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STATE-OF-THE-ART IN THE MANAGEMENT OF CANCER

LUNG CANCER — PART III
SMALL CELL LUNG CANCER-EPIDEMIOLOGY, TUMOR MARKERS, STAGING, PROGNOSIS, DISEASE MONITORING, AND CURRENT TREATMENT STRATEGIES

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Small-cell lung cancer (sclc), a subtype of primary lung cancer, is a rather rare but devastating disease with an overall 5-year survival estimated at about 3%. Although sensitive to chemotherapy, sclc is associated with a very high rate of recurrence of resistant disease within months after an initial favorable response. Newer multimodality and second-line therapies may have somewhat improved outcomes in sclc, but the benefits only translate into adding a few months with a cure nowhere in sight. Novel drugs and vaccines under development to treat lung cancer, in general, and sclc, in particular, will be presented in an upcoming issue of FUTURE ONCOLOGY.

EPIDEMIOLOGY

Small cell lung cancer accounts for about 20% of all primary lung cancer in the USA (Exhibit 1), and is most commonly diagnosed in men than women. It is comprised of three separate histologies, oat cell or small cell type (90%), intermediate type (5%), and mixed type (5%) that comprises both sclc and lung cancer of another histologic subtype. Of the different lung cancer subtypes, sclc is most closely associated with cigarettes, with over 95% of patients having a smoking history. Other environmental toxins or noxious inhalants may increase this risk.

Sclc is a subset of neuroendocrine carcinomas, which also include bronchial carcinoids, and well differentiated neuroendocrine carcinomas. Carcinoids are tumors of low metastatic potential which can occur in virtually any visceral organ. They are estimated to account for about 2% of primary lung cancer (Matthew H, etal, NEJM, 18 Mar 1999;340(11):858-68). These tumors often secrete neuroendocrine peptides which cause flushing, diarrhea and other symptoms in most patients. Well differentiated neuroendocrine lung carcinomas (also termed atypical or malignant carcinoids) appear to be of intermediate malignant potential. They occur primarily in cigarette smokers, but metastasize much less frequently, and the surgical cure rate approaches 50% in limited-stage disease. There is increasing evidence that the diverse histologic subtypes of bronchogenic carcinoma may all arise from the same epithelial cell lining the respiratory tract.

Rates of sclc vary around the world based on smoking habits of men and women. However, for the purposes of this report we have assumed a standard rate of 20% in the developed world comprised of Europe, excluding the former USSR, North America and Japan (Exhibit 2).

TUMOR MARKERS

Both molecular and neuroendocrine markers are being investigated in sclc (see Exhibit 3). These markers may prove useful in the diagnosis, prognosis and monitoring of sclc, and may also serve as therapeutic targets.

Oncogenes and Tumor Suppressor Genes

Despite extensive research into the biology of lung cancer, the basic molecular defect is not well understood. Numerous genetic changes have been observed in lung cancer cells as well as in lung cancer tissue *in vivo*, and carcinogenesis probably represents a multistep process involving several of these changes.

The most common chromosomal abnormality, present in over 90% of cases of sclc, are allelic losses on the short arm of chromosome 3 that may result in the loss of several tumor suppressor genes. Deletions in chromosome 3p occur early in the course of the disease while abnormalities in chromosomes 5q and 18q are noted during disease progression.

Neuroendocrine Markers

In addition to genetic mutations which affect cell cycle, growth and apoptosis, sclc may also produce numerous autocrine growth factors, among them neuron-specific enolase (NSE), gastrin-releasing peptide (GRP), insulin-like growth factor I (IGF-I), and arginine vasopressin (Exhibit 3).

DIAGNOSIS, STAGING, PROGNOSIS AND DISEASE MONITORING

Sclc typically presents as a centrally located lung tumor with mediastinal and extrathoracic spread. After identifying an abnormality, a diagnosis is made by histologic confirmation of malignancy in tumor or sputum samples. Patients usually undergo bronchoscopy, bronchoalveolar lavage, and mediastinoscopy (if necessary), to obtain sample tissue, and to detect presence of cancer spread to regional lymph nodes. If the suspected lesion is peripheral, or otherwise inaccessible by bronchoscopy, a needle biopsy, open lung biopsy, or (increasingly) video-assisted thoracoscopic surgery (VATS), is used to obtain a tissue sample. If the primary lesion is small enough, it may be resected entirely via VATS with minimal morbidity.

The diagnosis of sclc is based primarily on histology, characterized by small cells with scant cytoplasm, frequent mitoses, and "crush artifact". Staining for neuroendocrine markers such as NSE, may support the diagnosis, but is not specific for sclc. Needle biopsy is frequently used to obtain tissue in peripheral lung lesions, but pulmonary carcinoid tumors can be mistakenly diagnosed as sclc because of crush artifact associated with needle biopsies. The diagnosis of sclc in a solitary pulmonary nodule (SPN) by needle biopsy is confirmed by obtaining further tissue if there is any question.

Clinically, sclc, as a neuroendocrine tumor that ectopically produces neuroendocrine or hormonal polypeptides, is associated with a high incidence of paraneoplastic syndromes which distinguishes it from nsclc. Inappropriate secretion of antidiuretic hormone (SIADH) that occurs in approximately 40% of cases, and ectopic production of atrial natriuretic peptide (ANP), may cause hyponatremia and hypotension, respectively. Ectopic production of adrenocorticotrophic hormone (ACTH), occurring in about 30% of cases, may give rise to hypertension, hyperglycemia, or even psychosis, but often it is not associated with the typical moon facies and obesity seen with Cushing's disease. Ectopic production of other polypeptides such as vasoactive intestinal peptide (VIP), human growth hormone (hGH), calcitonin or vasopressin, to name a few, may all cause symptoms. However, hypercalcemia, a paraneoplastic syndrome associated with some solid tumors, is not typically seen in sclc.

In addition to paraneoplastic syndromes associated with increased hormone production, there are a series of syndromes which are related to autoantibodies. It appears that in some patients, the immune system generates antibodies against the tumor, and some of these antibodies can cross-react with normal tissue. Since sclc is of neuroendocrine origin, many of these antibodies recognize neural tissue. Syndromes associated with autoantibodies include a myasthenia gravis-like syndrome (Lambert-Eaton syndrome), cerebellar degeneration, encephalitis, autonomic dysfunction, and retinopathy. Most of these syndromes are rare, except for Lambert-Eaton which occurs in 5% of patients with sclc. Patients with Lambert-Eaton syndrome present with progressive weakness. The distinguishing feature of this syndrome is that there is increasing strength of muscle contraction upon repetitive stimulation.

Once a diagnosis of sclc is established, the extent of disease should be determined, because prognosis and therapy are dependent on disease stage. Sclc is divided into either limited- or extensive-stage disease (Exhibit 1). In patients with limited-stage sclc the tumor is confined to one hemithorax, and can be encompassed within a field of radiation. Extensive disease involves bilateral and/or metastatic disease. At presentation, one third of patients are found to have limited-stage sclc, and the remainder have extensive-stage. Metastatic sites at diagnosis include, most commonly, bone (30%), liver (25%), bone marrow (20%), brain (15%), and adrenals (10%).

Initial staging studies involve a chest CT scan that encompasses the liver and adrenal glands, a head CT scan, bone scans, and routine blood tests. If these studies indicate limited-stage disease, then bone marrow aspirate and biopsy should be performed as a final staging procedure. However, routine use of bone marrow aspiration and biopsy as part of the initial sclc work-up is controversial. If the

blood counts and serum lactate dehydrogenase (LDH) are normal, the risk of bone marrow involvement is low (<5%), and the bone marrow studies may be omitted. However, even in these cases, bone marrow aspiration may upstage as many as 10% of patients. Patients with malignant pleural effusions are usually classified as having extensive-stage disease.

Supraclavicular lymph node (SCLN) involvement in limited-stage sclc does not appear to be a significant prognostic contributor as was confirmed by Cox modeling of records of 1,370 patients with sclc who participated in four consecutive clinical trials. The relationship of SCLN involvement and outcome was as follows:

	Limited-stage Disease		Extensive-stage Disease		All Stages	
	SCLN	No SCLN	SCLN	No SCLN	SCLN	No SCLN
Number of patients (#)					234	1,136
Median survival (days)					258	297
Metastasis at baseline					169	65
Number of patients by stage and SCLN involvement	65	529	169	604		
Median survival (days)	332	375	228	244		
2-year survival rates (%)	12	17	4	2		

As expected, SCLN correlated highly with extensive (metastatic) sclc, explaining its overall prognostic value, but was only a minor poor prognostic factor in limited-stage disease (Urban T, etal, Chest, Dec 1998;114(6):1538-41).

Serum Markers

As a "neuroendocrine tumor," sclc often ectopically produces neuroendocrine or hormonal polypeptides. These biomarkers have been shown to correlate with the extent of disease and response to therapy in individual cases. Also, a majority of patients with sclc have normal CEA, but significantly elevated CEA is associated with distant metastases. In general, however, the spectrum of biomarker expression differs from tumor to tumor, and no single marker for all sclc has yet been identified. Biomarkers in the diagnosis, prognosis and monitoring of sclc remain investigational.

In a study combining several imaging modalities and tumor markers to distinguish between benign and malignant SPN, tumor markers used alone or in combination with imaging, did not result in additional benefits, in terms of sensitivity and accuracy, as compared to the diagnostic imaging methods alone. Specificity and sensitivity of the various methodologies employed on 104 consecutive cases (malignant=81, benign=23) was as follows:

Methodology	Sensitivity (%)	Specificity (%)	Accuracy (%)
Chest radiography	64.2	82.6	
Spiral computed tomography (SCT)	88.9	60.9	
High-resolution (HR) CT	91.4	56.5	
Carcinoembryonic antigen (CEA)	27.2	87.0	40.4
Cytokeratin marker (cyfra 21-1)	19.8	100.0	37.5
Neuron-specific enolase (NSE)	13.6	100.0	32.7

A precise morphological assessment of the periphery of the pulmonary lesion and the adjacent visceral pleura was necessary to distinguish malignant from benign nodules using chest radiography, SCT and HRCT. The tumor markers cyfra 21-1 and NSE exhibited a far superior specificity compared with the imaging methods (Seemann MD, etal, Eur J Med Res, 25 Aug 1999;4(8):313-27).

In a review of the literature for the best documented serum markers with prognostic value, independent of the usual radioclinical and histologic parameters of sclc, NSE

Exhibit 1
Incidence and 5-year Survival Estimates of Patients with Small-Cell Lung Cancer in the USA

Staging		Incidence in 1999		Survival	
Stage	Definition by the Veterans Administration Lung Cancer Study Group	Cases (#)	Total (%)	5-year Survival (#)	Total (%)
Limited-stage Disease	Tumor confined to 1 hemithorax and its regional hilar or mediastinal lymph nodes, with or without ipsilateral supraclavicular node involvement that can be encompassed in one radiation portal	8,580	25.0	686	8.0
Extensive-stage Disease	Disease that cannot be encompassed in one radiation portal; presence of ipsilateral malignant effusion	25,740	10.0	386	1.5
All Stages		34,320	100.0	1,072	3.1

appeared to exhibit a pretherapeutic prognostic value better than LDH and perhaps better than serum sodium, biocarbonates, and uric acid. However, based on only a few reports, thymidine kinase (TK), tissue polypeptide antigen (TPA), cyfra 21-1 and/or interleukin-2 (IL-2) secretion might have better pretherapeutic prognostic value than NSE. Despite all these findings, based on currently available data, it would appear that is not necessary to routinely measure serum tumor markers, and in particular NSE, for the prognostic evaluation of sclc. Iterative blood assays to follow therapeutic effects in patients with sclc have not been proven to provide independent prognostic information (Watine J and Charet JC, Presse Med, 25 Sep 1999;28(28):1541-6).

Neuron-specific enolase (NSE), an isoform of the dimeric glycolytic enzyme enolase, is predominantly found in neurons and neuroendocrine cells and was shown to be a marker for tumors derived from these cells. NSE is the most sensitive tumor marker of sclc at diagnosis.

NSE may be measured using a one-step enzyme immunoassay of the sandwich type, the Cobas Core NSE EIA II, that was developed by Roche Diagnostics (Basel, Switzerland). Cobas Core NSE EIA II is performed on the fully automated Cobas Core immunoassay analyzer with a total assay time of 45 minutes on a 10-microliter serum sample (Sterk M, etal, Anticancer Res Jul-Aug 1999;19(4A):2759-62). NSE is also measured using immunoradiometric assay (IRMA).

When the predictive value of serum NSE, in terms of CR and survival, measured before and after one cycle (28 days) of chemotherapy, was assessed in 135 patients with sclc (limited-stage disease=63 and metastatic disease=72), normal serum post-chemotherapy NSE value was a strong, independent early predictor of both CR and survival. Serum NSE levels were raised in 120 patients (88%) prior to therapy but the probability of a normal NSE value post-chemotherapy was not affected by the baseline value. Disease extension, performance status (PS), post-chemotherapy NSE levels, and CEA levels were predictive for survival, whereas age, gender, plasma sodium, serum protides, and baseline NSE levels were not. Median survival time (MST), and 2-year overall survival, were 15.3 months and 21%, respectively, when post-chemotherapy NSE levels were normal, and 8.1 months and 15%, respectively, when they were not. According to multivariate analysis, only PS disease stage, and post-chemotherapy NSE levels were independent prognostic parameters for survival. A simple prognostic index was developed using these 3 variables. Limited-stage disease, a normal value 28 days after chemotherapy (D28-NSE), and a normal CEA value prior to therapy, were the only parameters predictive for CR in the univariate analysis, and D28-NSE and disease extension were found to be independent variables in multivariate analysis. CR occurred in 62% with a normal post-chemotherapy NSE value, but in only 34% in the opposite case. Therefore, measuring NSE post-chemotherapy may provide a simple means for use in the clinic and in research, in association with an assessment of disease extension and PS, to predict the outcome of patients with sclc (Fizazi K, etal, Cancer, 15 Mar 1998;82(6):1049-55).

Pro-gastrin-releasing peptide (ProGRP), a more stable precursor of GRP, exhibits a very high specificity and good sensitivity for sclc, and may be used to diagnose this disease in patients with lung tumors of unknown origin as well as monitor therapeutic efficacy. Using an enzyme immunoassay, the sensitivity of ProGRP was compared with NSE, cyfra 21-1 and CEA in the sera of 272 patients with histologically confirmed lung cancer (sclc=87 and nsclc=185). At a specificity of 95%, ProGRP and NSE exhibited comparable sensitivities (47% versus 45%) in sclc, and a clear additive sensitivity of about 20% (Stieber P, etal, Anticancer Res, Jul-Aug 1999;19(4A):2673-8).

Chromogranin A (CgA), a protein present in neuroendocrine vesicles, is released into the circulation of sclc patients. When the plasma of 150 newly diagnosed patients with sclc was tested for the presence of chromogranin A (CgA) using a two-site EIA assay, 37% of samples exhibited elevated pretreatment values that were significantly related to disease stage. Moreover, multivariable analysis involving 9 known prognostic factors indicated that PS was the most influential prognostic factor, followed by stage of disease, CgA and LDH. Based on these four pretreatment features, a simple prognostic index was used that separated patients into three groups with significant different prognosis with MST of 424 days (311-537), 360 days (261-459) and 174 days (105-243) after a followed-up of a minimum of 5 years (Drivsholm L, etal, Br J Cancer, Oct 1999;81(4):667-71).

Multiple serum markers are being investigated as diagnostic, prognostic and disease monitoring options in sclc. To date, known tumor markers have proven to be of minor value in the primary diagnosis and staging of lung tumors but may play a role in prognosis and disease monitoring.

When the clinical usefulness of measuring serum NSE, and tissue polypeptide-specific antigen (TPS) using an immunoradiometric assay, and thymidine kinase (TK) using a radioenzymatic assay, was investigated in 41 patients with newly diagnosed sclc (limited-stage=11 and extensive-stage=30), none distinguished between limited- and extensive-stage. Among 9 patients treated with 2 courses, and 18 patients with 3 or more cycles of chemotherapy, consisting of IV carboplatin (300 mg/m^2) on the first day, and IV etoposide (120 mg/m^2) from day 1 to day 3, every 3 weeks, there were 18 PR and 9 CR. NSE and TPS were significantly more often abnormal than TK, either at the time of diagnosis or in patients experiencing PR or in non-responders. In relation to chemotherapy response, NSE and TPS serum patterns were shown to be more reliable than TK in PR and NR patients. No significant difference was observed between serum NSE and TPS patterns. Serum NSE and TPS seem to be more useful in

Exhibit 2
Estimated Incidence of Small-Cell Lung Cancer in the Triad in 1999

Region	Incidence of Primary Lung Cancer (#)	Incidence of Small Cell Lung Cancer (#)[1]
Europe[2]	386,529	77,305
North America	189,706	37,941
Japan	45,842	9,168
Triad, Total	622,077	124,414

[1] Based on 20% of total accross the board

[2] Excluding the former USSR; for a detailed country by country incidence estimate, see FO þ 1047

the diagnosis and follow-up of sclc patients undergoing chemotherapy (Abbasciano V, Cancer Detect Prev 1999; 23(4):309-15).

Measurement of a combination of markers as contributors to clinical decision-making processes with respect to diagnosis and assessment of response to therapy, found that they were clearly inferior to the yield of standard cytopathologic examinations. These conclusions are based on the assessment of cyfra 21-1, measured by an EIA marketed by Boehringer Mannheim/Roche, TPA-M measured by an IRMA provided by Sangtec Medical (Bromma, Sweden), TPS measured by an IRMA, provided by Beki Diagnostics (Bromma, Sweden), CEA and NSE in a series of 381 consecutive patients with lung tumors and benign pulmonary diseases. Although the diagnostic value of these tumor markers was minimal, detection of increasing marker levels may contribute to clinical decision making, at least in helping to decide which patients should no longer treated by ineffective and toxic drugs. In sclc, progressive disease was most effectively indicated by NSE (Ebert W, Anticancer Res, Jul-Aug 1997;17(4B):2875-8).

In a similar study designed to assess the degree of useful information of multiple markers, 184 patients suspected of having lung cancer and who underwent diagnostic bronchoscopy between July 1994 and May 1995, were tested for cyfra 21.1, detected by antibodies BM 19-21 and KS 19-1, CEA, NSE, TPS, and TPA. Of these patients, 87 were subsequently found to have intrathoracic malignancy, 93 benign lung disease and 4 were lost to follow-up. Cyfra 21.1 was the most efficient marker in differentiating benign from malignant disease, with a sensitivity of 54% and a positive predictive value of 96%. Among patients with a negative bronchoscopy, 37 subsequently turned out to have malignant disease. Either cyfra 21.1 or CEA was elevated in 26 (70%) of these patients. Multivariate analysis showed that only cyfra 21.1 and CEA contributed significantly to the discriminatory power of the data. Therefore, measurement of cyfra 21.1 and CEA at the time of bronchoscopy significantly increases the diagnostic yield in this population; this approach is especially useful in patients in whom tumor biopsy was not possible at bronchoscopy (Bates J, etal, Eur Respir J, Nov 1997;10 (11):2535-8).

In order to identify potential markers of prognosis, variables such as tumor, node, metastasis status, PS, body weight loss, blood leukocyte count, serum sodium, serum albumin, LDH, alkaline phosphatase, serum NSE, serum TPS, and serum cyfra 21-1, were established prior to treatment in 99 patients with sclc. Ten weeks after treatment, significant prognosticators of poor survival were lack of CR [hazard ratio (HR)=2.04], weight loss (HR=1.76), high serum LDH level (HR=1.64), and high serum TPS level (HR=2.47). A high serum TPS level was the only factor among those studied that predicted lack of achieving CR (odds ratio=0.39) (Ray P, etal, Cancer Detect Prev 1998;22(4):293-304).

In another study, investigators attempted to establish the relationship between risk of death with marker level and disease state during chemotherapy. For instance, if marker levels were altered during chemotherapy, i.e., if they were reversible disease indicators, it may be possible to link changes in marker levels to the effectiveness of the treatment, and arrive at a reliable patient prognosis. In order to test this hypothesis, tumor markers such as serum NSE, cyfra 21-2 and TPS, were used to monitor disease status during cisplatin-based chemotherapy administered to 52 patients with sclc. Results suggest that an increase in serum NSE level or a lack of patient response at any time during follow-up is strongly associated with a worse prognosis. However, a reversion to a low mortality risk state was possible (Boher JM, etal, Br J Cancer, Mar 1999;79(9-10):1419-27).

Angiogenesis Markers

Angiogenesis factors may also have prognostic significance in sclc. When samples from 46 patients (limited-stage=29, extensive-stage=17) were tested for the presence of matrix metalloproteinase (MMP)-1, -2, -3, -9, -11, -13, and -14 and tissue inhibitors of metalloproteinases (TIMP)-1, -2, -3, and -4, positive immunohistochemistry (IHC) staining was evident for MMP-1 and -9 in 60% to 70% of tumor cells, and for MMP-11, -13, and -14 and TIMP-2 and -3 in 70% to 100%. Stromal staining of TIMP-1 to -3 was present in less than 30% of specimens while it was 39% for TIMP-4. Based on multivariate analysis, only stage and decreased tumor expression of TIMP-1 were significant for response, and tumor stage, weight loss, and high tumor cell expression of MMP-3, -11 and -14, for survival. MMP and TIMP expression did not differ significantly between stages. Increased tumor expression of MMP-3, -11, and -14 were independent negative prognostic factors for survival (Michael M, etal, J Clin Oncol, Jun 1999;17(6):1802).

Exhibit 3
Selected Tumor Markers Associated with Small-Cell Lung Cancer

Markers	Comments
	Molecular Markers
c-kit	At least 70% sclc tumors ectopically express high levels of the c-kit receptor tyrosine kinase, and stem cell factor (SCF), its ligand (Krystal GW, etal, Cancer Res, 15 Oct 1998;58(20):4660-6)
c-myc	Amplification of the myc proto-oncogene occurs in 25% to 40% of sclc, and may be associated with a shortened survival
c-raf-1	Raf-1 proto-oncogene causes growth suppression and alteration of neuroendocrine markers in the DMS53 human sclc cell line; in DMS53, activated ras expression induced increased neuroendocrine differentiation and decreased cell proliferation; DMS53 cells underwent differentiation and G1-specific growth arrest in response to ras/raf/mitogen-activated protein kinase (MEK)/mitogen-activated protein kinase (MAPK) pathway activation; activation of the raf/MEK/MAPK signaling pathway can reduce growth of sclc cells, and may be clinically efficacious in some settings (Ravi RK, etal, Am J Respir Cell Mol Biol, Apr 1999;20(4):543-9); c-raf-1 simian virus 40 large tumor antigen-immortalized human bronchial epithelial cell transfectants, and c-raf-1 and c-myc double transfectants, were relatively radioresistant compared with c-myc transfectants, or controls (Pfeifer A, etal, Biochem Biophys Res Commun, 18 Nov 1998;252(2):481-6)
Fragile histidine triad (fhit) tumor suppressor gene at 3p14.2	Fhit was found to be abnormal in approximately 80% of sclc tumors, and loss of fhit function may result in stimulation of DNA synthesis and proliferation
Matrix metalloproteinases (MMP) and and their tissue inhibitors (TIMP)	MMPs and TIMPs are widely expressed in sclc; MMP-1 and -9 were expressed in 60% to 70% of sclc, and MMP-11, -13, and -14 and TIMP-2 and -3 in 70% to 100% of tumor cells; stromal staining of TIMP-1 to -3 was present in <30% of specimens (Michael M, etal, J Clin Oncol, Jun 1999;17(6):1802)
p16 (MTS-1/ CDKN-2/INK4A) tumor suppressor gene on chromosome 9p21	While pRb and cyclin D1 staining was negative in 161 specimens of sclc, expression of p16 was observed in 153 samples (95%) while a very weak p16 staining was observed in 5/20 nsclc samples, indicating different mechanisms in the tumorigenesis of sclc and nsclc (Yuan J, etal, J Pathol, Nov 1999;189(3):358-362)
p53 tumor suppressor gene on chromosome 17p	Deletions of 17p have been noted in 80% of sclc; mutation in lung cancer attributed to smoking is usually a guanine-to-thymidine (G-to-T) transversion; radon appears to mutate p53 differently; in a study of underground miners with lung cancer, none of the p53 mutations found in 37%, were of the G-to-T transversion type; the importance of the p53 gene in sclc pathogenesis is underscored by the observation that mice genetically engineered to lack p53 expression develop sclc at a very high frequency; p53 mutations between exons 5 and 9 were found in 37 (57%) of 65 patients (37 males and 28 females) with primary sclc tumors; none of the tumors from females contained more than one mutation, whereas four of the tumors from males contained more than one mutation with the most common mutation in this population being adenosine-to-guanine transition (27%), followed by G-T transversion (17%) and guanine-to-adenosine transition (12%); gender difference in p53 mutational rate may suggest that a higher proportion of sclc in females may develop through pathways not involving p53 mutations (Tseng JE, Cancer Res, 15 Nov 1999;59(22):5666-70)
Ras family	Ras mutations, although common in nsclc, are rarely found in sclc, suggesting that ras activation may not confer a growth advantage in these cells
Retinoblastoma (rb) gene	The rb gene expresses Rb protein that acts as a tumor suppressor; in more than 10% of sclc rb gene expression is either absent or abnormal (hypophosphorylated or with deletions or mutations of the pocket domain)
Telomerase	A suppressor gene for telomerase may lie on chromosome 3p in neuroendocrine tumors of the lung, and telomerase expression may be a useful prognostic marker for sclc (Rathi A, etal, AACR98, Abs. 2390:350)
	Neuroendocrine Markers
Arginine vasopressin (AVP)	Arginine vasopressin is detected in up to 67% of sclc tumors whereas normal physiological expression is essentially restricted to the hypothalamus; a 65-bp AVP minimal promoter fragment is sufficient to restrict activity to sclc *in vitro*, raising the possibility of targeting AVP by gene therapy in sclc (Coulson JM, etal, Br J Cancer, Aug 1999;80(12):1935-44)
Cholecystokinin (CCK)-B/gastrin receptors	CCK-B/gastrin receptors were found frequently in sclc (57%) but rarely expressed in nsclc (Reubi JC, etal, Cancer Res, 1 Apr 1997;57(7):1377-86)
Chromogranin A	Chromogranin A (CgA) is a protein present in neuroendocrine vesicles that is released into the circulation; sclc tumors expressing CgA seem to behave more aggressively and respond better to chemotherapy

— continued on next page

Cytokeratin marker (cyfra 21-1)	Cyfra 21-1 secretion may be a better pretherapeutic prognostic factor than NSE in sclc; cyfra 21-1 exhibited a sensitivity of 19.8% and a specificity of 100.0% (accuracy of 37.5%) in the identification of malignant solitary pulmonary lesions (Seemann MD, etal, Eur J Med Res, 25 Aug 1999;4(8):313-27)
Cytoplasmic secretory granules	Characteristic of sclc
Gastrin-releasing peptide (GRP)	GRP, the mammalian counterpart of amphibian bombesin, is expressed in about 1/3 of sclc; proGRP, a more stable precursor of GRP, demonstrated a very high specificity, and good sensitivity for sclc and, therefore, may enable diagnosis of sclc in patients with lung tumors of unknown origin and be an indicator of therapeutic efficacy
Insulin-like growth factor I (IGF-I), IGF-II and IGF binding protein (BP)-3	IGF-I is a polypeptide that is mitogenic for a variety of cell types secreted by both sclc and nsclc
Interleukin (IL)-2	IL-2 secretion may be a better pretherapeutic prognostic factor than NSE in sclc
Lacto-dehydrogenase (LDH)	May have a predictive value in sclc
Leu-7	The natural killer cell surface associated antigen (Leu-7) was expressed specifically only by sclc and not nsclc cell lines (Poola I and Graziano SL, J Exp Clin Cancer Res, Jun 1998;17(2):165-73)
Muscarinic acetylcholine receptor (mAChR)	Direct activation of PKC or stimulation of M3 subtype of mAChR, that in turn result in increased PKC activity, increases the binding activity of β1-integrins, resulting in increased adhesion of sclc cells to ECM proteins; the ability of mAChR to regulate sclc proliferation and adhesion suggests that activation of these receptors may be used to alter sclc tumorigenesis and metastasis (Quigley RL, etal, Chest, Sep 1998;114(3):839-46)
Neurone specific enolase (NSE)	NSE may have a pretherapeutic prognostic value in sclc, better than LDH and, perhaps, better than serum sodium, biocarbonates, and uric acid, but the superiority of NSE over serum albumin has not been proven (Watine J and Charet JC, Presse Med, 25 Sep 1999;28(28):1541-6)
Ranatensins (neuromedin B, neuromedin C, litorin)	Neuromedin B and its receptor which share significant homology with GRP and its receptor, are also expressed in many sclc cell lines; they may bind to each other's receptor at different affinities and, therefore, despite successful inhibition of GRP receptors, sclc growth may still be stimulated by neuromedin B
Thymidine kinase (TK)	TK secretion may be a better pretherapeutic prognostic factor than NSE in sclc
Tissue polypeptide antigen (TPA)	TPA secretion may be a better pretherapeutic prognostic factor than NSE in sclc
Transferrin (TF)	In a study performed in Sweden, a significant decrease in frequency of the TF variant C3 was observed in sclc and squamous epithelial lung cancer but not in adenocarcinoma, suggesting a protective effect of TF C3 in the former; however, this relationship was not consistent among populations from different regions of the country indicating that the association between TF C alleles and lung cancer may be secondary and dependent on linkage disequilibrium with allelic variants of newly discovered tumor-associated genes known to map to the same position (3q21) as TF, such as NCK and H-RYK (Beckman LE, etal, Oncology 1999;56(4):328-31)
Vasoactive intestinal peptide (VIP)	The gene encoding the human type I VIP receptor (hVR1), also termed the type II pituitary adenylyl cyclase-activating peptide (PACAP) receptor, was cloned, characterized, and localized to the short arm of human chromosome 3 (3p22), in a region associated with sclc; VIP inhibits proliferation of sclc cells in culture and dramatically suppresses the growth of sclc tumor-cell implants in athymic nude mice (Maruno K, etal, PNAS USA, 24 Nov 1998;95(24):14373-8)

Note: Also see FO, pp 87 and 89

Detection of Tumor Cells in Bone Marrow

Detection of tumor cells in bone marrow may be used to assess disease status, or establish the contamination of bone marrow with such cells in patients undergoing autologous bone marrow transplants (autoBMT). Recently, it has been reported that immunodetection of tumor cells in bone marrow of sclc patients may be far more effective than traditional cytohistologic methods of disease staging and that it may provide clinically valuable data. An immunostaining method combining the alkaline phosphatase-anti-alkaline phosphatase and streptavidin-biotin-alkaline phosphatase complex methods provided the best results in terms of sensitivity and specificity, and of intensity of immunoreaction and absence of staining background. Moreover, bone marrow micrometastases detected by this method were prognostically relevant and identified, among patients with apparently limited-stage disease according to conventional staging procedures, a subgroup with shorter survival (Pelosi G, J Histochem Cytochem, Aug 1999;47(8):1075-88). Detection of malignant cells in the bone marrow may also be important in transplant procedures using autologous hematopoietic cell expansion in

serum free medium, to prevent transferring tumor cells back to the patient (Peters R, etal, ASCO99, Abs. 1885:489a).

Noninvasive Imaging

Bone Scans

Bone scans are traditionally a part of the initial staging and follow-up of sclc. In the search for a lower cost alternative NSE assays were evaluate retrospectively, in 57 patients, as a means of selecting those patients that would go on to bone scans based on abnormal serum NSE levels. Both bone scans and NSE assays were performed in 47 patients referred for initial staging of sclc; NSE levels were normal in 8 but in 2 of these cases (25%) secondary bone localizations with great clinical significance were discovered during the bone scan. During follow-up, 59 bone scans were performed in conjunction with NSE assays; 45 NSE levels were in the normal range whereas 17 (38%) corresponding bone scans were suggestive of bone metastases. In conclusion, because of the frequent occurrence of false-negative results in patients with bone metastases, serum NSE levels proved to be useless in the selection for bone scans of patients suffering from sclc (Gendreau V, etal, Int J Biol Markers, Oct-Dec 1997;12(4):148-53).

Scintigraphy

Scintigraphy is becoming a common procedure in the staging and monitoring of sclc, although it is not part of the standard regimen. Sclc is a particularly attractive target for radioisotope imaging because most tumors (50%- 75%) express receptors for somatostatin, not found in normal lung tissue. In several different studies, the radiolabeled somatostatin analogs ^{111}In-pentetreotide (OctreoScan; Mallinckrodt) and ^{111}In-octreotide detected tumors in 92%-100% of patients tested, and may represent a more sensitive tool to follow disease prior to and after chemotherapy. OctreoScan, a modified version of octreotide (Sandostatin; Novartis) used with gamma scintigraphy/single photon emission computed tomography (SPECT), was approved and launched in the USA in 1994, and was also launched in Europe in 1995 for imaging sclc (see FO, p 90).

High-level expression of the 5 subtypes of the somatostatin receptor (SSTr) on the cell surface of various tumor cells provides the basis for the successful clinical use of radiolabeled ligands for the *in vivo* localization of tumor sites. Although SSTr scintigraphy is highly sensitive in detecting primary sclc, it fails in the detection of metastases and is not, therefore, useful for staging of sclc. However, because somatostatin uptake by the primary tumor is affected by chemotherapy, this technique may be used to monitor disease course. In 100 patients (134 examinations were performed), SSTr scintigraphy visualized the primary tumor with varying degrees of uptake in 96% of cases, but regional and distant metastases were detected in only 60% and 45% of cases, respectively. Among 27 patients examined before and after chemotherapy, uptake of the somatostatin analog by the primary tumor was significantly lower in patients examined during chemotherapy as compared to those examined before treatment, with a significant decrease observed in patients with remission at the time scintigraphy. However, there were no differences in the pretreatment uptake of octreotide by the primary tumor between patients with eventual tumor progression and responders (CR or PR) to subsequent treatment (Reisinger I, etal, J Nucl Med, Feb 1998;39(2):224-7).

A new scintigraphy approach, depreotide injection (P829; NeoTect), developed by Diatide (Londonderry, NH), was approved on August 3, 1999 for imaging somatostatin-bearing pulmonary masses, detected on CT and/or chest x-ray in patients previously diagnosed with sclc, or who are at great risk for the disease. NeoTect is an injectable imaging agent consisting of two active components, a small-molecule synthetic somatostatin-type, receptor-binding polypeptide, and a molecule of ^{99m}Tc. The peptide is designed to adhere to the somatostatin receptor that is present in several types of cancers while ^{99m}TC emits a gamma ray which is detectable by a gamma camera (see FO, pp 345 and 167). Diatide licensed a technology, involving a chemical procedure enabling the production of complex peptides, developed by Frank Robey, from the National Institute of Dental and Craniofacial Research (NIDCR) and has been issued at least 6 USA patents for the technology of coupling technetium with synthetic peptides. In August 1999, Diatide was issued patent #5,932,189, entitled "Cyclic hexapeptide somatostatin analogs", that covers composition and methods of use of somatostatin analogs, highly specific for the somatostatin receptors found on a wide range of tumors, including lung and breast, labeled with a radioisotope. This patent also covers use of the modified analogs for treating disease in both unlabeled and radioiodinated form, and for performing radioisotope-guided surgery.

In August 1998, Diatide received a $2 million milestone payment from Nycomed Amersham for the June 1998 submission of the NDA for NeoTect, but Nycomed Amersham subsequently decided to discontinue funding Diatide's R&D and sold its 1.5 million-share equity in Diatide. The company, however, maintains its marketing agreement with Diatide. In September 1999, Schering AG agreed to purchase Diatide for about $100 million based on $9.50 per common share.

In *in vitro* research, it was shown that ^{99m}Tc-P829 binds with high affinity to many different types of primary and cloned tumor cells. The agent targeted various subtypes of the SSTr, namely SSTr2, the VIP acceptor SSTr3, and SSTr5 which are frequently expressed at high levels on primary tumor cells. (Virgolini I, etal, Cancer Res, 1 May 1998;58(9):1850-9).

For imaging, NeoTect is administered as a peripheral IV injection at a single dose of 15 to 20 mCi containing approximately 50 µg of ^{99m}Tc-radiolabeled depreotide peptide. NeoTect is being promoted as a noninvasive means of differential diagnosis of lung nodules, and as a safe and use-

ful technique with sensitivity comparable to that reported for position emission tomography (PET). Using a combination of NeoTect and SPECT investigators imaged SPN in 30 patients with undeterminate SPN of ≥1 cm and significant risk factors for primary lung cancer. Tissue diagnosis was subsequently established by transthoracic needle biopsy. NeoTect correctly diagnosed 27 of 30 subjects. The specificity of NeoTect was 88% and the sensitivity 93% which compares favorably with the reported results of F-18 fluorodeoxyglucose (FDG)-PET imaging (Blum JE, etal, Chest, Jan 1999;115(1):224-32).

FDA approval was based on results from prospective multicenter phase III clinical trials, reported in May 1998, that enrolled a total of 269 patients by September 1997. The primary endpoint was the agreement of P829 blinded readings with the histopathologic diagnosis concerning the lesion under evaluation. The plan required an agreement rate of approximately 80%. Based on 226 evaluable patients, 112 from study A, and 114 from study B, the agreement rate for malignancy was 76.8% in study A and 81.6% in study B. The agreement of P829 to histopathology on a regional basis was also part of the trial's statistical plan. Because of the complexity of the lung anatomy and the hot spot nature of P829's detection of malignancy, the results did not support precise regional localization of the mass. Thus, the company did not pursue an indication for localization of lung cancer. NeoTect was launched in September 1999 at a cost of approximately $500 per procedure. The test, in addition to sclc, may be applicable in a variety of cancers that express SSTr, and is currently in phase II clinical trials in breast cancer and melanoma. Nycomed filed an MAA for approval in Europe as of November 1998.

In the phase III clinical trial that enrolled 114 patients with SPN, no benign calcification patterns on thoracic CT scan, and no demonstrable radiographic stability, patients were studied with NeoTect SPECT and tissue histology. Histology detected a malignancy in 88 patients with SPN with a mean nodule diameter of 2.8 cm. When compared to histology, NeoTect scintigraphy correctly identified 85/88 with 3 false negatives. There were also 7 false positive results, including 6 patients with granulomatous disease and one with a hamartoma. The sensitivity of NeoTect scintigraphy was 96.6% and the specificity 73.1% (Blum JE, etal, SNM99, Abs. 36). According to results from these trials, imaging using P829 may be an effective alternative to invasive procedures such as needle biopsy or lung surgery in the diagnosis and management of lung cancer.

A related study examined prospective cost savings using NeoTect, by analyzing the same group of 114 patients with SPN. The evaluation, conducted at the UCLA School of Medicine (Los Angeles, CA), compared four diagnostic approaches. Life expectancies of patients were calculated using an established model. The study found that NeoTect could save as much as $1,800 per year of life per patient, with up to $50.4 million potentially saved annually in the USA, compared with CT-based detection approaches (Gambhir S, etal, SNM99, Abs 231).

Another radioimaging approach based on nofetumomab merpentan (Verluma), an immunoconjugate consisting of MAb NR-LU-10 fragment that recognizes a glycoprotein expressed by sclc, linked to ^{99m}Tc, developed by NeoRx (Seattle, WA), failed in the market despite FDA approval in August 1996 to detect extensive disease in patients with biopsy-confirmed, previously untreated sclc. In the third quarter of fiscal 1997 NeoRx received a $4.5 million payment from DuPont Pharmaceuticals, upon FDA marketing clearance of Verluma but, in May 1998, DuPont gave one year's notice of termination of its license agreement involving Verluma. DuPont owned exclusive rights to market Verluma in North America and was required to pay NeoRx royalties on sales.

Various other radiolabeled conjugates to image sclc are actively under investigation, among them radiolabeled peptides targeting cholecystokinin (CKK)-B/gastrin receptor-expressing tumors. CCK-B/gastrin receptors are found in >90% of medullary thyroid tumors (MTC), and in a high percentage of sclc, some ovarian cancers, astrocytomas and possibly in a variety of adenocarcinomas (Behr TM, etal, J Nucl Med, Jun 1999;40(6):1029-44). In a pilot study, investigators at the Department of Nuclear Medicine, Georg-August-University (Gottingen, Germany) demonstrated the feasibility of radiolabeled gastrin-I to target CCK-B receptor-expressing tissues *in vivo* in animals and patients (Behr TM, etal, Eur J Nucl Med 1998;25: 424-430). A new study was undertaken to systematically optimize, in a preclinical model, suitable radioligands for targeting CCK-B receptors *in vivo*. Best tumor uptake and tumor:nontumor ratios were obtained with members of the gastrin family, probably because of their selectivity and affinity for the CCK-B receptor subtype. Pilot therapy experiments in MTC-bearing animals showed significant antitumor efficacy when compared with untreated controls. ^{111}In-labeled diethylene-triamine-penta-acetate derivatives of minigastrin effectively targeted CCK-B receptor-expressing tissues in animals and a healthy human volunteer. These data suggest that CCK/gastrin analogs may be a useful new class of receptor-binding peptides for the diagnosis and therapy of CCK-B receptor-expressing tumors, such as MTC or sclc. Nonsulfated gastrin derivatives may be preferable because of their CCK-B receptor selectivity and, hence, lower accretion in normal CCK-A receptor-expressing organs. Further preclinical as well as clinical studies are ongoing (Behr TM, etal, Clin Cancer Res, Oct 1999;5(10 Suppl):3124s-3138s).

Other imaging agents such as N-isopropyl-p-^{123}I-iodoamphetamine (^{123}I IMP) may also be applicable in imaging sclc (Watanabe N, etal, Lung Cancer 1999 Jul;25(1):1-6). A relationship was also established between ^{99m}Tc tetrofosmin, an imaging conjugate originally designed for myocardial infusion imaging, and accumulation in tumors and response to chemotherapy. Among 20

sclc patients, there was a higher incidence of positive ^{99m}Tc tetrofosmin lung SPECT findings in those with good chemotherapy (93%) response than those with poor response (33%). This correlation may relate to the expression of multidrug resistance (MDR)-mediated P-glycoprotein (P-gp) and multidrug resistance-associated protein (MRP) in patients with untreated sclc. Other prognostic factors (tumor size and stage) did significantly relate to ^{99m}Tc tetrofosmin lung scan findings and chemotherapy responses (Kao CH, etal, Anticancer Res, May-Jun 1999;19(3B):2311-5). Another radioimaging approach with a similar performance to ^{99m}Tc tetrofosmin is ^{99m}Tc sestamibi (Miraluma; DuPont Pharmaceuticals) that was approved by the FDA in May 1997 for planar imaging as a second-line diagnostic approach after mammography to assist in the evaluation of breast lesions in patients with an abnormal mammogram or a palpable breast mass.

Positron emission tomography (PET)

One of the most promising nuclear medicine techniques, FDG-PET scanning, may also be of value in the detection and staging of sclc, and the determination of response to therapy. For a comprehensive review of the role of FDG-PET scanning in oncology, in general, and in lung cancer, in particular, see FO, pp 875-884, 340-342. and 164-165.

The role of FDG-PET in lung cancer is multifaceted, and this imaging modality may prove indispensable in the optimal management of this disease. In sclc, FDG-PET is used in the differential diagnosis of SPN where its specificity is at least 81%, and specificity at least 73%, and both may be as high as 100%. In this application, FDG-PET is as accurate as transthoracic needle aspiration without its complications, such as pneumothorax. Other applications of FDG-PET include hilar evaluation and mediastinal staging where it was shown to be superior to CT. Whole body FDG-PET may also accurately detect extrathoracic metastases. FDG-PET may also provide more accurate information than CT or x-ray as to disease status during and after therapy. Early detection of recurrence using this imaging modality may extend survival. Also CR, confirmed by FDG-PET, correlates with complete eradication of local tumor. Monitoring disease status using FDG-PET may also determine the length of treatment required to achieve a lasting CR.

TREATMENT OF PRIMARY SCLC

Left untreated, sclc is one of the most aggressive of any malignancy, with an MST of 2-4 months. Unlike nsclc, sclc almost always presents with metastatic spread (often with occult metastases). But like nsclc, prognosis depends primarily on the extent of disease spread. For the one third of patients with limited-stage disease confined at diagnosis to one hemithorax, the mediastinum, or ipsilateral supraclavicular lymph nodes, MST is 10-16 months. Approximately 10%-25% of treated patients will be alive at 2 years, and about 50% of these will survive beyond 5 years. These long-term survivors die more often from concurrent disease, and second cancers than from recurrence of sclc. Patients with extensive-stage disease have a worse prognosis, with an MST of 9-12 months and a maximum survival of only 2% beyond 2 years.

In addition to limited-stage disease, other favorable prognostic factors in sclc include good physical condition and, for unknown reasons, female gender. Age does not seem to be a significant factor, although some elderly patients treated with "mild" chemotherapy may not survive as long because the treatment is not sufficiently cytotoxic for tumor eradication.

Currently, standard therapeutic approaches (Exhibit 4) rarely influence survival outcomes. Choice of therapy depends on disease stage, a patient's functional status, and concurrent diseases. Sclc, although often widely disseminated at presentation, is extremely sensitive to chemotherapy. Therefore, most patients are treated with chemotherapy. Surgery is rarely indicated, irrespective of disease stage. In patients with an SPN and negative staging studies, resection may be pursued, but systemic treatment is still needed. Because standard therapy in extensive-stage sclc has not resulted in favorable outcomes, clinical trials using novel combinations/agents are recommended in the majority of suitable patients.

USA sclc populations treated by first-line, or second-line chemotherapy and/or radiotherapy, are estimated in Exhibit 5. The totals reflect both monotherapies and concurrent multimodality regimens, with the latter, if feasible, being the chosen approach. Because sclc is very chemosensitive, responses to first-line chemotherapy/multimodality therapy tend to be very high at 50% to 60%; sometimes the overall response rate reaches 100%. However, most of these responses are short-lived, an MST of 7 to 11 months. In view of these dismal outcomes, novel second-line approaches are providing new hope to those who relapse with sensitive disease, and will undoubtedly increase the number of sclc patients treated aggressively after relapse.

Despite an accelerated clinical trials program in sclc, results have been disappointing. A retrospective review of a series of 594 consecutive patients with sclc, treated at the National Cancer Institute in 20 years (between April 1973 and April 1993), was undertaken to assess outcomes in toxicity and duration of survival related to various treatment regimens. Patients were followed for at least 2 years. When the outcome of patients with limited- and extensive-stage sclc, treated during the first decade of the study (1973 through 1983) with cyclophosphamide-based regimens was compared with that of those treated during the second decade (1983 through 1993) with cisplatin-based regimens, no significant differences were noted in terms of survival. Among patients with extensive-stage sclc, poor PS and metastatic lesions of the liver and CNS resulted in a significantly adverse effect on survival in both the first and the second decade. Among patients with limited-stage disease, poor PS was the most negative prognostic factor

regarding survival during the overall study period. A multivariate analysis revealed that chemoradiotherapy incorporating etoposide, cisplatin and twice-daily chest RT modestly improved survival when compared to the cyclophosphamide-based chemoradiotherapy regimen (Chute JP, etal, Mayo Clin Proc, Oct 1997;72(10):901-12).

Also, when results from 21 phase III clinical trials involving 5,746 patients with extensive-stage sclc, initiated by North American cooperative groups within the 1972-1990 period, were analyzed and compared with survival data from the SEER database, only a modest improvement in survival was discerned. The median of the MST of the 21 trials was 7 months during the 1972-1981 period, rising to 8.9 months in the 1982-1990 period, in line with overall SEER findings. Interestingly MST did not exceed 11.1 months with any regimen (Chute JP, etal, J Clin Oncol, Jun 1999;17(6): 1794). However none of these trials evaluated the newer agents such as taxanes and topoisomerase (topo) I inhibitors, among others, currently mostly in phase II clinical trials in both limited- and extensive-stage sclc as first- and second-line monotherapies or combination therapies.

Exhibit 4
Standard treatment Options for Small-cell Lung Cancer

Stage	Primary Therapy
Limited sclc	Chemotherapy [(cisplatin or carboplatin plus etoposide (PE) ± cyclophosphamide, doxoribicin and vincristine (CAV)] and concurrent radiation therapy (RT); occasionally surgery; prophylactic cranial irradiation (PCI) in selected patients
SPN	Surgery plus chemotherapy; concurrent chemotherapy and RT if positive mediastinoscopy
Multiple nodules	Chemotherapy [4-6 cycles of PE ± CAV; or any of the many other combinations (see Exhibit 6) under evaluation], and concurrent fractionated RT (45-60 Gy), administered with the early chemotherapy cycles for 3 to 5 weeks
Extensive-stage sclc	Primarily chemotherapy; radiation is used for palliation of painful bony metastases, symptomatic brain metastases, and lung obstruction causing shortness of breath or hemoptysis
Brain metastases	Chemotherapy + radiotherapy
Severely debilitated patients	Chemotherapy (oral etoposide)
Responders	PCI may be considered in patients with CR
Progressive disease after initial chemotherapy	Tumor responses, palliation of symptoms, and short-term local control may be achieved with external-beam RT
Relapsed disease	Second-line chemotherapy; brain metastases are treated with radiotherapy

Treatment of paraneoplastic syndromes is best accomplished by treating the primary tumor. Although ectopic peptide production often improves with tumor response to treatment, the autoimmune paraneoplastic syndromes often do not. Blocking autoantibodies with intravenous immune globulin, plasmapheresis, and steroids may provide benefit in certain cases.

Surgery

Surgery is rarely applicable exclusively for the treatment of sclc but it might play an important role in its diagnosis and staging. Among advantages of surgical intervention in sclc is staging that may be of prognostic significance and, possibly, prevent or reduce the chance of local relapses. Surgery does not in any way interfere with chemotherapy or affect the bone marrow. Surgery with curative intent may be of value in cases of limited-stage disease presenting with an SPN. Even in this case, however, treatment should include a round of chemotherapy. Five-year survival rates reported from small retrospective trials that either involved surgery alone, or in combination with adjuvant chemotherapy or radiotherapy, or in the neoadjuvant chemotherapy setting, have ranged from 10%-50%. Used in conjunction with new improved noninvasive staging procedures, such as PET, resection may lead to a cure in selected cases (Lassen U and Hansen HH, Cancer Treat Rev, Apr 1999;25(2):67-72). However, at present, it is not clear whether surgery is truly effective for patients with limited-stage sclc.

In a prospective clinical trial carried out at the University of Padua, in Italy, between 1981 and 1995, 104 patients with limited-stage sclc [Stage I=35 patients (33.6%), Stage II=16 (15.4%), and Stage III=53 (51%)] were treated with surgery, chemotherapy, and RT. In 51 patients with operable Stage I or II disease, resection of lesions was followed by adjuvant chemotherapy and RT. In 53 patients with Stage III disease, induction chemotherapy was followed by surgery and radiotherapy. All patients were treated with 4 to 6 courses of chemotherapy, and 36 with prophylactic cranial irradiation (PCI). All in all, there were 29 pneumonectomies, 8 bilobectomies and 66 lobectomies. All patients were followed-up for at least 1 year, with survival time calculated from the date of diagnosis until death, or most recent follow-up. Two patients died within 30 days after surgery, 14 (13.4%) experienced postoperative complications, and 51 (49%) relapsed. Within a median follow-up of 55 months, 78 (75%) patients had died. Survival correlated with disease stage and response. The overall 5-year survival rate was 32%, with an estimate MST of 28 months; 5-year survival rate was 52.2%, 30% and 15.3% for Stages I,

II and III, respectively. The 5-year survival was 41% among patients experiencing a CR after chemotherapy (Rea F, etal, Eur J Cardiothorac Surg, Oct 1998;14(4):398-402).

Radiotherapy (RT)

Radiotherapy is a standard approach to the management of all stages of sclc. In limited-stage sclc, RT is combined with chemotherapy to improve survival. PCI is used to prevent brain metastasis in patients achieving a CR under standard treatment. In extensive-stage disease, RT is used for palliation of painful bony metastases, treatment of symptomatic brain metastases, and for lung obstruction causing shortness of breath or hemoptysis.

Thoracic radiation therapy (RT) has been employed in sclc since the 1960s. RT is most effective when used in combination with chemotherapy. Combined modality approaches, such as RT administered concomitantly with the initiation of chemotherapy, induction chemotherapy followed by RT administered during subsequent courses of chemotherapy, sequential chemotherapy and RT, and courses of RT split between cycles of chemotherapy, have all been tried to improve survival in sclc.

Randomized clinical trials performed in the late 1980s confirmed a moderate advantage of chemoradiotherapy. In a meta-analysis, designed to evaluate the hypothesis that thoracic RT contributes to a moderate increase in overall survival in limited-stage sclc, individual data was collected on 2,140 patients (433 patient with extensive-stage sclc were excluded), enrolled before December 1988 in 13 randomized trials comparing chemotherapy alone or combined with thoracic RT. Overall, 1,862 of 2,103 evaluable patients had died at the time of the meta-analysis; median follow-up period for the surviving patients was 43 months. The relative risk of death in the combined therapy group as compared with the chemotherapy group was 0.86, corresponding to a 14% reduction in the mortality rate. The benefit in terms of overall survival at 3 years was 5.4 ± 1.4%. No differences in outcomes were discerned regarding the timing of RT but the relative risk of death in the chemoradiotherapy group as compared with the chemotherapy group, ranged from 0.72 for patients <55 years old to 1.07 for patients >70, indicating a trend toward a better survival outlook among younger patients (Arriagada R, etal, Anticancer Res, Jan-Feb 1994;14(1B): 333-5, and Pignon JP, NEJM, 1992;327(23):1618-24). In another meta-analysis the absolute survival odds ratio was 1.56 for those treated with chemoradiation compared to chemotherapy alone (Warde P and Payne D, J Clin Oncol 1992;10:890-5).

However, despite the early benefits of chemoradiation, most sclc patients relapse within 3 years after treatment. And, although chemoradiation has been shown to be beneficial in the treatment of limited-stage disease, it has yet to be established if the delivery mode of RT (sequential, early or late concurrent, or alternating) would significantly impact its effectiveness. Another issue is the radiation dose which currently stands at between 40-50 Gy in daily fractions over 3 to 5 weeks. However, because chest relapse at this dose level remains high, and in most cases relapse is only local, investigators are experimenting with higher thoracic RT doses. Fractionated RT approaches are used to deliver higher RT doses, or similar doses within shorter intervals.

Chemoradiation may also confer a survival advantage in extensive-stage sclc. In order to demonstrate such a benefit, investigators in Yugoslavia and Japan undertook a phase III randomized clinical trial that treated 210 patients between January 1988 and June 1993 with three cycles of standard combined cisplatin/etoposide (PE) chemotherapy. After PE, those with a CR at both the local and distant sites, or a local PR and distant CR, were treated with hyperfractionated RT with 54 Gy in 36 fractions over 18 treatment days, in combination with carboplatin and etoposide, followed by two cycles of PE (group 1, n = 55), or only by four more cycles of PE (group 2, n = 54). Patients with a lesser response were treated nonrandomly (groups 3, 4, and 5). All patients with a distant CR were treated with PCI. Among 206 assessable patients, the MST was 9 months and the 5-year survival rate was 3.4%. Survival rates of patients in group 1 were significantly better than those in group 2, with an MST of 17 months versus 11 months and a 5-year survival rate of 9.1% versus 3.7%, respectively. Local control was also better in group 1, but the difference was not significant. There was no difference in distant metastasis-free survival between groups 1 and 2. Acute high-grade toxicity was higher in group 2 (Jeremic B, etal, J Clin Oncol, Jul 1999;17(7):2092).

Prophylactic cranial irradiation (PCI) has been used in sclc to prevent the development of brain metastases because of the propensity of this tumor to metastasize to the brain. About 50% of patients with treated limited-stage sclc who survive for at least two years will develop brain metastases. In several trials, PCI has resulted in a marked reduction in the incidence of symptomatic brain metastasis, and was shown to improve survival. Concern has been raised over the impact of PCI on normal brain function, but several studies suggest that if the dose and amount of radiation per fraction are not excessive there is no increase in neurocognitive dysfunction. In general, PCI is recommended for limited-stage sclc patients who have experienced a CR after chemoradiotherapy.

To assess the role of PCI in prolonging survival, a meta-analysis was undertaken by the Prophylactic Cranial Irradiation Overview Collaborative Group, involving individual data on 987 patients with sclc who took part in 7 trials conducted between 1977 to 1994, that compared PCI with controls. Patients in CR after initial treatment were randomized to PCI (generally 24 to 40 Gy, administered in fractions of 2-3 Gy per day) or no treatment; median follow-up was 5.3 years in the control group and 5.9 years in the PCI group. Overall, 846 (85.7%) patients died during the study period. The relative risk of death in the treatment

Exhibit 5
Estimated Small-cell Lung Cancer Cases by Type of Treatment in the USA in 1999

Treatment	Cases (#)	Total (%)
First-line Chemotherapy[1]	22,220	76.4
First-line Radiation Therapy[1]	16,096	46.9
Second-line Chemotherapy[2]	7,777	35.0

[1] Alone or in combination

[2] Based only on patients originally treated with chemotherapy

group, as compared with the control group, was 0.84 which corresponds to a 5.4% increase in the rate of survival at 3 years (15.3% in the control group versus 20.7% in the treatment group). PCI also increased the rate of disease-free survival with a relative risk of recurrence or death of 0.75, and decreased the cumulative incidence of brain metastasis by 25% (relative risk=0.46). Larger doses of radiation led to greater decreases in the risk of brain metastasis, according to an analysis of four total doses (8 Gy, 24 to 25 Gy, 30 Gy, and 36 to 40 Gy) but the effect on survival did not differ significantly based on dose. There was also a trend toward a decrease in the risk of brain metastasis with earlier administration of PCI after the initiation of induction chemotherapy. This meta-analysis did not assess the neuropsychological effects of PCI because only 2 of the 7 clinical trials included testing for such toxicity (Auperin A, NEJM, 12 Aug 1999;341(7):476-84). Additional research is needed to optimize PCI in terms of radiation dose, tissue target, and duration and timing.

Chemotherapy

Chemotherapy is standard treatment for all stages of sclc. Sclc is sensitive to chemotherapy with 70% to 90% of those treated experiencing a favorable initial response only to relapse within a short period of time and expire soon thereafter, with only 10% surviving more than 2 years. Even in limited-stage disease, with multimodality therapy, the 5-year survival rate is under 20%. In patients with extensive sclc, in view of poor outcomes, the therapeutic benefit must be balanced against the burden of treatment (physical, psychological, and financial).

Chemoradiotherapy is standard treatment in limited-stage disease. Combination chemotherapy, either cisplatin- or cyclophosphamide-based or both, is more effective than single-agent chemotherapy, with a response rate of 80% and a 50% chance of eliminating all visible disease. Addition of chest RT to chemotherapy improves the chances of survival by about 5%. With chemoradiotherapy, 15-20% of those with limited-stage sclc are alive 3 years after diagnosis. RT is usually administered concurrently with chemotherapy. Typically, two cycles of chemotherapy are followed by 2 more cycles with concurrent RT. Extensive-stage disease is treated primarily with chemotherapy with RT reserved for palliation. In this setting, treatment clearly prolongs life but is not curative with only a small fraction of patients remaining alive after 2 years.

It appears that 4-6 cycles of chemotherapy provide the maximum benefit, and that further "maintenance" chemotherapy does not improve chances of survival. Other approaches to improving the effects of standard chemotherapy such as alternating non-cross resistant regimens (PE/CAV), or escalating doses of chemotherapy, have not proven to be more effective. In several small, single arm studies, high response rates have been noted with dose-intensified cisplatin/etoposide. However, the majority of larger, randomized studies have failed to show a survival benefit, and one meta-analysis recently published failed to show a benefit to dose escalation. Since higher doses of chemotherapy are associated with increased gastrointestinal, neurologic, and myelosuppressive toxicities (even with growth factor support), they are not routinely provided outside of a clinical trial.

On occasion, patients with sclc will present with obstruction of the large blood vessels which drain the head and neck (SVC sydrome), resulting in facial swelling, shortness of breath, and headache. In the past, many of these patients were treated with RT. However, chemotherapy may provide rapid reduction of the tumor mass and relief of the SVC syndrome. This is especially important in limited-stage disease where RT is reserved for potential curative therapy. Chemotherapy can also be used to treat symptomatic brain metastases, if followed up by whole brain irradiation, but symptomatic brain metastases should probably treated with RT at presentation.

Combination chemotherapy using etoposide (Vepesid; Bristol-Myers Squibb), cisplatin (Platinol; Bristol-Myers Squibb) or carboplatin (Paraplatin Bristol-Myers Squibb) with concurrent RT is the standard first-line treatment of sclc. Platinum agents are the mainstay of combination chemotherapy and are being evaluated with a variety of other chemotherapeutics. A new platinum agent, Lobaplatin, under development by Asta Medica (Frankfurt am Main, Germany), was approved in China in 1998 for treatment of metastatic and inoperable sclc.

Alternatively, regimens such as CAV (cyelphosphamide, doxorubicin, and vincristine), CAE (that substitutes etoposide for vincristine), and ICE (ifosfamide, cisplatin or carboplatin, and etoposide) have produced objective responses in 55% to 65% of patients. A clinical trial performed by the Hoosier Oncology Group randomized 171 sclc patients to treatment with either standard IV PE alone, on days 1-4, or PE and ifosfamide (1.2 g/m^2), on days 1-4. Among 165 patients evaluable for survival, the overall response rates were similar for PE and ICE (67% and 73%, respectively). MST was 7.5 months and 9.0 months, respectively, only modestly higher with the ICE regimen when corrected for PS, as were the 1-year (29% and 37%)

and 2-year (4.7% and 13%) survival rates. Overall incidence of Grade 3/4 toxicity was comparable between the two treatment arms but the ICE arm was associated with greater hematologic toxicity, notably anemia. There were 5 deaths in each regimen from drug-related toxicity (Ansari R, etal, ASCO94; Abs. 1091:330).

A combination regimen of vincristine, carboplatin, etoposide and methotrexate was also active in terms of response, MST and long-term survival but did not significantly differ from the historical results of the standard 2 drug regimen. Speed of response as well as response completeness was a predictor of long-term survival.

Recently, a number of new chemotherapeutic agents approved in the USA and elsewhere for other cancer indications have shown promise and are currently being tested in 2 or 3 drug combination regimens as first-line treatment of sclc. Exhibit 5 illustrates the variety of combination therapies currently under investigation in sclc (also see FO, p 93).

Among the newer agents, topotecan (Hycamtin; SmithKline Beecham), in combination with paclitaxel, has been proven to be highly active as first-line therapy in patients with previously untreated extensive-stage sclc, resulting in significantly greater MST than that seen with standard chemotherapy (see Exhibit 6). Topotecan and cisplatin combination chemotherapy is also active in both sensitive and refractory sclc with Grade 3/4 thrombocytopenia and neutropenia being the major side effects.

The combination of irinotecan (Camptosar; Pharmacia & Upjohn), a topoisomerase I inhibitor, with etoposide, a topoisomerase II inhibitor, was shown to be effective with acceptable toxicity in previously untreated patients with extensive-stage sclc. These two drugs exhibited a synergistic effect on sclc cells when administered sequentially, or concurrently, *in vitro* which provided an experimental basis for conducting clinical trials using this combination (Bahadori HR, etal, ACSO98, Abs. 1837:477a).

The taxanes paclitaxel (Taxol; Bristol-Myers Squibb) and docetaxel (Taxotere; Aventis), in various combinations, are also active as first-line treatment of sclc. Paclitaxel and carboplatin with/without etoposide is an active, well tolerated regimen in metastatic sclc, with a low hematologic toxicity profile with neutropenia being the major adverse event. Death from toxicity is estimated at 10%. A randomized phase III clinical trial was initiated in late 1998, to see if this regimen is superior to the standard carboplatin, etoposide and vincristine combination. The combination of docetaxel and cisplatin was also an effective regimen in patients with disseminated sclc (overall response rate=55%), in spite of poor PS and multiple metastatic sites. The main toxicity was hematologic, while nonhematologic side effects were mild.

Single-agent chemotherapy may also be effective in sclc, particularly in extensive-stage disease. Several drugs, among them the taxanes (paclitaxel, docetaxel), topoisomerase I inhibitors (irinotecan, topotecan), gemcitabine, and navelbine, have also demonstrated single agent activity, achieving MST that appears comparable to that obtained with combination therapy.

In a two-stage phase II clinical trial, 43 patients with previously untreated extensive-stage sclc were treated with IV paclitaxel (250 mg/m^2) during 24 hours with G-CSF support. Cycles were repeated at 21-day intervals. Patients who achieved CR were subsequently treated with a maximum of 10 cycles of chemotherapy, whereas those with PR/regression continued treatment until progression or undue toxicity developed. Patients with stable or progressive disease for six cycles were crossed over to PE. All patients were evaluable for analysis. Responses were observed in 23 (53%) patients. At the time of analysis, 39 patients had progressed with a median time to progression of 95 days, and 39 patients had died with an MST of 278 days. The 1-year survival rate was 24%. Myelosuppression was the main side effect with significant neutropenia occurring in 24 (56%) patients, but with only 2 experiencing ≥Grade 3 infection; there were no septic deaths. Although paclitaxel monotherapy was active against sclc, the response duration was short (MST=3.4 months), which suggests that this drug is not sufficient as a single agent in this setting (Kirschling RJ, etal, Am J Clin Oncol, Oct 1999;22(5):517-22).

Oral etoposide is an active single agent in sclc and is widely prescribed as first-line treatment as an alternative to combination IV chemotherapy in patients with extensive-stage disease. However, interim results from a phase III randomized clinical trial of palliative treatment in advanced sclc, conducted by the University College London Hospitals, in the UK, oral etoposide was found to be inferior to IV chemotherapy and it was recommended that it should not be used as first-line treatment of in this setting. In this trial, oral etoposide (100 mg), administered twice daily for 5 days, was compared with IV chemotherapy consisting of alternating cycles of cisplatin and etoposide (PE) and cyclophosphamide, doxorubicin, and vincristine (CAV). Six cycles of chemotherapy were administered every 21 days in both regimens.

An interim analysis conducted in January 1996, after 155 patients had been randomly assigned from a projected total enrollment of 365, survival at 9.8% at 1 year was inferior in the oral etoposide group compared with IV therapy at 19.3%, and there was a trend toward inferior overall survival. MST was 4.8 months in the oral etoposide group compared to 5.9 months for the IV therapy group. PFS was 3.6 months and overall response rate was 32.9% in the oral etoposide arm versus 5.6 months and 46.3% in the IV arm, respectively. With the exception of acute nausea and vomiting associated with IV chemotherapy, all aspects of symptom control and quality of life were either the same or worse in the oral etoposide group. Because of these results, it was recommended that the study be terminated (Souhami RL, JNCI, 16 Apr 1997;89(8):577-80).

Exhibit 6
Combination and Multimodality Clinical Trials in Small-cell Lung Cancer

Regimen	Toxicity	Results	Clinical Status➢ Location ❑ Indication ❑ Institution ❑ Reference
Cisplatin + etoposide (PE) with/ without epirubicin + cyclophosphamide for induction; patients are then randomized to one of two treatment arms: etoposide IV on days 1 and 3 + cisplatin IV on day 2 (arm I) or PE as in arm I, plus epirubicin IV on day 1 + cyclophosphamide IV on days 1 and 3 (arm II); treatment is repeated in both arms *q* 28 days for up to 6 courses; patients with PR or CR are treated with PCI and/or thoracic RT; those with residual tumor may be treated with oral etoposide for 3 of *q* 4 weeks			Phase III randomized, multicenter clinical trial (o4/99)➢ Europe ❑ extensive-stage sclc (a total of 210 patients will be accrued for this study within 2.5 years) ❑ Hôpital Arnaud de Villeneuve (Montpellier, France) FRE-FNCLCC-95012, EU-98021 ❑ Jean Louis Pujol, Chair
High-dose epirubicin (100 mg/m^2) + cisplatin (100 mg/m^2) on day 1, or (arm I) cisplatin (100 mg/m^2) on day 1 plus etoposide (100 mg/m^2) on days 1, 2, 3, (arm II), repeated *q* 3 weeks for up to 6 cycles; responders with limited-stage disease are treated with RT and PCI	As of 11/98, 383 patients were evaluated for toxicity; myelotoxicity was the main side effect, with neutropenic fever in 5% of the cycles; the treatment-related death rate was 8%; there were no differences in side effects between the arms	331 patients were evaluated for response and 379 for survival; although response rate, TTP and MST were slightly superior in the high-dose arm, significance was reached only in a higher ORR, 86% versus 76.7% in all cases and 79.2% versus 67.5% in extensive-stage disease	Phase III randomized clinical trial (o11/98)➢Europe limited-stage sclc ❑ (n=205) and extensive sclc (n=199) ❑ Gómez-Codina J, etal, ASCO99, Abs. 1810:469a
Cyclophosphamide + doxorubicin + vincristine (CAV) by IV bolus alternating with 3 days of daily etoposide IV over 60-120 minutes + cisplatin IV over 30 minutes, alternating *q* 3 weeks for 6 courses; patients are randomized to thoracic RT either with course 2 (arm I) or with course 6 (arm II) of chemotherapy; those in arm I are treated with 1 week of rest between RT and the second course of chemotherapy; if no disease progression after chemotherapy and locoregional RT, and a repeat negative brain scan, patients are treated with PCI			Phase III (o1/99)➢UK ❑ limited-stage sclc ❑ Middlesex Hospital-Meyerstein Institute (London, England) LLCG-TR8SCLC, EU-98011 ❑ Stephen G. Spiro, Chair
Cyclophosphamide IV + doxorubicin IV on day 1 + etoposide IV on days 1-3 *q* 3 weeks (arm I), compared to IV carboplatin followed by IV paclitaxel over 3 hours on day 1, *q* 3 weeks (arm II); stable patients and responders are treated for up to 5 courses			Phase III randomized clinical trial (o2/99)➢Europe ❑ extensive-stage sclc (n=250) ❑ Academisch Ziekenhuis der Vrije Universiteit (Amsterdam, Netherlands) DUT-KWF-CKVO-9802, EU-98059) ❑ Egbert F. Smit, PI
Cisplatin IV on day 1 + etoposide IV over 1 hour, on days 1-3, *q* 21 days, for 6 courses (arm I) or IV paclitaxel over 3 hours on day 1 and IV PE as in arm I followed by G-CSF SQ on days 4-18, *q* 21 days, for 6 courses (arm II)			Phase III randomized clinical trial (o2/99)➢USA ❑ extensive-stage sclc (n~670) ❑ CALGB-9732 ❑ Harvey B. Niell, Cancer and Leukemia Group B, Chair

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Vincristine (V) + ifosfamide (I) + carboplatin (C)+ etoposide (E)	Treatment-related toxicities, especially myelosuppression, have hindered efforts to accelerate the administration of ICE and VICE regimens and to incorporate them into combined-modality treatments; use of hematologic support, including growth factors and peripheral blood prognitor cells, may aid in maximizing the effectiveness of these regimens	ICE and ICE administered with vincristine (VICE) achieved ORR of 79% and 94% in limited-stage disease, and 77% and 100% in extensive-stage disease, respectively; 2-year survival rates were 24% and 33%, and 9% and 25%, respectively	Phase III (c6/95)➢UK ❑ limited- and extensive-stage sclc ❑ Weston Park Hospital (Sheffield, UK) ❑ Lorigan P, etal, Semin Oncol 1995 Jun;22(3 Suppl 7):32-41
Ifosfamide IV over 24 hours + carboplatin IV over 1 hour, on day 1, + etoposide IV over 1 hour, on days 1 and 2, (escalating-dose trial with dose level 1=4 patients, 2=17 and 3=2), repeated *q* 14 days, for 4 courses, and SQ G-CSF administered beginning on day 2 and continuing until blood-cell counts recover; PBSC are collected after course 1 and reinfused on day 3 of courses 2 and 3; patients who experience CR are treated with PCI on day 71; early intensification was feasible, but did not yield an overwhelming CR rate or TTP	MTD was at level 2 because of neuropathy and infection which was the DLT at level 3; overall, toxicity was ≤ Grade 2 for all patients up to dose level 2 with hematotoxicity being Grade 4 uniformly for all patients	Among 17 patients evaluable for response and TTP (6 patients too early), there were 7 CR (41%), 9 PR (53%), and 1 PD; median TTP was 7 months with 4 patients in continuous remission (5+, 6+, 7+, 13+ months); MST of 16 evaluable patients had not yet been reached at the time of this report	Open label, multicenter, phase II (o12/99)➢Europe ❑ mostly extensive-stage sclc ❑ University Hospitals (Münster and Greifswald); Kliniken Ibbenbüren, (Hemer and Chemnitz); and Amgen (Munich), FRE-FNCLCC-98003-CLEO, EU-98072, FRE-FNCLCC-CLEOPA RE03 ❑ Oelmann E, etal; T ASCO99, Abs. 1831:475a
Cisplatin (80 mg/m^2) on day 1 + etoposide (100 mg/m^2) on days 1-3 as a one cycle induction + concurrent thoracic RT of 45 Gy administered by 1.5 Gy *bid* 5 days/week for 30 fractions; cisplatin (25 mg/m^2) IV weekly, for 6 weeks, +vincristine (1 mg/m^2) IV on weeks 6, 8, and 10, + doxorubicin (40 mg/m^2) + etoposide (80 mg/m^2) x 3 days IV on weeks 5, 7 and 9 (CODE regimen), were started on week 5 and G-CSF (50 m/m^2) was administered SQ on the days when cytotoxic drugs were not administered	Main toxicity was hematologic with Grade 3/4 leukopenia in 8%/92%, anemia in 100%/0%, and thrombocytopenia in 33%/17%; no other Grade 3 toxicity nor treatment-related deaths occurred	11 patients (92%) completed 6 cycles of CODE, and 1 patient was treated with 5 cycles; 5 patients achieved CR and 7 PR; as of 9/98, among 13 evaluable patients there were 5 CR and 7 PR for an ORR of 100%	Phase II (o12/98)➢Japan ❑ limited-stage sclc (n=16) ❑ National Cancer Center Hospital (Tokyo, Japan); National Cancer Center Hospital (East Kashiwa, Japan) ❑ Kubota K, etal, ASCO99, Abs. 1978:513a
Cisplatin IV over 1 hour on days 1 and 8 + etoposide IV over 1 hour, daily, on days 1-15, *q* 4 weeks; RT (45 Gy to 54 Gy) is administered from the start of treatment for 5 days per week, for 7 weeks; in the absence of disease progression, patients are treated with paclitaxel IV over 3 hours, followed by carboplatin IV over 30 minutes, *q* 3 weeks, for 3 courses, within 8 weeks after completing RT	Among 10 patients accrued in phase I evaluable for toxicity, 5 experienced Grade 3/4 esophagitis, 5 Grade 4 neutropenia, and 1 Grade 3/4 nausea/vomiting during induction and 5 Grade 4 neutropenia, 2 Gade 4 anemia and 4 Grade 1/2 peripheral neuropathy occurred during consolidation	Among 9 patients accrued in phase I evaluable for response, there were 4 CR, 4PR, and 1 patient experienced a minimal response; MST had not been reached at the time of this report; median PFS was 14 months; 2 patients not treated with PCI relapsed exclusively in the brain. 1 relapsed systemically and 1 solely in the chest	Phase I (c98); phase II (o10/99)➢USA ❑ limited-stage sclc ❑ phase I: UC Davis Cancer Center (Sacramento, CA); VA Northern CA Health Care System (Martinez, CA); and David Grant Medical Center (Fairfield, CA) ❑ Hutchinson K, etal, ASCO99, Abs. 1964:509a) and phase II: SWOG-9713 ❑ Martin J. Edelman of SWOG, Chair
Topotecan (1 mg/m^2) was administered IV for 30 minutes, daily, for 5 days, followed by paclitaxel (135 mg/m^2), administered IV for 3 hours on day 5 with G-CSF support; this cycle was repeated *q* 28 days	Grade 3 leukopenia occurred in 12/15 patients treated with 6 cycles; there were no hospitalizations for neutropenic fever	Almost all patients responded to therapy within 2 cycles; there were 10 (66.7%) CR, and 5 (33.3%) PR, for an ORR of 100%; 1-year survival among 10 evaluable patients was 80%; MST had not been established at the time of this report	Phase II (c5/99)>USA ❑ extensive-stage sclc ❑ Amos Cancer Center (Columbus, GA) ❑ Tweedy CR, etal, ASCO99, Abs. 2025:525a

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Topotecan (1 mg/m^2) was administered IV for 30 minutes, daily, for 5 days, followed by paclitaxel (135 mg/m^2), administered IV for 24 hours, on day 5, with G-CSF support	Grade 4 myelosuppression was the primary toxicity occurring in at least 1 cycle in 27/28 patients; febrile neutropenia occurred in 21% of courses and there was 1 septic death; neutrophil recovery occurred by day 15 in greater than 90% of cycles; Grade 4 thrombocytopenia occurred in 18% of courses	The ORR was 60% with 21% CR and 39% PR; MST was 12.5 months, with 1- and 2-year survival probabilities at 50% and 15%, respectively	Phase II (c5/99)➢USA ❑ extensive-stage sclc ❑ U Pittsburgh Cancer Institute ❑ Samuel A, etal, ASCO99, Abs. 1814:470a
Topotecan + paclitaxel			Phase II (b4/98;o1/00)➢ USA ❑ recurrent or refractory sclc ❑ NCI NCCTG-972051 ❑ James R. Jett, North Central Cancer Treatment Group, Chair
Paclitaxel + carboplatin + topotecan+ G-CSF; peripheral blood stem cells (PBSC)			Phase II (o12/99)➢USA ❑ metastatic sclc ❑ NCI FCCC-98039, NCI-G99-1535 ❑ Russell J. Schilder, Fox Chase Cancer Center, Chair
Topotecan IV on days 1-5 + paclitaxel IV, over 3 hours, on day 1 + SQ G-CSF *q* day starting on day 6 until blood counts recover; the course is repeated once beginning on day 22; after restaging, patients begin thoracic RT daily, 5 days per week, for 6-7 weeks; simultaneously with RT, patients are treated with carboplatin IV over 1 hour, on day 43, and etoposide IV over 1 hour, daily, for on days 43-45, repeated *q* 21 days for a total of 3 courses; stable or responding patients undergo PCI			Phase II (o1/00)➢USA ❑ limited-stage sclc ❑ CALGB-39808 ❑ Alan Philip Lyss, Cancer and Leukemia Group B, Chair
Altretamine (150 mg/m^2) on days 1-14, and oral etoposide (50 mg/m^2) on days 1-14, *q* 21 days [median number of cycles delivered was 3; 9 patients (28%) were treated with 6 or more cycles, and 3 (10%) with 9 or more]	25 patients (81%) experienced nausea +/- vomiting, 9% Grade 3; 59% fatigue and asthenia, 28% Grade 3; Grade 3 (4) anemia occurred in 19% (0%), granulocytopenia in 19% (13%), and thrombocytopenia in 13% (3%)	ORR was 22%, with 1 CR (3%); ORR in previously treated patients was 20% (6/30); MDR was 7 months; disease progressed after only 2 cycles in 14 patients (44%); median PFS was 3.2 months and median overall survival was 5 months; 1-year survival rate was 21% and PFS was 9%; results are comparable to those observed with topotecan or CAV in a similar setting	Phase II (c12/98)➢USA ❑ relapsed (n=30) and chemonaive (n=2) extensive-stage sclc ❑ U.S. Bioscience ❑ Sprandio J, etal, ASCO99, Abs. 1845:478a
Carboplatin (AUC 6) + paclitaxel (200 mg/m^2) as a 3-hour infusion, administered on day 1, at 3 weekly intervals (a total of 147 cycles were administered); response was assessed after 2, 4 and 6 courses; nonresponders after each evaluation, were withdrawn from the study and treated with standard chemotherapy	Hematologic toxicity included Grade 3 and 4 neutropenia (27%), anemia (6%) and thrombocytopenia (4%); there was 1 Grade 3 febrile neutropenia; nonhematologic Grade 3 toxicity included muscle pain (9%), emesis (9%), asthenia (9%) and alopecia (9%); Grade 1/2 neuropathy occurred in 13% of cases	In an interim analysis of 35 patients (2 were non-assessable for efficacy), ORR was 67%, with 10% CR, 57% PR, 3% SD and 30% PD; overall MST was > 24 weeks and MDR was 20 weeks	Phase II (c11/98)➢France ❑ metastatic sclc ❑ Hôpital Ste-Marguerite (Marseille, France) ❑ Thomas P, etal, ASCO99, Abs. 2000:519a

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Paclitaxel (175 mg/m^2) IV over 3 hours on day 1, followed by carboplatin (AUC 5) on day 1 + oral etoposide (50 mg), on days 2-8; the regimen was repeated *q* 3 weeks (median=4 cycles)	88 patients were evaluable for toxicity (384 courses); Grade 3/4 hematologic toxicity included anemia in 3.5% of courses, thrombocytopenia in 5.1%, leukocytopenia in 16.0%, and neutropenia in 44.9%; main Grade 3/4 nonhematologic toxicities were PNP in 0.5% of courses, myalgia in 0.3% and vomiting in 0.8%	There were 15/84 CR (17.8%), 54/84 PR (64.3%), 13/84 SD (15.5%) and 2/84 PD (2.4%); 50 (56.8%) patients were alive at the interim analysis for an MST of 585 days (1.6 years) and an ORR of 82.1%	Phase II (c11/98); Phase III (o12/98)➢Germany ❑ limited-stage sclc ❑ U Gatzemeier, Hospital Großhansdorf (Germany); Community Hospital (Hamburg- Germany); Hospital Gauting (Germany); Bristol-Myers Squibb Oncology ❑ Reck M, etal, ASCO99, Abs. 1887:489a
Paclitaxel (200 mg/m^2) IV on day 1 + carboplatin (AUC 6) on day 1, *q* 3 weeks, for a maximum of 6 cycles (median=4)	The regimen was well-tolerated; among 75 patients evaluable for toxicity (307 courses) Grade 3/4 hematologic toxicities were anemia in 1.7% of courses, thrombocytopenia in 2.9%, leukocytopenia in 6.9% and neutropenia in 42.9%; Grade 2/3 nonhematologic toxicities were PNS in 29.3% of courses, myalgia in 14%, nausea in 8.5% and vomiting in 3.6%	Among 69 patients evaluable for response; ORR was 61.1%; there were 5 CR (7, 3%), 37 PR (53, 6%), 19 SD (27, 5%) and 8 PD (11, 6%); 36 patients (48%) were alive at the interim analysis with an MST of 359 days	Phase II (c1/98)➢Germany ❑ advanced, extensive-stage, chemonaive sclc ❑ Bristol-Myers Squibb Oncology ❑ Deppermann KM, etal, ASCO99, Abs. 1860:482a
Topotecan (0.75 mg/m^2), administered on days 1 to 5 as a 30-minute infusion, + cisplatin (60 mg/m^2) on day 1; cycles are repeated *q* 3 weeks (prophylactic G-CSF was not allowed during the first course)	Among 54 (30 sensitive and 24 refractory) evaluable patients, the main toxicity was hematologic with Grade 3/4 neutropenia in 65% of patients and Grade 3-4 thrombocytopenia in 54%; 19% of patients developed febrile neutropenia; myelosuppression was the main cause of dose-reduction (16 patients) and of toxicity-related treatment withdrawal (5 patients); Grade 3/4 nonhematologic toxicity was rare (lethargy 15%, diarrhea 4%, anorexia 9%, nausea 4%); there were no toxic deaths	There were 8 objective responses (1 CR and 7 PR) among 28 evaluable sensitive patients, and 4 PR among 24 refractory patients	Phase II (o12/98)➢UK ❑ second-line treatment of sensitive (n=67) and refractory (n=41) sclc ❑ EORTC LCCG (Brussels, Belgium); SmithKline Beecham ❑ Ardizzoni A, etal, ASCO99, Abs. 1817:471a
Irinotecan (60 mg/m^2) IV on days 1, 8 and 15 + etoposide (80 mg/m^2) IV on days 2-4; treatment was repeated *q* 4 weeks for at least 2 courses	Among 51 evaluable patients, Grade 3 or 4 toxicity included neutropenia (72%), leukopenia (28%), anemia (4%), thrombocytopenia (4%), pneumonitis (2%), and diarrhea (2%)	ORR was 66%, with 10% CR; MST was 12 months	Phase II (c5/98)➢Japan ❑ previously untreated extensive-stage sclc ❑ The West Japan Lung Cancer Group ❑ Nakamura S, etal, ASCO99, Abs. 1815:470a
Paclitaxel (175 mg/m^2) IV over 3 hours on day 1 + cisplatin (80 mg/m^2) IV, on day 1, + etoposide (80 mg/m^2) IV, on day 1 and 160 mg/m^{2}PO on days 2 and 3 of a 21 day cycle for 6 cycles; G-CSF (5 μg/kg) was administered SQ on days 4-14	Among 59 patients evaluable for toxicity, Grade 3/4 neutropenia was 3%/34%, and thrombocytopenia was 10%/10%; 5 patients died from neutropenic sepsis, and 1 patient from complications of renal failure, for a 10% overall rate of toxic death; this high death rate is most likely attributable to patient selection factors including those (27/59) with PS=2, but no significant predictors of fatal outcome were discovered in this trial; nonhematologic toxicity was tolerable with no ≥Grade 3 peripheral neuropathy or myalgias/arthralgias	In the phase I clinical trial using this combination, ORR was 83% with a median TTP of 7.5 months, an MST of 10 months, and a 1-year survival rate of 39%	Phase II (c12/98)➢USA ❑ extensive-stage, chemonaive sclc ❑ SWOG (San Antonio, TX) ❑ Bunn PA, etal; ASCO99, Abs 1807:468a; Kelly K, etal, Clin Cancer Res, Nov 1999;5(11):3419-24

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Vincristine + carboplatin + etoposide + methotrexate [203 cycles of chemotherapy were administered in total (mean: 5.1 per patient), with methotrexate and vincristine being administered on 150 (75%) of these cycles; 82%, 80%, 68% and 62% of patients were treated with at least 80% of the planned dose of carboplatin, etoposide, methotrexate and vincristine, respectively]	Myelosuppression was the main toxicity, with Grade 3 or 4 neutropenia occurring in 73% of patients; there were no treatment-related deaths	Among 31 (78%) responders, there were 19 (48%) CR; MTP was 10.9 months and MST 15.6 months; longest time to relapse was 27.6 months with 90% of relapses occurring within 18 months of diagnosis; actual 1-, 2- and 5- year survival rates were 60%, 27.5% and 12.5%, respectively; all 5-year survivors had achieved CR by the end of the third cycle of chemotherapy	Phase II (c12/98)➢New Zealand ❑ limited-stage, chemonaive sclc ❑ Auckland Hospital (New Zealand); Palmerston North Hospital (New Zealand); and Greenlane Hospital (Auckland, New Zealand) ❑ Redfern BD, etal, ASCO99, Abs. 2008:521a
Ifosfamide + paclitaxel + etoposide + carboplatin + G-CSF; RT [among 9 patients, 7 were treated with all 5 cycles (1 patient suffered from early-PD, 1 patient refused the last cycle) of intensive chemotherapy *q* 14 days]	Nonhematologic toxicities were Grade 3/4 (3/9) esophagitis, Grade 3/4 (2/9) infection and Grade 3 (9/9) alopecia	There were 5 CR, 3 PR and 1 PD; malignant cells were detectable in one patient only who progressed under therapy	Phase II (c12/98)➢Europe ❑ limited-stage sclc ❑ Betticher Institute of Medical Oncology, Radio-Oncology U Berne; Centre Pluridisciplinaire d'Oncologie, (Lausanne); Oncology St. Gallen; Hematology, (Berne, Switzerland) ❑ Calderoni A, etal, ASCO99, Abs. 1909:495a
Docetaxel + cisplatin (as of 12/98, 22 patients were enrolled and 5 median cycles and 95 total cycles delivered)	Among 22 patients evaluable for toxicity 12/22 (54.5%) experienced Grade 3/4 neutropenia, 3/22 (13.6%) febrile neutropenia, and 3/22 Grade 3/4 pulmonary infection; Grade 3-4 nonhematologic toxicities included Grade 3 alopecia (n=5) and asthenia (n=2), and Grade 3/4 nausea and vomiting (n=4), diarrhea (n=1), and stomatitis (n=2); 1 patient died from septic shock after 1 cycle	Among 20 patients evaluable for response, 82% had 2 or more involved sites (12 hepatic, 11 distant nodal, 9 contralateral lung, 7 bone, 4 bone marrow, 11 others); ORR was 55% with 11 PR, 3 SD and 6 PD	Phase II (o12/98)➢Europe ❑ disseminated sclc ❑ 12 de Octubre Hospital (Madrid); Virgen del Rocío Hospital (Sevilla); Virgen de la Victoria Hospital (Málaga); Durán i Reynals (Barcelona); Gregorio Marañón Hospital, (Madrid); Santa Creu i Sant Pau (Barcelona); Rhône-Poulenc Rorer ❑ Lianes P, etal, ASCO99, Abs. 1983:514a
Cisplatin IV on day 1 + etoposide IV daily on days 1-3 *q* 3 weeks for 4 courses + concurrent RT, 5 days/week for 5.5 weeks, starting with the first course of chemotherapy, + amifostine IV over 15 minutes 15-30 minutes prior to each dose of chemotherapy on days 1-3			Phase II (o11/98)➢USA ❑ limited-stage sclc ❑ Alza UF-G-97120405, NCI-V98-1475, ALZA-97-033-ii ❑ Dean Latain McCarley, U Florida, Chair
Paclitaxel (100 mg/m^2, 135 mg/m^2, or 170 mg/m^2 IV) over 3 hours on day 1 + cisplatin (60 mg/m^2) administered on day 2 + etoposide (60 mg/m^2) administered on days 1, 2 and 3, for cycles 1 and 2 and paclitaxel (170 mg/m^2) over 3 hours on day 1 + cisplatin on day 2 and etoposide (80 mg/m^2) on days 1, 2, and 3 and G-CSF in cycles 3 and 4; RT, at a weekly dose of 900 cGy, was administered in 5 fractions for 5 weeks, beginning on day 1 of cycle 1	In cycles 1 and 2, Grade 4 neutropenia occurred in 32% of courses with fever occurring in 7%, Grade 4 thrombocytopenia in 2%, and Grade 2/3 esophagitis in 13%; in cycles 3 and 4, Grade 4 neutropenia occurred in 20% of courses with fever occurring in 6%, Grade 4 thrombocytopenia in 4%, Grade 3/4 anemia in 12% and Grade 2/3 esophagitis in 16%	Among 28/31 evaluable patients, ORR was 96% (CR=39% and PR=57%); within a median follow-up of 23 months (range: 9-40 months) MST was 22 months	Phase I/II➢USA ❑ limited-stage sclc ❑ Multi-institutional ❑ Levitan N, etal, ASCO99, Abs. 1809:469a
Paclitaxel (230 mg/m^2) IV for 3 hours on day 1 and topotecan (1 mg/m^2) IV for 30 minutes daily for days 1-5 with G-CSF support [patient accrual was suspended after 3 treatment-related deaths occurred but was reopened using a lower dose of paclitaxel (175 mg/m^2), over 3 hours, on day one; cycles were repeated *q* 3 weeks; accrual target is 40 patients]	Among the first 13 patients treated with this modified regimen Grade 3/4 neutropenia occured in 69% and Grade 3/4 thrombocytopenia in 23%; there was 1 infection-related toxic death	MST was 13.8 months	Phase I (o5/99)➢USA ❑ previously untreated, extensive-stage sclc ❑ Cancer and Leukemia Group B (Chicago, IL) ❑ Lynch TJ, etal, ASCO99, Abs. 1987:515a

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Topotecan was administered as a 30-minute infusion, followed by a 30-minute saline flush, and then a 1-hour infusion of a fixed daily dose of etoposide (60 mg/m^2/day), *q* 3 weeks, for a maximum of 6 cycles; dose levels of topotecan commenced at 0.5 mg/m^2/day and escalated by 0.25 mg/m^2/day per cohort; a third cohort of topotecan (1 mg/m^2/day) with etoposide (60 mg/m^2/day) is planned if no further DLT is incurred in the second cohort	Among 7 patients treated in the first topotecan cohort Grade 4 neutropenia was seen in 6 courses (3 patients), and dose delays occurred in 7 cycles in 3 patients; in 5 patients, treated with 0.75 mg/m^2 of topotecan, daily for 16 courses, Grade 4 neutropenia was observed in 9 courses (5 patients) and dose delays occurred in 4 cycles in one patient; DLT involving Grade 4 neutropenia with fever requiring IV antibiotics, occurred in 1 patient in each cohort; there were no toxic deaths	All patients (n=12) were evaluable for response and all experienced at least a PR	Phase I (o12/98)➢UK ❑ untreated sclc ❑ Clatterbridge Centre for Oncology (Wirral, Merseyside, UK); SmithKline Beecham Pharmaceuticals ❑ Clark PI, etal, ASCO99, Abs. 1926:499a
Paclitaxel + ifosfamide + carboplatin [dose-escalation trial involving 10 patients treated between 5/98 and 11/98; 6 patients were treated with the first dose level until MTD was reached; 4 patients were treated by a lowered dose of ifosfamide (1000 mg/m^2/day)]	At MTD, 1 patient experienced >5 days of Grade 4 thrombocytopenia, 1 died at home on day 8 for unknown reasons, and 1 died from tumor lysis syndrome; Grade 3/4 hematologic toxicity occurred in 14 cycles, granulocytopenia in 6/4 cycles, and thrombocytopenia in 2/7 cycles; nonhematologic toxicity was mild	Among 6 patients evaluable for tumor response there were 3 PR and 3 SD	Phase I (o12/98)➢The Netherlands ❑ resistant sclc ❑ Netherlands Cancer Institute (Amsterdam); University Hospital (Groningen, The Netherlands) ❑ Kerbusch T, etal; ASCO99, Abs 833:217a
Gemcitabine (1000 mg/m^2) IV on days 1 and 8 + cisplatin (70 mg/m^2) on day 2, and etoposide on days 3, 4, and 5, administered as an initial dose of 50 mg/m^2 IV (Step 1), then escalated to 75 mg/m^2 (Step 2), and 100 mg/m^2 (Step 3); 8 patients were entered (Step 1=6 and Step 2=2); RT	Hematologic toxicities included anemia, leukopenia, thrombocytopenia, and neutropenia; 1 patient died from neutropenic fever; one cycle was delayed in each of 3 patients (Grade 2 neutropenia=1 and leukopenia and neutropenia=2)	There were 4 PR and 1 SD (Step 1); MTD was reached in Step 2 because of DLT at that dose level	Phase I (c12/98)➢Italy ❑ chemonaive limited-stage (n=3) and extensive-stage (n=5) sclc ❑ De Marinis F, etal, ASCO99, Abs. 1933:501a

Legend:

***CR**=complete response **DLT**=dose-limiting toxicity **MDR**=maximum duration of response **MST**=median survival time **MTD**=maximum tolerated dose **MTP**=median time to progression **ORR**=overall response rate **PCI**=prophylactic cranial irradiation **PD**=progressive disease **PFS**=progression-free survival **PR**=partial response **RT**=radiotherapy **SD**=stable disease **SQ**=subcutaneous **TTP**=time to progression*

Source: NEW MEDICINE Oncology KnowledgeBASE (nm|OK), January 2000.

Intensive chemotherapy/chemoradiotherapy

Because of its high chemosensitivity, both limited-and extensive-stage sclc has been the target of high-dose combination chemotherapy/chemoradiotherapy. However, despite high response rates achievable in limited-stage sclc patients with good PS scores with several high-dose chemotherapy (HDC) regimens, survival outcomes were not that much more favorable with HDC than with those obtained with standard-dose regimens in this setting. HDC has also been disappointing in terms of both response and survival in extensive-stage sclc. Failure of dose-intensive regimens may be attributed to limitations of optimizing maximum dose of all drugs in the combination because of overlapping toxicity. Lower than optimal high doses of each agent in the combination often severely compromise its cancer cell killing ability. At this point the role of dose-intensified chemotherapy in sclc remains unclear.

The feasibility and outcome of combination chemotherapy at moderately elevated doses with concomitant thoracic RT, was evaluated in a phase I/II clinical trial in limited-stage sclc using a combination of ifosfamide plus epirubicin (cycles 1 and 3) and of carboplatin plus etoposide (cycles 2 and 4) administered with G-CSF and peripheral blood stem-cell (PBSC) support and once daily thoracic RT (40 Gy) during the first 5 days of each cycle. Overall toxicity was acceptable with the most common side-effects being myelosuppression and asthenia. All 35 eligible patients responded with 23 (65.7%) CR, 12 (34.3%)

PR. Median time to progression was 15 months, and median overall survival was 24.6 months. Only 6/25 (24%) relapsing patients experienced locoregional recurrence while 12/25 (48%) relapsed in the CNS (van de Velde, etal, Ann Oncol, Sep 1999;10(9):1051-7).

A phase I/II trial was undertaken to assess the feasibility and activity of a combination chemotherapy regimen (VIP-E) consisting of etoposide (500 mg/m^2), ifosfamide (4000 mg/m^2), cisplatin (50 mg/m^2) or carboplatin, and epirubicin(50 mg/m^2), followed by G-CSF, administered to 100 patients with limited- or extensive-stage sclc. Thirty patients with qualifying responses to VIP-E proceeded to HDC with autologous peripheral blood stem-cell (PBSC) transplantation after etoposide (1,500 mg/m^2), ifosfamide (12,000 mg/m^2), carboplatin (750 mg/m^2) and epirubicin (150 mg/m^2) (VIC-E) conditioning. Among 97 patients evaluable for response after the standard-dose VIP-E regimen, the objective response rate was 81% in limited-stage disease (33% CR, 48% PR; excluding patients in surgical CR) and 77% in extensive-stage disease (18% CR, 58% PR). Treatment-related mortality of was 2% and 2 additional patients in CR developed secondary nsclc which was cured by surgery. MST was 19 months in limited-stage disease, and 6 months in extensive-stage disease, and the 5-year survival was 36% and 0%, respectively.

HDC was feasible in 16% of those with extensive-stage disease, and 58% of those with limited-stage disease. All HDC patients (n = 30) improved or maintained prior responses. Four (13%) patients died of early treatment-related complications, and 2 additional patients in CR developed secondary malignancies (esophageal cancer and secondary chronic myelogenous leukemia). MST was 26 months in limited-stage sclc, and 8 months in extensive-stage sclc, and the 5-year survival was 50% and 0%, respectively. Despite high response rates, survival after VIP-E and HDC VIC-E in patients with extensive-stage sclc was not superior to that achieved with less toxic traditional regimens. The high 5-year survival rates achieved with these protocols in limited-stage sclc probably reflect both patient selection (high proportion of patients with prior surgical resection), and the high activity of this chemotherapy regimen in combination with RT (Fetscher S, etal, Ann Oncol, May 1999;10(5):561-7).

A prospective clinical trial randomized 90 previously untreated extensive-stage sclc patients to standard-dose versus HDC PE to determine whether HDC PE would yield a higher CR rate, or longer survival. Another 25 patients at risk of excessive toxicity from HDC were treated with standard-dose therapy. During cycles 1 and 2 of PE, patients on standard-dose treatment were treated with IV cisplatin (80 mg/m^2), on day 1, plus etoposide (80 mg/m^2), on days 1 to 3, every 3 weeks; the HDC regimen consisted of IV cisplatin (27 mg/m^2) plus etoposide (80 mg/m^2) on days 1 to 5, every 3 weeks. All patients were treated with standard-dose PE in cycles 3 and 4. In cycles 5 through 8, those in CR continued standard-dose PE; all others were treated with either a CAV regimen, or (if possible) a combination drug program based on *in vitro* drug sensitivity testing of tumor-cell lines established from individual patients. Despite the administration of 68% higher doses and a 46% higher dose-rate intensity in the HDC group, CR rates (23% versus 22%) and MST (10.7 and 11.4 months) were virtually identical. In comparison, among the nonrandomized patients, CR occurred in 4% of cases and the MST was 5.8 months. Leukopenia, thrombocytopenia, febrile neutropenia, and weight loss were significantly more common in the HDC group. HDC PE, that was associated with a substantially worse toxicity than standard PE, did not confer neither a response nor a survival benefit in patients with extensive-stage sclc (Ihde DC, J Clin Oncol, Oct 1994;12(10):2022-34).

In another approach, termed dose-dense chemotherapy, multiple dose-escalated cycles of chemotherapeutics are administered in sequence, often alternating combinations with different toxicity profiles, i.e. those with hematologic toxicity with those primarily associated with non-hematologic side effects, with supportive measures. One example of a dose-dense regimen evaluated in sclc is CODE, that combines cisplatin, vincristine, doxorubicin, and etoposide, administered on a weekly schedule with extensive support including steroids and antibiotics. CODE increases two-fold the dose-intensity of these active drugs in sclc compared with a standard CAV/PE regimen while maintaining an approximately equal total dose. In a preliminary phase II clinical trial, CODE was found to be highly effective in extensive-stage sclc, yielding a 48% CR rate, and an MST of 55 weeks.

Based on this trial, a randomized study was undertaken by the National Cancer Institute of Canada and the Southwest Oncology Group (SWOG), to compare CODE with the standard CAV/PE regimen. The goal of the study was to enroll 400 patients <68 years-of-age, with a PS of 0 to 2, and free of brain metastases, but the study was terminated after results became available on 219 patients enrolled between 1992 and 1996 and randomized to either CODE or alternating CAV/PE. Each cycle of CAV, alternating with PE, was administered every 3 weeks, while CODE was administered on an alternating weekly schedule. Consolidative thoracic RT and PCI were administered to patients responding to CODE, and according to investigator discretion on the CAV/PE arm. More than 70% of all patients were treated with the intended chemotherapy protocol. According to this protocol, over a 9-week period, an equal total dose of cisplatin but more doxorubicin, vincristine and etoposide were administered with CODE than with the 18-week CAV/PE regimen. Although rates of neutropenic fever were similar, 9/110 (8.2%) patients on the CODE arm died during chemotherapy, compared to only 1/109 (0.9%) on the CAV/PE. The principal cause of death was infection. Cardiovascular and neurologic toxicity were also more common in the CODE arm. Overall response rates after chemotherapy were higher (87%) with CODE than with CAV/PE (70%), with the CR rate being 27% and 23% and the PR rate 60% and 47%, respectively. However,

PFS (median of 0.66 years on both arms) and overall survival (median 0.98 years for CODE and 0. 91 years for CAV/PE) were not statistically different. Despite supportive care including prophylactic antibiotics and G-CSF after episodes of febrile neutropenia (but not routine use of G-CSF prophylaxis), there was excessive toxic mortality with the CODE regimen. The response rate with CODE was higher than that of CAV/PE, but PFS and overall survival were not significantly improved. In view of increased toxicity and similar efficacy, this CODE chemotherapy regimen is not recommended for treatment of extensive-stage sclc (Murray N, etal, J Clin Oncol, Aug 1999;17(8):2300-8).

Results from a phase II CODE clinical trial (see Exhibit 6), conducted in Japan, in which subcutaneous G-CSF (50 m/m^2) was routinely administered on the days when cytotoxic drugs were not administered, revealed a significantly lower overall toxicity and no deaths despite high rates of hematologic toxicity. The overall response rate was 92.3% with 38.5% CR and 53.8 PR. Unfortunately these results are based on only 13 evaluable patients. Use of prophylactic G-CSF in this trial may have prevented toxic deaths. Therefore, use of G-CSF and/or PBSC in combination with HDC may improve outcomes. Also, HDC may be more effective using some of the newer drugs that have shown promise in the treatment of sclc.

Often the intended HDC doses are not delivered because of toxicity. One of the strategies employed to optimize HDC in order to eradicate minimal residual disease, involves use of hematopoietic support such as autoBMT, or stem-cell rescue, to treat responders to first-line therapy, those with relapsed/refractory sclc, and as first-line therapy in selected patients. However, a review of 10 trials involving 419 patients treated with autoBMT after induction chemotherapy, did not indicate a survival benefit with an MST <15 months in all stages of sclc and a 3.8% rate of treatment-related deaths (Krug LM, etal, Semin Oncol, Oct 1999;26(5 Suppl 15):55-61).

Although, generally, sclc is not considered a viable candidate for HDC with hematopoietic support, results of some trials using stem-cell rescue have been promising. In a phase II clinical trial, 36 patients <60 years-of-age with limited-stage sclc (Stage III) who responded to first-line chemotherapy (CR=9, near-CR=20 and PR=7), were treated with HDC consisting of cyclophosphamide (5,625 mg/m^2), cisplatin (165 mg/m^2) and carmustine (480 mg/m^2) with hematologic stem-cell support, chest RT, and PCI. There were 3 (8%) toxic deaths. The median PFS for all patients was 21 months. The 2- and 5-year survival rates after HDC were 53%, and 41%, respectively. Of the 29 patients with or near CR before undergoing HDC, 14 remained continuously progression-free for a median of 61 months (range=40-139 months) after HDC. Actuarial 2- and 5-year PFS rates were 57% and 53%. Late complications were infrequent, and most patients returned to full-time work and activity (Elias A, J Clin Oncol, Apr 1999;17(4):1175).

MANAGEMENT OF REFRACTORY/RELAPSED SCLC

Nearly 95% of sclc patients relapse after first-line chemotherapy, and many successfully treated patients develop secondary malignancies. As a result, only a very small percent of sclc patients survive for >5 years.

Drug Resistance in SCLC

Resistance is a principal limitation in the effectiveness of chemotherapy in the treatment of sclc. Identification of markers associated with resistance to chemotherapy may lead to new strategies in the treatment of this devastating disease. The exact mechanism of drug resistance in sclc remains unknown but a number of factors such as overexpression of P-gp encoded by the MDR1 gene, and MRP, as well alterations in topoisomerase (topo) IIα, and topo IIβ activity, have been shown to play a role.

Expression of DNA topoisomerase (topo) IIα, and topo IIβ genes appears to predict survival and response to chemotherapy in patients with sclc. In a study to evaluate the role of the expression of a number of markers of drug resistance, proliferation, and apoptosis, in relation to response to chemotherapy and survival in patients with sclc, tumor samples were obtained from the primary tumor site from 93 previously untreated patients who were randomized in a phase III study to either cyclophosphamide, epirubicin, and etoposide, or cyclophosphamide, epirubicin and vincristine, alternating with PE. Samples were analyzed for expression of markers implicated in drug resistance, including topo IIα, topo IIβ, and MRP, apoptosis (p53, p21, and bcl-2), or proliferation (Ki67). Shorter survival was seen in patients with extensive-stage sclc, and poorer PS, and in those whose tumors expressing high topo IIα and Ki67 levels. Based on multivariate analysis, factors predictive for worse survival were high expression levels of topo IIα, Ki67, and bcl-2, male sex, and extensive-stage disease. High topo IIβ expression was predictive of lower overall response and CR rates. There was no relationship between apoptotic pathway markers, or MRP, and response to chemotherapy. High expression of topo IIα was predictive of worse survival, and high expression of topo IIβ was predictive of lower response rates, and a lower survival probability was observed in patients with bcl-2-positive tumors (Dingemans AM, etal, Clin Cancer Res, Aug 1999;5 (8):2048-58).

One theory as to how drug resistance arises in sclc postulates that sclc cells are protected from apoptosis by an extensive stroma of extracellular matrix (ECM) that surrounds tumors at both primary and metastatic sites. Adhesion of sclc cells to ECM enhances tumorigenicity and confers resistance to chemotherapeutic agents as a result of β1 integrin-stimulated tyrosine kinase activation suppressing chemotherapy-induced apoptosis. Survival of cells bound to ECM could explain the partial responses and local recurrence of sclc often seen clinically after chemotherapy. Strategies based on blocking β1 integrin-mediated survival signals may represent a new therapeutic

approach to improve the response to chemotherapy in sclc (Sethi T, etal, Nat Med, Jun1999;5(6):662-8).

Second-line Chemotherapy

According to a review of records of 1,749 patients treated mainly in phase II clinical trials with second-line chemotherapy for sclc, reported in the literature between 1989-1999, the overall response rate was 20% (Huisman C, etal, Cancer Treat Rev, Aug 1999;25(4):199-206). However, responses did not translate to a survival benefit.

There are two types of patients with sclc who are candidates for second-line chemotherapy. The prognosis of those classified as refractory or resistant to first-line therapy that include patients experiencing only a PR, and/or stable or progressive disease, or responders who relapse within 6 months after chemotherapy, is very poor regardless of disease stage with an expected MST of 2 to 3 months. These patients may be offered palliative therapy or entered into phase I or single-arm phase II clinical trials with novel agents or new combination regimens.

To assess the value of disease stabilization (SD) as a predictor of survival following chemotherapy, data was analyzed from multicenter clinical trials in sclc and ovarian cancer using various second-line chemotherapy regimens. In both patient populations, SD (lasting >8 weeks) and PR were associated with a survival benefit versus progressive disease (PD); interestingly, the survival benefit was similar between the two groups (PR and SD). These results suggest that, at least in these populations, the distinction between SD and PR may not be useful (Cesano A, etal, Int J Oncol, Dec 1999;15(6):1233-1238).

Patients with sensitive sclc whose responded to first-line chemotherapy only to relapse after 6 months following initial treatment, are more likely to respond to second-line regimens. In sensitive sclc, second-line options include induction chemotherapy with standard regimens, and enrollment in phase III clinical trials comparing standard chemotherapy with newer single-agent or combination approaches, with response rate, toxicity and quality of life being the major endpoints.

At this point, there is no standard second-line chemotherapy regimen but various chemotherapies have shown activity in this setting including oral etoposide, PE, cyclophosphamide, doxorubicin and vincristine (CAV), lomustine and methotrexate, and topotecan. Single agent therapy is probably better in this palliative setting than combination treatment. For instance, topotecan was shown to be equally effective, but less toxic than CAV in relapsed patients. Brain metastases in this setting are common, rarely solitary, and are treated with XRT.

Gemcitabine (Gemzar; Eli Lilly) that is active in untreated sclc, may also be effective in resistant disease (Postmus PE, etal, Semin Oncol, Aug 1998;25(4 Suppl 9):79-82). In a phase II clinical trial, 38 heavily pretreated patients with resistant sclc were treated with gemcitabine (1000 mg/m^2), administered IV in 30 minutes, on days 1, 8 and 15 of each 28-day cycle; a maximum of 5 cycles were delivered. Treatment was discontinued in case of PD or unacceptable toxicity. Among 35 evaluable patients, after 2 courses of gemcitabine, there were 5 PR (14.2%) and disease stabilized in 6, and progressed in 24. TTP among responders varied from 1 to 5 months. Toxicity consisted of Grade 3/4 thrombocytopenia in 11/36 (30.6%) patients, and Grade 3 leukocytopenia in 7/36 (19.4%). Nonhematologic toxicity was mild and consisted of nausea in most patients, without significant emesis (Van der Lee I, etal, ASCO99, Abs. 1835:476a).

Topotecan was approved on November 30, 1998, for the treatment of chemotherapy-sensitive (defined as disease responding to chemotherapy, but subsequently progressing at least 60-90 days after chemotherapy) sclc after failure of first-line chemotherapy. Approval was based on results from four clinical trials conducted in relapsed sclc. A randomized, international, multicenter, 211-patient, phase III clinical trial, undertaken by the International Topotecan Study Group in 44 centers in Europe, North America and South Africa, compared topotecan (1.5 mg/m^2), administered on days 1-5, every 21 days, with a CAV regimen consisting of cyclophosphamide (1000 mg/m^2), doxorubicin (45 mg/m^2) and vincristine (2 mg), all administered on day 1, every 21 days, in the treatment of recurrent sclc in patients whose disease had not progressed within 60 days of cessation of first-line therapy. The overall response rate was 26/107 (24.3%) in the topotecan arm, and 18/104 (17.3%) in the CAV arm. MST was similar in both groups, 5.8 months with topotecan compared to 5.7 months with CAV, and TTP was 3.1 months and 2.8 months, respectively. More topotecan- than CAV-treated patients reported improvement in disease-related symptoms. Grade 4 neutropenia occurred in 69% of topotecan-treated patients (38% courses) and in 73% in CAV-treated patients (51% courses); Grade 4 thrombocytopenia was 29% (10%) and 5% (1.5%), respectively (Schiller J, etal, ASCO98, Abs. 1755:456a). Reports were also presented on 3 open-label, phase II clinical trials involving 319 patients with recurrent or progressive sclc after treatment with first-line chemotherapy. An oral formulation of topotecan is also undergoing clinical evaluation in ovarian cancer and sclc.

Paclitaxel is also being evaluated in various combination regimens (see Exhibit 6). On such combination regimen, consisting of a 3-hour IV infusion of paclitaxel (175 mg/m^2), followed by a 30-minute infusion of carboplatin (AUC 7), once every 3 weeks for five cycles with standard premedication before every cycle (dexamethasone, clemastine, and ranitidine), in 35 sclc patients (limited-stage=16 and extensive-stage= 19) who relapsed within 3 months after first-line treatment consisting of a CAV regimen, was evaluated in a phase II clinical trial. Based on a total of 232 cycles, hematologic toxicity consisted of Grade 3 or 4 leukopenia (27% and 6%), thrombocytopenia (21% and 13%), and anemia (17% and 0%); neutropenic fever

— continued on back page

— continued from page 1127

occurred in 2 patients, and there were no toxic deaths. Nonhematologic toxicity included Grade 3 paresthesia, Grade 4 diarrhea, and Grade 3 myalgia in one patient each. Reversible paresthesia (Grade 1 and 2) in toes and fingers was reported in 69% of patients. Among 34 patients assessable for response, there were 2 CR, 23 PR, for an overall response rate of 73.5%, and disease stabilized in 8 and progressed in 1. Median time to progression was 21 weeks, MST was 31 weeks (range=6 to 112 weeks) and 1-year survival was 9% (Groen HJ, etal, J Clin Oncol, Mar 1999;17(3):927-32).

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