New Agents in the Treatment of Small Cell Lung Cancer*

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The treatment of small cell lung cancer (SCLC) has evolved significantly over the past 3 decades. Single-agent and combination chemotherapy regimens with radiotherapy have greatly improved response rates and median survival. Combination regimens such as cisplatin/etoposide, carboplatin/etoposide, ifosfamide/carboplatin/etoposide, cyclophosphamide/doxorubicin/vincristine, and etoposide/ifosfamide/cisplatin have all achieved good response rates. Improving long-term survival, however, has remained problematic. Treatment with biological response modifiers (interferons alpha and gamma) has not shown promise in this setting. New agents showing good preliminary single-agent activity in untreated SCLC include paclitaxel, vinorelbine, gemcitabine, topotecan, and teniposide. Results obtained with single-agent docetaxel and CPT-11 are thus far inconclusive. Studies evaluating response and survival rates of these new agents in combination with agents of known activity are underway. (CHEST 1998; 113:868-915)

Mortality from all cancers in the United States has risen by 3% in men and 6% in women over less than 2 decades (from 1975 to 1979 to 1987 to 1991), mostly because of continuing increases in lung cancer mortality. An estimated 177,000 new cases of lung cancer are expected to occur in the United States in 1996, of which 40,000 will be of the small cell type. Most (80%) lung cancer cases are associated with tobacco use, and smoking is the major determinant of the rise in the incidence of lung cancer in women.

Over the past 3 decades the treatment of small cell lung cancer (SCLC) has undergone significant change. With the advent of effective chemotherapy and the incorporation of radiotherapy, response rates and median survival have improved greatly. Standard chemotherapeutic regimens have consistently produced 70 to 90% overall response rates in this disease. Limited-stage disease (LD) is confined to the hemithorax with or without ipsilateral supraclavicular lymph node metastases and encompassed in one radiation port, while extensive-stage disease (ED) comprises lesions at sites beyond the definition of LD. The Mayo Clinic and North Central Cancer Treatment Group database, which includes 1,617 patients in clinical trials, documented a median survival of 15.1 months for LD and 9.3 months for ED. The overall survival for LD and ED is 29% and 8% at 2 years, 12% and 2% at 5 years, and 4% and 1% at 10 years, respectively. These survival statistics clearly document the need to improve survival with new and innovative therapies. In this article, we will summarize currently employed chemotherapeutic regimens and review new agents in the treatment of SCLC.

Currently Used Regimens

Recent trials of combination chemotherapy for SCLC are summarized in Table 1.4-8 Cyclophosphamide/doxorubicin/vincristine (CAV) and cisplatin/etoposide are the most commonly used combination regimens in SCLC. Randomized studies have compared these two regimens. Einhorn et al9 compared the effect of consolidation with cisplatin/etoposide vs no consolidation after induction with CAV or CAV plus thoracic irradiation in patients with LD. In the 148 patients evaluated, median survival for patients randomized to cisplatin/etoposide was 24 months, compared with 17 months for the no consolidation arm (p=0.0094). At 65 weeks of follow-up, 36% of patients who received cisplatin/etoposide were alive vs only 18% of the no consolidation arm.

Following this study, Roth et al6 evaluated cisplatin/etoposide alternating with CAV (CAV/PE) vs either regimen alone. In terms of response and median survival, all three regimens were equally effective. (Cisplatin/etoposide, CAV, and CAV/PE response rates were 61%, 51%, and 59%, respectively; median survival was 8.6, 8.3, and 8.1 months, respectively.) Fukuoka et al7 also compared CAV, cisplatin/etoposide, and CAV/PE in 288 patients with ED and LD. Overall response rates were 55%, 78%, and 76%, respectively, with median survivals of 9.9, 9.9, and 11.8 months. The alternating regimen produced significantly better survival than either regimen alone. When corrected for prognostic factors, however, overall survival in the three arms did not differ. Severe leukopenia was noted in the CAV arm. Thus, CAV and cisplatin/etoposide have similar efficacy, but CAV appears to be more toxic. In the 1990s, cisplatin/etoposide has become the standard treatment for SCLC.

Carboplatin/Etoposide

Carboplatin, an analogue of cisplatin, has been investigated in ovarian cancer, non-small cell lung cancer, head and neck cancer, and SCLC. In SCLC, the standard regimen of cisplatin/etoposide has been compared with carboplatin/etoposide. In a phase III study,2 the Hellenic Cooperative Oncology Group for Lung Cancer Trials randomized 147 patients to receive either etoposide, 100 mg/m² on days 1 to 3, and cisplatin, 50 mg/m² on days 1 and 2, or etoposide, 100 mg/m² on days 1 to 3, and carboplatin, 300 mg/m² on day 1 plus radiation. Median survivals were similar, 12.5 months and 11.8 months, respectively, for the etoposide/cisplatin and etoposide/carboplatin arm. The majority (79%) of complete responders with LD had chest irradiation; 38% of complete responders among ED patients had chest irradiation. However, toxic reactions, particularly nausea, vomiting, nephrotoxicity, and neurotoxicity, were significantly lower.

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in the carboplatin/etoposide arm. Thus, carboplatin/etoposide is well tolerated and appears to be as effective as cisplatin/etoposide.

**IfoxamidContaining Regimens**

Ifoxamide, an analogue of cyclophosphamide, has been widely used. As a single agent in untreated SCLC patients, ifosfamide has produced an overall response rate of 49%. Ettenger has investigated ifosfamide as part of combination therapy with carboplatin and etoposide (ICE) in ED SCLC. This ICE regimen consisted of the following: ifosfamide, 5 g/m² on day 1; carboplatin, 300 mg/m² on day 1; oral etoposide, 50 mg/m² on days 1 to 21; and mesna. At these doses, 67% of patients had grade 4 hematologic toxicity, which necessitated reductions in the dosages of ifosfamide and etoposide to 3.75 g/m² on day 1 and 50 mg/m² on days 1 to 14, respectively. The overall response rate was 83%, with 63% of patients achieving a partial response (PR) and 20% a complete response (CR). Median survival was 9 months, and the 2-year survival rate was 14%. An overview of ICE regimen trials shows that in LD, overall response rates range from 76 to 94%, with a median survival of 14 to 19 months and a 2-year survival rate of 24 to 37%. In ED, overall response rates range from 72 to 90%, with a median survival of 9 to 14 months and a 2-year survival rate of 14 to 22%.

Ifoxamide has also been tested in combination with cisplatin and oral etoposide (VIP). A phase II study conducted by the Hoosier Oncology Group showed that in previously treated patients and patients with recurrent SCLC, VIP achieved an objective response rate of 55% (23/42 patients). However, myelosuppression was significant such that the duration of etoposide therapy was decreased from 21 to 14 days. The Hoosier Oncology Group also compared the standard cisplatin/etoposide regimen with VIP in previously untreated patients with ED in a phase III study. One hundred seventy-one patients were randomized to receive either etoposide, 100 mg/m², and cisplatin, 20 mg/m², on days 1 to 4, or etoposide, 75 mg/m² on days 1 to 4, ifosfamide, 1.2 g/m² with mesna on days 1 to 4, and cisplatin, 20 mg/m² on days 1 to 4. Myelosuppression was more severe in the VIP arm, but granulocytopenic fever and sepsis rates were not significantly different. Objective response rates were 67% and 73% for cisplatin/etoposide and VIP, respectively. Median survival was 9 months for patients receiving VIP and 7.5 months for those given cisplatin/etoposide. Survival rates for VIP and cisplatin/etoposide were 36% and 27% at 1 year, 13% and 5% at 2 years, and 5% and 0% at 3 years, respectively. These differences represent a statistically significant advantage for the VIP regimen with regard to both median and overall survival (p=0.03).

Both the VIP and ICE regimens have activity in SCLC. The hematologic toxicity associated with their use may be countered by administration of granulocyte colony-stimulating factor (G-CSF). These regimens, along with cisplatin/etoposide and carboplatin/etoposide, have produced comparable overall response rates, although long-term survival in patients with ED has been suboptimal (10 to 15% at 2 years). Therefore, the identification of new and innovative agents is of paramount importance.

**NEW AGENTS**

Trials of new agents in previously untreated ED SCLC are summarized in Table 2. The rationale for studying new antitumor agents in previously untreated SCLC is based on necessity and ethics. First, despite good response rates and a fivefold increase in median survival in ED patients from 6 weeks without treatment to 9 months with treatment, combination chemotherapy has not produced significant long-term survival gains. The use of new agents in SCLC, however, causes a dilemma. On the one hand, testing new agents in previously treated patients may produce low response rates (<20%), thus masking the potential activity of these agents in untreated SCLC. On the other hand, using these agents in previously untreated patients may result in decreased survival, as compared with standard chemotherapy.

**Menogaril**

The Eastern Cooperative Oncology Group (ECOG) conducted a randomized study comparing a new agent, menogaril, with CAV as first-line therapy in ED SCLC. Both groups received cisplatin/etoposide as the salvage regimen. Menogaril produced only a 5% overall response rate. However, the 27.9% 12-month survival obtained with menogaril was not significantly different from that obtained with CAV (24.4%). A number of major cooperative oncology groups have adopted the philosophy of enrolling previously untreated ED SCLC patients in phase II trials.
Patients should be selected by the following eligibility criteria: (1) good performance status and ED; (2) no emergent situations requiring rapid reduction of tumor (ie, superior vena cava syndrome or major airway obstruction); and (3) rapid crossover to a salvage regimen (eg, cisplatin/etoposide).15

**Paclitaxel**

Paclitaxel, a new agent with a unique mechanism of action, has received much attention in the treatment of solid tumors. Extracted from the bark of the Pacific yew *Taxus brevifolia*, paclitaxel exerts its antitumor activity by binding to microtubules, promoting microtubule assembly, and interfering with the depolymerization of the tubulin molecules, therefore inhibiting cell division. The ECOG performed a phase II study of paclitaxel in previously untreated ED SCLC.12 A total of 32 patients received paclitaxel, 250 mg/m² over 24 h every 3 weeks for four cycles. Nonresponders received salvage therapy with cisplatin/etoposide. First-line paclitaxel therapy yielded no CRs and 11 PRs in 32 evaluable patients, for an overall response rate of 34%. Median response duration for the 11 responders was 12 weeks, whereas median survival for the whole group was 45 weeks. Grade 4 leukopenia occurred in 56% of paclitaxel-treated patients.

Following this study, the North Central Cancer Treatment Group conducted a similar trial in previously untreated ED SCLC.13 Paclitaxel was again given at a dose of 250 mg/m² over 24 h, but with G-CSF added on days 2 to 15. Cisplatin/etoposide was given as salvage therapy. This time, grade 4 leukopenia occurred in only 14% of patients, and the overall response rate was 53% among 43 evaluable patients. Median survival of all patients was 278 days, with a 1-year survival rate of 24%. Thus, paclitaxel is both active against SCLC and, with the addition of G-CSF, generally well tolerated.

**Paclitaxel-Containing Regimens**

Phase I trials have been conducted to determine the maximum tolerated dose of paclitaxel in combination with etoposide and cisplatin in previously untreated patients. The University of Colorado Cancer Center administered paclitaxel as a 3-h infusion in three treatment groups with dose escalations.10 The highest doses tested were as follows: etoposide, 80 mg/m² on day 1 and 160 mg/m² orally on days 2 and 3; cisplatin, 80 mg/m² on day 1; and paclitaxel, 175 mg/m² on day 1. The dose-limiting toxicity reaction was neutropenia; however, the maximum tolerated doses of paclitaxel/etoposide/cisplatin were not reached. For all dose levels tested, 56% of patients achieved a CR (five patients) and 44% a PR (four patients). Survival data are pending.

The Ireland Cancer Center is also performing a phase 1/II study with escalating doses of paclitaxel (135 mg/m², 170 mg/m², and 200 mg/m²) given on day 1 with the following: cisplatin, 60 mg/m² on day 1; etoposide, 80 mg/m² on days 1 to 3; and G-CSF on days 5 to 14.20 Significant GI toxic reactions (grade 3 and 4 diarrhea in two patients) were observed at the second paclitaxel dose (170 mg/m²). Among eight patients evaluated thus far at the first two dose levels, there have been one CR and six PRs. Further studies will be necessary to determine the role and optimal doses of paclitaxel in single-agent and combination chemotherapy for patients with SCLC.

**Docetaxel**

Docetaxel, another taxane, was synthesized in 1986 from the needles of the European yew tree *Taxus baccata*. As with paclitaxel, docetaxel stabilizes microtubules and induces a mitotic block in proliferating cells. Docetaxel, however, is twice as efficient as paclitaxel in inhibiting the depolymerization of microtubules.21 Phase 1 studies of docetaxel have shown antitumor activity in patients with SCLC. Extra et al22 evaluated 65 patients at 10 distinct doses (5 to 115 mg/m²) given over 1 h to 2 h each. The main dose-limiting toxic reaction was leukopenia. Grade 4 neutropenia occurred in 40% of patients treated at 70 mg/m². Other toxic reactions included alopecia, anemia, paresthesias, erythema, and edema. Unlike paclitaxel, docetaxel did not cause significant hypersensitivity reactions.

The European Organization for Research and Treatment of Cancer conducted a phase II study of docetaxel in 34 previously treated SCLC patients.23 Docetaxel, 100 mg/m², was infused over 1 h every 21 days. The overall response rate was 25%, and the response duration was 3.5 to 12.6 months. Another phase II trial, conducted in Japan in both NSCLC and SCLC,24 reported a 13.3% overall response rate (2/15) in previously treated SCLC patients with a docetaxel dose of 60 mg/m².

**Vinorelbine**

Vinorelbine, a vinca alkaloid, is a semisynthetic product that prevents tubulin polymerization in mitosis. The recommended dose from phase I studies is 30 mg/m² weekly. The European Organization for Research and Treatment of Cancer conducted a phase II study of vinorelbine in

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Table 2—Trials of New Agents in Previously Untreated ED SCLC

<table>
<thead>
<tr>
<th>Trial</th>
<th>Agent</th>
<th>No. of Patients</th>
<th>Response Rate, %</th>
<th>Response Duration, wk</th>
<th>Median Survival, wk</th>
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<td>DePierre et al14</td>
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<td>Genetabine</td>
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<td>12.5</td>
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<tr>
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refractory SCLC.25 Among 23 evaluable patients, 4 achieved a PR, 7 had stable disease, and 12 had progressive disease. Duration of response was between 9.5 and 17 weeks. Grade 3 and 4 leukopenia was seen in 32% of patients and other toxic reactions included anemia and parasthesias. Furuse et al26 administered vinorelbine at a dose of 25 mg/m² weekly to 24 previously treated patients, 76% of whom had previously received a vinca alkaloid. The overall response rate was 12.5%.

DePierre et al27 tested vinorelbine’s activity in previously untreated patients. Among 30 patients who received 30 mg/m² weekly, there were eight PRs, for an overall response rate of 26.7%. Toxic reactions included grade 3 and 4 leukopenia (12 patients), constipation, peripheral neuropathy, and nausea/vomiting. Twenty-six patients then received salvage chemotherapy with cisplatin/etoposide, with a response rate of 46%. Vinorelbine has shown single-agent activity in previously untreated patients, but further studies will be needed to determine its role in combination therapy.

**Gemcitabine**

Gemcitabine, a difluorodeoxycytidine, is a new antitu- mor agent that has proven activity in advanced pancreatic cancer.27 It is a pyrimidine antimetabolite that blocks cells at the S and G2 phases.29 Phase I studies have shown gemcitabine to have more dose-limiting thrombocytopenia and anemia than granulocytopenia.30 The National Cancer Institute of Canada Clinical Trials Group conducted a phase II study of gemcitabine in previously untreated ED SCLC.15 The first 17 patients received gemcitabine at a dose of 1,000 mg/m², which was then increased to 1,250 mg/m² weekly ×3. Among 29 evaluable patients, there were six PRs and one CR, for an overall response rate of 27%. Median duration of response was 12.5 weeks. Response to second-line gemcitabine therapy was 63%, which suggests that clinical drug resistance did not develop. Thus, gemcitabine has single-agent activity against SCLC. Because of mild hematologic toxic reactions, it may be used in combination with other agents.

**CPT-11**

CPT-11 is a semisynthetic derivative of camptothecin, an extract from stem wood of the Chinese tree *Camptotheca acuminata*. It stabilizes topoisomerase I and DNA adducts and impairs cell repair in S phase.30 Masuda et al31 conducted a phase II study of CPT-11 in 16 patients with refractory or relapsed SCLC. CPT-11 was given at 100 mg/m² as a 90-min infusion every week. The most common toxic reaction was leukopenia (33% of patients); other toxic reactions included transient eosinophilia, nausea and vomiting, diarrhea, and pneumonitis. In the 15 assessable patients, there were no CRs and seven PRs, for an overall response rate of 47%. This rate is high for relapsed and refractory SCLC, and perhaps indicates noncross-resistance from two different mechanisms of action.

As a follow-up study, Fujitaka et al32 performed a phase II trial with the combination of CPT-11 and cisplatin. Seventy-five previously untreated patients received CPT-11, 80 mg/m² over 90 min on days 1, 8, and 15, and cisplatin, 60 mg/m² on day 1. At 50 mg/m² of CPT-11, hematologic toxic reactions, diarrhea, and liver toxic reactions warranted reduction of the dose to 60 mg/m² in 65 patients. Among 32 patients evaluated, overall response rates were 78% (4 CRs and 10 PRs) in LD and 79% (3 CRs and 8 PRs) in ED. Survival data were forthcoming. CPT-11 is a highly active agent against SCLC, but further studies are warranted to elucidate its role.

**Topotecan**

Topotecan, another topoisomerase I inhibitor, is a water-soluble derivative of camptothecin. The ECOG administered topotecan at a dose of 2.0 mg/m² for 5 days every 3 weeks to 41 previously untreated patients with ED SCLC.19 Of 18 patients evaluable for response, there were no CRs and seven PRs, for an overall response rate of 39%. Median time to treatment failure was 4.3 months, and median survival was 7.2 months. The occurrence of grades 3 and 4 leukopenia in 61% of patients prompted investigators to give G-CSF with topotecan. The final results of this study are pending.

Topotecan has also been evaluated in patients refractory to the topoisomerase II inhibitor etoposide.33 Patients were given topotecan, 1.25 mg/m²/d, for 5 consecutive days. Three of 25 patients (12%) evaluated thus far had a PR. Thus, topotecan has moderate activity in SCLC as first-line therapy. At the University of Pittsburgh, we are currently conducting a phase II trial of combination chemotherapy in previously untreated patients with ED SCLC using paclitaxel (135 mg/m² infused over 24 h on day 5) and topotecan (1.0 mg/m² IV on days 1 through 5). Initial results are very encouraging.

**Teniposide**

Teniposide, a derivative of epipodophyllotoxin, like etoposide, inhibits topoisomerase II. It has been evaluated as a single agent in patients refractory to first-line therapy and in patients with brain metastases. In a phase II study of 16 patients refractory to standard therapy,34 teniposide was administered at a dose of 100 mg/m² every 7 days. Results showed only one PR, for an overall response rate of 6.25%. Two patients had life-threatening hematologic toxic reactions.

In previously untreated patients, however, teniposide has fared much better. Bork et al35 conducted a phase II trial in 33 previously untreated patients, most of whom had LD and were older than 70 years of age (27 patients). Teniposide was given at a dose of 60 mg/m² on days 1 to 5 every 3 weeks. Side effects consisted of leukopenia and alopecia. The overall response rate was 90% (30/33), and median remission duration was 8+ months, with a median survival of 37 weeks.

The ECOG also tested teniposide as a single agent in a phase III trial, comparing it with CAV and with ifosfamide in previously untreated patients with ED SCLC.19 Teniposide was administered at a dose of 60 mg/m² for 5 days every 3 weeks. Salvage therapy consisted of cisplatin and etoposide. Overall response rates and median survivals
were 58% and 42 weeks for CAV, 48% and 43 weeks for ifosfamide, and 43% and 38 weeks for teniposide. The authors concluded that teniposide is an active agent, and that etoposide/cisplatin can be used in salvage therapy in nonresponders to teniposide with no adverse impact on survival in terms of drug resistance.

**Biological Response Modifiers**

Biological response modifiers have been used in the treatment of SCLC. Interferons have direct antiproliferative and immunopotentiating effects. Interferon-gamma, specifically, has been tested by the Cancer and Leukemia Group B in SCLC patients who have responded to combination chemotherapy.30 The Cancer and Leukemia Group B administered 0.2 μg interferon-gamma subcutaneously daily to 71 patients who achieved CR or PR with cisplatin, doxorubicin, cyclophosphamide, and etoposide. The objective response rate was 6.7% (2/30 patients). The North Central Cancer Treatment Group confirmed the inactivity of interferon-gamma in SCLC in a randomized phase III study.37 One hundred patients who achieved CR after six cycles of chemotherapy were randomized to observation or interferon-gamma at 4 million units subcutaneously every day for 6 months. In this study, median time to progression and survival were inferior in the interferon-gamma arm, although the differences were not statistically significant. Likewise, the Southwest Oncology Group demonstrated in a randomized trial that maintenance therapy with interferon-alpha in LD SCLC patients who respond to chemotherapy does not affect time to relapse or survival.38 In another randomized study, Mattson et al39 reported that natural interferon-alpha did not improve median survival but did prolong 5-year survival in LD patients only (11% vs 2% in the control arm). In summary, interferons do not appear to have a substantial role in SCLC therapy.

**DISCUSSION**

The treatment of SCLC is in evolution. Combination chemotherapeutic regimens (ie, cisplatin/etoposide, carboplatin/etoposide, ICE, VIP, CAV) all produce good response rates; however, the goal of long-term survival has been elusive. In addition, maintenance therapy with interferon-alpha and interferon-gamma has not improved survival. New agents with unique mechanisms have shown promise in the treatment of SCLC. By adopting the philosophy of performing phase II trials in previously untreated patients, study groups have begun to collect data on new and innovative agents. Of the agents discussed in this article, high single-agent response rates in previously untreated patients have been demonstrated for pachutaxel (34 to 53%), vinorelbine (25.7%), gemcitabine (27%), topotecan (39%), and teniposide (43 to 90%). The response data for single-agent docetaxel and CPT-11 in untreated patients are not yet conclusive. Studies evaluating response and survival rates of these new agents in combination with agents of known activity are underway. As these new and innovative agents progress to phase III trials, they may prove to be more effective in prolonging the survival of SCLC patients. Progress will continue to be made only through the translation of basic scientific research to the clinical setting.

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