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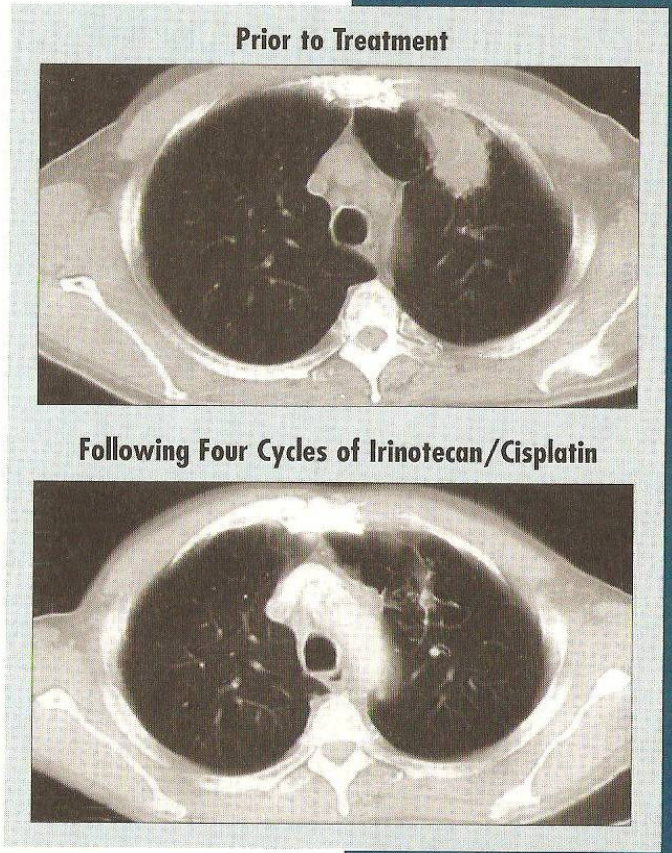

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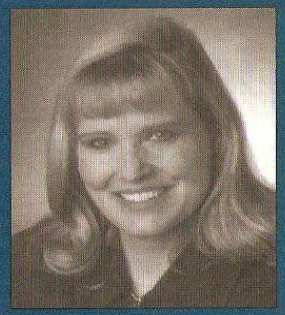

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Introduction

Small-cell lung cancer (SCLC) is one of the most aggressive and lethal cancers in humans.[1] In the United States, SCLC accounts for approximately 15% of all lung cancer and will afflict an estimated 25,000 adults in 2002.[2,3] At presentation, the majority of patients will have extensive disease progressing outside of the chest. Combination chemotherapy is the treatment of choice for these patients, producing objective response rates (RRs) in 65%-85% of patients with a 10%-15% complete response (CR) rate.[4] Although RRs are high, median survival time is a disappointing 8-11 months.[4] Cisplatin or carboplatin with etoposide remain the most commonly utilized regimens. Although these combinations are no more effective than older regimens, they are less toxic.[5] Unfortunately, research efforts over the past 20 years have failed to produce any major advances in the treatment of extensive-stage SCLC ES-SCLC.[6] Despite this frustration, continued evaluation of new agents and new strategies is vital.[7]

Irinotecan in Small-Cell Lung Cancer

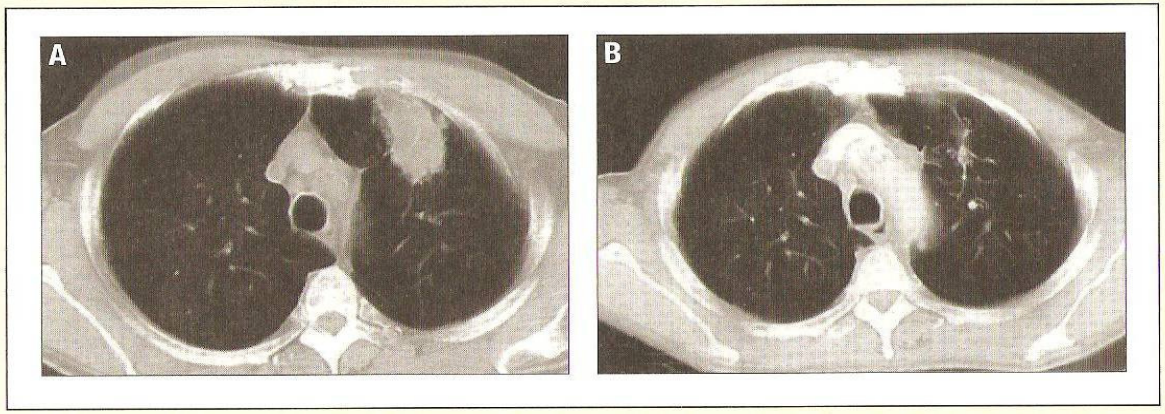
Of the several newer chemotherapy agents being explored, the topoisomerase I inhibitor irinotecan is the most promising new agent for SCLC. This stems from extensive work with irinotecan and irinotecan combinations by our Japanese colleagues. Most recently, the Japanese Clinical Oncology Group (JCOG) reported their positive findings from a randomized trial comparing irinotecan/cisplatin to etoposide/cisplatin in patients with untreated ES-SCLC.[8] Seventy-seven patients on the irinotecan/cisplatin arm received irinotecan 60 mg/m^2 on days 1, 8, and 15 with cisplatin 60 mg/m^2 on day 1 every 4 weeks for 4 cycles; 77 patients on the etoposide/cisplatin arm received etoposide 100 mg/m^2 on days 1-3 with cisplatin 80 mg/m^2 on day 1 every 3 weeks for 4 cycles.

Table 1 summarizes the efficacy and toxicity results. The overall RR (ORR) was 84% for irinotecan/cisplatin and

Table 1. Results From the JCOG Phase III Trial Comparing Irinotecan/Cisplatin Versus Etoposide/Cisplatin in Extensive-Stage Small-Cell Lung Cancer

Parameter	Irinotecan/ Cisplatin (n = 77)	Etoposide/ Cisplatin (n = 77)	*P* Value
Objective Response	84%	68%	0.02
Complete response	3%	9%	–
Partial response	82%	58%	–
Median Survival	12.8 months	9.4 months	0.002
1-Year Survival	58%	38%	–
2-Year Survival	20%	5%	–
Grade 3/4 Toxicity			
Neutropenia	65%	92%	< 0.001
Leukopenia	27%	52%	0.002
Thrombocytopenia	5%	18%	0.02
Diarrhea	16%	0	< 0.001

Figure 1. Computed Tomography Scans Before and After Treatment With Irinotecan/Cisplatin



A chest computed tomography scan before treatment shows a left peripheral mass (A). After 4 cycles of irinotecan/cisplatin, a marked decrease in the size of the mass observed (B).

68% for etoposide/cisplatin (P = 0.02), with CR rates of 3% for irinotecan/cisplatin and 9% for etoposide/cisplatin. The median survival times, and the 1- and 2-year survival rates were 12.8 months versus 9.4 months (P = 0.002), 58% versus 38%, and 20% versus 5%, for irinotecan/cisplatin and etoposide/cisplatin, respectively. The incidence of grade 3/4 neutropenia (65% vs. 92%; P < 0.001), leukopenia (27% vs. 52%; P = 0.002), and thrombocytopenia (5% vs. 18%; P = 0.02) was higher in the etoposide/cisplatin group, while grade 3/4 diarrhea was significantly higher on the irinotecan/cisplatin arm (16% vs. 0; P < 0.001). Overall, irinotecan/cisplatin produced a statistically superior survival benefit over the standard regimen with less hematologic toxicity but with a higher rate of diarrhea.

In the United States, irinotecan/cisplatin for SCLC is only beginning to be evaluated. Thus, we describe a patient with ES-SCLC who has been successfully treated with irinotecan/cisplatin in the setting of a clinical trial.

Case Report

Presentation and Diagnosis

The patient is a 67-year-old Caucasian male who was in his usual state of health until February 2002 when he developed a progressive cough, chest pain, and shortness of breath that did not completely resolve with antibiotic treatment. He also admitted to a poor appetite with a 5-pound weight loss over the previous 3 months. His social history disclosed 80 pack years of smoking. He quit smoking when he developed symptoms, which was 1 month prior to the examination. The patient denied a family history of cancer.

On physical examination, he had bilateral supraclavicular lymphadenopathy. Two palpable lymph nodes on the right side measured 2 cm and 4 cm, respectively, and 1 lymph node on the left side measured 1 cm. Auscultation of his lungs revealed crackles in the left base. A chest x-ray showed left perihilar and suprahilar consolidation. A computed tomography (CT) scan of the chest demonstrated a 6.0 x 3.5-cm mass in the left perihilar area extending down from the level of the aortic arch to the superior pulmonary veins. In addition, there was a peripheral component to this mass, also measuring 6.0 x 3.5 cm (Figure 1A), as well as associated left hilar, pretracheal, subcarinal, and aortic-pulmonary window lymphadenopathy. A bronchoscopic biopsy of the left upper lobe revealed SCLC. A metastatic workup, including an abdominal CT scan, magnetic resonance imaging of the brain, and bone scan, showed no evidence of tumor spread. The patient was seen in consultation by radiation oncology who determined that the patient's disease could not be encompassed within a single radiation port. He was considered to have ES-SCLC. Systemic chemotherapy was recommended.

Treatment With Irinotecan/Cisplatin

The patient agreed to participate in a randomized clinical trial comparing irinotecan/cisplatin to etoposide/cisplatin. He received the experimental arm consisting of irinotecan 65 mg/m^2 with cisplatin 30 mg/m^2 on days 1 and 8 every 3 weeks for 4 cycles. The patient tolerated chemotherapy very well with resolution of chest pain, shortness of breath, and anorexia. He developed grade 3 neutropenia (absolute neutrophil count = 1000/μL) during cycle 2, which required a dose reduction of both agents. Physical examination after 4 cycles of treatment revealed complete disappearance of all 3 supraclavicular lymph nodes. A chest CT scan obtained at this time showed significant improvement in the left hilar mass, decreasing to 3.4 x 2.5 cm, and in the peripheral parenchymal mass, decreasing to 2.0 x 1.0 cm (Figure 1B). After evaluation of all sites of disease, the patient had achieved a partial response (PR) to irinotecan/cisplatin.

Discussion

Irinotecan/Cisplatin for Small-Cell Lung Cancer

The evaluation of irinotecan for the treatment of SCLC has been limited in the United States. Dr. DeVore and his colleagues from Vanderbilt University Medical Center administered irinotecan 125 mg/m^2 for 4 of 6 weeks to 44 previously treated SCLC patients; 27 had refractory disease.[9] The ORR was 16%, including 6 of 17 patients (35%) with sensitive relapse and 1 of 27 patients (4%) with refractory disease. The median survival time for all patients was 4.8 months, with a median survival time of 5.9 months and 2.8 months for sensitive and refractory patients, respectively. Twelve patients (27%) each experienced grade 3/4 diarrhea and neutropenia. This trial demonstrated that irinotecan was an active agent in SCLC and deserved further evaluation.

Typically, additional phase II studies are conducted, but with extensive data from Japan suggesting a survival advantage for irinotecan/cisplatin in the treatment of SCLC, it was prudent to move ahead with randomized phase III trials of this promising combination. Two trials have been designed (Figure 2). The Southwest Oncology Group (SWOG) plans to confirm the Japanese data[8] by conducting a larger duplicate trial involving 620 patients. This is important because of the small sample size and the unclear role that thoracic radiation therapy might have played in the outcome of the Japanese trial. The SWOG trial will be activated this fall. The second trial is being conducted by Pharmacia Oncology to evaluate a weekly regimen of

Figure 2. Randomized Trials of Irinotecan/Cisplatin Versus Etoposide/Cisplatin

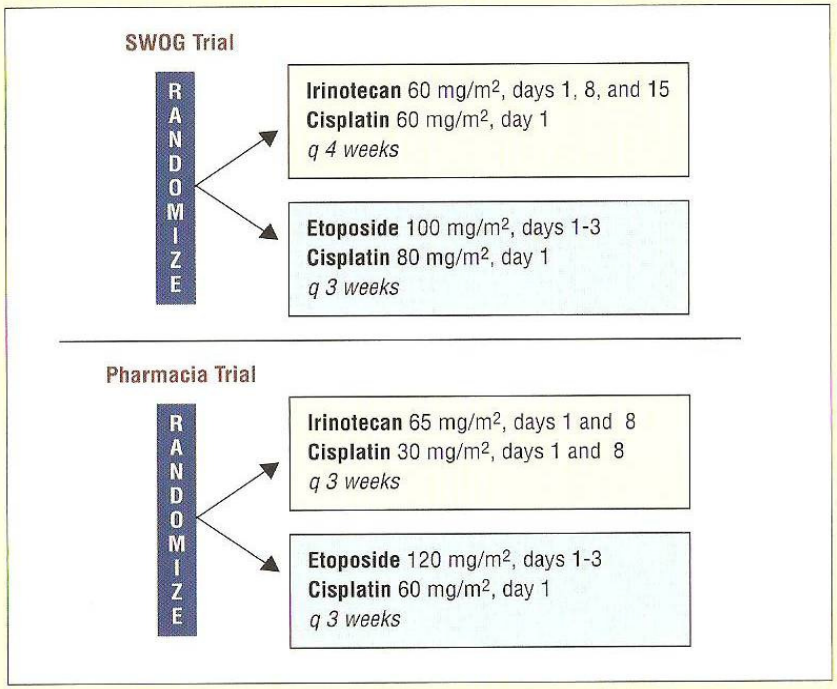


Table 2. Phase I and II Trials of Irinotecan/Carboplatin in Small-Cell Lung Cancer

	Phase	Regimen	Number of Evaluable Patients	ORR Number of Patients (%)	Toxicity
Fukuda et al[12]	I	Irinotecan 40-60 mg/m^2 days 1, 8, and 15 Carboplatin AUC = 5 day 1	25	15/25 (60%) 11/13 (85%)*	DLT: Neutropenia Thrombocytopenia Diarrhea
Kinoshita et al[14]	II	Irinotecan 50 mg/m^2 days 1, 8, and 15 Carboplatin AUC = 5 day 1	60	51/60 (85%)	Grade 3/4 toxicity: Leukopenia (35%) Neutropenia (76%) Thrombocytopenia (42%) Anemia (42%) Diarrhea (13%)
Sato et al[15]	I	Irinotecan 40-60 mg/m^2 days 1, 8, and 15 Carboplatin 300 mg/m^2 day 1	10†	NR	DLT: Neutropenia Thrombocytopenia Diarrhea
Sato et al[15]	II	Irinotecan 50 mg/m^2 days 1, 8, and 15 Carboplatin 300 mg/m^2 day 1	16	13/16 (81%)	Grade 4 leukopenia: 1 patient Grade 3 diarrhea: 1 patient Grade 3 nausea: 1 patient

* Small-cell lung cancer patients
† 3 small-cell lung cancer patients
Abbreviations: AUC = area under the curve; DLT = dose-limiting toxicity; NR = not reported

irinotecan/cisplatin in an attempt to minimize toxicity and decrease dose delays and reductions while maintaining dose intensity over the cycle period. In this trial, patients will receive irinotecan 65 mg/m^2 and cisplatin 30 mg/m^2 on days 1 and 8 every 3 weeks. The standard arm will consist of etoposide 120 mg/m^2 on days 1-3 with cisplatin 60 mg/m^2 on day 1 every 3 weeks. The rationale for this design was based on detailed information from the randomized JCOG study in which day 15 irinotecan was omitted in 50% of courses.[8]

Additional support for a weekly schedule is provided from a phase I trial in patients with non–small-cell lung cancer (NSCLC).[10] Patients were treated with fixed doses of irinotecan at 60 mg/m^2 on days 1, 8, and 15 with cisplatin at 27, 33, and 40 mg/m^2 on days 1, 8, and 15 every 28 days. Twenty-four patients were accrued to the 3 cohorts. Leukopenia was a dose-limiting toxicity (DLT), and cisplatin 33 mg/m^2/week was determined to be the maximum tolerated dose. Significant diarrhea was infrequent.

Irinotecan/Carboplatin for Small-Cell Lung Cancer

Area Under the Curve Dosing of Irinotecan/Carboplatin. Etoposide/carboplatin is a popular regimen in the United States for treating ES-SCLC because it is less toxic than and is as efficacious as etoposide/cisplatin[11]; therefore, clinical trials substituting carboplatin for cisplatin with irinotecan have been conducted (Table 2). Dr. Fukuda et al conducted a phase I trial of irinotecan/carboplatin in untreated patients with advanced solid tumors, focusing primarily on lung cancer patients.[12] Irinotecan was administered in escalating doses starting at 40 mg/m^2 on days 1, 8, and 15 with carboplatin at an area under the curve (AUC) of 5 on day 1 every 28 days. DLTs occurred at irinotecan 60 mg/m^2 and included neutropenia, thrombocytopenia, and diarrhea. Fifteen of the 25 evaluable patients (60%) achieved an objective response, including 11 of 13 patients with SCLC. Irinotecan 50 mg/m^2 on

days 1, 8, and 15 with carboplatin at an AUC of 5 on day 1 was recommended for future testing.

In a phase II study by Dr. Mukohara and colleagues using these recommended doses to treat patients with advanced NSCLC, < 50% of the patients received day 15 irinotecan, which might have contributed to the low RR of 25%.[13] Recently, Dr. Kinoshita and colleagues reported their results from a larger phase II study.[14] Sixty-one SCLC patients, 27 with limited disease and 34 with extensive involvement, were given irinotecan 50 mg/m^2 on days 1, 8, and 15 with carboplatin at an AUC of 5 on day 1. The overall ORR was 85% (89% limited stage, 84% extensive stage). Seventeen patients (28%) achieved a CR. The median overall survival time was 15.7 months, with 1- and 2-year survival rates of 56% and 30%, respectively. For patients with ES-SCLC, the median survival time was 9.7 months, with a 1-year survival rate of 27% and a 2-year survival rate of 11%. Grade 3/4 toxicities included leukopenia (35%), neutropenia (76%), thrombocytopenia (42%), anemia (42%), and diarrhea (13%).

Body Surface Area Dosing for Irinotecan/Carboplatin. Dr. Sato and colleagues completed a phase I trial beginning with irinotecan 40 mg/m^2 on days 1, 8, and 15 with a carboplatin dose fixed at 300 mg/m^2 on day 1 every 4 weeks in 10 patients with lung cancer.[15] DLTs including neutropenia and diarrhea occurred at irinotecan 60 mg/m^2.

Sato et al subsequently performed a phase II trial in chemonaive patients with SCLC.[15] Sixteen patients (14 with limited-stage disease and 2 with extensive-stage disease) received irinotecan 50 mg/m^2 on days 1, 8, and 15 with carboplatin 300 mg/m^2 on day 1 every 4 weeks. The regimen was active; 11 limited-stage patients (79%) achieved an ORR including 2 patients with a CR. Two additional patients (100%) with extensive-stage disease had a PR. Grade 4 leukopenia was seen in 1 patient, grade 3 diarrhea in 1 patient, and grade 3 nausea in 1 patient. Although this regimen was modestly active, the authors did not recommend pursuing body surface area dosing of carboplatin for future studies.

Ongoing Study at the University of Colorado Cancer Center. The University of Colorado Cancer Center is currently conducting a phase I trial of irinotecan/carboplatin utilizing an every-3-week schedule. The starting dose of irinotecan was 60 mg/m^2 on days 1 and 8 with carboplatin at an AUC of 6 on day 1. Due to neutropenia and diarrhea, the doses have been modified. Enrollment is continuing at the second dose level (irinotecan 50 mg/m^2 on days 1 and 8 with carboplatin at an AUC of 5 on day 1) with acceptable toxicity. Once doses are established, a phase II trial will commence.

Summary

Irinotecan/cisplatin represents the first major advance in the treatment of ES-SCLC in several decades and is considered the new standard of care in Japan. In the United States, we are optimistic that similar results will be achieved from the 2 ongoing randomized trials, but we must await their completion and analysis. Meanwhile, investigators are pursuing the evaluation of other regimens containing irinotecan, especially irinotecan/carboplatin.

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Cover Illustration: Computed tomography scans of a peripheral parenchymal mass due to small-cell lung cancer prior to treatment and following 4 cycles of irinotecan/cisplatin. The patient achieved a partial response with resolution of symptoms.

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