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Lung Cancer 38 (2002) 303–308

LUNG CANCER
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Phase II study of irinotecan and carboplatin for advanced non-small cell lung cancer

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Received 2 April 2002; received in revised form 19 July 2002; accepted 14 August 2002

Abstract

A phase II study was conducted to assess the activity and toxicity of irinotecan (CPT-11) and carboplatin (CBDCA) combination chemotherapy for advanced non-small-cell lung cancer (NSCLC). Eligibility included chemo-naive advanced NSCLC patients with measurable disease and a good performance status. CPT-11 of 50 mg/m^2 was administered as a 90-min intravenous infusion on days 1, 8, and 15. CBDCA dosed to an area under the concentration-time curve of 5 mg min/ml, using Calvert's formula, was administered by 90-min infusion after the CPT-11 infusion on day 1. Treatment was repeated 28 days interval for at least two cycles. Haematopoietic growth factors were not routinely used. From December 1997 to January 1999, 36 patients were entered into the study. The overall response rate was 25.0% (95% confidence interval: 12.1–42.2%). The median survival time and the 1-year survival rate were 10.2 months and 42.2%, respectively. Major toxicity by Japan Clinical Oncology Group criteria was as follows: grade 3–4 neutropenia 76.5%; grade 3 anemia 26.5%; grade 3/4 thrombocytopenia 47.1%; grade 3 nausea/vomiting 36.1%; grade 3–4 diarrhoea 5.9%; grade 3 alopecia 5.9%; grade 3–4 skin rush 2.9%. Four patients developed febrile neutropenia and only one had serious diarrhea induced by CPT-11. Actual relative delivery dose of CPT-11 to the projected one on days 8 and 15 were 0.86 and 0.43, respectively. It seemed that CPT-11 and CBDCA was more toxic regimen than CPT-11 and CDDP in advanced NSCLC. The relatively disappointing response rate could be related with low dose intensity of CPT-11.

Keywords: Phase II study; Irinotecan; Carboplatin; Non-small-cell lung cancer; Chemotherapy

1. Introduction

The recent development of new drugs for the treatment of non-small-cell lung cancer (NSCLC) has made several systemic chemotherapy regimens available for this disease [1].

Irinotecan (CPT-11), a new derivative of camptothecin, has been found to have clinical activity against various tumors, including small cell lung cancer (SCLC) [2], and NSCLC [3]. Its major active metabolite, 7-ethyl-10-hydroxycamptothecin (SN-38), is also active against these tumors [4]. The dose-limiting toxicities (DLTs) of CPT-11 are diarrhea and leukopenia [2,3].

Carboplatin (CBDCA) is an analogue of cisplatin (CDDP), but produces less nonhematologic toxicity. It is active against NSCLC and its DLTs are thrombocytopenia and leukopenia. The area under the plasma concentration versus the time curve (AUC) of CBDCA correlates well with the degree of myelosuppression, especially thrombocytopenia and with the response rates of patients with ovarian carcinoma. CBDCA is a unique antineoplastic agent, for which the desired AUC can be controlled on the basis of individual renal function. AUC-based dosing of CBDCA is a reasonable strategy for ensuring constant drug exposure, reducing the risk of unnecessary toxicity, and possibly improving the response rate [5].

Furthermore, CBDCA shows no cross-resistance with CPT-11 [6], and a synergistic effect has been observed with combined CBDCA and CPT-11 in a preclinical

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0169-5002/02/$ - see front matter
PII: S0169-5002(02)00304-5

study [7,8]. When compared with other chemotherapy regimens by a cooperative group study, CBDCA was associated with modest improvement in the 1-year survival rate of patients with advanced NSCLC [9].

Therefore, we conducted a dose escalation study of CPT-11 combined with fixed dose of CBDCA (target AUC; 5 mg min/ml) for advanced NSCLC [10]. The maximum tolerated dose of CPT-11 with this regimen was 60 mg/m^2, while 50 mg/m^2 could be recommended for future use. The overall response rate of 35.3% and the median survival time of 10.5 months were encouraging.

The objective of this phase II study was to assess the response and toxicity of combination chemotherapy of CPT-11 and CDBCA in patients with advanced NSCLC.

2. Patients and methods

2.1. Patients' selection

Patients with histologically or cytologically documented, TNM stage IIIB or IV NSCLC according to the criteria reported by Mountain [11] were enrolled in this study. However, patients who had received previous chemotherapy were excluded. Patients who had experienced postoperative recurrence and those who had received radiotherapy to metastatic sites were eligible for the current study. A complete history and physical examination were performed in all patients. The nature and purpose of the study were fully explained to each patient. All patients signed an informed consent approved by the institutional review boards of Osaka City General Hospital.

Patients were required to have measurable or assessable disease, an Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0–2, an age <75 years, and no active concomitant malignancy. Measurable or assessable disease meant that the tumor was demonstrated by conventional chest roentgenograms or computed tomography (CT) of the whole body. In addition, all patients underwent a routine staging evaluation that consisted of standard radiological studies (including CT of the abdomen and brain) as well as bone scanning.

Eligibility requirements also included the following: white blood cell (WBC) count $\geqslant 4000/\mu l$, platelet count $\geqslant 100\,000/\mu l$, hemoglobin $\geqslant 9.5$ g/dl, serum bilirubin <1.5 mg/dl, serum AST/ALT $\leqslant$ twice the upper limit of normal, creatinine clearance $\geqslant 40$ ml/min. Patients with massive pleural effusion or ascitis were excluded from this study.

Height, weight, PS, and tumor stage were recorded. Initial laboratory data obtained included a complete blood count, differential WBC count, platelet count, serum electrolytes, blood urea nitrogen (BUN), creatinine, total protein, albumin, calcium, phosphate, uric acid, alkaline phosphatase, total bilirubin, AST, and ALT.

2.2. Treatment schedule

CPT-11 of 50 mg/m^2 was administered as a 90-min intravenous infusion on days 1, 8, 15. CBDCA was administered by 90-min infusion after the CPT-11 infusion on day 1, with the dose targeted to a specific AUC as described by Calvert et al. [5]. The dose was determined by multiplying the targeted AUC by the sum of the glomerular filtration rate (GFR) plus 25. The 24-h creatinine clearance was substituted for GFR. The target AUC of CBDCA was fixed 5 mg min/ml in this study. This dose definition was leaded by our previous phase I study of CPT-11 and CBDCA [10]. The regimen was repeated every 28 days for at least 2 cycles.

CPT-11 was withdrawn if the leukocyte count was less than 3000/μl, the platelet count was less than 100 000/μl, or diarrhea Grade 1 or higher occurred on days 8 and 15. This withdrawn criterion was amended according to the guideline from the Ministry of Public Welfare at that time. In our previous phase I study, CPT-11 was withdrawn if the leukocyte count was less than 2000/μl, the platelet count was less than 70 000/μl, or diarrhea Grade 2 or higher occurred on days 8 and 15 [10].

For CPT-11-induced diarrhea, high dose loperamide treatment, as described by Abigerges et al. [12], was administered.

Subsequent courses of chemotherapy were initiated when the leukocyte and platelet counts were $\geqslant 4000$ /μl and $\geqslant 100\,000$ /μl after day 28, respectively. If the leukocyte or platelet counts had not returned normal levels or diarrhea had not disappeared by day 1 of the next course of chemotherapy, both drugs were withheld until full recovery. If more than 8 weeks passed from the time of the last treatment before these criteria were satisfied, the patient was removed from the study.

Dose adjustments were made for both CBDCA and CPT-11 based on toxicity. Patients who experienced grade 4 leukopenia or grade 3 or higher diarrhea had their CPT-11 dose reduced by 10 mg/m^2 for the subsequent cycle. Patients who experienced thrombocytopenia grade 4 had their target AUC of CBDCA reduced by 1 mg min/ml for the subsequent cycle.

Haematopoietic growth factors were not administered routinely, but were used as needed according to published guidelines [13].

2.3. Evaluation of efficacy and toxicity

For the assessment of response and toxicity, the following tests were done once a week during treatment: complete blood count, AST, ALT, alkaline phospha-

tase, lactate dehydrogenase, bilirubin, creatinine, BUN, serum electrolytes, urinalysis, and chest X-ray film. WHO response criteria [14] were used for efficacy analysis; responses were assessed in alternate therapy cycles with CT scan or radiologic and ultrasound evaluation of the lesions.

Toxicity was evaluated in accordance with Japan Cooperative Oncology Group (JCOG) toxicity criteria [15].

Survival was calculated on the basis of the period from the start of treatment to death or the last follow-up evaluation. Survival curves were drawn using the Kaplan–Meier method [16].

This phase II study was conducted using a two-stage design [17]. Twenty patients were to be treated, if two or fewer responses were observed, accrual would terminate. This would ensure, with 95% confidence interval (CI), that the combination had a response rate $< 30\%$.

3. Results

3.1. Patients characteristics

From December 1997 to January 1999, 36 patients were entered into this study. The main clinical characteristics of the 36 eligible patients are listed in Table 1.

Table 1
Patients characteristics

No. of patients entered	36	
Eligible	36	(100%)
Male/female	26/10	
Age (year)		
Median	66	
Range	42–74	
Performance Status (ECOG)		
0	9	(25.0%)
1	23	(63.9%)
2	4	(11.1%)
Histology		
Adenocarcinoma	20	(55.6%)
Squamous cell carcinoma	14	(38.9%)
Unclassified carcinoma	2	(5.6%)
Stage		
IIIA	2	(5.6%)
IIIB	7	(19.4%)
IV	27	(75.0%)
Prior therapy		
No	22	(61.1%)
Yes	14	(38.9%)
Surgery alone	7	
Chest radiotherapy after surgery	1	
Gamma knife or WBI	5	
Craniotomy	1	

ECOG; Eastern Cooperating Oncology Group, WBI; whole brain irradiation.

Thirty-two (88.9%) had an ECOG PS of 0 or 1. Two patient (5.6%) was in TNM stage IIIA, 7 (19.4%) had stage IIIB, and 27 (75.0%) had stage IV disease at the enrollment. Twenty-two patients (61.1%) had no prior therapy, and 14 had prior therapy including lobectomy for primary lesion, whole brain irradiation, gamma knife, or craniotomy for brain metastasis, and chest radiotherapy for residual mediastinum lymph node after surgery.

3.2. Drug delivery

A total of 78 cycles of CPT-11 and CBDCA were administered. The median number of cycles received was two (range 1–4), with a median cycle interval of 34 days (range 28–50). Cycle delays were almost due to prolongation of neutropenia. Nine (25%) of 36 patients were given at only first cycle for the following reasons: tumor progression ($n = 5$), severe toxicity ($n = 3$), and patient refusal ($n = 1$). Four patients were adjusted the doses of CPT-11 and CBDCA over the subsequent cycle according to the previous described criteria. An actual delivered dose of CPT-11 compared to the projected one was shown in Fig. 1.

In 27 patients treated with two or more cycles, the achieved dose intensity compared to the projected one of CPT-11 and CBDCA were 26.5 mg/m^2/wk and 1.1 mg min/ml/wk, respectively, considering both the dose adjustment and the treatment interval. Furthermore, the achieved dose intensity of CPT-11 and CBDCA were 0.71 and 0.89, respectively.

3.3. Toxicity

The major toxicity was myelosuppression (Table 2). A dose reduction was required in four and two patients at the second and third cycles, respectively. Recombinant human granulocyte colony-stimulating factor (rhG-CSF) support was used in seven treatment cycles (9.0%). The median number of days required rhG-CSF support was seven (range, 3–13). Four patients occurred with grade 3 or 4 febrile neutropenia were given

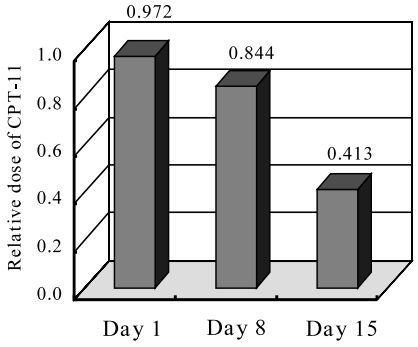

Fig. 1. Relative dose intensity of CPT-11 on days 1, 8, and 15. Relative dose of CPT-11 = actual delivered CPT-11/projected dose of CPT-11.

Table 2
Major toxicity in 36 eligible patients

JCOG grade	1	2	3	4	3–4(%)
Neutropenia	5	4	12	14*	76.5
Thrombocytopenia	6	7	8	8	47.1
Leukopenia	4	15	14	1	44.1
Anemia	8	15	9	–	26.5
Nausea/vomiting	15	10	3	–	8.8
Diarrhoea	10	3	1	1	5.9
Alopecia	11	5	2	–	5.9
Skin rash	2	2	1	0	2.9
Constipation	1	2	0	1	2.9
Creatinine	2	1	0	0	0
AST/ALT	4	2	0	0	0

* Including 4 febrile neutropenia.

antibiotics intravenously, and two of them were also required rhG-CSF support. All of them had recovered until 4 days. Grade 3 anemia occurred in nine patients (26.5%), and 4 patients required a total of 24 units of packed RBCs. Grade 4 thrombocytopenia was developed in eight patients, and nine patients, including one of grade 3 thrombocytopenia, required a total 200 units of platelet transfusions. There was no episode of bleeding tendency.

Nonhaematological toxicities were generally modest. However, diarrhea induced CPT-11 was sometimes serious. One patient developed grade 4 diarrhea with grade 4 neutropenia and infections, and subsequently ileus of grade 4 was documented. These series were very serious and life-threatening toxicities. Another patient developed a temporary grade 3 diarrhea. No treatment related death had been experienced in this study.

3.4. Response and survival

Among 36 eligible patients, there were no complete and 9 partial responses, for an overall response rate of 25.0% (95%CI, 12.1–42.2%). Nineteen patients experienced stable disease, and 8 had progressive disease. Seven responses were apparent after the first cycle, and two responses were the initial two cycles of therapy.

With a minimum follow-up duration of 26 months, the median survival time is 10.2 months and 1- and 2-year survival rate are 42.2 and 20.5%, respectively. The survival curve was shown in Fig. 2.

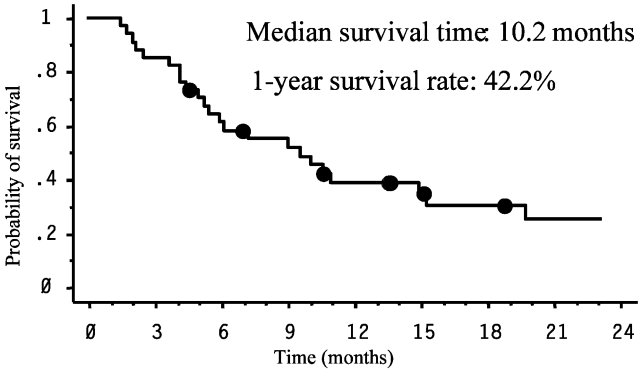

Fig. 2. Kaplan–Meier curve for time to death.

4. Discussion

Over the past few years, a number of new drugs have been shown to posses good activity against NSCLC, including paclitaxel, docetaxel, vinorelbine, gemcitabine, and CPT-11. CPT-11 combined with CDDP has been defined to be one of the most aggressive regimens against NSCLC. In Japan, a phase III trial of CPT-11, either alone or in combination with CDDP, versus vindesine (VDS) and CDDP, the reference arm, was conducted [18]. A total of 385 evaluable patients enrolled, 246 of who had stage IV disease. Patients were randomized to one of three arms: (1) VDS at 3 mg/m^2 days 1, 8, and 15 and CDDP at 80 mg/m^2 day 1 every 4 weeks; (2) CPT-11 at 60 mg/m^2 days 1, 8, and 15 and CDDP 80 mg/m^2 day 1 every 4 weeks; or (3) CPT-11 at 100 mg/m^2 days 1, 8, and 15 every 4 weeks. Overall response rate were observed in 32, 44 and 21% of patients for VDS and CDDP, CPT-11 and CDDP, and CPT-11 alone arm, respectively, with corresponding median survival times of 45.6, 50.0, and 46.0 weeks. There were no significant differences in response rate or survival between treatment groups for all patients. However, when the subset of stage IV patients was analyzed separately, the survival advantage for CPT-11 and CDDP was significant; the median survival time was 50 weeks for patients receiving CPT-11 and CDDP, 36.4 weeks for VDS and CDDP, and 42.1 weeks for CPT-11 alone ($P = 0.004$ for CPT-11 and CDDP arm vs VDS and CDDP; $P = 0.018$ for CPT-11 vs VDS and CDDP). This established CPT-11, along with vinorelbine [19] and paclitaxel [20], as one of three 'new' drugs, which, in combination with CDDP, has proven superior to 'standard' older CDDP combinations. However, a separate phase III study comparing CPT-11 and CDDP to VDS and CDDP in 210 patients with advanced NSCLC failed to show a survival difference [21].

Recently reported from the JCOG, CPT-11 plus CDDP is more effective treatment than etoposide plus CDDP for extensive SCLC [22].

Among the numerous drugs evaluated over the 10 years, only CBDCA has achieved similar survival prolongation as a single agent in advanced NSCLC [9]. These findings, coupled with the excellent toxicity profile of CPT-11 and CBDCA in combination, prompted us investigated this regimen in advanced NSCLC.

Our previous dose escalation study of CPT-11 combined with fixed dose of CBDCA (target AUC; 5

mg min/ml) for advanced NSCLC was conducted. The maximum tolerated dose of CPT-11 was 60 mg/m^2, while 50 mg/m^2 could be recommended for this phase II study. The response rate was 35.3% (95%CI: 18.0–49.9%), indicating that this therapy was also promising for the treatment of advanced NSCLC. Furthermore, the median survival time and the 1-year survival rate were 10.5 months and 35.3%, respectively, resulted that were comparable with those for CPT-11 and CDDP [10].

In this phase II study, we observed a relatively disappointing objective response rate of just 25%, not much better than that achieved with CPT-11 combined with CDDP, as well as CPT-11 alone. The response rate of CPT-11 alone was 34.3% in a phase II trial [3], and 21% in a randomized multicenter phase III trial [18].

Myelosuppression induced by this combination chemotherapy was more toxic, especially neutropenia, than CPT-11 and CDDP previously reported [18,21,22]. Although neutropenia of CPT-11 and CDDP ranged Grade 3 or 4 neutropenia was developed in 76.5% of 36 patients. Febrile neutropenia occurred in 4 patients, all of them, however, had recovered until 4 days. According to the withdrawal criteria of CPT-11 on days 8 and 15, CPT-11 was not administered on day 15 for most patients. An actual delivered dose of CPT-11 to the projected one on days 1, 8, and 15 were 0.972, 0.844, and 0.413, respectively. Furthermore, cycle delays due to prolongation of neutropenia decreased dose intensity of both CPT-11 and CBDCA. Thrombocytopenia was also so severe that 25% of 36 patients treated with CPT-11 and CBDCA required platelet transfusions. In this phase II study, CPT-11 was withdrawn if the leukocyte count was less than 3000/μl, the platelet count was less than 100 000/μl, or diarrhea Grade 1 or higher occurred on days 8 and 15. Few patients could be delivered CPT-11 on days 8 and 15, even if the withdrawal criteria of CPT-11 on days 8 and 15 were not strict. Myelosuppression induced by this combination of CPT-11 and CBDCA was too severe to satisfy dose intensity as much as projected.

Nonhematological toxicities, including CPT-11 induced diarrhea, were developed generally modest. Only one patient was developed sever diarrhea and ileus induced by CPT-11. No treatment related death was occurred in this study.

In conclusion, it seemed that the efficacy of CPT-11 combined with CBDCA was not encouraging in treatments of advanced NSCLC. This combination of CPT-11 and CBDCA was more toxic, in especially myelosuppression, than CPT-11 and CDDP. The relatively disappointing response rate could be related with low dose intensity of CPT-11.

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