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ORIGINAL ARTICLE

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Dose escalation study of irinotecan combined with carboplatin for advanced non-small-cell lung cancer

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Abstract From December 1994 to July 1997, we conducted a dose escalation study of irinotecan combined with carboplatin in 17 patients with advanced non-small-cell lung cancer (NSCLC) to determine the maximum tolerated dose and the dose-limiting toxicities. Irinotecan was administered intravenously over 90 min on days 1, 8 and 15, with carboplatin given at an area under the concentration-time curve dose of 5 mg/ml·min (calculated using Calvert's formula) on day 1. The starting dose of irinotecan was 30 mg/m^2 and dose escalation was done in 10-mg/m^2 increments. Treatment was repeated at 28-day intervals for at least two cycles. The dose-limiting toxicities were neutropenia and thrombocytopenia, since three out of five patients given 60 mg/m^2 of irinotecan developed grade 4 neutropenia and thrombocytopenia. The overall response rate was 35.3%. The median survival time and the 1-year survival rate were 10.5 months and 35.3%, respectively. The maximum tolerated dose of irinotecan with this regimen was 60 mg/m^2, while 50 mg/m^2 can be recommended for future use. Further studies of this combination in advanced NSCLC are warranted.

Keywords Irinotecan · Calvert's formula · Carboplatin · Non-small-cell lung cancer · Phase I study

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Introduction

Irinotecan is a derivative of camptothecin that shows activity against leukemia, lymphoma [21], small-cell lung cancer [14], non-small-cell lung cancer (NSCLC) [9], and colorectal cancer [23]. Its major active metabolite, 7-ethyl-10-hydroxycamptothecin, is also active against these tumors [11]. The dose-limiting toxicities of irinotecan are diarrhea and leukopenia [9, 11, 14, 21, 23]. Irinotecan combined with cisplatin has been shown to be one of the most active regimens against NSCLC, with response rates in the range 31–54% [15, 16, 17, 18].

Carboplatin is an analogue of cisplatin that shows less nonhematologic toxicity [4]. It is also active against NSCLC, and its dose-limiting toxicities are thrombocytopenia and leukopenia. The area under the plasma concentration versus time curve (AUC) of carboplatin correlates well with the extent of the myelosuppression caused by this drug, especially thrombocytopenia, as well as with the response rate in patients with ovarian carcinoma [10, 24]. The target AUC of carboplatin can be modified on the basis of a patient's renal function and dosing can be individualized using Calvert's formula [5]. AUC-based administration of carboplatin is a reasonable strategy for ensuring constant drug exposure and reducing the risk of toxicity, and may also improve the response rate [6].

Furthermore, carboplatin shows no cross-resistance with irinotecan [19], and a synergistic effect has been observed with the combination of these two drugs in preclinical studies [12]. When compared with other chemotherapy regimens in an Eastern Cooperative Oncology Group (ECOG) study, carboplatin achieved modest improvement of the 1-year survival rate in patients with advanced NSCLC [3].

Therefore, we conducted a dose escalation study of irinotecan combined with carboplatin for advanced NSCLC. The objectives of this study were (1) to determine the optimum doses of the two drugs in combination, (2) to detect and quantify the clinical toxicity of

this combination therapy, and (3) to assess the activity of this therapy against advanced NSCLC.

Material and methods

Patient selection

Patients with histologically documented NSCLC of TNM stage IIIB or IV according to the criteria of Mountain [20] could be enrolled in this study. Patients who had received previous chemotherapy were excluded, as were patients with massive pleural effusion or ascites, but patients with postoperative recurrence and those who had received radiotherapy for metastatic disease were eligible. A complete history and physical examination were performed in all patients. After the nature and purpose of the study were fully explained, each patient gave written informed consent. The study was approved by the institutional review board of Osaka City General Hospital.

Patients were required to have measurable or assessable disease, an ECOG performance status ≤ 2, an age < 75 years, and no active concomitant malignancy. Measurable or assessable disease meant that the tumor could be demonstrated on conventional chest roentgenograms or by computed tomography (CT). All patients underwent routine staging evaluation that consisted of standard radiologic studies (including CT of the abdomen and brain) and bone scanning.

Eligibility requirements also included the following: white blood cell (WBC) count $\geq 4000/mm^3$, platelet count $\geq 100{,}000/mm^3$, hemoglobin ≥ 9.5 g/dl, serum bilirubin < 1.5 mg/dl, serum AST/ALT not more than twice the upper limit of normal, serum creatinine less than the upper limit of normal, and creatinine clearance ≥ 40 ml/min.

Dose escalation procedure

Irinotecan was administered as a 90-min intravenous infusion on days 1, 8, and 15. Carboplatin was administered as a 90-min infusion after the irinotecan infusion on day 1, with the dose targeting a specific AUC as determined by Calvert's formula: dose(mg) = AUC $\times$ [glomerular filtration rate (GFR) + 25] [5]. The 24-h creatinine clearance was substituted for GFR. The target AUC of carboplatin was fixed at 5 mg/ml·min based on the finding that this is the minimum AUC producing a tumor response with manageable toxicity in patients with ovarian carcinoma [10]. The regimen was repeated at 28-day intervals and at least two cycles were given. Hematopoietic growth factors were not administered routinely, but were used as needed according to published guidelines [2].

The starting dose of irinotecan was 30 mg/m^2. Three patients were entered at each dose level, and the dose was escalated in increments of 10 mg/m^2 for successive groups of patients until dose-limiting toxicity was observed during the first course of treatment. No intrapatient dose escalation was performed.

Dose-limiting toxicity was defined as grade 3 or 4 nonhematologic toxicity, excluding nausea/vomiting and alopecia, or grade 4 hematologic toxicity according to the Japan Clinical Oncology Group (JCOG) toxicity criteria [25]. If one or two instances of dose-limiting toxicity were observed among three patients treated at a certain dose level, an additional three patients were scheduled to be treated at the same dose level, and dose escalation would only continue if dose-limiting toxicity was observed in no more than two out of six patients. The maximum tolerated dose (MTD) was defined as the dose causing three instances of dose-limiting toxicity among six patients, and the dose recommended for further studies was set one level lower.

High-dose loperamide therapy, as described by Abigerges et al. [1], was used to manage diarrhea induced by irinotecan. From the first episode of diarrhea, the patient took 2 mg of loperamide every 2 h and treatment was only stopped after a 12-h diarrhea-free interval.

Subsequent courses of chemotherapy were started after day 28 when the leukocyte and platelet counts were $\geq 4000/mm^3$ and $\geq 100{,}000/mm^3$, respectively. If the leukocyte or platelet count had not reached these levels or diarrhea had not resolved by day 1 of the next scheduled course of chemotherapy, both drugs were withheld until full recovery. If more than 6 weeks passed from the time of previous treatment before these criteria were satisfied, the patient was removed from the study.

The doses of both carboplatin and irinotecan were adjusted for toxicity as follows. Patients who experienced grade 4 leukopenia or grade 3–4 diarrhea had their irinotecan dose reduced by 10 mg/m^2 for the next cycle, while patients who experienced grade 4 thrombocytopenia had their target carboplatin AUC reduced by 1 mg/ml·min for the next cycle. Irinotecan was withheld if the leukocyte count was less than $2000/mm^3$, the platelet count was less than $75{,}000/mm^3$, or there was diarrhea of grade 2 or worse on days 8 and 15.

Evaluation

For the assessment of tumor response and the toxicity of therapy, the following tests were done once a week during treatment: complete blood count, AST, ALT, alkaline phosphatase, lactate dehydrogenase, bilirubin, creatinine, BUN, serum electrolytes, urinalysis, and chest radiography. Tumor response was also evaluated by CT scan. Tumor responses were evaluated according to WHO criteria [26], while toxicity was evaluated in accordance with JCOG toxicity criteria [25]. Complete response (CR) was defined as the disappearance of all lesions for at least 4 weeks. Partial response (PR) was defined as a $> 50\%$ decrease in the sum of the products of the greatest perpendicular diameters of all measurable lesions for at least 4 weeks without the development of new lesions. If no change in the lesions occurred during treatment, the patient was defined as having stable disease (SD). Progressive disease (PD) was defined as a $> 25\%$ increase in the sum of the products of the perpendicular diameters of all measurable lesions or the appearance of new lesions.

Differences in the response rate between groups of patients were compared using the chi-squared test. Survival was calculated on the basis of the period from the start of treatment to death or the last follow-up and survival curves were drawn using the Kaplan-Meier method [13].

Results

Patients characteristics

From December 1994 to July 1997, 17 patients were enrolled in this study through four dose escalations. The main clinical characteristics of these patients are listed in Table 1. There were 14 men and 3 women, with a median age of 63 years (range 41 to 74 years). Of the 17 patients, 15 (88.2%) had an ECOG performance status of 1. Seven patients (41.2%) had squamous cell carcinoma, five (29.4%) had adenocarcinoma, three (17.6%) had large-cell carcinoma, and two (11.8%) had adenosquamous carcinoma. Five patients (29.4%) were in TNM stage IIIB and 12 (70.6%) had stage IV disease. Three patients had undergone prior therapy which included surgery (lobectomy) for the primary tumor and whole brain irradiation or gamma knife therapy for brain metastasis, and the other 14 patients had not undergone prior therapy. The mean 24-hour creatinine clearance of all the patients was 91 ml/min (range 57–142 ml/min).

Table 1 Patients characteristics

	No. of patients
Enrolled	17
Gender	
Male	14
Female	3
Age (years)	
Median	63
Range	41–74
Performance status (ECOG)	
1	15
2	2
Histology	
Squamous cell carcinoma	7
Adenocarcinoma	5
Large-cell carcinoma	3
Adenosquamous carcinoma	2
Stage	
IIIB	5
IV	12
Patients without prior therapy	14
Patients with prior therapy	3
Surgery	1
WBI	1
Gamma knife	1
24-h creatinine clearance (ml/min)	
Mean	91
Range	57–142

WBI: whole brain irradiation

The number of patients and courses at each irinotecan dose level and the actual doses of irinotecan delivered are listed in Table 2. The percentages of the irinotecan dose actually delivered relative to the planned dose were more than 80% at each dose level. Some patients did not received irinotecan on day 15 due to hematologic toxicities. Most patients completed irinotecan and carboplatin as scheduled. Of the 17 patients enrolled, 5 received only one cycle of this combination chemotherapy. Two patients had disease progression during the first treatment cycle and three did not receive the treatment due to toxicity. The median number of treatment cycles was two, and maximum was four for the responders.

Toxicity

Leukopenia, neutropenia, and thrombocytopenia were the dose-limiting toxicities of this combination chemotherapy. Major toxicities stratified by dose levels of irinotecan for cycle one only are shown in Table 3. Grade 4 neutropenia occurred in one patient at the 50 mg/m^2 dose level, but there was no other severe toxicity. At 60 mg/m^2, grade 4 neutropenia and grade 4 thrombocytopenia occurred in one patient each. When treatment was extended to another three patients at this dose level, one more patient developed grade 4 leukopenia, grade 4 neutropenia, and grade 4 thrombocytopenia, while

Table 2 Dose escalation schedule and actual given to patients: CPT-11 and carboplatin

Dose level	CPT-11 dose (mg/m^2)	Carboplatin AUC (mg/ml·min)	No. of patients	Total no. of courses	CPT-11 dose intensity (mg/m^2/week), delivered/projected	CPT-11 percentage dose delivered[a]
1	30	5	6	9	18.3/22.5	81.5
2	40	5	3	9	30.0/30.0	100.0
3	50	5	3	7	30.4/37.5	81.0
4	60	5	5	8	39.4/45.0	87.5

[a]Percentage of the CPT-11 dose actually delivered vs the planned dose

Table 3 Major toxicities for the cycle one stratified by dose level of irinotecan (number of patients at each dose level: six, three, three and five at 30, 40, 50 and 60 mg/m^2, respectively)

	Dose level (mg/m^2)															
	30				40				50				60			
	JCOG grade				JCOG grade				JCOG grade				JCOG grade			
	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
Leukopenia	1	3	1	0	0	2	0	0	0	1	2	0	0	1	3	1
Neutropenia	0	2	3	0	0	1	2	0	0	0	2	1	0	0	2	3
Anemia	1	1	3	0	1	0	0	0	0	3	0	0	2	2	0	0
Thrombocytopenia	2	1	0	0	1	1	0	0	0	0	0	0	0	0	1	3
Diarrhea	0	0	0	0	1	0	0	0	0	1	0	0	1	2	0	0
Skin rash	0	2	0	0	0	0	0	0	0	0	0	0	2	0	0	0
Fever	1	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0
Nausea/vomiting	1	1	0	–	1	0	0	–	1	2	0	–	2	2	1	–
Alopecia	2	0	0	–	2	0	0	–	0	0	0	–	3	0	1	–

another developed grade 4 neutropenia and grade 4 thrombocytopenia. Since three out of five patients developed severe toxicity, the MTD of irinotecan was defined as 60 mg/m^2 (days 1, 8, and 15) when combined with carboplatin at a target AUC of 5 mg/ml·min, while the recommended dose of irinotecan for subsequent studies of this combination was 50 mg/m^2. Patients who developed grade 4 neutropenia and grade 4 thrombocytopenia received treatment with recombinant human granulocyte stimulating factor and platelet transfusion. Only one patient developed febrile neutropenia at the dose level of 60 mg/m^2. No treatment-related deaths occurred in this study.

Irinotecan caused diarrhea, but this was mild (grade 1–2). Some patients developed noninfectious fever without neutropenia. Higher doses of irinotecan caused more severe nausea and vomiting. At the starting dose level, two out of three patients developed grade 2 skin rash due to an allergic reaction to irinotecan or carboplatin. Although this was not a dose-limiting toxicity, three more patients were entered at the 30 mg/m^2 dose level and did not develop skin rashes. Grade 1 skin rash also occurred in two patients at the 60 mg/m^2 dose level, but no severe allergic reactions were noted during the study.

Response and survival

The response achieved at each dose level of irinotecan is shown in Table 4. No significant differences in response was observed among the four dose levels. Of the 17 patients treated, 6 achieved a PR and 8 had SD. The overall objective response rate was 35.3% (95%CI 18.0–49.9%). During follow-up, 16 patients died of disease progression and one patient was still alive after 36 months at the time of analysis. The 1-year survival rate was 35.3% and the median survival time was 10.5 months for all eligible patients.

Discussion

The present phase I study showed that the MTD of irinotecan was 60 mg/m^2 when combined with carboplatin at a target AUC of 5 mg/ml·min. The recommended dose of irinotecan for subsequent investigation was determined to be 50 mg/m^2. As expected, the dose-limiting toxicities were leukopenia, neutropenia, and thrombocytopenia. However, irinotecan-induced diarrhea was very mild (grade 1–2). This may have been because a lower dose of irinotecan was given in this study than in previous phase II studies of single-agent therapy [9] and high-dose loperamide treatment [1].

Okamoto et al. [22] have reported the results of a phase I clinical and pharmacologic study of irinotecan and carboplatin with recombinant human granulocyte-colony stimulating factor prophylaxis in patients with advanced NSCLC. They recommended an irinotecan dose of 60 mg/m^2 and a target AUC for carboplatin of 5 mg/ml·min using Calvert's formula. In their study, the dose-limiting toxicity was grade 4 diarrhea at an irinotecan dose of 70 mg/m^2 and a target AUC for carboplatin of 5 mg/ml·min. At an irinotecan dose of 60 mg/m^2 and a target AUC for carboplatin of 6 mg/ml·min, the dose-limiting toxicities were diarrhea, leukopenia, neutropenia, and thrombocytopenia.

Another phase I study of irinotecan combined with carboplatin in patients with previously untreated solid cancer was reported by Fukuda et al. [8]. As in the present study, granulocyte colony-stimulating factor was not used prophylactically, but the dose of carboplatin was determined using Chatelut's formula [7] instead of Calvert's formula. The dose-limiting toxicities were leukopenia, thrombocytopenia, and diarrhea, with one treatment-related death occurring at an irinotecan dose of 60 mg/m^2 and a target AUC for carboplatin of 5 mg/ml·min, indicating that this was the MTD. They also concluded that the recommended dose of irinotecan is 50 mg/m^2 with a target AUC for carboplatin of 5 mg/ml·min when treatment is done without prophylactic colony-stimulating factor support. The former study was different from our study in the use of prophylactic colony-stimulating factor and the latter was different in the determination of the dose of carboplatin and the eligible cancer type. This combination chemotherapy of irinotecan and carboplatin aimed to evaluate for NSCLC.

The response rate to irinotecan in patients with advanced NSCLC who have not previously received chemotherapy is reported to be 32% [9]. When used in combination with cisplatin, it has been found that irinotecan is very active against NSCLC, with response rates in the range 31–54% [15, 16, 17, 18]. In the present study, the response rate was 35.3% (95%CI 18.0–49.9%), indicating that this therapy is also promising for the treatment of advanced NSCLC. The median survival time and the 1-year survival rate were 10.5 months and 35.3%, respectively, results that are comparable with those for irinotecan plus cisplatin [18]. Because

Table 4 Response

Irinotecan dose level (mg/m^2)	*n*	Complete response	Partial response	Stable disease	Progressive disease	Response rate (%)
30	6	0	1	3	2	16.7
40	3	0	1	2	0	16.7
50	3	0	2	1	0	66.7
60	5	0	2	2	1	40.0
Overall	17	0	6	8	3	35.3[a]

[a]95%CI 18.0–49.9%

carboplatin is easier to administer than cisplatin, this combination chemotherapy for advanced NSCLC deserves to be assessed in phase II studies.

In conclusion, the MTD and the recommended dose for irinotecan combined with carboplatin were 60 mg/m^2 and 50 mg/m^2, respectively, when the target AUC for carboplatin was set at 5 mg/ml·min using Calvert's formula. We are planning to conduct a phase II trial of this combination chemotherapy in patients with advanced NSCLC.

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