

Small Cell Lung Cancer

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Small cell lung cancer accounts for approximately 15% of bronchogenic carcinomas. It is the cancer most commonly associated with various paraneoplastic syndromes, including the syndrome of inappropriate antidiuretic hormone secretion, paraneoplastic cerebellar degeneration, and Lambert-Eaton myasthenic syndrome. Because of the high propensity of small cell lung cancer to metastasize early, surgery has a limited role as primary therapy. Although the disease is highly sensitive to chemotherapy and radiation, cure is difficult to achieve. The combination of platinum and etoposide is the accepted standard chemotherapeutic regimen. It is also the accepted standard therapy in combination with thoracic radiotherapy (TRT) for limited-stage disease. Adding TRT increases absolute survival by approximately 5% over chemotherapy alone. Thoracic radiotherapy administered concurrently with chemotherapy is more efficacious than sequential therapy. Furthermore, the survival benefit is greater if TRT is given early rather than late in the course of chemotherapy. Regardless of disease stage, no relevant survival benefit results from increased chemotherapy dose intensity or dose density, altered mode of administration (eg, alternating or sequential administration) of various chemotherapeutic agents, or maintenance chemotherapy. Prophylactic cranial radiation prevents central nervous system recurrence and can improve survival. In Japan and some other Asian countries, the combination of irinotecan and cisplatin is the standard chemotherapeutic regimen. Clinical trials using thalidomide, gefitinib, imatinib, temsirolimus, and farnesyltransferase inhibitors have not shown clinical benefit. Other novel agents such as bevacizumab have shown promising early results and are being evaluated in larger trials.

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CI = confidence interval; ED = extensive-stage disease; EGFR = epidermal growth factor receptor; EP = etoposide plus cisplatin; GRP = gastrin-releasing peptide; IGF1 = insulin-like growth factor 1; IGF1R = IGF1 receptor; IP = irinotecan plus cisplatin; IV = intravenous; LDH = lactate dehydrogenase; LD = limited-stage disease; MMP = matrix metalloproteinase; mRNA = messenger RNA; NSCLC = non-small cell lung cancer; PCI = prophylactic cranial irradiation; SCLC = small cell lung cancer; TRT = thoracic radiotherapy; VEGF = vascular endothelial growth factor

In 2007, an estimated 213,380 new cases of lung cancer were diagnosed in the United States, with 160,390 resultant deaths.¹ Small cell lung cancer (SCLC) accounts for approximately 15% of new cases of lung cancer diagnosed annually and for up to 25% of lung cancer deaths each year.² However, the overall incidence and mortality rates of SCLC in the United States have decreased during the past few decades.^{2,3} Possible causes for this trend include the decrease in smoking prevalence (especially in white men) and a change to low-tar filters.³ Recent evidence suggests that women of all ages are more likely to present with SCLC than men, and that younger women are more likely to present with SCLC than older women. Women who

begin smoking at an early age are more susceptible to SCLC.⁴⁻⁶

PATHOLOGY

Histologically, the tumor cells are small, round to ovoid or spindle shaped, with scant cytoplasm. The mitotic count is high; cells grow in clusters that exhibit neither glandular nor squamous organization. Electron microscopy shows dense-core neurosecretory granules 100 nm in diameter. Nearly all SCLC are immunoreactive for keratin, thyroid-transcription factor 1, and epithelial membrane antigen. Neuroendocrine and neural differentiation result in the expression of dopa decarboxylase, calcitonin, neuron-specific enolase, chromogranin A, CD56 (also known as nucleosomal histone kinase 1 or neural cell adhesion molecule), gastrin-releasing peptide (GRP), and insulin-like growth factor 1 (IGF1). One or more markers of neuroendocrine differentiation can be found in approximately 75% of SCLCs.⁷

Whereas preinvasive and in situ malignant changes are frequently found in non-small cell lung cancer (NSCLC), these findings are rare in SCLC.⁸

ETIOLOGY AND PATHOGENESIS

The most important known cause of SCLC is cigarette smoking,⁹ accounting for approximately 95% of cases. Interaction of environmental factors with the genome of the respiratory epithelium results in carcinogenesis in susceptible patients.

Increasing evidence has implicated autocrine growth loops, proto-oncogenes, and tumor-suppressor genes in the pathogenesis of SCLC. Several chromosome and oncogene abnormalities have been identified in fresh SCLC tissues and cell lines, such as deletions on the short arm of chromosome 3 found in more than 95% of cases of SCLC.¹⁰ Some genetic abnormalities occur early in the disease, such as inactivation of tumor suppressor genes on chromosome 3.

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TABLE. Molecular Abnormalities in SCLC and NSCLC*

Characteristic	SCLC (%)	NSCLC (%)
Point mutations		
K ras	NA	30-50
P53	90	60
Rb	80-100	20-40
c-met	12.5	7
Increased gene copy number		
EGFR	NA	22-32
MYC (formerly c-MYC)	18-30	8-22
Protein overexpression		
BCL2	75-95	10-35
EGFR	NA	60-70
ERBB2 (formerly Her2/neu)	0-13	20-40
GRP	50-75	NA
CCND1	NA	43
MYC (formerly c-Myc)	10-45	10
c-kit	60-90	<10
c-met	80-90	90-100
VEGF	80	75

*EGFR = epidermal growth factor receptor; GRP = gastrin-releasing peptide; NA = not applicable; NSCLC = non-small cell lung cancer; SCLC = small cell lung cancer; VEGF = vascular endothelial growth factor.

Certain genetic changes characteristic of the malignant phenotype also occur in the benign bronchial epithelium of patients with lung cancer. This *field carcinogenic* effect occurs more frequently with SCLC than with NSCLC.⁸ The common molecular abnormalities found in SCLC vs those found in NSCLC are shown in the Table.

The basic tenets that underlie our understanding of carcinogenesis can be categorized into overlapping processes that mediate proliferation, antiapoptosis, angiogenesis, and metastasis. In SCLC, the presence of multiple neuropeptides and polypeptides, such as GRP, stem cell factor, and IGF1, which are coexpressed with their specific receptors (GRP receptor, c-kit, and IGF1 receptor [IGF1R], respectively), promote the growth of SCLC via the establishment of autocrine growth loops. Moreover, IGF1R activates the PIK3-AKT1 pathway, a major mediator of resistance to apoptosis and chemotherapy.

Constitutive activation, either by mutations or overexpression of 1 or more components of the various proliferative pathways, is another mechanism for dysregulated growth in cancers. The activation of c-met, a receptor tyrosine kinase that is highly expressed in SCLC, results in proliferation, angiogenesis, and motility.¹¹ Mutations, including activating mutations in the juxtamembrane domain leading to a more aggressive phenotype, have been reported in SCLC.¹² However, coexpression of c-met with its cognate ligand hepatic growth factor/scatter factor (HGF/SF) is rare,¹¹ although it is interesting to note that serum levels of HGF in patients with SCLC are higher than in healthy controls.¹³ Invasive properties and increased cell

motility are seen with concomitant induction of tyrosine phosphorylation of a number of cellular proteins such as the focal adhesion proteins paxillin and focal adhesion kinase via activation of the PIK3-AKT1 pathway.¹⁴⁻¹⁶

The epidermal growth factor receptor (EGFR), a member of the *ErBB* receptor tyrosine kinase family, is known to trigger cell proliferation, migration, survival, and angiogenesis on its activation. Although its role in lung cancer has been predominantly demonstrated in NSCLC, some evidence suggests that SCLC expresses low but functional levels of EGFR that could confer more invasive properties than EGFR-negative cells.^{17,18} Another member of the *ErBB* receptor tyrosine kinase family, *ERBB2* (formerly *HER2/neu*), acts as a potent oncogene when overexpressed in mouse fibroblasts¹⁹ and can mediate malignant transformation of cells independently of EGFR.²⁰ Although it has been thought that *ERBB2* is not expressed in patients with SCLC, more recent evidence suggests that *ERBB2* is expressed in a small proportion of these patients. Moreover, the presence of *ERBB2* seems to be a prognostic indicator of poorer survival outcomes among patients with extensive-stage disease (ED) SCLC and poor performance status.²¹ The best characterized signal transduction pathway stimulated by these growth signals is the ras-raf-MAPK pathway that mediates proliferation, cell cycle regulation, cell migration, and angiogenesis.²²

Dysregulation of the programmed cell death or apoptotic process has been implicated in both tumorigenesis and therapeutic resistance. Key regulators of this process that are relevant in SCLC biology include *BCL2* and *TP53*. Overexpressed in most patients with SCLC,^{23,24} *BCL2* confers resistance to treatment with cytotoxic chemotherapy, radiotherapy, and monoclonal antibodies.^{25,26} In more than 90% of SCLC cases, *TP53* is mutated,²⁷ with most mutations affecting the DNA-binding core domain, thereby abolishing the *TP53*-dependent transcriptional regulation of target genes. Mutant *TP53* is typically expressed in higher levels in cancer cells because of its inability to up-regulate its own negative regulator, *MDM2*.²⁸ It is thought that survival of tumor cells with mutant *TP53* depends largely on the presence of mutant *TP53*. Restoration of wild-type *TP53* in patients with SCLC has been shown to restore chemosensitivity and radiation sensitivity.²⁹

As more data are generated from studies on angiogenesis and the tumor microenvironment, the integral role of these complex systems in carcinogenesis is becoming better appreciated. Vascular endothelial growth factor (VEGF) is one of the most important promoters of angiogenesis and has been associated with poorer prognosis in various malignancies. The interplay of various elements, such as cytokines, chemokines, adhesion molecules, and matrix metalloproteinases (MMPs), affects the cellular in-

teraction with the extracellular matrix and contributes to angiogenesis and metastasis.³⁰ One of the crucial signaling targets that regulate these myriad processes is nuclear factor κ B, a transcription factor that regulates the expression of genes that control inflammation, cell growth, apoptosis, angiogenesis, cell adhesion, and metastasis. It is highly expressed in various malignancies including SCLC.³¹

HEREDITARY PREDISPOSITION TO LUNG CANCER

The Genetic Epidemiology of Lung Cancer Consortium (GELCC) conducted the first family linkage study searching for susceptibility genes for lung cancer. This study identified linkage of lung, laryngeal, and pharyngeal cancer in families to a region on chromosome 6q23-25.³²⁻³⁴ Attempts at defining genetic susceptibility are ongoing. Studies have identified people with certain alleles of the *CYP1A1* gene to have an increased capacity to metabolize procarcinogens derived from cigarette smoke and thus to be at greatest risk of developing lung cancer. The *CYP3A4*1B* allele has also been linked to an increased SCLC risk, particularly in female smokers, who were at an 8-fold higher risk of lung cancer.³⁵ Patients with a mutagen-sensitivity genotype resulting from chromosomal breakages in peripheral blood lymphocytes after exposure to tobacco-related carcinogens have a greater than 10-fold risk of developing lung cancer. In contrast, a correlation has been noted between a promoter allelic variant of the myeloperoxidase gene *MPO* and reduced susceptibility of smokers to develop SCLC.³⁶

CLINICAL DIAGNOSIS AND STAGING

The most common presenting symptoms are dyspnea, persistent cough, and hemoptysis. Postobstructive pneumonia may be the presenting clinical syndrome. Small cell lung cancer is the most common malignant cause of superior vena cava syndrome. Metastatic disease can produce pain, headache, malaise, seizures, fatigue, anorexia, and weight loss. Common sites of metastasis include bone, liver, lymph node, the central nervous system, adrenal glands, subcutaneous tissue, and pleura.³⁷ Pancoast tumor, ie, tumors located at the apex, which can present ipsilaterally, with Horner syndrome, and with pain in the upper extremities in the T1 dermatome location, is an uncommon presentation, perhaps because of the early propensity for widespread dissemination and the typical central location of SCLC. In a review of 413 cases from different series, Johnson et al³⁸ found only 5 cases (1.2%). As noted in another review, only 12% of patients with SCLC presented with a peripheral lung lesion and only 2% had an apical lung mass.³⁹

Paraneoplastic syndromes are very commonly associated with SCLC. Cancer cachexia and the syndrome of inappropriate antidiuretic hormone secretion (SIADH) occur in approximately 40% of cases. Cushing syndrome can result from increased serum and tissue levels of immunoreactive adrenocorticotrophic hormone. Often seen in patients with NSCLC, hypercalcemia is distinctly uncommon in those with SCLC.⁴⁰ Paraneoplastic neurologic syndromes include Lambert-Eaton myasthenic syndrome, manifested as weakness of proximal muscles of the lower and upper extremities with relative sparing of respiratory and bulbar muscles. In contrast to patients with other myasthenic syndromes, motor strength in patients with Lambert-Eaton myasthenic syndrome may initially improve after exercise, subsequently weakening if activity is sustained. This phenomenon is called postexercise facilitation. Cerebellar degeneration presents as loss of coordination, truncal and limb ataxia, dysarthria, and nystagmus, whereas encephalomyelitis can present as limbic, brainstem, or focal encephalitis in combination with subacute sensory and autonomic neuropathy. Pathogenesis involves immunologic cross-reactivity between tumor-associated antigens and P/Q-type voltage-gated calcium ion channels (Lambert-Eaton myasthenic syndrome), anti-Purkinje cell antibodies (cerebellar degeneration), and anti-Hu antibodies (encephalomyelitis). The neurologic syndromes are usually progressive and run their own course independently of the cancer and outcomes of cancer therapy. The endocrine syndromes related to peptide production by the tumor usually abate with effective treatment of cancer.⁴¹⁻⁴³

A detailed history, careful physical examination, and appropriate testing, including complete blood cell count, electrolyte panel, and radiologic evaluation, are key to establishing a diagnosis of SCLC. Chest radiograph, computed axial tomography of the chest extending through bilateral adrenal glands, and brain imaging are standards of care. Ongoing studies are investigating the role of positron emission tomography in disease staging. There is as yet no proven role for spiral computed tomography in screening for lung cancer. Radionuclide bone scans are also typically obtained because of the frequency of bony metastasis. Standard in the past, routine bone marrow aspiration and biopsy are not performed today. In patients with negative findings on bone scan and normal serum levels of lactate dehydrogenase (LDH), isolated bone marrow involvement with disease is found in fewer than 5% of cases. In several large retrospective studies, increased LDH concentrations positively correlated with the finding of bone marrow involvement by SCLC.⁴⁴⁻⁴⁷

Small cell lung cancer is typically staged according to the Veterans Administration Lung Cancer Study Group (VALCSG) staging system. Disease confined to 1 hemitho-

rax with the tumor encompassed in 1 radiation port is classified as limited-stage disease (LD); disease that is any less confined, as ED. This distinction is important because patients with ED are treated with palliative chemotherapy and/or radiotherapy, whereas patients with LD are treated with curative intent to achieve a 5-year survival rate of approximately 20%.

NATURAL HISTORY

Historical survival data for people with untreated SCLC came from an early VALCSG trial in which cyclophosphamide treatment was compared with placebo. In this trial, median survival was 12 weeks for patients with LD and 6 weeks for patients with ED. Small cell lung cancer is very responsive to chemotherapy, with major responses in 70% to 90% of cases on initial treatment. However, most patients relapse and die within 2 years. The most important prognostic features are disease stage, performance status, and extent of weight loss. Patients who are nonambulatory and patients who have lost 5% or more of their body weight in the preceding 2 to 6 months have a poor prognosis. Elevated LDH is associated with a poorer prognosis.

THERAPY

LIMITED-STAGE DISEASE

At diagnosis, approximately 30% of patients with SCLC have LD.⁴⁸⁻⁵⁰ Combined modality treatment with chemotherapy and concurrent radiotherapy is the current standard of treatment. Addition of radiation to chemotherapy produces modest but significant improvement in survival. Two meta-analyses have shown a 5% improvement in 3-year survival rates for patients receiving a combination of chemotherapy and radiation vs those receiving chemotherapy alone.^{51,52}

With its propensity for early hematogenous spread, SCLC is a systemic disease and is rarely cured with surgical resection. Surgery alone is no longer used in the United States for SCLC.^{53,54} In a prospective randomized trial conducted by the Lung Cancer Study Group (LCSG), pulmonary resection after at least partial response to combination chemotherapy followed by thoracic radiotherapy (TRT) and prophylactic cranial irradiation (PCI) in patients with LD-SCLC neither improved survival rates nor influenced the pattern of relapse.⁵³ A very small subset of patients with SCLC who have small peripheral tumors and a documented absence of nodal and metastatic disease may be considered for surgical resection followed by adjuvant therapy, although this practice remains debatable.⁵⁵ Because they can harbor a focus of NSCLC, resection of tumors that are partially responsive to therapy and have residual mass that remains confined to the chest can result in long-term survival.⁵⁶

Chemotherapy. Several chemotherapeutic agents, including doxorubicin, methotrexate, vincristine, cyclophosphamide, etoposide, cisplatin, and carboplatin, produce single-agent response rates of 30% or greater in patients with SCLC. Combination regimens yield higher responses and superior survival compared with the use of single agents. The relative efficacy of 2- to 5-drug regimens appears to be similar. Alternating chemotherapeutic regimens have not proven more effective than consistent use of a single regimen. Randomized studies evaluating the role of maintenance therapy did not reveal any survival advantage for prolonged treatment after the first 4 to 6 cycles of chemotherapy.⁵⁷

Currently, etoposide plus cisplatin (EP) is the regimen of choice for patients with LD because of the superior efficacy of cisplatin vs carboplatin and because of the favorable toxicity profile of EP.⁵⁸⁻⁶⁰ Many trials evaluating this combination have found it superior to other regimens; it causes less mucosal, hematologic, and pulmonary toxicity than the older cyclophosphamide-based regimen. In a randomized phase 3 study, EP was compared with a regimen of cyclophosphamide, epirubicin, and vincristine in 436 patients with either LD (214 patients) or ED (222 patients). Patients with LD received TRT concurrently with the third cycle of chemotherapy, and PCI was administered to those with complete response. In patients with LD-SCLC, EP resulted in better 2- and 5-year survival rates than cyclophosphamide, epirubicin, and vincristine (14% and 5% vs 6% and 2%). In patients with ED, no difference in survival was noted.⁶¹

Clinical studies have shown carboplatin to have good activity in patients with SCLC. In a German multicenter study, Wolf et al⁶² evaluated 350 patients randomized to receive doxorubicin, ifosfamide, and vincristine alternating with either EP or carboplatin-etoposide. Median survival in patients receiving cisplatin was higher than in those receiving carboplatin (14 vs 12 months), but no difference was seen in patients with ED. Thus, unless contraindicated, cisplatin should be the preferred compound for treating patients with LD until further studies demonstrate an equal efficacy for carboplatin.

Given the exponential gompertzian growth kinetics of SCLC, the concept of dose density, defined as increased chemotherapy dose per unit of time, to overcome the resistance to chemotherapy has been studied. Steward et al⁶³ randomized patients with LD and ED to ifosfamide, etoposide, carboplatin, and vincristine given every 3 (intensified) or 4 (standard) weeks. Patients were also randomized to receive granulocyte-macrophage colony-stimulating factor or placebo. Patients in the dose-dense arm were found to have a higher median survival time and higher 2-year survival rate than those in the standard arm. Although multiple

other studies support the safety and tolerability of this approach, no survival benefit has been observed.⁶⁴

In a meta-analysis of 60 published SCLC studies, no significant correlation was found between dose intensity and either response rates or median survival in patients with LD or ED.⁶⁵ Subsequent studies have yielded conflicting results.^{66,67} Similarly, high-dose chemotherapy with autologous bone marrow transplant has yielded disappointing results. In the first reported randomized trial, 45 patients who achieved a response to induction chemotherapy were randomized to high-dose chemotherapy and autologous bone marrow transplant or conventional treatment. No significant difference in overall survival was observed between the 2 arms, but a statistically significant difference in relapse-free survival was noted in favor of high-dose therapy.⁶⁸ Because of the small sample size, no meaningful conclusion can be drawn. Another randomized trial of 100 patients also yielded similar results.⁶⁹

Radiotherapy. As mentioned earlier, combination therapy with radiation and chemotherapy significantly improves survival in patients with LD-SCLC. If these benefits are to be realized, careful attention must be paid to the appropriate timing and dosage of radiation and the appropriate fractionation strategies.

Because of the radiosensitivity of SCLC, modest doses of TRT (45-50 Gy) were typically administered in daily fractions of 1.8 to 2.0 Gy in earlier studies. Subsequent data suggested that more aggressive TRT to improve local control can improve the long-term outcome of patients with LD-SCLC as well.⁷⁰ However, adoption of a twice-daily TRT dose of 45 Gy as a routine treatment is limited by increased esophageal toxicity as well as scheduling inconvenience for patients. Because of the demonstrable radiation dose-response effect in patients with SCLC,⁷¹ it has been suggested that delivery of a biologically equivalent once-daily TRT dose of 60 to 70 Gy might yield survival benefit comparable to that of twice-daily TRT.⁷² A phase 3 trial is needed to address this issue, and one is currently under development by The Cancer and Leukemia Group B (CALGB) and Radiation Therapy Oncology Group (RTOG).

Integrating TRT With Chemotherapy. Sequential, concurrent, and alternating approaches have been tried in integrating TRT with chemotherapy. With the sequential approach, 1 modality is used at a time. In alternating therapy, TRT is given on days when chemotherapy is not given; in concurrent therapy, TRT is given simultaneously with chemotherapy.

An early meta-analysis evaluating the effect of TRT on survival in patients with LD-SCLC indirectly compared the method of treatment integration (sequential vs alternating vs concurrent). No statistically significant difference was

found among the different approaches.⁵² Subsequently, a European Organization for Research and Treatment of Cancer (EORTC) trial treating 335 patients with LD-SCLC with a regimen of cyclophosphamide, adriamycin, and etoposide did not show any survival benefit with alternating therapy.⁷³

Studies that failed to show the superiority of concurrent thoracic irradiation used cyclophosphamide- or doxorubicin-based chemotherapy, wherein the accelerated toxicity of the combined-modality therapy inevitably required reduced dose intensity. In contrast, an EP-based concurrent regimen did not increase pulmonary toxicity or lead to the radiation recall phenomenon.⁷³ The Japanese Clinical Oncology Group (JCOG) 9104 study showed an improved trend in overall survival with concurrent vs sequential therapy. However, small sample size and an imbalance of baseline characteristics such as performance status were cited as reasons for the lack of statistical significance. Adjustment with Cox regression analysis suggested a greater benefit of concurrent radiotherapy; the hazard ratio for death in the concurrent arm to death in the sequential arm was 0.70 (95% confidence interval [CI], 0.52-0.94; $P=.02$).⁷⁴ With EP as the systemic chemotherapeutic regimen of choice, the concurrent chemoradiation approach is currently the standard treatment approach for patients with LD-SCLC.

Early vs Late Concurrent TRT. Multiple randomized trials have evaluated the relative efficacy of early vs late integration of TRT into chemotherapy. Early meta-analyses were unable to show any difference in survival.^{52,75} However, a more recent meta-analysis of 7 randomized trials comprising 1524 patients showed a small 2-year survival benefit favoring early TRT.⁷⁶ Although the magnitude of the survival benefit remained similar at 3 years, the lack of statistical significance could be attributable to insufficient power in the analysis. Moreover, certain factors related to the timing of TRT likely influence the outcomes. Subset analyses of this meta-analysis revealed that the survival benefit was most evident in studies using platinum-based chemotherapy, as well as in studies using hyperfractionated TRT. No difference in survival was noted with timing of TRT in studies using once-daily fractionation schemes. With non-platinum-based chemotherapeutic regimens, survival difference was not statistically significant. Thus, although the available data do not conclusively settle the question of TRT timing, early delivery of concurrent TRT is favored in current clinical practice.

Once- vs Twice-Daily TRT. On the basis of SCLC biology, it has been postulated that hyperfractionated radiotherapy is superior to conventional (once-daily) radiation. *Standard radiation fractionation* refers to schedules using daily treatments of 1.8 to 2.0 Gy, 5 times per week,

continuously for approximately 6 weeks. *Accelerated hyperfractionation* refers to delivering a course of radiation during a shorter total treatment period (acceleration) and with a greater number of treatment fractions (hyperfractionation). In this schedule, TRT is typically delivered 2 to 3 times a day and the size of individual fractions is reduced.

Contrasting results were reported by 2 major trials that addressed this issue. In a randomized study by Turrisi et al,⁷⁷ 417 patients received 4 cycles of EP, starting with 45 Gy of concurrent TRT, given either twice daily for 3 weeks or once daily for 5 weeks. At median follow-up of 8 years, the median survival was 23 months for patients who received twice-daily radiation and 19 months for the group who received once-daily radiation. The 2- and 5-year survival rates for patients receiving once-daily radiotherapy were 41% and 16%, respectively; for those receiving radiotherapy twice a day, 47% and 26%, respectively.

Bonner et al⁷⁸ reported a study of LD-SCLC in which patients received 3 cycles of EP, followed by randomization to twice-daily TRT of 48 Gy in 32 fractions, with a 2.5-week break after the initial 24 Gy, or once-daily TRT with 50.4 Gy in 28 fractions, both given concomitantly with 2 additional cycles of chemotherapy. After TRT, a sixth cycle of chemotherapy was given, followed by PCI for those showing a complete response. In contrast to the study by Turrisi et al,⁷⁷ no differences in local progression rates, overall progression rates, or overall survival were observed.⁷⁸ The lack of benefit in this latter study of twice-daily TRT has been ascribed to the treatment break that occurred in the delivery of TRT, which could counteract the potential benefit of this intensified regimen. Another reason for the negative results in this study could be the delayed initiation of TRT. Although patient adherence and concerns of acute toxicity are often cited to account for difficulty in uniformly implementing twice-daily TRT (45 Gy), this is currently a standard treatment option for patients with LD-SCLC, particularly for patients with good performance status.

EXTENSIVE-STAGE DISEASE

Chemotherapy is the mainstay of treatment in ED-SCLC. An overview of phase 3 trials between 1972 and 1990 revealed that the median survival time of patients treated in the control arms of trials from 1972 to 1981 was 7 months. Patients enrolled in control arms between 1982 and 1990 had a median survival time of 8.9 months. During the same period, the Surveillance Epidemiology and End Results database suggested a similar (2-month) prolongation in median survival in patients with ED-SCLC. These improvements have been attributed to improved supportive care.⁷⁹

Chemotherapy. The current standard chemotherapy for ED-SCLC is EP.⁸⁰ This regimen provides response rates of 60% to 80% (in frontline settings), with median survival time of 8 to 10 months. As is the case with LD-SCLC, there is no survival advantage of prolonged maintenance cytotoxic chemotherapy for patients with ED-SCLC after the first 4 to 6 cycles of treatment.⁵⁷

Various substitutions and additions to EP have been investigated. Skarlos et al⁸¹ performed a randomized study comparing EP to carboplatin and etoposide in 147 patients with LD and ED. No significant differences were seen in response rate or median survival time; however, less toxicity was reported in the carboplatin arm.

In JCOG 9511, Noda et al⁸² reported a phase 3 study of irinotecan and cisplatin (IP) (60 mg/m² of intravenous [IV] irinotecan on days 1, 8, and 15 plus 60 mg/m² of IV cisplatin on day 1, once every 28 days) compared with EP (100 mg/m² of IV etoposide days 1 to 3 plus 80 mg/m² of IV cisplatin on day 1, every 21 days) in 154 patients with ED-SCLC. They found significant differences in overall survival and toxicity profile in favor of the irinotecan arm. This finding was evaluated in the United States in a phase 3 study by Hanna et al⁸³ in which 331 patients with ED-SCLC were randomized to receive either IP or EP. The EP (120 mg/m² of IV etoposide on days 1 through 3 plus 60 mg/m² of IV cisplatin on day 1 every 21 days) and IP (65 mg/m² of IV irinotecan on days 1 and 8 plus 30 mg/m² of IV cisplatin every 21 days) regimens in this study were modified from the JCOG regimens to improve delivery, reduce toxicity, and be more consistent with dosages and schedules given in the United States. No statistically significant difference in survival was found in the 2 groups. The 1-year survival rate for the IP group was 35.0% compared with 36.1% for the EP group. In the IP vs EP group, median survival was 9.3 months vs 10.2 month, and the response rate was 52.0% vs 51.0%. Patients receiving irinotecan had less myelosuppression but more diarrhea.

The Southwest Oncology Group (SWOG) presented the preliminary data from the comparative and pharmacogenomic analysis of SWOG 0124 and JCOG 9511. A phase 3 study that used the same protocol as JCOG 9511 study, SWOG 0124 found significant differences in treatment-related toxicities between the 2 populations. This study examined different allelic variants in genes associated with irinotecan metabolism and found different allelic variants correlating with hematologic and gastrointestinal toxicities. The pharmacogenomics could explain the different toxicity profile of Japanese and American populations. The survival data from SWOG 0124 are eagerly awaited.⁸⁴

In another recent phase 3 study, Hermes et al⁸⁵ randomized 220 patients with ED-SCLC to either IV carboplatin

(area under the curve of 4) and IV irinotecan (175 mg/m²) on day 1 or IV carboplatin (area under the curve of 4) on day 1 and oral etoposide (125 mg/m²/d) on days 1 through 5 of a 21-day cycle. Overall survival was 255 days in the irinotecan arm and 214 days in the etoposide arm. In the irinotecan arm, 18 complete responses were observed; in the etoposide arm, 7 complete responses. No significant difference in grade 3 or 4 hematologic toxicities was observed. This study demonstrated the efficacy of irinotecan in combination with carboplatin vs the oral etoposide combination regimen.

With disease recurrence, the overall median survival of patients is 2 to 3 months. If relapse occurs more than 3 to 4 months after initial treatment, then 40% response rates to further chemotherapy can be attained, as opposed to only 10% if relapse is within 3 to 4 months of primary treatment. Long-term survival is possible if relapse is more than 8 months after primary treatment; these patients might respond to agents used in primary treatment.⁸⁶ In a multicenter randomized trial, topotecan was at least as effective as cyclophosphamide, doxorubicin, and vincristine for patients with recurrent disease, improving dyspnea, fatigue, and anorexia.⁸⁷ Currently, topotecan is approved by the Food and Drug Administration for treatment of patients with SCLC who experience relapse at least 60 days after completion of first-line therapy.

Pemetrexed is a multitargeted antifolate that is effective as a single agent in NSCLC. A phase 2 study of pemetrexed as single agent in sensitive and refractory relapsed SCLC showed modest response rates (complete response, partial response, and stable disease) of 20% and 14% in patients with sensitive and refractory relapsed SCLC, respectively, at a dose of 500 mg/m². This study was later amended to increase the pemetrexed dose to 900 mg/m². This increase in dose did not increase the grade 3 or 4 toxicities; however, no increase in efficacy was noted.⁸⁸ On the basis of the demonstrated activity and tolerability of pemetrexed with platinum combinations in NSCLC, a randomized phase 2 study in patients with untreated ED-SCLC evaluated the use of either cisplatin or carboplatin in combination with pemetrexed.⁸⁹ Favorable results paved the way for the Global Analysis of Pemetrexed in SCLC Extensive Stage (GALES), an ongoing multicenter international randomized phase 3 trial of pemetrexed in combination with carboplatin vs etoposide plus carboplatin as first-line therapy for patients with ED-SCLC.

Other cytotoxic agents such as vinorelbine, gemcitabine, and taxanes have shown variable activity as single agents or in combination in clinical trials. Although these combinations have not led to a change in the current standard for first-line therapy, they can be considered in relapsed disease.

Prophylactic Cranial Irradiation. The risk of central nervous system metastasis developing 2 years after successful treatment of SCLC is approximately 35% to 60%.⁹⁰⁻⁹² Thus, PCI was introduced, primarily for responsive LD-SCLC. A meta-analysis of the efficacy of PCI in 847 patients with LD-SCLC and 140 patients with ED-SCLC who took part in 7 trials and who had complete remission with chemotherapy, with or without TRT, demonstrated a 25.3% decrease in cumulative incidence of brain metastasis at 3 years with PCI. An absolute increase in overall survival of 5.4% at 3 years was also seen.⁹³ Neurotoxicity from PCI is more frequent and severe when it is given concurrently with or before chemotherapy, when radiation fractions are greater than 2.5 Gy, and when total radiation dose is more than 30 Gy.⁹⁴

Prophylactic cranial irradiation has traditionally been limited to patients with LD-SCLC after meaningful response from combined-modality treatment has been achieved. However, recent results from a randomized study provide evidence that PCI not only reduces the incidence of symptomatic brain metastases but also prolongs disease-free and overall survival in patients with ED-SCLC. The EORTC Radiation Oncology and Lung Cancer group randomized 286 patients with ED-SCLC who responded to 4 to 6 cycles of chemotherapy to receive PCI (dose ranging from 20 Gy/5 fractions to 30 Gy/12 fractions) or no PCI. Primary quality-of-life end points were global health status, hair loss, fatigue, and cognitive and emotional functioning. The 1-year cumulative incidence of symptomatic brain metastasis in the PCI group was 14.6% (95% CI, 8.3%-20.9%) compared with 40.4% in the control group (95% CI, 32.1%-48.6%). At 1 year, the survival rate in the PCI group was 27.1% vs 13.3% in the control group.⁹⁵

On the basis of these studies the National Comprehensive Cancer Network recommends PCI for patients with either LD or ED who achieve a complete response, have only radiation scarring, or have a tumor with a mass that is 10% or less that of the tumor before systemic treatment.

NEW CYTOTOXIC AGENTS

Picoplatin. Picoplatin is a sterically hindered platinum analogue designed to overcome platinum resistance. Moreover, clinical studies with picoplatin have shown it to be less nephrotoxic and neurotoxic than currently marketed platinum agents. In a phase 2 study of single-agent picoplatin as second-line therapy in patients with SCLC, 4 (8%) of 48 patients had a partial response and 21 (44%) had stable disease. Median survival was 27 weeks (95% CI, 16-35 weeks). In another multicenter phase 2 study of picoplatin as a single-agent second-line therapy in SCLC, the median overall survival was 28.1 weeks (95% CI, 26.0-37.0 weeks).⁹⁶ A randomized phase 3 trial of best supportive

therapy with or without picoplatin in patients with refractory SCLC or disease progression within 6 months of completing a first-line platinum-containing regimen is ongoing.

Amrubicin. Amrubicin is a novel, completely synthetic 9-aminoanthracycline derivative. Like other anthracycline derivatives, such as doxorubicin and daunorubicin, amrubicin is converted to its C-13 alcohol metabolite amrubicinol. However, in contrast to doxorubicinol and daunorubicinol, amrubicinol has much higher antitumor activity than the parent drug in vitro. In addition, amrubicin has been shown to be less cardiotoxic than doxorubicin in long-term animal experimental models.⁹⁷⁻¹⁰⁰

Amrubicin had been studied as a second-line single agent in patients with refractory and sensitive relapsed SCLC. The overall response rate in each group was approximately 50%. The progression-free, overall, and 1-year survival in the refractory and sensitive group was 2.6 months and 4.4 months, 10.3 months and 11.6 months, and 40% and 46%, respectively.¹⁰¹ Amrubicin is currently being tested in the United States against topotecan in a multinational randomized phase 3 trial for patients with SCLC that does not respond to first-line chemotherapy. It is already an approved agent in Japan.

NOVEL TARGETED THERAPIES

Proliferative Pathways as Target. EGFR Inhibitors. Gefitinib is a small-molecule inhibitor of the EGFR tyrosine kinase with activity in NSCLC and pancreatic cancer. A phase 2 trial of 250 mg/d of gefitinib as salvage therapy in patients with chemosensitive relapsed or chemorefractory SCLC showed that this drug is not active in this patient population. No responses were observed, and all but 2 of the 18 patients had progressive disease. However, rare cases of nonsmokers with SCLC associated with activating EGFR mutations in the tyrosine kinase domain, either de novo or arising at the time of or after a diagnosis of NSCLC, have been reported.¹⁰²⁻¹⁰⁵ Anecdotal responses were seen in such cases after treatment with gefitinib or erlotinib, another oral EGFR tyrosine kinase inhibitor.

Ras/Raf Inhibitors. To be biologically active, ras proteins must be localized to the inner face of the plasma membrane via farnesylation, which affects cell cycle, the cytoskeleton, and apoptosis and is an important process for other proteins as well.¹⁰⁶ Despite the lack of known activating ras mutations, SCLC cells have shown sensitivity to farnesyltransferase inhibitors in preclinical studies.^{107,108} The farnesyltransferase inhibitor zarrestin (R115777) has been tested in patients with SCLC with good performance status and sensitive relapsed disease. However, no objective responses were noted in the 22 study patients. The median time to progression was 1.4 months.¹⁰⁹

Sorafenib is a multiple kinase inhibitor that was initially developed as a raf kinase inhibitor but subsequently was shown to have potent antiangiogenic activity via its inhibition of KDR (formerly VEGFR2), FLT4 (formerly VEGFR3), and PDGFRB. It is currently being evaluated in a phase 2 trial for patients with platinum-treated ED-SCLC.

C-kit Pathway. The high coexpression of stem cell factor/c-kit was shown to be relevant to SCLC biology with in vitro data demonstrating inhibition of SCLC growth after exposure to imatinib, an inhibitor of the PDGFR-related tyrosine kinases, including c-kit.¹¹⁰ This finding led to several phase 2 studies of SCLC in various clinical contexts. Johnson et al¹¹¹ reported their findings in 19 patients with SCLC, either with chemosensitive relapsed disease or previously untreated ED, who were enrolled in a phase 2 trial using 600 mg/d of imatinib mesylate for up to 12 months. No antitumor activity was observed in this group of patients. However, the study was weakened by at least 2 limitations: only 21% of the patients had c-kit–positive tumors on immunohistochemistry, and 26% of the patients had non-SCLC histology on an unplanned post hoc central pathology review. In another study, 30 patients with c-kit–positive relapsed SCLC were enrolled in 2 groups: arm A (7 patients) included patients with disease progression within 3 months; arm B (23 patients), those with disease progression more than 3 months after treatment. No objective response was identified. Despite careful selection of patients with c-kit–expressing tumors, this study showed no efficacy for imatinib.¹¹²

Imatinib has also been studied in combination with chemotherapy. In a recently reported phase 2 study, 68 patients with chemonaïve ED-SCLC were treated with irinotecan, carboplatin, and imatinib. The addition of imatinib provided no benefit.¹¹³ Imatinib also did not show clinical activity as maintenance therapy among patients with c-kit–positive ED-SCLC that responded to first-line chemotherapy.¹¹⁴

Cell Survival Pathways as Target. BCL2. Oblimersen sodium (G3139) is an 18-base antisense phosphorothioate oligonucleotide complementary to *BCL2* messenger RNA (mRNA). Its binding to the cognate sequence of *BCL2* mRNA results in inhibition of mRNA translation and ribonuclease H–mediated mRNA degradation.¹¹⁵ Preclinical models in SCLC have shown antitumor effects with this approach, as well as synergistic effects with cytotoxic chemotherapy.^{116,117} In a pilot study of 12 patients with chemorefractory SCLC who received oblimersen with paclitaxel, 2 patients achieved stable disease beyond cycle 4. One patient who had a progression-free interval of more than 1 year had consistently high plasma oblimersen levels. In a randomized phase 2 study (CALBG 30103) of first-

line chemotherapy using carboplatin and etoposide with or without oblimersen to treat patients with ED-SCLC, increased toxicities were observed in the oblimersen arm. The mature results of this trial are awaited with interest.

Oral small molecule inhibitors of BCL2 are modeled after the BH3-interacting domain death agonist (BID), a naturally occurring BCL2 inhibitor; AT-101 (gossypol), ABT-263, and ABT-737 are BH3 mimetics that inhibit both BCL2 and the related apoptotic inhibitors BCL2L1 (formerly BCLX) and BCL2L2 (formerly BCLW). Single-agent activity against SCLC xenografts has been shown with this approach.¹¹⁸ These agents are currently being evaluated in combination with chemotherapy in patients with SCLC.

Expression of the antiapoptotic protein BCL2 is regulated in part by the inhibitor of NF- κ B (I κ B), a target of the ubiquitin-proteasome degradative pathway. The 26S proteasome is a multienzyme unit that regulates intracellular protein homeostasis via proteolytic degradation. Proteasomal inhibition in lung cancer cell lines causes cell-cycle arrest and apoptosis associated with increased levels of p21 and decreased levels of BCL2 through diminished I κ B degradation.¹¹⁸ Lara et al¹¹⁹ reported a phase 2 study of the proteasome inhibitor bortezomib as salvage therapy for relapsed platinum-sensitive or -refractory ED-SCLC. Although an objective response was seen in a patient with platinum-refractory disease, bortezomib had limited single-agent activity in this patient population. Combination with cytotoxic chemotherapy, such as topotecan, is currently being evaluated in early-phase clinical trials.

IGF1R/PIK3/AKT1/FRAP1 Pathway. On binding to its receptor, IGF1 promotes antiapoptotic effects via activation of the *PIK3-AKT1-FRAP1* (formerly mTOR) survival pathway. This pathway has been implicated in mediating chemoresistance as well as resistance to novel agents such as imatinib in SCLC.¹²⁰ An inhibitor of IGF1 receptor kinase, NVP-ADW742, sensitizes SCLC cells to chemotherapy in vitro.¹²¹ Monoclonal antibodies to IGF1R are in early clinical development. These agents are currently being investigated in combination with chemotherapy and other targeted therapies. Temsirolimus (CCI-779) is a FRAP1 inhibitor that has been evaluated in a phase 2 study in 2 weekly doses (25 mg and 250 mg) in patients with ED-SCLC who had responsive or stable disease after induction chemotherapy. No difference was found in progression-free survival between the 2 doses.¹²²

Angiogenesis Pathways as Target. Despite an abundance of preclinical data supporting the use of MMP inhibitors, high-profile clinical trials of these agents in various tumor types including SCLC not only showed that they lacked antitumor efficacy but also that they were associated with worse outcome in patients.¹²³ This discrepancy be-

tween preclinical and clinical data likely stemmed from an inadequate understanding of the complexity of the physiologic roles assumed by individual members of this large family of MMPs.

Bevacizumab, a monoclonal antibody against VEGF, has shown clinical benefit in various clinical contexts for different malignancies, such as colon cancer and NSCLC. Sandler et al¹²⁴ reported a phase 2 study in 64 patients with previously untreated ED-SCLC. A 21-day cycle of IV cisplatin (60 mg/m², day 1), IV etoposide (120 mg/m², days 1, 2, and 3), and bevacizumab (15 mg/kg, day 1) was repeated 4 times or until disease progression. An overall response rate (4 complete responses and 23 partial responses) of 69% (95% CI, 55%-81%) was reported. At 6 months, 33% of patients were alive with no disease progression. In another nonrandomized single-arm phase 2 trial, Ready et al¹²⁵ studied 72 patients with untreated ED-SCLC. The treatment regimen involved 30 mg/m² of cisplatin on days 1 and 8, 65 mg/m² of irinotecan on days 1 and 8, and 15 mg/kg of bevacizumab on day 1 of a 21-day cycle for a maximum of 6 cycles. The most common adverse events (grade \geq 3) were neutropenia (25.0%) and diarrhea (16.0%). One patient died of left ventricular systolic dysfunction, 1 of brain hemorrhage, and 1 of pneumonitis/pulmonary infiltrates.¹²⁵ The treatment regimen resulted in 3 complete responses and 48 partial responses, for an overall response rate of 75.0%. Eleven other patients had stable disease. The 12-month overall survival was 48.9%, and median survival was 11.7 months. The 12-month progression-free survival rate was 18.3%, with a median survival time of 7.1 months. Vascular endothelial growth factor and platelet-derived growth factor levels revealed no correlation with response, overall survival, or progression-free survival. Given these findings, phase 3 evaluation of bevacizumab is warranted.

Vandetanib (ZD6474), a small molecule inhibitor of the tyrosine kinase domain of the VEGF receptor and EGFR, was evaluated as a maintenance therapy in a double-blind randomized phase 2 trial in patients with SCLC who had attained complete or partial response to standard chemotherapy. Of 107 patients enrolled, 46 (43%) had LD and 61 (57%) had ED. The overall survival was 10.6 months in the vandetanib arm and 11.9 months in the placebo arm. No difference in progression-free and overall survival was observed. Of patients receiving vandetanib, those with LD were found to have longer overall survival and those with ED shorter overall survival than patients receiving placebo.¹²⁶

Thalidomide, a pleiotropic agent with potent antiangiogenic effect via reduced tumor production of VEGF and basic fibroblast growth factor (FGF2, formerly BFGF),¹²⁷ has also been studied in SCLC. Despite promising results

in early-phase studies, results from several phase 3 trials were disappointing. Pujol et al¹²⁸ randomized 92 patients with ED-SCLC responding to 2 cycles of cisplatin, etoposide, cyclophosphamide, and epirubicin to 4 additional chemotherapy cycles plus 100 mg/d of thalidomide or placebo until disease progression or unacceptable toxicity. The lack of statistical significance for survival outcome was attributed to low accrual rate leading to an underpowered study that closed at approximately 50% of the estimated sample size. Poor toleration of long-term thalidomide therapy led to poor adherence or short treatment duration and ultimately to only a transient survival benefit, at best. Exploratory analyses showed that patients with performance status of 1 or 2 had slower disease progression (hazard ratio, 0.54; $P=.02$), but this benefit did not reach statistical significance for the whole population (hazard ratio, 0.74; $P=.15$). A larger European phase 3 trial of 720 patients randomized to receive up to six 3-week cycles of once-weekly carboplatin and etoposide with placebo or 100 mg/d of thalidomide followed by up to 2 years of maintenance with placebo or thalidomide did not show any difference in the survival outcomes between the 2 groups. There was also no evidence of benefit in the subgroup analysis.¹²⁹

Other novel agents being evaluated in phase 2 trials include cediranib (ZD2171) and sunitinib. Both agents show potent inhibition of FLT1 (formerly VEGFR1), KDR (formerly VEGFR2), c-kit, and PDGFRB. Cediranib is being tested as a single agent in patients with previously treated ED-SCLC in the California Cancer Consortium trial PHII-64. Sunitinib is being evaluated in combination with first-line chemotherapy using EP in ED-SCLC. Inhibitors of c-met are in early-phase clinical development and testing in SCLC warrants exploration.

Immunotherapy. The identification of unique tumor-associated antigens and demonstration of the feasibility of targeting cell surface antigens in various tumor types have led to clinical investigations of immunotherapeutic approaches. Monoclonal antibodies or vaccines have been developed to target cell surface antigens, such as glycolipids (eg, GD2, GD3, GM2, fucosyl GM1, sialyl Lewis x, globoH, and polysialic acid) and CD56 that are abundantly expressed in SCLC.

An anti-idiotypic antibody, BEC2 mimics GD3 ganglioside. In conjugation with bacille Calmette-Guérin, BEC2 was studied as adjuvant therapy in a phase 3 randomized trial in patients with LD-SCLC with clinical response to 4 to 6 cycles of multiagent chemotherapy and TRT. No difference in overall or progression-free survival was noted; however, data suggested improved survival in patients with an immunologic response.¹³⁰

The initial data from a phase 2 study of HuN901-DM1 (also known as BB-10901), an immunoconjugate of hu-

manized anti-CD56 antibodies linked to maytansinoid 1, a microtubule-depolymerizing compound, showed promising clinical activity and safety in the first 14 patients enrolled with relapsed SCLC. Mature results of this study are much awaited.^{131,132}

A vaccine consisting of dendritic cells transduced with wild-type *TP53* was tested in patients who had completed conventional cytotoxic chemotherapy for ED-SCLC.¹³³ Despite induction of antigen-specific immunity, the objective response rate from vaccine therapy was disappointing. Interestingly, most vaccinated patients had objective clinical responses to second-line chemotherapy. Whether vaccine therapies are best used before, after, or concurrently with chemotherapy warrants further investigation.

CONCLUSION

Small cell lung cancer remains a therapeutic challenge despite high initial responses to chemotherapy and radiotherapy. The 5-year survival is 15% to 25% for patients with LD-SCLC and less than 1% for patients with ED-SCLC. Concurrent chemoradiation therapy in patients with LD-SCLC and PCI are the primary advances made in therapy during the past decade. The fact that several promising molecularly targeted agents have not shown adequate activity in the clinical setting does not spell the doom of novel targeted therapies for SCLC; instead, it shows that, however rational our approaches to therapy, medicine remains an empirical process. Nevertheless, a better understanding of SCLC biology and better preclinical models of SCLC are needed to improve the therapies available for this challenging disease.

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The Symposium on Solid Tumors will continue in the April issue.