Phase II Trial of Irinotecan and Cisplatin With Early Concurrent Radiotherapy in Limited-Disease Small-Cell Lung Cancer

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BACKGROUND. A Phase II trial of irinotecan and cisplatin (IP) with early concurrent radiotherapy was performed in limited-disease small-cell lung cancer (LD-SCLC) to evaluate the efficacy and toxicity.

METHODS. For untreated LD-SCLC patients, irinotecan (60 mg/m^2, Days 1, 8, and 15) and cisplatin (40 mg/m^2, Days 1 and 8) were repeated every 4 weeks for a maximum of 6 cycles. Thoracic radiotherapy of 1.8 Gy/day was begun on Day 1 of the second chemotherapy cycle, up to a total of 45 to 54 Gy. Prophylactic cranial irradiation (30 Gy in 10 fractions) was performed on patients with a complete response (CR).

RESULTS. Thirty-three LD-SCLC patients were enrolled. The median age was 60 years and 31 patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1. Twelve (36.4%) patients had N3 disease. The response rate was 87.9%, with a CR rate of 45.5%. At a median follow-up period of 27 months the median progression-free survival (PFS) and overall survival (OS) were 14.4 and 26.1 months, respectively, with 2-year PFS and OS rates of 26.8% and 54.9%. The dominating toxicity was neutropenia, with grade 3–5 of 81.8%. The most common grade 3–5 nonhematologic toxicities were diarrhea (21.2%), anorexia (21.2%), and fatigue (21.2%). Grade 3–5 radiation esophagitis and pneumonitis occurred in 18.2% and 9.1% of patients, respectively. There were 2 treatment-related deaths from sepsis and radiation pneumonitis.

CONCLUSIONS. IP with early concurrent radiotherapy was effective and tolerable in untreated LD-SCLC. ***Cancer* 2007;109:1845–50.** © *2007 American Cancer Society.*

KEYWORDS: irinotecan, cisplatin, limited-disease small-cell lung cancer.

Small-cell lung cancer comprises about 20% of all lung malignancies and chemotherapy, rather than surgery, plays a pivotal role in the treatment. Limited-disease small-cell lung cancer (LD-SCLC) is defined as a disease confined to 1 hemithorax, which is generally regarded as potentially curable. For LD-SCLC, to date, concurrent chemoradiotherapy based on an etoposide/cisplatin (EP) regimen and early radiation treatment has been the standard protocol since the early 1990s.[1–5] In spite of the good response of tumors to chemoradiation, most patients still die as a result of systemic metastasis, with a median survival of 17–27 months and a 2-year survival rate of 33% to 54%.[4–7] Therefore, more effective systemic chemotherapy regimens are needed to improve patient outcomes for LD-SCLC.

Irinotecan, a topoisomerase I inhibitor, showed a synergistic activity with cisplatin and seemed to be an active radiosensitizer in preclinical studies.[8,9] Moreover, for extensive-disease small-cell lung

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cancer (ED-SCLC), irinotecan was combined with cisplatin and showed a better survival than an EP regimen in a prospective Phase III randomized study.[10]

With this background, we conducted a trial of irinotecan and cisplatin (IP) with early concurrent chemoradiotherapy in order to evaluate the clinical efficacy and toxicities in LD-SCLC.

MATERIALS AND METHODS

Eligibility Criteria

LD-SCLC was defined as a tumor confined to 1 hemithorax where a primary tumor and regional nodes, including ipsilateral supraclavicular nodes and contralateral hilar/mediastinal nodes, were included. Patients with ipsilateral pleural effusion were regarded as LD-SCLC and enrolled in this study. Patients with LD-SCLC were eligible if the following criteria were met: 1) age $\geq$18 years; 2) histologically or cytologically proven SCLC; 3) Eastern Cooperative Oncology Group (ECOG) performance status of $\leq$2; 4) adequate bone marrow (neutrophils $\geq 1.5 \times 10^3/\mu L$, platelets $\geq 100 \times 10^3/\mu L$, and Hb $\geq$10.0 g/dL), renal (serum creatinine $\leq 1.5 \times$ upper normal limit), and liver function (serum bilirubin $\leq 1.5 \times$ upper normal limit and aspartate aminotransferase [AST] and alanine aminotransferase [ALT] $\leq 1.5 \times$ upper normal limit); 5) no previous chemo- or radiotherapy; and 6) no history of other malignancies excluding nonmelanoma skin cancer or carcinoma in situ of the uterine cervix. All the patients were required to provide written informed consent and this protocol was approved by the institutional ethics committee.

Treatment Protocol

For pretreatment staging, chest x-ray, chest and abdominal computed tomography (CT) scan, and radionuclide bone scan were conducted within 4 weeks before enrollment. Brain magnetic resonance imaging was performed only in symptomatic patients. Irinotecan (60 mg/m^2, 90-minute intravenous infusion on Days 1, 8, and 15) and cisplatin (40 mg/m^2, 60-minute intravenous infusion on Days 1 and 8) were administered every 4 weeks for a maximum of 6 cycles. Modifications of doses and dosing schedules were as follows: current chemotherapy was omitted if grade 2 or worse hematologic toxicity (neutropenia or thrombocytopenia) or grade 3–4 nonhematologic toxicity (eg, radiation pneumonitis or esophagitis) was observed. The dose was reduced at the subsequent week or cycle if hematologic toxicity was grade 3–4 or nonhematologic toxicity was grade 2 or worse. In detail, when grade 3 or 4 hematologic toxicity was observed the next dose of irinotecan was reduced to 50 mg/m^2 or 40 mg/m^2, respectively, with an unchanged dose of cisplatin. In the case of grade 2–3 nonhematologic toxicity, the next doses were reduced to irinotecan/cisplatin of 50/30 mg/m^2. In the case of grade 4 nonhematologic toxicity, the next doses were reduced to irinotecan/cisplatin of 40/20 mg/m^2.

Once-daily thoracic radiotherapy (TRT) of 1.8 Gy/day was begun on Day 1 of the second chemotherapy cycle, up to a total of 45 to 54 Gy. Postchemotherapy treatment volumes were used for radiotherapy. The target volume included the lung tumor and involved lymph nodes with a margin of 1.5 cm. Prophylactic cranial irradiation (PCI) with a total of 30 Gy in 10 fractions was started in patients who achieved a complete response (CR) within 2 weeks of completion of chemotherapy.

Granulocyte colony-stimulating factor (G-CSF) was administered in the case of neutropenic fever. Prophylactic G-CSF use was not permitted. Cholinergic symptoms including early diarrhea within 24 hours of irinotecan administration were treated with atropine 1 mg intravenously. Loperamide was administered for late diarrhea 1 day to several days after irinotecan administration in the following manner: 4 mg at the first onset of diarrhea, then 2 mg every 2 hours until diarrhea stopped for 12 hours.

Follow-up of the patients was performed at 1-month intervals for the first year, at 3-month intervals for the second year, and at 6-month intervals thereafter. Evaluations during these follow-up visits included history taking, physical examination, complete blood count, biochemical profile, chest x-ray, chest CT, abdominal CT scan, and bone scan.

Endpoints Evaluation

Response was assessed, using chest CT scan, abdominal CT scan, and/or bone scan after the first, third, and sixth cycle of IP. Tumor response was classified according to the Response Evaluation Criteria in Solid Tumors[11] as follows: CR, disappearance of all target and nontarget lesions; partial response (PR), a minimum of a 30% decrease in the sum of the longest diameter of target lesions; progressive disease (PD), a minimum of a 20% increase in the sum of the longest diameter of target lesions, appearance of 1 or more new lesions, or unequivocal progression of existing nontarget lesions; stable disease (SD), neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD. Patients who achieved a response were required to take a confirmative CT scan at least 4 weeks later. Response duration was defined as the time from the first documented day of response until disease progression or death. Progression-free survival (PFS) was

defined as the time from commencement of the treatment until disease progression or death. Overall survival (OS) was measured from the first date of the treatment to death from any cause. Toxicity was assessed weekly by history taking, physical examination, and complete blood count and monthly by biochemical profile and chest x-ray during the treatment. The toxicity was graded based on the National Cancer Institute's Common Toxicity Criteria v. 3.0.[12]

Stastistical Considerations

The sample size was calculated by the Fleming single-stage design,[13] based on an anticipated response rate of 90%, threshold response rate of 65%, a 2-sided significance level of 0.05, and a power of 0.8. The minimum sample size was 28 and assuming a 10% of dropout rate, a final sample size was calculated to be 31 patients. All statistical calculations were performed, using SPSS Windows program, v. 11.0 (SPSS, Chicago, Ill). Survival was estimated by the Kaplan-Meier method. We measured the tumor volumes before and after the first cycle of chemotherapy using CT scan and the paired *t*-test was used for statistics.

RESULTS

Patients Characteristics

Thirty-three patients were enrolled in the study between November 2002 and September 2005. The median follow-up period was 27 months (range, 7.5–41.4), as of April 20, 2006. All the patients had histologically confirmed small cell carcinoma with clinically limited stage. The median age was 60 years (range, 38–76). Twenty-eight (84.8%) patients were male. ECOG performance status was 0–1 in 31 (93.9%) and 2 in 2 (6.1%) patients. Twelve (36.4%) patients had N3 disease: 9 had ipsilateral supraclavicular nodes involvement; 5 had contralateral hilar nodes involvement; and 7 had contralateral mediastinal nodes involvement. Ipsilateral pleural effusion was observed in 3 patients. The patient characteristics are summarized in Table 1.

Response

Of the 33 patients, 2 were not assessable for response: 1 case was due to treatment-related death and the other was removed from the study because of the adverse event after the first cycle of chemotherapy without response evaluation. The response rate was 87.9% (29/33 patients), with a CR rate of 45.5% (15/33 patients) according to the intent-to-treat analysis. The median response duration was 13.1 months (95% confidence interval [CI]: 6.6–19.6).

TABLE 1
Characteristics of the Patients

	No. of patients (%)
Total no. of patients	33
Median age, y	60 (range, 36–76)
Sex	
Men	28 (84.8)
Women	5 (15.2)
ECOG performance status	
0	1 (3.0)
1	30 (90.9)
2	2 (6.1)
N3 nodes	
Present	12 (36.4)
Absent	21 (63.6)
Pleural effusion	
Present	3 (9.1)
Absent	30 (89.9)

ECOG indicates Eastern Cooperative Oncology Group.

Progression-Free and Overall Survival

At a median follow-up period of 27.0 months (range, 7.5–41.4), 17 of the 33 patients experienced disease progression. The median PFS was 14.4 months (95% CI: 10.3–18.5). The 1- and 2-year PFS rates were 54.1% and 26.8%, respectively. Over the same follow-up period, 16 of the 33 patients died and the median OS was 26.1 months (95% CI: 9.0–43.2). The 1- and 2-year OS rates were 76.6% and 54.9%, respectively (Fig. 1). Twelve patients died from disease progression and 2 from treatment-related sepsis and radiation pneumonitis, respectively. The remaining 2 patients died from treatment-unrelated bacterial pneumonia and a traffic accident, respectively. Patients with N3 disease had lower 2-year PFS (0% vs 43.5% in patients without N3; $P = .093$) and OS (40.0% vs 65.5% in patients without N3; $P = .037$) rates.

Toxicity Profiles

The dominating toxicity was neutropenia, of which a grade 3–5 was observed in 81.8% (27/33 patients). The most common grade 3–5 nonhematologic toxicities were diarrhea (21.2%), anorexia (21.2%), and fatigue (21.2%). Grade 3–5 radiation esophagitis and pneumonitis occurred in 6 (18.2%) and 3 (9.1%) patients, respectively. There were 2 treatment-related deaths from sepsis and radiation pneumonitis (Table 2).

Treatment Delivery and Dose Intensity

A total of 165 cycles of chemotherapy were delivered and 20 (60.6%) of the 33 patients completed 6 cycles of chemotherapy. Reasons for not completing chemotherapy were as follows: 5 disease progressions, 4

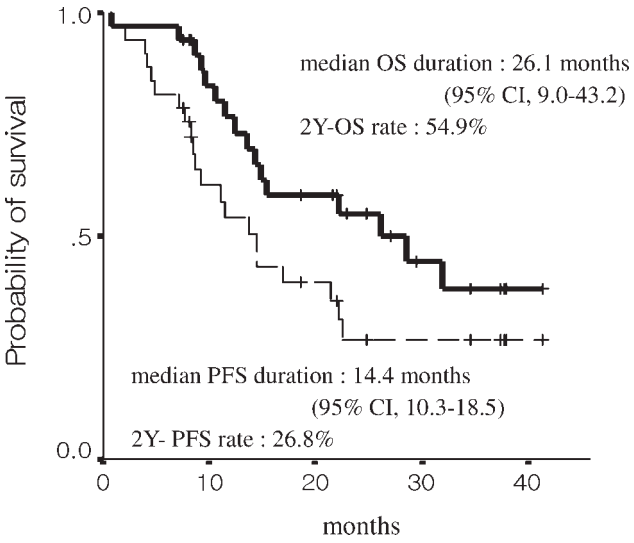

FIGURE 1. Progression-free survival (PFS, dotted line) and overall survival (OS, continuous line). Median OS duration, 26.1 months (95% confidence interval [CI], 9.0-43.2); 2-year OS rate, 54.9%. Median PFS duration, 14.4 months (95% CI, 10.3-18.5); 2-year PFS rate, 26.8%.

TABLE 2
Toxicity Profiles (by Patient)

	NCI-CTC grade					
Toxicity	**G1**	**G2**	**G3**	**G4**	**G5**	**G≥3 (%)**
Hematologic						
Neutropenia	0	6	17	9	1	27 (81.8)
Anemia	6	21	6	0	0	6 (18.2)
Thrombocytopenia	10	9	6	2	0	8 (24.2)
Nonhematologic						
Diarrhea	7	5	6	1	0	7 (21.2)
Anorexia	4	16	7	0	0	7 (21.2)
Fatigue	0	12	7	0	0	7 (21.2)
Nausea	5	14	6	0	0	6 (18.2)
Esophagitis	3	12	6	0	0	6 (18.2)
Pneumonitis	7	5	1	1	1	3 (9.1)
Hyperbilirubinemia	0	1	1	0	0	1 (3.0)
Vomiting	2	6	1	0	0	1 (3.0)
Constipation	2	7	0	0	0	0 (0)
Neuropathy	1	3	0	0	0	0 (0)

NCI-CTC indicates the National Cancer Institute's Common Toxicity Criteria.

treatment-related adverse events, 3 self-refusals, and 1 pulmonary thromboembolism. Planned dose intensities for irinotecan and cisplatin were 45 mg/m^2/week and 20 mg/m^2/week, respectively. The median relative dose intensities for irinotecan and cisplatin were 0.65 (range, 0.33–0.96) and 0.80 (range, 0.46–1.00), respectively. TRT was performed in 30 patients (90.9%): 29 patients completed it with a median dosage of 54.0 Gy (range, 45.0–64.8) and 1 patient received a dosage of only 750 cGy because of self-refusal. The remaining 3 patients could not receive TRT due to early progression, death after first cycle of chemotherapy, and self-refusal, respectively. PCI was performed in 12 (80.0%) of the 15 CR patients. Among the remaining 3 patients, 2 refused PCI and 1 died from radiation pneumonitis before PCI.

TABLE 3
Patterns of First Failure

	No. of patients (%)
Patients with progression	17 (100)
Site of progression	
Locoregional	5 (29.4)
Locoregional and distant	7 (41.2)
Liver	2
Adrenal	2
Brain	2
Neck node	1
Distant	5 (29.4)
Brain	3
Bone	1
Neck node	1

Patterns of First Failure and Salvage Chemotherapy

Among the 17 patients who had documented disease progression, there were 5 locoregional failures alone, 5 distant metastases alone, and 7 both locoregional and distant failures as the first failure. During the whole follow-up period, brain metastasis occurred in 7 (21.2%) of 33 patients: 3 with PCI and 4 without PCI (Table 3).

Twelve of the 17 patients who experienced disease progression received salvage chemotherapy.

Comparisons of Tumor Volumes at the Baseline and After the First IP Chemotherapy

We compared tumor volumes at baseline and after the first IP chemotherapy in 22 patients whose tumor volumes could be measured by CT scan. Tumor volumes were decreased in all but 1 patient after the first IP chemotherapy. The median decrease of tumor volume was 73.8% relative to the baseline volume ($P = .000$).

DISCUSSION

Topoisomerase I inhibitors and cisplatin showed synergism in in vitro assays by increased interstrand cross-linking (ICL), decreased DNA repair after ICL formation, and enhanced topoisomerase I inhibitor activity by cisplatin, as determined by the relaxation of supercoiled DNA.[8] Additionally, these 2 drugs do

TABLE 4
Comparisons of Clinical Trials in Limited-Disease Small-Cell Lung Cancer

		Chemotherapy			Thoracic radiotherapy			Treatment outcome			
Author	Year	No.	Induction	Concurrent	Dose, Gy	Fraction, Gy	Timing	2-Year PFS (%)	MST, m	2-Year OS (%)	Toxicity (Grade ≥3) by patient (%)
Turrisi et al.[6]	1999	206	None	EP q 3 wk ×4	45	1.5 bid	Concurrently with cycle 1	29	23	47	N(80), E(32), P(6); D(2.9)
Glisson et al.[18]	2000	67	None	PIEo q 4 wk ×4	45	1.5 bid	Concurrently with cycle 1	30	23.7	50	N(66), E(43), P(13); D(1.5)
Takada et al.[4]	2002	114	None	EP q 4 wk ×4	45	1.5 bid	Concurrently with cycle 1	28.9	27.2	54.4	N(88), E(9), P(0); D(2.6)
Schild et al.[19]	2004	130	EP q 4 wk ×3	EP q 4 wk ×3	50.4	1.8 daily	Concurrently with cycle 4	31.3	20.6	44.3	N(>86), E(5), P(5); D(0)
		131	EP q 4 wk ×3	EP q 4 wk ×3	48	1.5 bid	Concurrently with cycle 4	30.8	20.6	44	N(>88), E(12), P(8); D(3)
Han et al.[15]	2005	35	IP q 3 wk ×2	EP q 3 wk ×2	45	1.5 bid	Concurrently with cycle 3	36.1	25	53.9	N(100); E(29), P(9); D(0)
Current study	2006	33	IP q 4 wk ×1	IP q 4 wk ×5	54	1.8 daily	Concurrently with cycle 2	26.8	26.1	54.9	N(81.8), E(18.2), P(9.1), D(21.2)

N indicates number of patients; EP, etoposide plus cisplatin; PIEo, cisplatin plus ifosfamide plus oral etopside; IP, irinotecan plus cisplatin; q, every; wks, weeks; 2 Y PFS, 2 year progression-free survival; MST, median survival time; OS, overall survival; Mo, months; NA, not available; In the toxicity column: Gr, grade; N, neutropenia; E, esophagitis; P, paeumonitis; L, leukopenia; D, death.

not overlap in their dominating toxicities. As such, combinations of these 2 drugs have been tested in several clinical trials since the late 1990s.[10,14,15]

Although a recent confirmative Phase III trial[16] reported a different result in contrast to a Japanese study reported by Noda et al,[10] regarding an IP regimen compared with EP regimen in ED-SCLC, we had been encouraged to conduct this trial to evaluate irinotecan plus cisplatin with early concurrent TRT in LD-SCLC based on the positive result of the study in ED-SCLC at that time. We were further prompted by a Phase I study that showed tolerability of the IP regimen with thoracic radiotherapy in LD-SCLC.[17]

The response rate (87.9%) and CR rate (45.5%) in this study were similar or superior to rates in studies using EP with TRT. Although this is a single-institution Phase II trial, the 2-year survival rate of 54.9% with once-daily TRT is considerably more promising over the previous results of the EP regimen-based once daily or hyperfractionated concurrent radiotherapy studies (Table 4).[4,6,15,18,19] Moreover, in this trial patients with more advanced disease were included. For example, patients with ipsilateral pleural effusion and/or contralateral mediastinal nodes that had been exclusion criteria in other studies[4,6,15,18,19] accounted for 24.2% of the total patient population in this study.

Two Phase I trials of IP-based concurrent chemoradiotherapy have ever been reported: Yokoyama et al.[20] reported that they could not find a clinically recommended dose of the IP regimen in unresectable stage III nonsmall-cell lung cancer because of the toxicities such as leukopenia or diarrhea. In an LD-SCLC trial reported by Oka et al.[17] irinotecan/cisplatin of 40/60 mg/m^2 with split-course radiotherapy was recommended. In our study we did not want to compromise the systemic dose of irinotecan/cisplatin in chemosensitive diseases such as SCLC, just as with EP-based concurrent chemoradiotherapy (CCRT). However, unlike the classic EP-based CCRT protocol, in which radiotherapy was administered from the first cycle of chemotherapy, we started with a full dose of IP chemotherapy, with once-daily radiotherapy administered on the first day of the second cycle of chemotherapy. This chemoradiotherapy schedule was aimed at reducing the tumor volume after the first cycle of chemotherapy. Actually, tumor volumes decreased by a median of 73.8% relative to baseline volume after the first IP chemotherapy and finally would lead to a decreased radiation field and toxicity. Although hyperfractionated radiation has been a preferred strategy based on a positive result in 1 large intergroup Phase III study,[6] TRT was administered once daily in this study because the safety of hyperfractionated radiation used concurrently with our IP regimen has not yet been studied. Additionally, we adopted a strict dose modification schedule so that we could continue the radiotherapy to the end.

The median relative dose intensity was lower in irinotecan (0.65) vs cisplatin (0.80). The major reason for irinotecan being delivered less than cisplatin was due to neutropenia. However, TRT was completed in most of the patients (87.9%). Although neutropenia was the dominating toxicity, treatment-related death from severe neutropenia was observed in only 1 patient. A strict dose modification might improve this relatively safe result. The rates of severe (≥grade 3) radiation esophagitis (18.2%) and pneumonitis (9.1%) were comparable to the previous reports from EP-based concurrent chemoradiotherapy trials (Table 4).[4,6,15,18,19] Diarrhea, which was rare in EP-based trials, was rela-

tively common, but was manageable in most cases with antidiarrhetics.

Recently, an important association between genetic polymorphism in the uridine diphosphate glucuronosyltransferase (UGT) 1A1 and irinotecan toxicity has emerged.[21] UGT1A1 is known to inactivate the potent topoisomerase inhibitor SN-38, the active metabolite of irinotecan.[22] UGT1A1*28, a common polymorphism of UGT1A1, is significantly higher in Caucasians than Asians.[23] Therefore, the toxicities of this regimen in the current study might be more severe in Caucasians than Asian patients, necessitating further trials for Caucasian patients.

Recently, a Phase II trial of irinotecan plus cisplatin induction followed by concurrent twice-daily thoracic irradiation with etoposide plus cisplatin chemotherapy in patients with LD-SCLC was reported, with a promising efficacy (response rate, 97%; 2-year survival rate, 53.9%) and tolerability.[15] Our study is the first Phase II report that demonstrates that irinotecan/cisplatin-based chemoradiotherapy is also effective and tolerable in LD-SCLC.

In conclusion, IP with early concurrent radiotherapy was effective and tolerable in untreated LD-SCLC.

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