC and the woeful inadequacy of local therapy alone in improving survival, interest turned to systemic therapies. A 1969 study of various alkylating agents in lung cancer patients noted that intravenous cyclophosphamide doubled median survival in patients with SCLC.[32] In 1972, Bergsagel and colleagues reported on a randomized trial in which SCLC patients received radiotherapy alone or radiotherapy with four or eight cycles of cyclophosphamide. Again, a small survival advantage was seen in patients who received systemic therapy in addition to radiation.[33]

Attempts to improve the modest success of single-agent cyclophosphamide initially revolved around the addition of other cytotoxic agents with different mechanisms of action. With this approach, Hansen and colleagues noted superior response rates but no significant difference in survival rates of extensive-disease patients treated with a three-drug regimen, as compared with a two-drug regimen.[34] Comparing cyclophosphamide, doxorubicin, and dacarbazine (DTIC) to single-agent cyclophosphamide in SCLC patients, Lowenbraun and associates demonstrated superior response rates as well as survival rates in patients receiving combination chemotherapy.[35]

**CAV and PE Regimens**

Building on the success of the study by Lowenbraun et al, Livingston and colleagues piloted a phase II study of cyclophosphamide, Adriamycin, and vincristine (CAV) in extensive-disease SCLC patients. Again, improved response and survival rates were achieved.[36] These studies established combination chemotherapy in general and CAV in particular as the standard of care for the management of SCLC in the 1980s.

Although both cisplatin (Platinol) and etoposide have marginal tumor activity in previously treated patients, in vitro studies of these agents in the late 1970s demonstrated synergistic activity. Evans and associates studied the combination of Platinum and etoposide (PE) in CAV-refractory SCLC patients and noted a 55% overall response rate.[37] In a phase II study of patients with previously untreated SCLC, Evans et al demonstrated an 86% response rate; survival, however, was similar to that seen with CAV (median survival, 71 weeks for limited disease and 43 weeks for extensive disease).[38] In addition to these good response and survival rates, the PE regimen has an excellent toxicity profile, which makes it one of the most popular regimens for SCLC in the 1990s. **TABLE 3**
With the above regimens, patients with limited-disease SCLC demonstrate overall (complete plus partial) response rates of 60% to 90%, complete response rates of 40% to 70%, median survival of 12 to 20 months, 2-year survival rates of 20% to 40%, and 5-year survival rates of 6% to 12%. Predictably, similar measures of therapeutic efficacy show inferior results of these regimens in patients with extensive disease. Overall response rates range from 40% to 70%; complete response rates, from 15% to 30%; and median survival, from 7 to 11 months. Also, the rate of 2-year survival is £ 5%, and there are only anecdotal reports of survival beyond 5 years (Table 3).[16] These improvements translate into an absolute survival increase of 9 to 13 months in limited-disease SCLC and 5 to 9 months in extensive disease.[16]

Despite the four- to fivefold increase in median survival with combination chemotherapy, the absolute survival advantage is still modest.[16] Presumably, the failure to cure SCLC more consistently reflects the presence of drug-resistant tumor cells. The Goldie-Coldman model of drug resistance predicts that maximum tumor kill can be achieved if all effective agents are used as early as possible at their optimal doses.[39] Because myelosuppression is the dose-limiting toxicity of most of the effective antineoplastic agents for SCLC, it frequently is impossible to deliver all effective agents in this manner.

Another option, therefore, is to alternate non-cross-resistant chemotherapy regimens. The success of this approach with the MOPP-ABVD (mechlorethamine, Oncovin, procarbazine, prednisone, Adriamycin, bleomycin, vinblastine, and dacarbazine) regimen in Hodgkin’s disease served as the impetus for numerous trials of presumptively non-cross-resistant regimens SCLC.

CAV Alternating With PE

Testing the clinical utility of the Goldie-Coldman hypothesis, the National Cancer Institute of Canada (NCIC) compared six cycles of CAV alone to CAV alternating with PE in extensive-disease SCLC patients.[40] Evans and associates noted a small but statistically significant survival advantage for patients receiving the latter regimen.[40] This study has been frequently criticized because it is impossible to know whether the superiority of the alternating regimen is real or whether it simply reflects the better efficacy of the PE regimen.

In their three-arm study of CAV, PE, and CAV alternating with PE, Fukuoka and colleagues noted statistically significantly higher response rates for all patients treated with CAV-PE and PE. Subset analysis revealed a slight survival advantage only in limited-disease patients.[41] In a similar study, Roth and associates noted no significant difference in response or survival rates in extensive-disease patients receiving PE, CAV, or alternating CAV-PE.[42] It is noteworthy that although alternating regimens do not significantly improve survival, they do decrease total dose-dependent treatment toxicity, such as doxorubicin-induced cardiomyopathy and cisplatin-induced neurotoxicity.[16]

Dose Intensification

The literature is replete with various studies of chemotherapy intensification in SCLC.

• Early Intensification—in early intensification, patients initially receive higher-dose chemotherapy followed by standard-dose chemotherapy. Johnson and associates reported markedly increased toxicity (infections, ≥ grade 3 nausea) without significant improvement in response or survival rates when they prospectively compared higher-dose CAV to standard CAV in SCLC.[43] Ihde and colleagues also prospectively randomized patients to higher-dose or standard-dose PE.[44] The higher-dose regimen did not produce any significant improvement in overall response rates or median survival. Also, as in the study by Johnson et al, toxicity was substantially increased in the higher-dose arm.[44]

• Late Intensification—Dose intensity can also be achieved by late intensification, in which higher-dose chemotherapy is delivered after maximal response to conventional-dose chemotherapy. This approach is theoretically attractive because: (1) patients most likely to benefit would be identified by their response to conventional treatment; (2) decreased tumor burden at the time of intensification should improve responsiveness to intensive therapy; and (3) residual tumor at the time of intensification is more likely to be chemosensitive than is relapsed tumor.[16] In 1988, Einhorn and associates described their experience with late intensification, or consolidation, in limited-disease SCLC.[45] In this trial, patients were randomized to six cycles of CAV with or without thoracic radiotherapy; responding patients were then rerandomized to either observation or two cycles of PE. Statistically significant improvements in median duration of response (49 weeks) and median survival (98 weeks) were noted in patients on the consolidation arm, whereas the control arm patients had a median duration of response of 28 weeks and a median survival of 68
weeks.[45]
Autologous bone marrow transplantation (BMT), another form of late intensification, has been studied in several small phase I and II trials. Ihde and colleagues reported on one of the earliest American trials of autologous marrow transplantation in SCLC.[46] After 12 weeks of two conventional chemotherapy regimens, responding eligible patients were given chest radiotherapy and high-dose etoposide and cyclophosphamide followed by autologous bone marrow infusion. Only 34% of initially registered patients were eligible for late intensification. Despite high response rates (21% complete response rate, 52% partial response rate) and a prolonged duration of response, patients of receiving autologous marrow grafts showed no obvious improvement in overall survival, and treatment-related deaths occurred in 25%.[46]
In a phase III trial, Humblet and associates also reported high response rates and improved duration of responses with late intensification via high-dose chemotherapy followed by autologous BMT. Again, however, this aggressive approach did not improve overall survival and resulted in treatment-related deaths in 18% of patients.[47]
Finally, Souhami and colleagues described four sequential studies of autologous BMT in 75 highly selected SCLC patients.[48] Again, although this approach produced superior response rates and a prolonged duration of response, it did not yield significant gains in survival, and treatment-related deaths occurred in 6% of transplanted patients.[48]

- Growth Factor Support—Leukopenia is the dose-limiting toxicity of most chemotherapeutic agents used in SCLC. Moderately intensive drug doses (producing leukocyte nadirs of 1,000 cells/µL) yield results superior to less myelosuppressive doses. Thus, the availability of hematopoietic growth factors has perpetuated interest in dose intensity in the management of SCLC.
In a randomized, placebo-controlled trial of granulocyte colony-stimulating factor (G-CSF, filgrastim [Neupogen]) after CAE (cyclophosphamide, Adriamycin, and etoposide) in SCLC patients, Crawford and associates demonstrated a significant decrease in the incidences of febrile neutropenia and neutropenic infections in patients receiving G-CSF.[49] Hamm and colleagues reported similar success in decreasing chemotherapy-associated neutropenia and neutropenic infections in SCLC patients receiving granulocyte-macrophage colony-stimulating factor (GM-CSF, sargramostim [Leukine, Prokine]) after more dose-intensive CAE.[50]
Using recombinant human (rHu) glycosylated G-CSF (lenograstim), Woll and associates attempted to determine the ability of hematopoietic growth factor to increase cytotoxic dose-intensity in SCLC patients.[51] Patients were prospectively randomized to VICE (vincristine, ifosfamide with mesna, carboplatin, and etoposide) with or without post-treatment G-CSF. There were no significant differences between the two arms with regard to the incidence of neutropenic fever (70% vs 65.5%), response rates (93.5% vs 94.1%), or median survival (65 vs 69 weeks). Although treatment-related mortality was higher in patients receiving G-CSF than in those not receiving this adjunct (6 vs 1 death, respectively), 2-year survival was somewhat longer in the G-CSF-treated group.[51]
In a review of dose escalation in hematologic and solid malignancies, Savarese and associates demonstrated marked toxicity without significant gains in response or survival rates in SCLC patients treated with the following regimens: (1) dose-intensive chemotherapy without bone marrow support; (2) dose-intensive chemotherapy with growth factor support; and (3) dose-intensive chemotherapy with bone marrow or stem-cell support.[52]

**Summary**

| TABLE 4 |
Commonly Used Chemotherapy Regimens for Small-Cell Lung Cancer

Combination chemotherapy has clearly improved the survival of patients with SCLC, albeit modestly. Although the optimal chemotherapeutic regimen remains to be defined, either PE or CAV offers acceptable response, survival, and toxicity profiles (Table 4). Alternating these regimens does not appear to significantly improve survival.[16] For elderly SCLC patients or those at risk of excessive toxicity from combination chemotherapy, oral etoposide as a single agent may offer some palliative effect, although it is clearly inferior with regard to its impact on survival and quality of life.[16,53] Numerous controlled clinical trials have yielded no evidence that treatment beyond 6 months positively affects response or survival rates.[16,53] To date, no study has demonstrated that the incorporation of hematopoietic growth factors in the management of SCLC offers a clear survival advantage. Thus, neither dose-intensive therapy nor growth factor support should be employed in SCLC patients outside of the context of clinical trials.

New Chemotherapeutic Agents

Clearly, more effective new treatments are necessary to improve the cure rate of SCLC. Several new agents with novel mechanisms of action may provide additional tools to combat this disease.

**Gemcitabine**

Although many antimetabolites have traditionally been ineffective in the treatment of SCLC, the deoxycytidine analog gemcitabine (Gemzar) is stimulating interest among researchers.[54,55] The drug is well tolerated and only modestly myelosuppressive, making it a potentially promising addition to combination regimens.

In a phase II trial of gemcitabine in patients with previously untreated extensive SCLC, a 27% overall response rate was noted. Although median duration of response was only 12.5 weeks, median survival was 12 months, as relapsed patients tended to respond to second-line therapy.[54] A phase I study of the combination of gemcitabine and etoposide has demonstrated that both drugs can be given at full doses without undue hematologic or nonhematologic toxicity. Responses were noted in 5 of 44 patients.[55] Results of a phase II study of this combination in patients with previously untreated extensive SCLC are expected in the near future.

**Paclitaxel**

The tubulin toxin paclitaxel (Taxol) has been noted to produce a 68% response rate when given as a 24-hour infusion at a dose of 250 mg/m² in patients with extensive SCLC. Median survival was 29 weeks.[56] Paclitaxel has been added to the PE regimen in patients with previously untreated extensive-stage SCLC with promising early results: Complete responses were noted in 33% of evaluable patients and partial responses in 67% patients, with a median survival of 11.3 months.[57] When given in combination with carboplatin (Paraplatin) and oral etoposide, paclitaxel (135 mg/m² infused over 1 hour) resulted in an 83% overall response rate (29% complete responses, 54% partial responses). Median survival was 7 months for extensive-disease patients and 17 months for limited-disease patients.[58]

**Docetaxel**

The tubulin toxin docetaxel (Taxotere) has been noted to produce a 75% response rate when given as a 1-hour infusion at a dose of 100 mg/m² in patients with extensive SCLC. Median survival was 19.6 months.[59] Docetaxel has been added to the CAV regimen in patients with previously untreated extensive-stage SCLC with promising early results: Complete responses were noted in 20% of evaluable patients and partial responses in 59% patients, with a median survival of 13.3 months.[60] When given in combination with carboplatin (Paraplatin) and etoposide, docetaxel (75 mg/m² infused over 1 hour) resulted in an 81% overall response rate (22% complete responses, 59% partial responses). Median survival was 10 months for extensive-disease patients and 16 months for limited-disease patients.[61]
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Docetaxel (Taxotere), a semisynthetic taxane, has been studied in SCLC patients previously treated with no more than one chemotherapy program. A 25% response rate was noted, with a median duration of response of 4.7 months. As anticipated, neutropenia was the dose-limiting toxicity.[59]

**Topotecan**

Topotecan (Hycamtin) is a water-soluble analog of camptothecin, a DNA topoisomerase I inhibitor.[60] In vitro data have suggested that treatment of leukemia cell lines with topoisomerase II inhibitors, such as etoposide, results in a population of cells that are dependent on topoisomerase I for DNA transcription and, thus, are more susceptible to topoisomerase I inhibitors.[60] In a phase II study of topotecan in patients with PE-refractory SCLC, Perez-Soler and colleagues noted an overall response rate of 12%. Duration of response was not reported, but median survival was 20 weeks.[61] The authors concluded that cross-sensitivity to topoisomerase I inhibitors after treatment with topoisomerase II inhibitors probably develops only rarely.

Ardizzoni and associates studied topotecan in previously treated SCLC patients,[62] who were prospectively identified as “sensitive” (ie, patients who responded to first-line therapy for at least 3 months) or “refractory” (ie, patients who never responded to first-line therapy or relapsed within 3 months of initial response). Median survival duration was longer in the sensitive patients than in the refractory patients (6.9 vs 4.7 months). Prior treatment with an etoposide-based regimen did not correlate with response to topotecan.[62]

In 48 patients with previously untreated extensive SCLC, Schiller and associates noted a response rate of 40% to topotecan. Median duration of response was 4.8 months, and median survival was 10 months.[63]

**Irinotecan**

**TABLE 5**

 Novel Agents in Small-Cell Lung Cancer

Irinotecan (CPT-11 [Camptosar]), another camptothecin analog, has elicited a response rate of 47% in 16 previously treated SCLC patients and a 78% response rate in combination with cisplatin in patients with chemotherapy-naive limited disease (Table 5).[64]

**Summary**

Gemcitabine, the taxanes, and the camptothecins, with their novel mechanisms of action, offer potentially promising avenues for the management of patients with SCLC.

**Thoracic Radiotherapy**

As mentioned above, 3 decades ago, surgery was the standard of care for SCLC despite a 5-year survival rate of 1%.[16] In the mid-1960s, a randomized trial of surgery vs radiotherapy in operable patients demonstrated superior median and overall survival rates for patients receiving chest radiotherapy.[30] With mounting evidence of the importance of chemotherapy in the management of SCLC, the role of thoracic radiotherapy was called into question.

In 1992, Pignon and colleagues performed a meta-analysis of 13 randomized trials of chemotherapy with or without thoracic radiation in 2,140 patients with limited SCLC.[65] They also noted a small survival advantage with chest radiotherapy: a 5.4% improvement in 3-year survival due to a 14% reduction in mortality. The timing of radiation did not appear to have an impact on survival.[65] Although gender was not a significant prognostic variable, age ≤ 55 years appeared to be associated with a decreased risk of death. Toxicity was not reported.

**Treatment Controversies**

Although the survival advantage of chest radiotherapy in limited-disease SCLC is now well
established, there is still considerable controversy over the proper timing of radiation therapy in relation to chemotherapy, as well as the optimal dose, treatment volume, and fractionation scheme.

**Timing**—Chest radiotherapy can be administered in a sequential, alternating, or concurrent manner. With sequential therapy, patients receive a full course of chemotherapy followed by radiotherapy. This strategy should theoretically lead to less treatment-related toxicity. With alternating therapy, radiotherapy is sandwiched between chemotherapy cycles in such a way that chemotherapy is not delayed. Finally, with concurrent therapy, both treatment modalities are delivered simultaneously—yielding higher response rates and toxicities.\[65,66\] The meta-analysis of thoracic radiation does not demonstrate significant differences in toxicity and survival for sequential and nonsequential approaches.\[65\] Trials of early vs late chest radiotherapy have yielded conflicting results with regard to survival.\[65,66\] Thus, although there is a small but definite survival advantage to thoracic radiation, its timing in relationship to chemotherapy (early vs late) remains undefined.

**Dose**—It is well documented that SCLC is a very radiosensitive tumor. Like chemotherapy, radiotherapy appears to have a dose-response curve in this cancer.\[66\] Studies have demonstrated decreased local recurrence rates with increasing radiation dose.\[66\] However, the maximum tolerated dose per fraction and the most effective total dose for SCLC remain to be determined.

**Treatment Volume**—Integrally related to dose is treatment volume, which also contributes to the success and toxicity of radiation. The optimal treatment volume in SCLC remains unclear. Retrospective studies suggest that the optimal volume is based on post-chemotherapy volume of disease.\[66\]

Only one prospective randomized trial has addressed this issue.\[67\] Unfortunately, the pretreatment vs post-treatment volume issue was addressed only in patients demonstrating stable disease or partial response to chemotherapy. This study failed to demonstrate a significant difference in the efficacy of radiation based on pretreatment or post-treatment volumes.\[67\]

**Fractionation**—refers to the manner in which the total radiation dose is divided over a period of time.\[66\] In a standard fractionation schedule, patients receive single daily doses for 4 to 6 weeks. In a hyperfractionated schedule, patients receive multiple daily doses over a shorter period of time. With accelerated and hyperfractionated treatments, maximal tumor kill and minimal normal tissue toxicity may be achieved more readily.

Johnson and colleagues compared once- to twice-daily thoracic radiotherapy with concurrent PE in 419 patients with limited-stage SCLC. They reported an 87% overall response rate for both arms. Likewise, median duration of response (8.4 vs 10.9 months) and median survival (18.6 vs. 22.7 months) did not differ significantly between the two arms. Grade 3 toxicity occurred in 26% of patients receiving twice-daily chest radiation.\[67\] The median survival durations of both patient groups are among the best reported in cooperative group studies.\[68\]

**Summary**

Outside of clinical trials, radiation therapy should probably be delivered to the post-chemotherapy volume, and dose should be in the range of 45 to 50 Gy given in 1.8 to 2.0 cGy single daily fractions.

**Prophylactic Cranial Radiation**

Approximately 10% of SCLC patients present with CNS metastasis at diagnosis, and another 20% to 25% of patients will develop CNS metastasis at some point during their life.\[16\] The actuarial probability of developing CNS recurrence is 50% to 80% in patients living for 2 years or more.\[16\] In the absence of effective intervention, it seems reasonable to anticipate an increased incidence of CNS metastases if improved management of SCLC results in more long-term survivors. Central nervous system metastasis also is a major source of morbidity and mortality in SCLC patients. Although 60% to 85% of patients with CNS metastasis can look forward to prompt relief of their symptoms with therapeutic cranial irradiation, the duration of response is quite brief: Only 20% of patients are still effectively palliated 12 months after radiation therapy.\[16\] Systemic therapy without total cranial irradiation has been reported to result in a 76% response rate (37% complete response rate) in patients with CNS metastasis, but the duration of response remained short (mean, 5 months) and survival was not influenced.\[16\]

The interest in prophylactic cranial irradiation, another controversial area in the management of SCLC, stems from this grim natural history. At the heart of the controversy are two issues: (1) the impact of prophylactic cranial irradiation on survival; and (2) its effect on quality of life. Multiple prospective randomized trials have demonstrated that prophylactic cranial irradiation can decrease the rates of isolated and concomitant CNS recurrence in patients responding to initial
treatment of their SCLC.[16,69] To date, no study has demonstrated a survival advantage of prophylactic irradiation, possibly because the magnitude of any benefit is too small to be detected.[16,69] However, given the morbidity of CNS metastases, their prevention is probably a worthwhile endeavor.

If prophylactic cranial irradiation is to be pursued as a means of improving quality of life, its toxicity must be well defined. Earlier trials in patients with SCLC reported variable neurotoxicity, ranging from subtle radiologic changes to psychometric abnormalities to clinical syndromes resembling dementia.[16,69] However, in more recent studies in which neurologic status was assessed prospectively, late neurotoxicity appears to be less prevalent.

Arriagada and associates prospectively assessed neurologic function in SCLC patients, who, after complete response to chemotherapy, were randomized to prophylactic cranial irradiation or observation.[70] Neuropsychiatric testing and CT imaging of the brain were performed at baseline and repeated at 6, 18, 30, and 48 months. Of note, over half of each group demonstrated baseline abnormalities in neuropsychiatric testing, and 17% of patients in each group had baseline brain abnormalities on CT imaging.

In addition to demonstrating a significant decline in the incidence of CNS metastasis with prophylactic cranial irradiation, Arriagada and associates found no significant difference in neuropsychiatric function or CT abnormalities between the treated and control groups.[70] Those studies that have reported the highest incidence of neurotoxicity with prophylactic cranial irradiation frequently used chemotherapeutic agents thought to be capable of crossing the blood-brain barrier, thus introducing another potential source of neurotoxicity.[16,69] Moreover, SCLC is not infrequently associated with neurologic paraneoplastic syndromes, which also confound this issue. Finally, tobacco abuse, the biggest risk factor for SCLC, is also one of the most important risk factors for cerebrovascular disease, yet another potential source of neurotoxicity in SCLC patients.

Surgery

Although SCLC is largely considered to be a nonsurgical disease, there are two clinical scenarios in which surgery may be considered. In ≤ 5% of cases, SCLC may present as a peripheral (solitary) pulmonary nodule. In patients with such a nodule, resection with curative intent, followed by adjuvant chemotherapy, has produced a 5-year survival rate of 50%. Thoracic radiotherapy could conceivably add to local control in these patients and perhaps improve survival.[71]

In another scenario, “salvage” surgery can be performed in clinical stage I patients who appear unresponsive to initial chemotherapy. Approximately 10% of these patients harbor a NSCLC component in their tumor.[71] Lad and associates reported four long-term survivors out of nine patients treated with such an approach.[71]

References:
8. Bouchard C, Benhamou S, Dayer P: The effect of tobacco on lung cancer risk depends on CYP2D6


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