

## IRINOTECAN PLUS CISPLATIN COMPARED WITH ETOPOSIDE PLUS CISPLATIN FOR EXTENSIVE SMALL-CELL LUNG CANCER

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### ABSTRACT

**Background** Irinotecan hydrochloride, a topoisomerase I inhibitor, is effective against small-cell lung cancer. In a phase 2 study of irinotecan plus cisplatin in patients with extensive small-cell lung cancer, there was a high response rate and a promising median survival time.

**Methods** We conducted a multicenter, randomized, phase 3 study in which we compared irinotecan plus cisplatin with etoposide plus cisplatin in patients with extensive (metastatic) small-cell lung cancer.

**Results** The planned size of the study population was 230 patients, but enrollment was terminated early because an interim analysis found a statistically significant difference in survival between the patients assigned to receive irinotecan and cisplatin and those assigned to receive etoposide and cisplatin; as a result, only 154 patients were enrolled. The median survival was 12.8 months in the irinotecan-plus-cisplatin group and 9.4 months in the etoposide-plus-cisplatin group ( $P=0.002$  by the unadjusted log-rank test). At two years, the proportion of patients surviving was 19.5 percent in the irinotecan-plus-cisplatin group and 5.2 percent in the etoposide-plus-cisplatin group. Severe or life-threatening myelosuppression was more frequent in the etoposide-plus-cisplatin group than in the irinotecan-plus-cisplatin group, and severe or life-threatening diarrhea was more frequent in the irinotecan-plus-cisplatin group than in the etoposide-plus-cisplatin group.

**Conclusions** Irinotecan plus cisplatin is an effective treatment for metastatic small-cell lung cancer. (N Engl J Med 2002;346:85-91.)

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THE usual chemotherapy for extensive small-cell lung cancer is etoposide plus cisplatin or this combination in alternation with a regimen of cyclophosphamide, doxorubicin, and vincristine.<sup>1-4</sup> In preliminary studies, irinotecan hydrochloride, a topoisomerase I inhibitor, was effective against small-cell lung cancer,<sup>5</sup> and a phase 2 study of irinotecan plus cisplatin yielded a rate of complete response of 29 percent and an overall response rate of 86 percent (median survival, 13.2 months) in patients with extensive small-cell lung cancer.<sup>6</sup> For these reasons, we conducted a randomized, phase 3 study to compare irinotecan plus cisplatin with etoposide plus

cisplatin in patients with extensive small-cell lung cancer.

### METHODS

#### Patients

To be included in the study, patients had to have cytologically or histologically confirmed small-cell lung cancer; extensive disease (defined by distant metastasis, contralateral hilar-node metastasis, or both; those with pleural effusion alone were excluded); no prior radiotherapy, chemotherapy, or surgery; measurable lesions; an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2; a life expectancy of at least three months; an age of 70 years or less; and adequate organ function. Staging of the tumor was based on the results of physical examination, chest radiography, fiberoptic bronchoscopy with biopsy and cytologic examination, computed tomography (CT) of the chest and the brain, ultrasonography or CT of the abdomen, radionuclide bone scanning, bone marrow aspiration or biopsy, and other tests as needed. Adequate organ function (adequate function of the bone marrow, liver, and kidney) was defined as indicated by a leukocyte count of at least 4000 per cubic millimeter, a platelet count of at least 100,000 per cubic millimeter, a hemoglobin level of at least 9.5 g per deciliter (5.9 mmol per liter), aspartate aminotransferase and alanine aminotransferase levels no higher than 100 IU per milliliter, a serum creatinine level no higher than 1.2 mg per deciliter (106  $\mu$ mol per liter), and a creatinine clearance of at least 60 ml per minute.

The exclusion criteria were infection, diarrhea, ileus, interstitial pneumonitis, pulmonary fibrosis, uncontrolled diabetes mellitus, myocardial infarction within the preceding three months, massive pleural or peritoneal effusion, symptomatic brain metastases requiring whole-brain irradiation or administration of corticosteroids, a paraneoplastic syndrome, an active synchronous cancer, a metachronous cancer within three disease-free years, and pregnancy or breast-feeding.

#### Treatment Assignment and Drug Administration

The patients were randomly assigned to receive either a combination of irinotecan and cisplatin or a combination of etoposide and cisplatin by the minimization method of balancing the groups according to the institution and the patients' performance status. Randomization was performed at the Japan Clinical Oncology Group

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\*Other participating institutions and investigators are listed in the Appendix.

(JCOG) data center according to the order in which information on enrollments was received by telephone or fax. The regimen of irinotecan and cisplatin consisted of four four-week cycles of 60 mg of irinotecan per square meter of body-surface area on days 1, 8, and 15 and 60 mg of cisplatin per square meter on day 1. The regimen of etoposide and cisplatin consisted of four three-week cycles of 100 mg of etoposide per square meter on days 1, 2, and 3 and 80 mg of cisplatin per square meter on day 1. Both regimens required hydration and administration of antiemetic drugs. If the leukocyte count fell below 2000 per cubic millimeter or the neutrophil count fell below 1000 per cubic millimeter, recombinant human granulocyte colony-stimulating factor was administered until the leukocyte or neutrophil count was restored. Because not all patients received the planned dose intensity (due to toxicity), we considered the planned intensity of cisplatin to be 15 mg and 26.7 mg per square meter per week in the irinotecan-plus-cisplatin group and the etoposide-plus-cisplatin group, respectively.

#### Dose Modifications and Modifications in the Treatment Schedule

Toxic effects were graded according to the JCOG Toxicity Criteria,<sup>7</sup> in which a grade of 1 indicates a mild effect, grade 2 a moderate effect, grade 3 a severe effect, and grade 4 a life-threatening effect. Administration of irinotecan was skipped on day 8 or 15 if the leukocyte count was 2000 per cubic millimeter or less, if the platelet count was 50,000 per cubic millimeter or less, or if there was diarrhea. Administration of subsequent cycles of irinotecan was allowed when the leukocyte count reached at least 3500 per cubic millimeter, the platelet count reached at least 100,000 per cubic millimeter, and the diarrhea had subsided. The dose of irinotecan in subsequent cycles was reduced by 10 mg per square meter from the planned dose if there were grade 4 hematologic toxic effects or if grade 2 or 3 diarrhea developed. Treatment was discontinued in patients with grade 4 diarrhea.

Etoposide was discontinued if the leukocyte count was 3500 per cubic millimeter or less, if the platelet count was 75,000 per cubic millimeter or less, or if the serum creatinine level was 1.5 mg per deciliter (132.6  $\mu$ mol per liter) or higher. In patients with grade 4 hematologic toxic effects, the doses of etoposide and cisplatin in subsequent cycles were reduced to 75 percent of the planned doses. In both study groups, the dose of cisplatin was reduced to 75 percent of the planned dose in patients with grade 2 renal toxic effects. Subsequent cycles of treatment were suspended entirely in patients with grade 2 hepatic toxic effects until the results of liver-function tests were normal. Treatment was terminated in patients with renal toxic effects rated grade 3 or higher, pulmonary toxic effects rated grade 2 or higher, or hepatic toxic effects rated grade 3 or higher.

A second randomization to evaluate subsequent thoracic radiotherapy as a means of inhibiting local relapse was canceled because of an inadequate number of eligible patients.

#### Evaluations

All the patients underwent weekly evaluations that included an assessment of symptoms, a physical examination, chest radiography, a complete blood count, blood-chemistry studies (including measurements of aspartate aminotransferase and alanine aminotransferase, lactate dehydrogenase, bilirubin, serum creatinine, blood urea nitrogen, total protein, serum albumin, serum electrolytes, and calcium), and urinalysis. Tumor response was evaluated according to World Health Organization criteria<sup>8</sup> and was assessed by chest radiography or chest CT and by the same tests used initially to stage the tumor. A complete response was defined as the disappearance of all clinical and radiologic evidence of tumor for at least four weeks; a partial response was defined as a decrease of 50 percent or more in the sum of the products of the longest perpendicular diameters of all measurable lesions for at least four weeks; and progressive disease was defined as an increase of more than 25 percent in the sum of the products of the perpendicular diameters of all

measurable lesions or the appearance of new lesions. All other circumstances were considered to indicate no change. All the observed responses were reviewed by an extramural panel at regular study-group meetings. A planned quality-of-life study<sup>9</sup> was terminated because of poor compliance.

#### Study Design and Statistical Analysis

This trial was designed as a multicenter, prospective, randomized phase 3 study. The study protocol was approved by the Clinical Trial Review Committee of JCOG and the institutional review board of each participating institution before the initiation of the study, and all the patients provided written informed consent before randomization in accordance with the policies of JCOG in effect in 1995, when enrollment began. The primary end point was overall survival, and the secondary end points were the rates of complete and overall response, progression-free survival, sites of relapse, and toxicity. The sample size initially planned was 230 patients from 54 participating sites, with 115 patients in each group. The planned duration of accrual was 3 years, and the planned follow-up time was 1.5 years. This sample size was designed to provide the study with 80 percent power to detect an improvement of 9 months in the median survival of the patients in the etoposide-plus-cisplatin group and an improvement of 13 months in the median survival of patients in the irinotecan-plus-cisplatin group (hazard ratio, 0.69) with a one-sided type I error of 0.05.

All comparisons of patients' characteristics, prognostic variables, response rates, and rates of toxic effects were performed with Fisher's exact test, except for age, for which the t-test was used. Survival was measured as the date of randomization to the date of death or the date of the most recent follow-up. Progression-free survival was measured as the date of randomization to the date of the first observation of disease progression or the date of death from any cause if there had been no progression. If there was no progression and if the patient had not died, data on progression-free survival were censored as of the date that the absence of progression was confirmed. If a patient died without information on progression, data on progression-free survival were censored as of the last date on which progression could be ruled out by review of follow-up forms. Survival curves were calculated by the Kaplan-Meier method<sup>10</sup> and compared with use of the log-rank test.

Two interim analyses were planned, with adjustment for multiple comparisons taken into account by the method of Lan and DeMets.<sup>11</sup> The O'Brien-Fleming type alpha spending function was used. The first interim analysis was planned for the date on which half the planned number of patients had been enrolled, and the second for the date on which all the patients had been enrolled. The boundaries were calculated with the use of computer programs provided by Reboussin et al.<sup>12</sup> The current study was designed and conducted on the basis of one-sided testing, but the results are presented with two-sided P values. Unadjusted P values are reported because of the conservative spending function used.

All patient-information forms were collected and managed at the data center. In-house interim monitoring was performed at the data center to ensure the submission of data, the eligibility of the patients, compliance with the protocol, safety, and progress of the study on schedule. The monitoring reports were submitted to and reviewed by an independent monitoring committee semiannually.

## RESULTS

Enrollment in the study began in November 1995. The first interim analysis, performed in August 1998, suggested a difference in overall survival between the two study groups; the monitoring committee therefore recommended that the second interim analysis be performed earlier than planned. The second analysis, performed in December 1998, found a significant dif-

ference in overall survival between the two groups ( $P < 0.001$ ), and the monitoring committee therefore recommended termination of the study. Enrollment was discontinued and the study was terminated in January 1999.

Between November 1995 and November 1998, 154 patients were enrolled in the study at 27 sites among the 54 institutions planned, with 77 randomly assigned to receive irinotecan and cisplatin and 77 randomly assigned to receive etoposide and cisplatin (Table 1). All the enrolled patients were included in the analyses of survival, progression-free survival, and tumor response. However, two patients in the irinotecan-plus-cisplatin group were given no chemotherapy, one because of rapid progression of disease and the other because of an acute gastric ulcer that was diagnosed immediately after randomization. Both of these patients were excluded from the analysis of toxicity. The average follow-up time was 16.8 months in the irinotecan-plus-cisplatin group and 11.7 months in the etoposide-plus-cisplatin group. None of the patients were lost to follow-up.

**Toxicity**

Hematologic toxic effects are shown in Table 2. JCOG grade 3 or 4 leukopenia and neutropenia and grade 3 or 4 thrombocytopenia were more frequent in the etoposide-plus-cisplatin group than in the irinotecan-plus-cisplatin group. Grade 3 or 4 diarrhea occurred in 16.0 percent of the irinotecan-plus-cisplatin group and in none of the etoposide-plus-cisplatin group ( $P < 0.001$ ). Grade 1 or 2 diarrhea was also frequent in the irinotecan-plus-cisplatin group. The incidence of nausea and vomiting and other nonhematologic toxic effects did not differ significantly between the two groups.

Major deviations from the protocol were the failure to reduce the dose of chemotherapy despite the presence of grade 4 neutropenia (in six patients in the irinotecan-plus-cisplatin group and seven in the etoposide-plus-cisplatin group), administration of irinotecan despite the presence of grade 1 or 2 diarrhea (in nine patients in the irinotecan-plus-cisplatin group), continuation of the study treatment despite grade 2 or 3 pulmonary toxic effects (in three patients in the irinotecan-plus-cisplatin group and six in the etoposide-plus-cisplatin group), and continuation of the study treatment despite grade 3 hepatic toxic effects (in one patient in the irinotecan-plus-cisplatin group and three in the etoposide-plus-cisplatin group).

There were four treatment-related deaths, three in the irinotecan-plus-cisplatin group and one in the etoposide-plus-cisplatin group. In the irinotecan-plus-cisplatin group, a 63-year-old man died of bleeding from a metastatic site in the lung, a 62-year-old man died of sepsis associated with neutropenia and diar-

**TABLE 1. CHARACTERISTICS OF THE PATIENTS.**

CHARACTERISTIC	IRINOTECAN PLUS CISPLATIN (N=77)	ETOPOSIDE PLUS CISPLATIN (N=77)	P VALUE
Age (yr)			0.12
Median	63	63	
Range	30-70	41-70	
Sex			0.25
Male	63	69	
Female	14	8	
ECOG performance status*			0.61
0	10	9	
1	61	58	
2	6	10	
Weight loss during previous 6 mo			0.76
<5% of body weight	55	56	
5-10% of body weight	14	11	
>10% of body weight	8	10	
Lymph-node metastasis			1.00
Contralateral mediastinal			
Absent	51	50	
Present	26	27	
Supraclavicular			0.24
Absent	64	57	
Present	13	20	
Distant metastasis†			0.43
Absent	6	10	
Present	71	67	
Liver	14	13	
Lung	18	20	
Brain	10	17	
Bone	28	18	
Adrenal gland	5	5	
Bone marrow	5	4	

\*ECOG denotes Eastern Cooperative Oncology Group.

†Some of the patients had distant metastasis to more than one site.

rhea, and a 64-year-old woman died of pneumonia associated with neutropenia. In the etoposide-plus-cisplatin group, a 69-year-old man died of radiation pneumonitis after completion of subsequent thoracic radiotherapy.

**Delivery of Treatment**

There were no significant differences between the two groups in the delivery of treatment (Table 3). The proportion of patients who received the planned four cycles of chemotherapy was approximately 70 percent in each group. More patients in the etoposide-plus-cisplatin group (38 percent) than in the irinotecan-plus-cisplatin group (29 percent) completed their assigned study treatment with no modifications in the doses or delivery schedule. The dose intensity (the actual dose delivered as a proportion of the planned dose) was 80.4 percent for irinotecan and 95.3 percent for cisplatin in the group assigned to receive irinotecan

TABLE 2. TOXIC EFFECTS, ACCORDING TO STUDY GROUP AND JCOG GRADE OF TOXICITY.\*

TOXIC EFFECT	IRINOTECAN PLUS CISPLATIN (N=75)						ETOPOSIDE PLUS CISPLATIN (N=77)						P VALUE†
	GRADE 1	GRADE 2	GRADE 3	GRADE 4	GRADE 3 OR 4	GRADE 4	GRADE 1	GRADE 2	GRADE 3	GRADE 4	GRADE 3 OR 4	GRADE 4	
	no. of patients			% of patients			no. of patients			% of patients			
<b>Hematologic</b>													
Neutropenia	8	17	30	19	65.3	25.3	0	5	21	50	92.2	64.9	<0.001
Leukopenia	16	38	17	3	26.7	4.0	5	30	35	5	51.9	6.5	0.002
Anemia	10	38	20	—	26.7	—	9	43	23	—	29.9	—	0.72
Thrombocytopenia	6	9	1	3	5.3	4.0	19	13	14	0	18.2	0	0.02
<b>Nonhematologic</b>													
Diarrhea	19	21	8	4	16.0	5.3	8	5	0	0	0	0	<0.001
Nausea or vomiting	26	28	10	—	13.3	—	36	23	5	—	6.5	—	0.18
Infection	17	9	3	1	5.3	1.3	23	9	1	2	3.9	2.6	0.72
Decrease in arterial oxygen pressure	20	5	1	1	5.0‡	2.5‡	27	9	2	1	5.8‡	1.9‡	1.0
Increase in alanine aminotransferase	30	7	3	0	4.0	0	28	6	2	1	3.9	1.3	1.0
Increase in aspartate aminotransferase	30	5	0	0	0	0	24	2	1	1	2.6	1.3	0.5
Fever	12	17	1	0	1.3	0	14	16	2	0	2.6	0	1.0
Increase in bilirubin	—	16	0	0	0	0	—	20	0	0	0	0	—
Increase in creatinine	15	4	0	0	0	0	16	5	0	0	0	0	—
Peripheral neuropathy	4	0	0	—	0	—	10	1	0	—	0	—	—

\*Two patients in the irinotecan-plus-cisplatin group were not included in the analysis of toxicity because they received no chemotherapy (one because of disease progression and one because of acute gastric ulcer). JCOG denotes Japan Clinical Oncology Group. Dashes indicate that there was no scale of grading in the JCOG toxicity criteria. A grade of 1 indicates a mild effect, a grade of 2 a moderate effect, a grade of 3 a severe effect, and a grade of 4 a life-threatening effect.

†P values are for the comparison between the two study groups of the incidence of grade 3 or 4 toxic effects.

‡Data were missing for 35 patients in the irinotecan-plus-cisplatin group and 25 patients in the etoposide-plus-cisplatin group.

plus cisplatin and was 83.9 percent for etoposide and 84.6 percent for cisplatin in the group assigned to receive etoposide plus cisplatin. The actual intensity of the dose of cisplatin in the etoposide-plus-cisplatin group was 1.58 times that in the irinotecan-plus-cisplatin group (22.6 vs. 14.3 mg per square meter per week, respectively).

#### Rates of Response

The rate of complete response and the overall response rate were 2.6 percent (95 percent confidence interval, 0.3 to 9.1 percent) and 84.4 percent (95 percent confidence interval, 74.4 to 91.7 percent), respectively, in the irinotecan-plus-cisplatin group and 9.1 percent (95 percent confidence interval, 3.7 to 17.8 percent) and 67.5 percent (95 percent confidence interval, 55.9 to 77.8 percent), respectively, in the etoposide-plus-cisplatin group (Table 4). The rate of overall response in the irinotecan-plus-cisplatin group was significantly higher than that in the etoposide-plus-cisplatin group ( $P=0.02$ ).

#### Overall Survival

As of March 2001, when the final analysis was conducted, the median overall survival was 12.8 months (95 percent confidence interval, 11.7 to 15.2) in the

irinotecan-plus-cisplatin group and 9.4 months (95 percent confidence interval, 8.1 to 10.8) in the etoposide-plus-cisplatin group; 70 patients in the irinotecan-plus-cisplatin group and 74 in the etoposide-plus-cisplatin group died ( $P=0.002$  by the log-rank test) (Fig. 1). The rate of overall survival in the irinotecan-plus-cisplatin group was 58.4 percent (95 percent confidence interval, 47.4 to 69.4 percent) at one year and 19.5 percent (95 percent confidence interval, 10.6 to 28.3 percent) at two years; in the etoposide-plus-cisplatin group, the rates of overall survival at these time points were 37.7 percent (95 percent confidence interval, 26.8 to 48.5 percent) and 5.2 percent (95 percent confidence interval, 0.2 to 10.2 percent). The risk of death in the irinotecan-plus-cisplatin group relative to that in the etoposide-plus-cisplatin group was 0.60 (95 percent confidence interval, 0.43 to 0.83). Similar results were obtained in analyses that adjusted for age, sex, performance status, and weight loss and in an analysis that excluded the 23 patients randomly assigned to the radiotherapy portion of the study, which was canceled.

#### Progression-free Survival

The median known progression-free survival was 6.9 months (95 percent confidence interval, 6.1 to 7.3)

**TABLE 3. NUMBER OF CYCLES OF TREATMENT AND ACTUAL DOSES DELIVERED.**

VARIABLE	IRINOTECAN PLUS CISPLATIN (N=77)		ETOPOSIDE PLUS CISPLATIN (N=77)	
	no. of patients (%)		no. of patients (%)	
Cycles				
0	2 (2.6)		0	
1	6 (7.8)		2 (2.6)	
2	8 (10.4)		13 (16.9)	
3	8 (10.4)		7 (9.1)	
4	53 (68.8)		55 (71.4)	
	delivered dose (mg/m <sup>2</sup> /wk)	% of planned dose	delivered dose (mg/m <sup>2</sup> /wk)	% of planned dose
Agent				
Cisplatin	14.3	95.3	22.6	84.6
Irinotecan	36.2	80.4	—	—
Etoposide	—	—	83.9	83.9

in the irinotecan-plus-cisplatin group and 4.8 months (95 percent confidence interval, 4.3 to 5.5) in the etoposide-plus-cisplatin group. The rate of known progression-free survival in the irinotecan-plus-cisplatin group was 65.3 percent (95 percent confidence interval, 54.3 to 76.3 percent) at six months and 12.5 percent (95 percent confidence interval, 4.9 to 20.1 percent) at one year; in the etoposide-plus-cisplatin group the rates of progression-free survival at these time points were 35.6 percent (95 percent confidence interval, 24.8 to 46.3 percent) and 7.9 percent (95 percent confidence interval, 1.8 to 14.0 percent), respectively (P=0.003 by the log-rank test) (Fig. 2). Progression was known to have occurred in 68 patients in the irinotecan-plus-cisplatin group and 75 patients in the etoposide-plus-cisplatin group. The relative risk of disease progression in the irinotecan-plus-cisplatin group as compared with that in the etoposide-plus-cisplatin group was 0.61 (95 percent confidence interval, 0.44 to 0.84). The estimates of progression-free survival, however, may be biased because information on progression was not monitored continuously and because there were 10 instances of early censoring because of death without data on progression (8 instances in the irinotecan-plus-cisplatin group and 2 in the etoposide-plus-cisplatin group).

**DISCUSSION**

The current standard chemotherapy for extensive small-cell lung cancer — a regimen of etoposide and cisplatin or this combination alternating with a combination of cyclophosphamide, doxorubicin, and vincristine — yields a median survival of 8 to 10 months

**TABLE 4. OBJECTIVE TUMOR RESPONSE.\***

RESULT	IRINOTECAN PLUS CISPLATIN	ETOPOSIDE PLUS CISPLATIN
	no. of patients (%)	
Response		
Complete	2 (2.6 [0.3–9.1])	7 (9.1 [3.7–17.8])
Partial	63 (81.8)	45 (58.4)
Overall	65 (84.4 [74.4–91.7])†	52 (67.5 [55.9–77.8])
No change	2 (2.6)	16 (20.8)
Progression	3 (3.9)	9 (11.7)
Not evaluated	5 (6.5)	0
Not treated	2 (2.6)	0

\*Values in brackets are 95 percent confidence intervals.

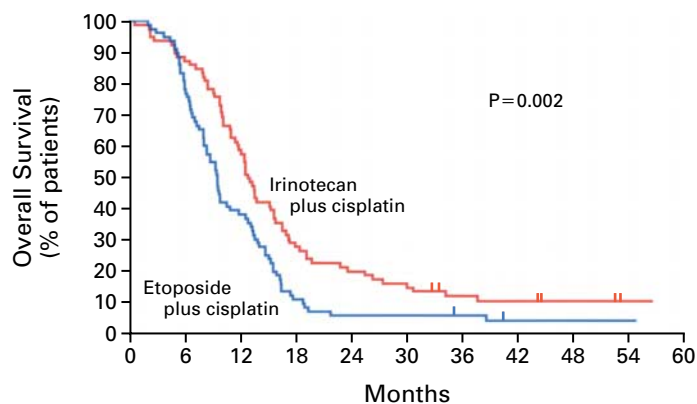
†P=0.02 for the comparison with the rate of overall response in the etoposide-plus-cisplatin group. The absolute difference between the two groups in overall response rate was 16.9 percent (95 percent confidence interval, 3.7 to 30.1 percent).

and a 2-year survival rate of 10 percent. In this phase 3 study, 77 patients with metastatic small-cell lung cancer who were treated with irinotecan plus cisplatin had a median survival of 12.8 months, whereas the group that received etoposide plus cisplatin had a median survival of 9.4 months (P=0.002). The overall rates of survival in these two groups at two years were 19.5 percent and 5.2 percent, respectively.

Myelosuppression was the most frequent toxic effect in both groups and was more frequent in the etoposide-plus-cisplatin group than in the irinotecan-plus-cisplatin group. There was, however, a significantly higher incidence of grade 3 or 4 diarrhea among the patients who received irinotecan than among those who received etoposide.

The three treatment-related deaths in the irinotecan-plus-cisplatin group occurred during the first or second cycle of treatment and were attributed to hematologic toxic effects of the first cycle. Severe hematologic toxic effects, as well as diarrhea, during the initial cycles of chemotherapy should therefore be managed carefully. All cases of grade 1 to 4 diarrhea occurred during the first and second cycles of irinotecan-plus-cisplatin treatment, but early suspension of treatment prevented death associated with diarrhea in all but one case, which involved a protocol violation in which the patient was given irinotecan on day 8 of the first cycle despite the presence of grade 1 diarrhea. We administered loperamide hydrochloride or a Chinese herbal drug such as hange-shashin-to to ameliorate the diarrhea at the discretion of the attending physicians.

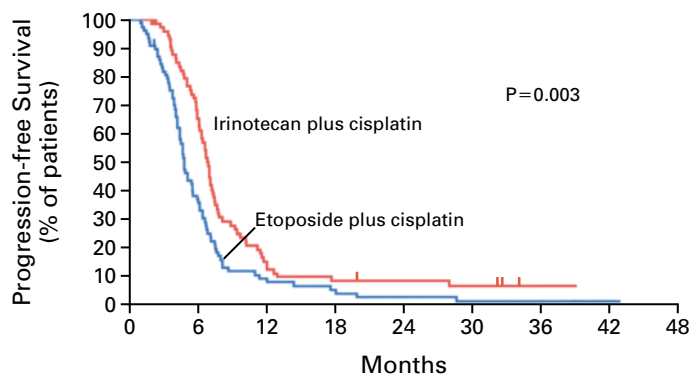
The proportion of patients who received all four



NO. AT RISK							
Irinotecan plus cisplatin	77	67	45	21	15	11	7
Etoposide plus cisplatin	77	60	29	8	4	4	3

**Figure 1.** Overall Survival of Patients with Extensive Small-Cell Lung Cancer Who Were Assigned to Treatment with Irinotecan plus Cisplatin or Etoposide plus Cisplatin.

The tick marks indicate patients whose data were censored.



NO. AT RISK				
Irinotecan plus cisplatin	77	47	9	9
Etoposide plus cisplatin	77	27	6	2

**Figure 2.** Progression-free Survival of Patients with Extensive Small-Cell Lung Cancer Who Were Assigned to Treatment with Irinotecan plus Cisplatin or Etoposide plus Cisplatin.

The tick marks indicate patients whose data were censored.

cycles of chemotherapy was similar in the two groups (approximately 70 percent), and thus the observed difference in survival is not thought to be attributable to a difference in the actual delivery of treatment.

Our study had several weaknesses. The planned second randomization to allow us to assess the benefit of subsequent thoracic radiotherapy was not completed; the planned quality-of-life study was not completed; and full information concerning treatment after dis-

ease progression was not available. The estimates of overall survival, however, should be highly reliable because, as of March 2001 (the final analysis), no patient had been lost to follow-up.

We consider that the trend toward a higher complete-response rate in the etoposide-plus-cisplatin group than in the irinotecan-plus-cisplatin group is due to chance. Although it is possible that these results occurred by chance, we believe that the decision to ter-

minate the trial early was based on generally accepted scientific and ethical principles and that, despite the small sample size, we can conclude that the combination of irinotecan and cisplatin is an attractive option for patients with metastatic small-cell lung cancer who have a good performance status.

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## APPENDIX

This study was coordinated by the Japan Clinical Oncology Group (M. Shimoyama, former chairperson) and was performed with the cooperation of the following institutions and investigators: National Dohoku Hospital, Hokkaido (T. Fujikane, K. Takahashi, and Y. Yamazaki); Hokkaido Keiaiikai Minami-ichijo Hospital, Hokkaido (A. Fujita); Asahikawa Medical College Hospital, Hokkaido (Y. Osaki and Y. Nishizaki); Yamagata Prefectural Central Hospital, Yamagata (T. Tsukamoto); Tsukuba University Hospital, Ibaragi (S. Hasegawa and M. Tajima); Tochigi Cancer Center, Tochigi (T. Hirose, S. Machida, and M. Noda); National Nishi-Gunma Hospital, Gunma (S. Tsuchiya and H. Nakano); Saitama Cancer Center, Saitama (S. Yoneda, H. Sakai, T. Ikeda, and K. Kobayashi); National Cancer Center Hospital East, Chiba (F. Houjo, R. Kakinuma, Y. Ohe, T. Matsumoto, H. Ohmatsu, K. Kodama, E. Moriyama, and Y. Hosomi); National Cancer Center Central Hospital, Tokyo (T. Shinkai, H. Kunitoh, K. Kubota, and I. Sekine); International Medical Center of Japan, Tokyo (K. Kudo and Y. Takeda); Kanagawa Cancer Center, Yokohama (I. Nomura, K. Yamada, F. Oshita, Y. Kato, and M. Kondo); Yokohama Municipal Citizen's Hospital, Yokohama (H. Kunikane and A. Nagatomo); Niigata Cancer Center Hospital, Niigata (H. Tsukada, S. Mitsuma, and Y. Ichikawa); Aichi Cancer Center, Nagoya (K. Yoshida and T. Hida); National Nagoya Hospital, Nagoya (K. Nishiwaki and M. Hiraiwa); National Kinki Central Hospital for Chest Diseases, Osaka (M. Ogawara, T. Tsuchiyama, N. Kodama, K. Moriya, K. Okishio, N. Naka, S. Nobuyama, and S. Yamamoto); Kinki University School of Medicine, Osaka (N. Yamamoto, K. Nakagawa, T. Nogami, Y. Ieda, and M. Yoshida); Osaka Prefectural Habikino Hospital, Osaka (I. Kawase, N. Masuda, T. Nitta, and M. Kobayashi); Osaka City General Hospital, Osaka (K. Takeda, N. Yoshimura, H. Uejima, N. Nishikubo, T. Nitta, N. Takifuji, R.

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