Small Cell Lung Cancer

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In the United States, lung cancer is the leading cause of cancer-related death,

Of all patients with lung cancer, approximately 14% will have small cell lung cancer (SCLC) .

Only a small percentage of patients with limited-stage SCLC are curable. In patients with more advanced disease, the overall outcome remains dismal, with 5-year survival rare

Etiology

A)smoking : The most common carcinogen associated with SCLC is tobacco smoke. Approximately 98% of all cases of SCLC occur in patients with smoking histories

Tobacco smoke has over **50 known carcinogens**, including polycyclic aromatic hydrocarbons and *N*-nitrosamines .

A dose-response relationship between cigarette smoking and the development of lung cancer has been reported by the Cancer Prevention Study II established by the American Cancer Society

Men who smoked 20 cigarettes per day had a22-fold increased risk of dying from lung cancer as compared with nonsmokers. For men who smoked more than 41 cigarettes a day, the risk was increased 45 times .

The risks of lung cancer and death are increased by

initiating smoking at an earlier age,

inhaling greater amounts of tobacco smoke,

smoking cigarettes with higher tar and nicotine levels .

smoking unfiltered cigarettes

Smoking cessation : as NSCLC

B) Additional carcinogenic agents associated with SCLC are asbestos, radon—especially in the case of miners exposed to uranium, coal tar, benzene, and halogenated ethers

These other agents typically act as cocarcinogens with tobacco, amplifying risk of lung cancer development.

Epidemiology

Age : peak at ages 55 to 65 years.

Sex : The incidence of lung malignancy is higher in men than in women.

However, over the last two decades, an increasing incidence of lung cancer has been seen in women, while a decreasing trend has been seen in men . This upward trend of lung cancer incidence in women has been attributed to an increase in smoking and the use of tobacco-related products.

Biology

Often in lung cancer, the aerodigestive tract epithelium has been exposed to carcinogens (field cancerization), and lung cancer arises from a stem cell that develops genetic abnormalities (Table 11-1).

Mutated Genes Associated with Small Cell Lung Cancer	
Tumor Suppressor Genes	**Protooncogenes**
RASSF1A	Myc
FHIT	Bcl-2
Retinoic acid receptor-beta	c-Kit
P53	c-Met
RB	IGF-1
Telomeres	TGF-B
	G protein-coupled receptors

Tumor Suppressor Genes

Tumor suppressor gene products are important regulators of cell growth. When these genes are mutated, a significant loss of function and unregulated cell growth can occur.

1)In SCLC, the most common genetic mutation is the deletion of a region on chromosome 3 [3p] (17). The loss of this allele at 3p is seen in 90% of SCLC tumors and in 80% of NSCLC .Chromosome 3p contains several genes potentially associated with the development of SCLC

a)Ongoing research has shown that hypermethylation occurs at certain regions on chromosome 3p, specifically the CpG island of the promotor sequence of the Ras-association domain **(RASSF1A) .** Hypermethylation and the silencing of this promotor were found to correlate with a loss of RASSF1A protein expression in

100% of SCLC tumors.

RASSF1A is believed to respond to DNA damage and suppress cell growth. Loss of this protein's function enables unregulated cell growth (23).

b) **The fragile histidine triad (FHIT**) gene is also located on chromosome 3p and encodes for a product involved in the metabolism of diadenosine tetraphosphate into adenosine triphosphate and adenosine monophosphate (25). Loss of the FHIT gene leads to accumulation of diadenosine tetraphosphate and increased DNA synthesis and cell proliferation

Some 80% of all SCLC tumors have been shown to have FHIT abnormalities (28).

c) the gene encoding for the **retinoic acid receptor-beta** isoform is located at 3p24 (29). Retinoic acid receptors are nuclear hormone receptors that regulate the retinoic acid response elements and may be promising tumor suppressors.

In the majority of SCLC tumors, abnormal retinoblastoma (RB) and p53 gene products have been identified.

2) **The RB gene** is located on chromosome 13q14.11 and encodes for a nuclear protein that regulates the G1-phase to S-phase transition (30).

3) **The *p53* gene** is located on chromosome 17q13.1 and encodes for a transcription factor that blocks the progression of cells from the G1 phase. In aerodigestive tract tumors, it is particularly interesting that mutations in *p53* leading to loss of protein function have been associated with cigarette smoking. Benzopyrene, a common tobacco smoke carcinogen, has been shown to cause a common point mutation in the *p53* gene.

4)Another genetic component under investigation in SCLC is the telomere. Telomeres are tandem repeats of DNA sequences that assist in stabilizing chromosomes. Abnormal telomeres have been found in lung malignancies. Over 98% of SCLC tumors have **upregulated telomerase** activity and overexpression of the telomerase RNA subunit

Protooncogenes:

1) The protooncogene **Myc** (c-Myc, N-Myc, L-Myc) is a nuclear DNA-binding protein that regulates cell proliferation, apoptosis, and differentiation. Gene amplification and gene product overexpression lead to oncogenic activity (34). Although the frequency of Myc overexpression in SCLC is variable, the amplification of c-Myc genes has been associated with a worse prognosis

2**) Bcl-2** is a negative regulator of cell death, expressed in 75% of SCLC cases,

The overexpression of insulin-like growth factor 1 (IGF-1), c-Kit, hepatocyte growth

factor, c-Met, and transforming growth factor beta (TGF-) has also been

associated with SCLC.

Autocrine Factors:

In SCLC, certain proteins are associated with neuroendocrine and neural differentiation.. **IGF-1** is found in 95% of SCLC tumor cell lines, and IGF-1 and **gastrin-releasing peptide** may enable autoproliferative paracrine and autocrine loops in SCLC

Autocrine loop pathways in SCLC have been targeted by monoclonal antibodies. In a phase II trial testing a murine monoclonal antibody to gastrin-releasing peptide in patients with recurrent SCLC, one patient responded, demonstrating proof of the concept that targeting an autocrine loop pathway can effect cytoreduction in SCLC

Drug Resistance

Although SCLC is initially highly sensitive to chemotherapy and radiation, the majority of patients relapse with resistant disease.

A) The best-established mechanism of drug resistance in oncology is the multidrug resistance 1 (MDR-1) gene, which encodes for the 170-kDa multidrug efflux pump P-glycoprotein. This pump transports drugs across the cytoplasmic membrane and, if rendered abnormal, will promote cell resistance to vinca alkaloids, anthracyclines, and epipodophyllotoxins.

Multidrug resistance–related protein (MRP) is another commonly transmembrane transporter that is overexpressed in drug-resistant SCLC cell lines

It is 190 kDa and is associated in vitro with resistance to doxorubicin, vincristine, etoposide, and cis-diamminedichloroplatinum II (48).

Although in vitro studies have shown an association between MDR-1 and drug resistance, **the effect of MDR-1 in SCLC in vivo is controversial**.

In one study, Hsia et al. reported that 11 of 23 bronchial biopsies from patients with SCLC who responded poorly to chemotherapy showed positive immunohistochemical staining for P-glycoprotein and MRP (49). In 27 patients with SCLC who responded well to treatment, no immunohistochemical staining for P-glycoprotein or MRP was found (49).

Another study, however, reported no correlation between the expression of the MDR-1 gene and response to treatment in SCLC cell lines

B) In tumors where MDR-1 and MRP are not overexpressed, resistance to certain cytotoxics has been attributed to changes in activity in **topoisomerase I or II.**

C) An additional study also suggested that **Bcl-2** may have a role in drug resistance

To further investigate the mechanism of drug resistance in SCLC, a phase III trial randomizing patients to cyclophosphamide, etoposide, epirubicine or cyclophosphamide, epirubicine, and vincristine alternating with carboplatin and etoposide was conducted.

The investigators performed pretreatment biopsies of the tumors and looked for immunohistochemical expressions of topoisomerase II, MRP, Bcl-2, Ki-67, p53, and p21

The results indicated that the expression of high levels of topoisomerase II, Bcl-2, and Ki-67 conferred a worse clinical prognosis.

In this study, no relationship was found between clinical outcome and MRP.

Pathology

In 1988, the **International Association for the Study of Lung Cancer** suggested using the following subtypes for SCLC:

small cell carcinoma, mixed small cell and large cell carcinoma, and combined small cell carcinoma. It has been suggested that SCLC originates from a pluripotent stem cell that can differentiate along different pathways, which would account for the variable histologies in the mixed form.

In 1999, the **World Health Organization (WHO)** classified SCLC into two categories,

1) classic or lymphocyte-like,

2)and as being either intermediate subtypes or combined tumors (adenocarcinoma, squamous cell, or large cell) (Table 11-2).

World Health Organization Classification of Small Cell Lung Cancer
Small cell carcinoma
Mixed small cell/large cell carcinoma
Combined small cell carcinoma*

* Combinations can occur with any other histologic subtype.

More than half of the patients present with perihilar masses and extensive mediastinal lymph node involvement. The cells usually involve only the submucosal layer of the airway, and often there is no exophytic endobronchial component. Tumor cells are

therefore unlikely to be found in sputum or bronchoscopic washings (56).

Light microscopy usually reveals monotonous "small round blue cells" with occasional spindle morphology Occasionally, the cells organize in a rosette formation with high mitotic counts with foci of necrosis.

Cellular atypia or pleomorphism with a high nuclear-to-cytoplasmic ratio can be seen.

The nuclear chromatin has been described as having a " salt and pepper" pattern because of its granularity.

No pathologic grading is reported because all SCLCs are considered high grade ..

Electron microscopy often shows sparse, dense granules in the cytoplasm, scanty cytoplasm

Immunohistochemical staining is often positive for chromagranin, synaptophysin, and CD56. Additional hormonal markers include calcitonin, glucagon, corticotropin, insulin, and vasoactive intestinal polypeptide

The common differential diagnosis of small blue round cell tumors includes SCLC, extrapulmonary small cell carcinomas,

carcinoid, atypical carcinoid,

small cell sarcomas, and lymphomas, Ewing

Merkel cell carcinoma,

.

Staging

In the modern era, tumor-node-metastasis staging can be used to identify patients with stage I disease who may benefit from resection.

However, SCLC is commonly staged using a modified version of the two-stage **Veterans Administration Lung Cancer Study Group system**, which classifies SCLC as limited-stage or extensive-stage disease

Approximately one-third of patients with SCLC will have limited-stage disease on initial presentation; the remainder will have extensive-stage disease (62).

Staging System for Small Cell Lung Cancer
Limited: Confined to a single hemithorax, where the tumor can be encompassed by a single tolerable radiation port
Extensive: Malignant pleural or pericardial effusion or disease that extends beyond limited stage

In the era of definitive chemoradiation, limited stage also frequently excludes patients with lymphadenopathy in the contralateral hilum and/or the contralateral supraclavicular fossa due to the large size of the required radiation port. Patients with malignant pericardial or pleural effusion or disease beyond what is described in limited-stage disease are considered as having extensive-stage disease.

Natural History :

Unfortunately, if left untreated, SCLC is rapidly fatal. MS in limited stage 6 w ,extensive stage 12w

Patients who present with limited-stage disease are also at high risk for having occult metastasis.

Treatment of SCLC with polychemotherapy and combined-modality treatment has increased the median survival rate of patients with SCLC. Currently, **the median survival time for limited-stage disease is 20 months**, with a 2-year survival rate of 45% and a 5-year survival rate of 20% (60). **The median survival time for extensive-stage disease is 1 year**, with a 2-year survival rate of 10% and a 5-year survival rate of less than 5% (60,66).

Prognostic Factors

Age has also been investigated as a prognostic factor and remains controversial

Sex no difference in survival outcome was seen between men and women when the dose intensity of treatment was adjusted .

the most important adverse prognostic features are a **poor performance status and advanced stage.**

In limited-stage SCLC, having an early stage I is favorable, but an elevated level of lactate dehydrogenase (LDH) is a poor prognostic feature

The level of serum LDH can predict a poor outcome because it is elevated in up to 85% of patients with extensive-stage disease .

In extensive disease, the extent of disease or stage, If more organ sites are involved,

the patient will have a worse prognosis. Metastatic disease to the liver, in particular, is considered highly unfavorable.

And presence of bone marrow metastases affect prognosis and long-term survival.

To date, **no molecular markers** have been proven to reliably predict the clinical outcome in SCLC.

For clinical purposes, **the creation of a prognostic model for SCLC** has been important. In one study, the combination of

poor performance status,

clinical hepatomegaly, low serum albumin, and

elevated levels of blood urea nitrogen and serum alkaline phosphatase

predicted higher mortality rates during treatment

Diagnostic Evaluation

CP as usual **Because SCLC is an aggressive tumor, patients will often develop symptoms over a short period of time (8 weeks) .A typical clinical presentation consists of the following symptoms: fatigue, anorexia, weight loss, cough, shortness of breath or dyspnea on exertion, and occasionally hemoptysis and debilitation with or without evidence of obstructive pneumonia. Additional symptoms associated with the spread of intrathoracic cancer are superior vena cava obstruction, hoarseness (resulting from recurrent laryngeal nerve involvement), phrenic nerve palsy, dysphagia (resulting from esophageal compression), and stridor (resulting from tracheal compression). SCLC often metastasizes to the central nervous system, bones, or liver, resulting in neurologic deficits or seizures, bone pain, or right-upper-quadrant pain, respectively .**

Paraneoplastic Processes

1)The most common of these **are hormonally mediated** and include syndrome of inappropriate antidiuretic hormone (SIADH) and Cushing's syndrome. These conditions result from ectopic secretion of the polypeptide hormones vasopressin and adrenocorticotropic hormone, respectively. The endocrine syndrome will generally subside with cytoreduction of tumor.

2)Paraneoplastic disorders of **neurologic origin** are less common. Some of these disorders occur as the result of onconeuronal antibodies recognizing tumor antigens as well as neuronal cell antigens (Table 11-4) (4,81–86). The most common disorder is **Eaton-Lambert myasthenic syndrome**, which is seen in 3% of patients with SCLC.

Onconeuronal Antibiotic-Recognizing Tumor Antigens as Neuronal Cell Antigens	
Onconeuronal Antigens	**Antibody**
Hu	Anti-Hu
Nova	Ri
Yo/cdr2	Anti-Yo
Nb	Anti-Nb
Tr	Anti-Tr
Ma1	Anti-Ma1

Autoantibodies impair acetylcholine release from the presynaptic motor terminal at the neuromuscular junction and cause transient cranial nerve palsies, proximal muscle weakness with lower extremity predominance, and depressed tendon reflexes (87).

Additional paraneoplastic central nervous system disorders include

stiff-man syndrome," resulting from antiamphiphysin antibodies

encephalomyelitis resulting from anti-Hu antibodies

Despite a more indolent course of SCLC, patients with paraneoplastic neurologic syndromes have a poor prognosis from progressive neurologic decline. This is largely due to limited treatment options and the observation that often, by the time clinical neurologic dysfunction is observed, significant permanent damage to neuronal tissue has occurred, and neurologic function is unlikely to improve with treatment. The recommended approach is to combine the removal of the antigen stimulus (by treating the underlying malignancy) with plasma exchange to remove antibodies and immunosuppression

Invetigations:

SCLC tumors are usually centrally located, although occasional peripheral satellite nodules are found.

Initial radiographic images often show a large hilar mass with bulky mediastinal lymphadenopathy.

The initial clinical evaluation should include

chest x-ray; computed tomography (CT) scans of the chest, liver, and adrenal glands;

a magnetic resonance imaging (MRI) or CT scan of the brain; a bone scan; and

The use of positron emission tomography is not standard.

Bone marrow aspirates and biopsies are no longer routine; these should be performed

to evaluate cytopenias or

in the case of patients with apparent limited-stage disease and significant elevations of LDH and/or alkaline phosphatase.

In the presence of obvious extensive disease (e.g., metastasis to liver), staging may be clinically directed. The goal of complete staging is to identify the limited-stage patient who is a candidate for definitive therapy.

baseline laboratory tests.

Additional studies may be necessary if clinical findings demonstrate other abnormalities.

If a pleural effusion is present, a thoracentesis should be performed and sent for cytologic testing. If the fluid is exudative or if malignant cells are present, the patient is diagnosed with extensive-stage disease.

Sampling of cerebrospinal fluid is indicated if there is suspicion of leptomeningeal spread.

Pulmonary function tests should be performed in patients who are candidates for definitive chemoradiation (4).

Treatment Recommendations

Limited-Stage Disease

A) Patient with good PS

1)After the clinical staging studies are completed, patients with very limited-stage SCLC (clinical stage T1, T2, N0) should proceed to mediastinoscopy. If the mediastinoscopy is negative, the patient's tumor should be surgically resected, including a lobectomy and mediastinal lymph node dissection.

If the lymph node dissection is negative for disease, adjuvant chemotherapy with cisplatin and etoposide (PE) or carboplatin and etoposide for four to six cycles is recommended.

If the lymph node dissection is positive, chemotherapy and concurrent mediastinal radiotherapy are advised (identical to the treatment of unresected limited-stage disease).

2) For the typical patient with node-positive limited stage disease who has good performance status, definitive chemoradiation should be given . Chemotherapy with PE and thoracic radiotherapy with 1.5 Gy twice a day (total dose, 45 Gy) or 1.8 Gy per day (total dose 45 Gy) are recommended by the National Comprehensive Cancer Network (4). Radiotherapy should begin with the first or second chemotherapy cycle.

Prophylactic cranial radiation (PCI) is recommended in limited-stage SCLC if there is good regression of intrathoracic disease following completion of treatment. Acceptable regimens for PCI include 24 Gy in eight fractions to 36 Gy in 18 fractions

B) Patients a poor performance status should receive chemotherapy without radiotherapy initially, with the potential of integrating it in subsequent cycles should performance improve (4). In some cases it may be prudent to delay chemotherapy and palliate with radiation initially to reduce the risk of early treatment-related death.

Extensive-Stage Disease

In extensive-stage SCLC, **chemotherapy is the primary treatment**. PE or carboplatin and etoposide for four to six cycles is recommended

Palliative radiation can also be considered for relief of symptoms from painful bony metastases or superior vena cava syndrome.

Whole-brain irradiation in patients with brain metastasis is considered part of the initial treatment if the brain metastasis is symptomatic. If the brain metastasis is asymptomatic, the radiation may be delayed until after the chemotherapy has been completed as long as the brain disease is responding to treatment (4).

Patients without brain metastasis who have a complete or near-complete response to chemotherapy should be offered **PCI**, as discussed above. Patients with established cerebrovascular disease and the elderly in general are at higher risk for neurotoxicity; PCI is not recommended in this setting.

Chemotherapy

Chemotherapy in Limited-Stage Disease :

Randomized trials conducted in the latter 1970s and 1980s, and reported in two metaanalyses documented the survival benefit of adding thoracic radiation to chemotherapy for limited SCLC

In the mid-1980s the PE regimen was studied in extensive-stage disease and found effective and well tolerated.

Because it is minimally myelosuppressive and lacking in mucosal toxicity, the PE regimen proved to be much better tolerated than older regimens in concurrent schedules with radiation (96).

The current standard of care for chemoradiation was established by a phase III trial (Intergroup 0096) in which four cycles of PE were evaluated in 416 patients with limited-stage SCLC. **Twice-daily concurrent fractionation radiotherapy over 3 weeks was compared with standard once-daily radiotherapy over 5 weeks**. Patients receiving the twice-daily radiotherapy fractionation lived a median of 4 months longer and had 10% improvement in 5-year survival as compared with the patients receiving once-daily radiotherapy (23 months versus 19 months and 26 versus 16%, respectively)

This study showed that early dose-intense radiation can improve locoregional control and prolong long-term survival rates; it confirmed that PE is a tolerable and effective regimen with concurrent thoracic radiotherapy.

The superiority of PE as the standard regimen in limited-stage SCLC was confirmed in additional studies. In a phase III trial, PE was compared with a regimen of cyclophosphamide, epirubicin, and vincristine in patients with limited-stage and others with extensive-stage SCLC (98). The results showed that in patients with limited-stage disease, PE was superior to cyclophosphamide, epirubicin, and vincristine for survival rates at 2 and 5 years In patients with extensive-stage disease, no survival difference was noted.

The addition of other cytotoxins to the PE regimen—either as a triplet with ifosfamide or paclitaxel or alternating therapy with cyclophosphamide, doxorubicin, and vincristine—has also been studied, but to date a new standard in the treatment of limited-stage SCLC has not emerged

A recent phase III clinical trial reported that irinotecan combined with cisplatin was significantly more beneficial than PE in extensive-stage SCLC disease. Whether this combination regimen will replace PE in limited-stage disease is the topic of ongoing research.

Chemotherapy in Extensive-Stage Disease

The current standard chemotherapy regimen for extensive-stage SCLC consists of

PE or **PE alternating with CAV**. These regimens typically provide median survival times of 8 to 10 months and a 15% survival rate at 2 years.

A recent phase III trial from Japan established that a superior regimen to PE comprised irinotecan and cisplatin. However, studies are ongoing in North America and Europe to confirm this trial. Until additional studies have been conducted, the current standard remains PE or PE alternating with CAV in the United States.

Single-Agent versus Combinations

It has been well established that combination chemotherapy is superior to single-agent chemotherapy in treating extensive-stage SCLC.

Maintenance Chemotherapy

Patients with extensive-stage SCLC were previously treated with multiple chemotherapeutic regimens, often for the duration of their lives. However, several trials have compared the four to six courses of induction chemotherapy with or without the addition of maintenance chemotherapy. Although the results were not all consistent (106,107), no significant overall survival advantage has been reported in patients receiving maintenance chemotherapy

1) In a large trial, Beith et al. concluded that **CAV maintenance** did not confer a survival advantage to patients receiving induction chemotherapy with PE and only provided more toxicity

2) Schiller et al. presented a phase III trial . Patients received PE every 3 weeks for four cycles and then were randomized to four cycles of **topotecan maintenance** (1.5 mg/m^2 per day for 5 days every 3 weeks) or observation.

demonstrating that maintenance chemotherapy beyond four to six cycles was able to prolong the duration of response but did not affect overall survival

Optimal Number of Induction Cycles

The optimal number of induction chemotherapy cycles has been evaluated in several trials. IN Trial enrolled 610 patients with extensive- and limited-stage disease

Patients received **four or eight courses of chemotherapy** The patients in both the four- and eight-cycle arms were found to have equivalent overall response rates

Patients who relapsed were then randomized to receive second-line chemotherapy or supportive care. The results of this trial showed that patients who received four cycles of initial chemotherapy before salvage treatment had better response rates than those who received eight cycles and better median survival times.

This trial illustrated that brief courses of induction chemotherapy (four to six cycles) provided the most benefit for patients with extensive-stage SCLC.

Substitutions and Additions to Induction Therapy

Substitutions Adjustments to the PE regimen have been investigated. Carboplatin has often been substituted for cisplatin in clinical practice, especially for patients with extensive-stage disease (116).

randomized study comparing PE to carboplatin and etoposide in 147 patients with limited- or extensive-stage SCLC showed , no significant differences were seen in response rate or median survival time, but less toxicity was reported in the carboplatin-containing arm.

Additions

1)Loehrer et al. conducted a randomized trial that added **ifosfamide** to the PE regimen

and reported that it provided a survival advantage to patients with extensive-stage disease

2)In a recent phase III trial by the French Federation of Cancer Institutes, PE was compared to PE plus **cyclophosphamide and 4'-epidoxorubicin** in patients with extensive-stage SCLC (119). This study reported that the four-drug regimen conferred improved survival and response rates..

Alternating or Sequential Combinations

Rational SCLC has a high relapse rate despite initial chemosensitivity. Several theories have been proposed to account for this phenomenon. One theory is that resistant clones develop during induction treatment. Based on this, the Goldie and Coldman hypothesis proposed that non-cross-resistant regimens could be rapidly alternated to eliminate resistant clones (162).

Three randomized phase III trials have evaluated PE and CAV regimens in direct and alternating sequences (199,121,122). Although the Fukuoka et al. trial reported that patients with limited-stage disease benefited from alternating PE and CAV, alternating combination regimens have failed to confer a consistent survival advantage to patients with extensive-stage SCLC .

In another approach, rapid sequencing of several active agents over a short treatment period was evaluated. The most studied regimen comprised weekly treatments of CODE. Although early studies indicated that CODE conferred a possible survival advantage to patients with extensive disease, subsequent phase III trials did not show that it was any better than alternating CAV and PE (123,124).

Altering Dose Intensity :

Higher-dose chemotherapy remains controversial as a solution to resistant SCLC.

A metaanalysis showed that in patients with extensive-stage SCLC, **dose-intense CAV** provided a clinically insignificant increase in median survival time (125). Several randomized trials have also been conducted, with primarily negative results

Two recent trials using cisplatin-based regimens have reported conflicting results The National Cancer Institute randomized 90 patients with extensive disease to standard or **high-dose PE for cycles 1 and 2.** No differences in overall survival were seen between the standard and high-dose arms.

The second trial was performed in France and reported a positive result in patients with limited-stage disease .As most studies do not show that high-dose therapy increases survival, high-dose therapy is not a standard of care (4).

Dose-Dense Chemotherapy

Dose-dense chemotherapy is another means of addressing SCLC resistance. The proposed mechanism of action is to reduce the time interval between cycles of chemotherapy by using hematopoietic growth factors.

Several trials evaluated this hypothesis. Steward et al. randomized patients with limited- and extensive-stage disease Given the **conflicting results of these trials**, and the added expense of hematopoietic support, dose-dense therapy remains in the realm of clinical research.

Studies have assessed the value of **autologous bone marrow transplant** and peripheral blood stem cell support and dose escalation in SCLC.

Although there was an improvement in relapse-free survival, the high toxicity rate (four deaths in the high-dose arm) and the absence of a clear impact on overall survival make this approach problematic.

New Chemotherapeutic Agents

Single-Agent Studies

Irinotecan (CPT-11) is a camptothecin derivative that inhibits the nuclear enzyme topoisomerase I.

Topotecan is a semisynthetic camptothecin analog that also inhibits topoisomerase I..

Docetaxel and paclitaxel are taxoids and have been studied as single agents in SCLC.

Gemcitabine is a pyrimidine antimetabolite that is an analog of deoxycytidine.

Ifosfamide is a derivative of cyclophosphamide that causes less myelosuppression.

Vinorelbine is a semisynthetic vinca alkaloid that prevents tubulin polymerization.

Combinations of the Newer Agents

The combination of etoposide, **ifosfamide**, and cisplatin (VIP) has been studied in clinical trials and shown mixed results (152–154). In one randomized phase III trial comparing VIP to PE in previously untreated patients with extensive-stage SCLC, there was **no statistically significant difference in response rate, but the overall survival time was better in the VIP arm** (VIP versus PE: 9.1 versus 7.3 months, respectively; $p = 0.044$) Higher rates of myelosuppression occurred in the VIP arm. Another phase III trial comparing VIP to PE in both limited- and extensive-stage SCLC did not show any difference in response or overall survival rates (154).

Two randomized trials have compared **paclitaxel, etoposide, and cisplatin (PET**) to PE (155,156). In both trials,. No differences in overall response or median survival rates were seen, but an increase in toxicity (myelosuppression, neurotoxicity, toxic

death) was seen in the PET arm (155).

Irinotecan in combination with cisplatin (PI) has been evaluated in multicenter phase III trial comparing PI to PE in previously untreated patients with extensive-stage SCLC. **a clear median survival advantage was seen at an interim analysis** of 177 patients (PI versus PE: 12.8 versus 9.4 months; $p = 0.0021$). Thus the study was closed early. **Progression-free survival time** was also improved in the PI arm

The 2-year survival rate was 19.5% in the PI arm and 5.2% in the PE arm.

The results of this trial have brought PI under consideration as a new standard, replacing PE. Ongoing trials in both North America and Europe are comparing PI to PE in more heterogeneous populations (Table 11-5) (160).

National Comprehensive Cancer Network Guidelines for Small Cell Lung Cancer
1. In limited-stage disease, concurrent chemoradiotherapy is recommended. Four to six cycles of a platinum- and etoposide-based regimen combined with 45 Gy of thoracic radiotherapy is the most common regimen. Thoracic radiotherapy should begin by cycle 3 of chemotherapy.
2. Prophylactic cranial irradiation (PCI) is recommended for patients with limited-stage SCLC who achieve a complete response.
3. In extensive-stage disease, combination chemotherapy is recommended, as combination of platinum and etoposide is superior to single-agent etoposide therapy.
4. Patient participation in clinical trials should be encouraged.
5. Smoking cessation should be encouraged.

Salvage Regimens

Recurrent SCLC carries a poor prognosis because patients often die within a few months of diagnosis.

There are several prognostic factors that determine clinical outcome.

Positive features include :

having a sensitive relapse (SR), A SR is defined as having a positive response to induction therapy and remaining free of progressive disease for at least 3 months after treatment is discontinued

maintaining a good performance status (0–1),

maintaining stable weight

general guideline,

1)patients with recurrent SCLC with good performance status should be offered a clinical trial.

2)If this is not possible, additional chemotherapy is reasonable for patients in sensitive relapse (see above). Benefit of therapy for patient with refractory disease is less clear

3)If the relapse occurs more than 6 months after completion of initial therapy, the induction regimen can be repeated (4).

Single-Agent Therapy

Topotecan was approved for second-line treatment of SR disease in 1998 by the U.S. Food and Drug Administration. This agent has been evaluated in three randomized trials in patients with SR disease. The first phase III trial compared CAV with single-agent topotecan given at 1.5 mg/m^2 on days 1 through 5 (168). The study reported that response rates, progression-free survival rates, and overall survival rates were similar between the two arms. Patients on the topotecan arm experienced better symptom improvement.

The second trial was a phase II and compared the intravenous and oral routes of topotecan administration. There was no difference in efficacy, but the intravenous formulation appeared to cause less severe neutropenia (169).

this trial concluded that oral administration of topotecan was an acceptable alternative to intravenous therapy.

For single-agent therapy, numerous phase II trials have assessed the newer ctyotoxins.
1)**Irinotecan** demonstrated 30% response rate in SR disease but had considerably less activity in refractory disease (RD), with a response rate of less than 10%

2)**paclitaxel** demonstrated 30% response rate, but the median survival time was poor at 100 days

3)**Docetaxel** was evaluated in two separate trials and had a cumulative response rate of 20%.

4) **gemcitabine and vinorelbine** had response rates of 15.

Combination Regimens

. **This is especially promising for patients with RD.**

Masuda et al. studied **irinotecan and etoposide** in patients with refractory or relapsed SCLC overall response rate of 70%..

Ando et al. used **irinotecan and cisplatin** in 22 patients with relapsed or refractory

disease (172). The overall response rate was 78%

Fujita et al. reported an overall response rate of 90 % in 18 patients with SCLC treated with **irinotecan , cisplatin, ifosfamide**

The EORTC LCCG performed a multicenter phase II study of topotecan and cisplatin in patients with SR and RD SCLC 30 % RR IN RD

Domine et al. reported a 40% response rate in patients with RD SCLC treated with gemcitabine and paclitaxel. Patients with SR disease in this study had a 60% overall These combination treatments show promising results for patients with RD SCLC and should be studied further in larger phase III trials.

Thoracic Radiation

The impact on survival by duration of radiotherapy, overall radiotherapy treatment times, and accelerated hyperfractionation has been investigated in several trials (179). The Intergroup 0096 study randomized patients with limited-stage SCLC to receive PE and then concurrent radiotherapy, either 45 Gy given as 1.8 Gy daily for 25 fractions in 5 weeks or given as 1.5 Gy twice daily for 30 fractions in 3 weeks. Patients in the accelerated, hyperfractionated arm had a 5-year survival rate of 26%, compared with 16% in patients on conventional radiotherapy (97).

One potential explanation for this difference is that accelerated, hyperfractionated regimen may control tumor cell repopulation. .

With PE as the chemotherapy regimen, it is clear that earlier and concurrent integration of thoracic RT is more effective. Three trials have been reported with PE or carboplatin and etoposide. These compared radiation in the second cycle versus the sixth cycle of chemotherapy (181), in the first versus the third cycle (182), or in the first cycle versus giving it as consolidation after the fourth cycle (183). A long-term survival benefit for earlier radiation has been reported in all of these trials.

Prophylactic Cranial Radiation

Rational

1)In SCLC, recurrence in the brain imparts substantial morbidity and mortality.

2)The risk of developing brain metastasis by 2 years after diagnosis has been reported to range between 50 to 80%

3)The intact blood-brain barrier prevents effective chemotherapy from reaching micrometastatic disease in the brain.

Therefore PCI has been studied in an effort to treat and control metastatic disease before it becomes clinically evident.

Indication In SCLC, the benefit of PCI is greatest in patients who have complete response to induction therapy. Patients with persistent systemic disease can "re-seed" the brain and are therefore not good candidates for PCI

Benefit In the Prophylactic Cranial Irradiation Overview Collaborative Group metaanalysis, which evaluated seven randomized trials, PCI was determined to benefit patients with a complete remission from induction therapy (186). PCI is effective in decreasing the rate of brain metastasis in SCLC, and this has a small impact on long-term survival (5% at 3 years).

It is important to separate PCI from chemotherapy and to use radiation regimens with a dose and schedule that have been documented safe as regards the incidence of late neurotoxic effects.

DOSE One method of decreasing toxicity is to use twice-daily treatments with smaller radiation doses per fraction—that is, 1.2 to 1.5 Gy with at least a 6-h interval (185). In a phase II trial, hyperfractionated PCI was reported to be efficacious at 30 to 36 Gy twice daily in 1.5-Gy fractions (187).

Gregor et al. conducted a three-arm randomized trial comparing PCI given at 36 Gy in 18 fractions, PCI given at 24 Gy in 12 fractions, and no PCI in patients with limited-stage SCLC who were in complete remission (189). This trial unfortunately had poor accrual, and the limited number of patients made interpretation difficult. There was suggestion of greater benefit with the higher dose.

Volume : In delivering PCI, the whole brain should be irradiated, including the temporal fossae. Radiation fraction sizes of 2 to 3 Gy, with total doses of 25 to 40 Gy, should be considered. In the Prophylactic Cranial Irradiation Overview Collaborative Group, the most common schedule was 24 Gy given in eight fractions (185,186).

. PCI should not be given concurrently with chemotherapy and should be offered to patients who have had a complete or, in the case of limited-stage patients postchemoradiation, near-complete response to induction treatment.

Special Populations: Elderly and Infirm

Approximately 25% of patients with SCLC are over the age of 70 years. This population of patients has often been excluded from clinical trials because of concerns for greater toxicity due to lowered organ reserves, especially myelosuppression and frequently lowered functional status due to comorbid conditions. However, retrospective studies have shown that elderly patients with retained performance have improved outcomes with more aggressive treatment (190). In a Canadian analysis, elderly patients of age 70 years or above who received four or more cycles of chemotherapy (CAV or PE) had a median survival time of 10.7 months (191). Elderly patients who received less than three cycles had a median survival time of 3.9 months, and patients with no treatment survived a median time of 1.1 months. Multivariate analysis showed that neither increasing age nor comorbid disease were adverse prognostic factors. This review reported that performance status, stage of disease, and treatment were the most important prognostic features. Additional studies have

confirmed these conclusions, whereas only one retrospective Australian review reported that the complications from therapy adversely affected outcome in the elderly population (192–197).

With regard to radiation tolerance in the case of limited-stage disease, elderly patients have been reported to have increased toxicity. Analysis of the patients above 70 years of age in the Intergroup trial 0096 (PE with conventional thoracic radiation versus hyperfractionated and accelerated treatment) showed that they experienced a higher

rate of treatment-related death (>0 years versus 70 years: 10 versus 1%, respectively) (91). However, the 5-year overall survival rate for elderly patients in this trial was 16%, similar to the survival for the entire group of patients on the control arm. Altered fractionation did not appear to benefit the elderly subgroup.

General recommendations for this population are as follows: Patients with good performance status and no significant organ dysfunction should receive full-dose chemotherapy and radiotherapy. Their higher risk of treatment-related death implies a need for close monitoring and intense supportive care. The prophylactic use of marrow growth factors after completion of radiation can be considered.

Patients with severe comorbid conditions, a worse performance status prior to diagnosis, or the very elderly may require a change in strategy from standard of care. However, randomized trials in patients with "poor risk" SCLC (and generally extensive disease) have consistently shown a benefit to combination chemotherapy relative to single-agent oral etoposide (198,199). These trials reported that intravenous combination regimens palliated symptoms better and improved median progression-free and overall survival. It can be concluded from these trials that in patients with a poor performance status, initial treatment should be combination chemotherapy.

Previously, PE for three to four cycles was recommended over cyclophosphamide- or doxorubicin-based regimens in the elderly population because it is less myelosuppressive (190). More recent studies have evaluated the combination of carboplatin and etoposide (200–203). With the exception of the trial reported by Samantas et al. (202), which used low doses of both agents, studies using carboplatin and etoposide have shown good response rates and tolerance in elderly patients.

In conclusion, carboplatin (AUC 5) and etoposide (100 mg/m^2 for 3 days) can be recommended for most patients with SCLC considered "high-risk" on the basis of age, comorbidities, or reduced functional status. It is clear that the time of highest risk for treatment-related mortality is in the first cycle. Close monitoring and support are critical during this time. Continued research in this area, especially in the very elderly, is needed.