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Phase I study of irinotecan and cisplatin with concurrent split-course radiotherapy in limited-disease small-cell lung cancer

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Abstract

We conducted a phase I study of irinotecan (CPT-11) and cisplatin with concurrent split-course radiotherapy in limited-disease small-cell lung cancer (LD-SCLC). This study aimed to determine the maximum tolerated dose (MTD) and dose-limiting toxicity (DLT) of this therapy. Four chemotherapy cycles of CPT-11 (days 1, 8 and 15) and cisplatin (day 1) were repeated every 28 days. Radiotherapy of 2 Gy/day commenced on day 2 of each chemotherapy cycle with 20 Gy administered from the first to the third cycles (a total of 60 Gy). 17 patients were enrolled at three dose levels (CPT-11/cisplatin: 40/60, 50/60 and 60/60 mg/m^2), and 16 were evaluable for toxicity and outcome. 2 of 4 patients at 60/60 mg/m^2 refused continuation of therapy because of general fatigue, and the relative dose intensity of CPT-11 at 50/60 mg/m^2 was approximately 50%. These levels were considered as the MTD. Tumour responses included four complete responses (CR), 11 partial responses (PR) and one no change (NC), and the overall response rate was 93.8% (95% confidence interval: (CI) 71.7–98.9%). This combined modality is tolerable, and CPT-11/cisplatin of 40/60 mg/m^2 in this modality is recommended for phase II study.

Keywords: Lung cancer; Small-cell lung cancer; Clinical trial; Chemoradiotherapy; Radiation therapy; Topoisomerase I inhibitor; Cisplatin; Combined modality

1. Introduction

Small-cell lung cancer (SCLC) is relatively chemosensitive among human solid cancers, and systemic chemotherapy is the mainstay of the treatment [1]. SCLC is often divided into two groups of limited (LD)- and extensive-disease (ED) [1], and PE (cisplatin and etoposide) and/or CAV (cyclophosphamide, doxorubicin (adriamycin), vincristine) regimens have been used worldwide as first-line chemotherapy over the past 20 years [2]. Patients with LD-SCLC sometimes have the benefit of a prolonged survival and cure by the addition of thoracic radiotherapy (TRT) to the chemotherapy [1,3,4]. This is based on two meta-analyses of randomised trials in LD-SCLC that showed a improvement in local control and 3-year survival by using combined chemoradiotherapy compared with chemotherapy alone [5,6]. Therefore, a combined modality of chemotherapy and TRT has been recognised as standard treatment for LD-SCLC patients with good performance scores [3,4]. PE has been incorporated into the modality because of its radiosensitising effects and reduced myelotoxicity compared with the CAV regimen

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[3,4,7], and TRT has been used in an early concurrent schedule during four cycles of PE [4,8].

Recently, newer active agents for SCLC have been extensively investigated in clinical trials [9,10]. These include the taxanes, paclitaxel and docetaxel, topoisomerase I inhibitors, irinotecan (CPT-11) and topotecan, vinorelbine, gemcitabine and amrubicin [9,10]. Among these agents, in combination with cisplatin, CPT-11 alone has been shown to be superior to PE for ED-SCLC in a phase III randomised trial [11]. Moreover, an in vitro study showed synergism between the action of cisplatin and the active metabolite of CPT-11, SN-38, in SCLC cells [12], and a preclinical study showed an enhancement effect of CPT-11 on tumour radiosensitivity [13]. Based on these results, we conducted a phase I study of CPT-11/cisplatin with TRT in LD-SCLC. A previous trial of CPT-11/cisplatin with concurrent and continuous standard TRT treatment of 60 Gy failed in non-small cell lung cancer (NSCLC) patients because of unacceptable toxicity and the low radiation therapy completion rate [14]. Accordingly, the present study incorporated concurrent split-course TRT during four cycles of CPT-11/cisplatin.

The primary objective of this phase I dose-escalation study was to determine the optimal doses of CPT-11/cisplatin when administered concurrently with split-course TRT. The second goal of this study was to define the toxicity associated with this chemoradiotherapy.

2. Patients and methods

2.1. Patients and evaluation

The study was approved by the Ethics Committee of the Nagasaki University School of Medicine. Patients with previously untreated LD-SCLC were enrolled. LD was defined as disease confined to one hemithorax, with or without ipsilateral hilar or bilateral mediastinal or supraclavicular lymph node involvement; no malignant pleural or pericardial effusion. Tumour staging was performed on the basis of a complete medical history and physical examination, routine chest radiography, bone scintiscanning, computed tomography (CT) of the chest and abdomen, magnetic resonance imaging of the head, bronchoscopy, and bone marrow aspiration. Staging was performed according to the tumour, node, metastasis (TNM) system [15]. Eligibility criteria included the following: histologically- or cytologically-confirmed SCLC; no previous chemotherapy; measurable or assessable disease; age <75 years with 0-2 performance status (PS) of Eastern Cooperative Oncology Group (ECOG); adequate haematological (leucocyte $\geqslant 4\times10^9$ cells/l, haemoglobin $\geqslant 100$ g/l, platelet count $\geqslant 100\times10^9$ #/l), hepatic (total bilirubin $\leqslant 25.65$ μmol/l, alanine aminotransferase (ALT) and asparate aminotransferase (AST) levels $\leqslant$ double the normal upper limit) and renal function (serum creatinine $\leqslant 105$ μmol/l); no serious cardiac or pulmonary dysfunction ($PaO_2 \geqslant 70$ torr); no other serious illnesses; no concomitant malignancies; no pregnancy; no stage I disease; the ability to provide informed consent.

Prior to the first course of therapy, a complete blood cell count including differential white blood cell count and platelet count, biochemistry tests (renal and hepatic function and electrolytes) and urinalysis were performed. Complete blood cell count and biochemistry were repeated at least once weekly after treatment, while other investigations were repeated as necessary to evaluate various markers. After completion of the chemoradiotherapy, each patient was restaged with all of the tests used during the initial work-up.

2.2. Treatment

Treatment commenced within 1 week of enrollment, and four cycles of CPT-11/cisplatin therapy were repeated every 28 days, as shown in Fig. 1. On day 1, CPT-11 dissolved in 250 ml of 5% dextrose was infused intravenously (i.v.) over 90 min followed 2 h later by cisplatin, which was infused i.v. over 60 min. The CPT-11 infusion alone was repeated on days 8 and 15. The starting doses of CPT-11 (days 1, 8 and 15) and cisplatin (day 1) were 40 and 60 mg/m^2, respectively, and the CPT-11 dose was increased in 10 mg/m^2 increments as shown in Table 1. However, our dose escalation was limited to a level of 60/60 mg/m^2 because this was the recommended dose for CPT-11/cisplatin chemotherapy alone in SCLC [16]. 3 patients were enrolled into each dose level. The dose was escalated to the next level if none of the 3 patients experienced dose-limiting toxicity (DLT) as described below. If 2 of the 3 patients experienced DLT, the dose level was defined as the maximum-tolerated dose (MTD). If 1 of the 3 patients experienced DLT, 3 more patients were treated at that level. If none

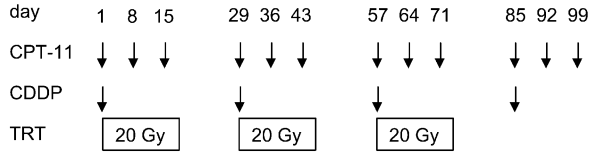

Fig. 1. Treatment schema. CPT-11, irinotecan; CDDP, cisplatin; TRT, thoracic radiotherapy.

Table 1
Dose escalation schedule

Level	CPT-11 (mg/m^2)	Cisplatin (mg/m^2)
1	40	60
2	50	60
3	60	60

CPT-11 on days 1, 8 and 15; cisplatin on day 1.

of the additional three patients experienced DLT, the dose was escalated to the next level. If one or more of the additional 3 patients experienced DLT, the dose level was then defined as the MTD. The dose level preceding that defined as the MTD was then defined as the recommended dose of this chemoradiotherapy for phase II study.

Thoracic radiation was administered once daily with a split schedule: 5 days/week with 2 Gy/day from day 2 of each chemotherapy cycle, with 20 Gy administered for the first to the third cycles (a total of 60 Gy). There was a break in the split-course radiation of 14 days. Based on recent chest CT scan, the radiation volumes and fields were individualised for each patient. The radiation fields encompassed areas of gross primary lesion with a 2 cm margin, and the ipsilateral hilar and mediastinal nodes. If supraclavicular and/or scalene node metastasis were found, the nodes were included in the fields. The area of the lung field included in the radiation field was not greater than half of the area of the ipsilateral lung. Patients received the intended radiotherapy with a total dose of 60 Gy, which was administered with a 10-MeV linear accelerator using two antero-posterior opposed beams.

Blood transfusion was only performed in cases with haemoglobin <75 g/l or platelet count $<20\times10^9$ cells/l. Patients who developed diarrhoea were treated with 2 mg loperamide hydrochloride, which was repeated 6-hourly until diarrhoea was under control.

Patients who achieved a complete response (CR) on re-evaluation received prophylactic cranial irradiation (PCI) with a total dose of 20 Gy in 10 fractions, 2.0 Gy once a day after completion of the four cycles of chemotherapy.

2.3. Dose modification

2.3.1. Chemotherapy

CPT-11 treatment was omitted on days 8 or 15 if the leucocyte count fell below 3×10^9 cells/l, platelet count was $<50\times10^9$ cells/l or any diarrhoea occured. Leucocytes $\geqslant3\times10^9$ cells/l and platelets $\geqslant75\times10^9$ cells/l were mandatory to commence the next cycle of treatment, and if the levels fell below these limits, the next cycle was postponed until the counts had recovered. Doses of CPT-11 and cisplatin were reduced to 75% when DLT occurred during the first treatment cycle.

2.3.2. Radiation therapy

If grade 4 haematological toxicity occurred during radiation, radiation was interrupted and restarted after recovery to grade 3 or less. If grade 3 or greater oesophagitis occurred, it was interrupted and restarted after recovery to grade 2 or less. If oesophagitis did not recover, it was discontinued. If the PaO_2 fell to 10 torr or a patient had a fever of 38 °C or higher, both radiation therapy and chemotherapy were interrupted and restarted as soon as possible after recovery.

2.4. Toxicity and response evaluation

Eligibility, assessability and tumour responses were determined by external reviewers. Tumour response and drug toxicity were classified according to the criteria of the World Health Organization (WHO) [17] except for oesophagitis and pneumonitis. Grading of oesophageal toxicity due to radiation was based on the ECOG criteria [18] and pneumonitis was clinically and radiographically graded according to the Radiation Therapy Oncology Group (RTOG) acute and late lung morbidity scoring criteria [19]. DLT was evaluated during three cycles of treatment at each dose level. DLT was defined as grade 4 leucopenia or neutropenia lasting 4 days or more, neutropenic fever, grade 4 thrombocytopenia, and grade 3 or greater non-haematological toxicities, except for nausea and vomiting. Omission of the CPT-11 dose on both days 8 and 15 in each chemotherapy cycle was also defined as a DLT, indicating a low dose intensity of CPT-11.

Tumour response was classified according to the WHO criteria [17]. A complete response (CR) was defined as the disappearance of any evidence of tumours for at least 4 weeks. A partial response (PR) was defined as $\geqslant50\%$ reduction in the sum of the products of the greatest perpendicular diameters of all lesions for at least 4 weeks. No change (NC) was defined as $<50\%$ reduction or $<25\%$ increase in the products of the greatest perpendicular diameters of all lesions without any evidence of new lesions. Progressive disease (PD) was defined as an increase of $\geqslant25\%$ or the appearance of new lesions. Response duration was measured from the start of the treatment to disease progression.

3. Results

3.1. Patient characteristics

17 patients were enrolled between October 1995 and November 1998, 16 of whom were eligible for evaluation of toxicity and efficacy. One patient was ineligible because pathological review evaluated the histological type as squamous cell carcinoma. The characteristics of the remaining 16 patients are shown in Table 2.

3.2. Dose escalation

Firstly, 3 patients were treated at each of the first two dose levels and no patients experienced DLT. 2 of 4 patients at dose level 3 refused to continue therapy because of severe general fatigue (a fall in PS), resulting in a MTD. In an extension study to confirm the safety

Table 2
Patient characteristics ($n=16$)

Characteristic	N
Age (years)	
Median (range)	65 (43–74)
Sex	
Male	15
Female	1
PS (ECOG)	
0	4
1	11
2	1
Stage	
IIB	1
IIIA	7
IIIB	8

PS, performance status; ECOG, Eastern Cooperative Oncology Group.

at dose level 2, an additional 2 patients were enrolled. However, the 2 patients received less than half of the scheduled CPT-11 dose because of leucocytopenia and fatigue, resulting in a MTD. Following this, an additional 4 patients were enrolled at dose level 1, and no DLT was experienced by this group. Therefore, level 1 was regarded as the recommended dose of this regimen for phase II study.

Table 3
Haematological toxicities: all dose levels ($n=16$)

Dose level	Pts (*n*)	WBC	ANC	Platelets	Hgb
		Grade			
		2 3 4	2 3 4	2 3 4	2 3 4
1	7 (4)	3 3 1[a]	1 3 3[a]	0 1 0	1 4 0
2	5 (2)	2 2 1	2 1 2[a]	1 3 0	0 1 1
3	4	1 3 0	0 4 0	2 1 0	0 2 1

Data in parentheses represent the number of patients in the extension study. WBC, white blood cells; ANC, absolute neutrophil count; Hgb, haemoglobin; pts, patients.

[a] Leucopenia and neutropenia of grade 4 did not last for the 4 days defined as a dose-limiting toxicity (DLT).

3.3. Toxicity

Haematological toxicities during treatment are summarised in Table 3. The principal adverse effects were leucopenia, neutropenia, anaemia, and 15 (94%) patients experienced grade 3-4 toxicities. Although 2 (13%) and 5 (31%) patients experienced grade 4 leucopenia and neutropenia, respectively, only 1 patient at dose level 2 experienced DLT in the extension study. No neutropenic fever or documented infection was observed. Thrombocytopenia was mild. Anaemia occurred during the third rather than the first and the second treatment cycles, with 9 (56%) patients experiencing grade 3-4 anaemia. 2 patients with grade 4 anaemia required a blood transfusion during the third treatment cycle.

The major non-haematological toxicities were gastrointestinal toxicity, pneumonitis and fatigue (Table 4). However, except for fatigue these were all mild. 5 patients (31%) experienced grade 3-4 fatigue, and 2 at dose level 3 and 1 at dose level 2 refused to continue the therapy because of this fatigue. This was considered as the DLT. Oesophagitis and diarrhoea were mild (none $>$grade 3). Grade 2 liver dysfunction was observed in 3 (19%) patients. Grade 2 late radiation pneumonitis was observed in 2 (13%) patients only.

3.4. Treatment delivery

A total of 53 chemotherapy cycles was administered to the 16 patients through at the three dose levels. Fifty-two (33%) of a planned 159 doses of CPT-11 for the 53 cycles were omitted. 6 patients had CPT-11 omitted on both days 8 and 15 during four cycles, with 2 patients having both omissions in the first cycle, 3 in the second, 3 in the third and 4 in the fourth. One patient at dose level 2 of the extension study had both omissions in three cycles because of leucopenia and fatigue, resulting in DLT. The ratio of actual dose intensity to planned dose intensity of CPT-11 was 0.76 at dose level 1, 0.51 at level 2 and 0.72 at level 3. The major reasons for CPT-11 omission were leucopenia in 32, diarrhoea in 7, fatigue in 6, thrombocytopenia in 2. Particularly, at the recommended dose level 1, compliance to the treatment including TRT was relatively favourable.

Table 4
Non-haematological toxicities: all dose levels ($n=16$)

Dose level	Pts (*n*)	Oesophagitis	Diarrhoea	Pneumonitis	Fatigue	Liver
		Grade				
		1 2$\geqslant$3	1 2 3 4	1 2$\geqslant$3	1 2 3 4	1 2$\geqslant$3
1	7	0 2 0	0 2 0 0	0 2 0	0 2 1 0	0 1 0
2	5	0 1 0	0 4 0 0	0 0 0	0 3 2 0	0 2 0
3	4	0 0 0	0 2 0 0	0 0 0	0 0 1 1	0 0 0

Pts, patients.

3.5. Response and survival

16 patients were assessed for response, and the tumour responses at each dose level are shown in Table 5. 15 (93.8%, 95% Confidence Interval (CI): 71.7–98.9%) patients achieved an objective response comprising 4 CR (25.0%, 95% CI: 10.2–49.5%) and 11 PR (68.8%, 95% CI: 44.4–85.8%), and the remaining patient was evaluated as NC. Although survival was not an endpoint in this study, the median survival time, and 1-, 2-, and 3-year survival rates were 25.2 months (95% CI: 0–51.2 months), 75.0% (95% CI: 53.8–96.2%), 56.2% (31.9–80.5%), and 43.8% (19.5–68.1%), respectively.

4. Discussion

Several new active agents including CPT-11 have been extensively investigated as chemotherapy for SCLC [9,10]. However, only two agents, CPT-11 and paclitaxel, have been incorporated into clinical trials of chemoradiotherapy for LD-SCLC [4,20–23]. Although a small number of patients with LD-SCLC were enrolled and analysed, the present study is the first trial to study CPT-II treatment with TRT in LD-SCIC. A phase II trial of CPT-11/cisplatin therapy for SCLC yielded an 84% overall response rate with a 29% CR rate [16]. This therapy induced 60 mg/m^2 CPT-11 (given days 1, 8 and 15) and 60 mg/m^2 cisplatin (given on day 1) every 28 days, of which four and six cycles were given to LD- and ED-SCLC patients, respectively. Interestingly, quite similar response rates were obtained in the LD- and ED-SCLC patients. A phase III trial in Japan, comparing four cycles of CPT-11/cisplatin with PE in ED-SCLC patients, demonstrated that CPT-11/cisplatin was significantly superior to PE with regard to the overall response rate and survival, and was associated with less myelotoxicity [11]. The overall response and the 1-year survival rates were 84.4 and 58.4% for the CPT-11/cisplatin treatment, and 67.5 and 37.7% for the treatment PE, respectively. These results were consistent with those in the above phase II and earlier trials. Thus, taken together with the radiosensitising effects *in vitro* and the most active regimen of CPT-11/cisplatin for SCLC, the present combined modality for LD-SCLC was considered to be worthwhile.

Table 5
Tumour responses at each dose level

Dose level	Pts (*n*)	CR	PR	CR + PR
1	7	3	4	7
2	5	0	5	5
3	4[a]	1	2	3
Total (%)	16 (100)	4 (25.0)	11 (68.8)	15 (93.8)

CR, complete response; PR, partial response.
[a] One of 4 patients had no change.

In general, PE with concurrent TRT has been used in the treatment of LD-SCLC patients with good PS [4,8]. The major reason for this was that four cycles of PE for SCLC had been shown to be more active and associated with less myelotoxicity compared with other regimens, such as CAV and carboplatin/etoposide [1,2]. Thus, the incorporation of CPT-11/cisplatin into chemoradiotherapy for LD-SCLC was a logical modality to test. Paclitaxel has been added to PE or carboplatin/etoposide in clinical trials for SCLC [9,23,24], and these three-drug regimens with concurrent TRT have also been investigated in LD-SCLC [21–23]. However, there have been no studies comparing the three-drug regimens with PE, and no phase II trials of these regimens demonstrating the superiority to PE in terms of toxicity, response and survival.

The principal toxicities in this study were myelotoxicity and general fatigue. No severe oesophagitis and CPT-11-induced diarrhoea were observed. Among these, general fatigue only was a DLT in the present study, which was evaluated during three cycles of treatment. Combined modality with concurrent TRT usually increases the risk of toxicities such as oesophagitis, myelosuppression and pneumonitis [3,4]. However, these were all mild in our study. In addition, the relative dose intensity 0.76 of CPT-11 at the recommended dose level was reasonable. The main reason for this is probably the incorporation of the split-course TRT. Concerning oesophagitis, approximately 10% of patients treated with PE and standard 45 Gy TRT were unable to swallow solids [8], and it is still one of the major toxicities in paclitaxel-containing PE with concurrent TRT [20–22]. Moreover, paclitaxel-containing PE with concurrent TRT caused grade 3 or 4 neutropenia in 50% or more of patients, and a few treatment-related deaths [21,22]. The major toxicities of oesophagitis and neutropenia sometimes caused dose reductions and a rest from TRT [21,22]. Thus, our CPT-11/cisplatin with concurrent split-course TRT is tolerable in comparison with these previous studies.

We incorporated a split-course TRT of 60 Gy into three cycles of CPT-11/cisplatin therapy. Several randomised trials with PE and TRT demonstrated that earlier concurrent TRT, particularly twice-daily accelerated hyperfractionated TRT, was superior to sequential and once-daily standard TRT with regard to survival [8,25,26]. Therefore, earlier concurrent TRT with PE is widely recognised as the standard treatment for LD-SCLC patients with a good PS [4]. However, particularly in new drug-containing regimens with TRT, there has been no consensus on the optimal sequencing, timing and dose of TRT. Perhaps the major reason for this is that the toxicity profiles of new drugs with TRT

are different from those of conventional drugs with TRT. In fact, in early trials for NSCLC, severe oesophagitis developing stricture and perforation, and fatal pulmonary toxicity occurred following treatment with vinorelbine, docetaxel, gemcitabine or paclitaxel with concurrent TRT [27–30]. In addition, a phase I/II trial of weekly CPT-11 with concurrent TRT of standard 60 Gy caused severe oesophagitis, pneumonitis, and diarrhoea at doses of 45 and 60 mg/m^2, and 1 patient died of pneumonitis [31]. Accordingly, together with the results from the present study and two previous trials of CPT-11 with continuous TRT of 60 Gy [14,31], this suggests a split-course TRT is favourable and safe until CPT-11 in a concurrent setting.

The overall response rate in this study was 93.8% (25.0% CR, 68.8% PR), which is similar or superior to rates in studies of PE with TRT [4,8,21,22]. At the recommended dose level 1 there was a good compliance and, the overall response rate was 100% (43% CR, 57% PR). Despite a low CR rate of 25%, our survival data were relatively favourable compared with those of standard treatment with PE and TRT [4,8,25]. However, the survival data needs to be confirmed in future clinical trials. Moreover, as it is difficult to evaluate the DLT in such split-course regimes, in future we recommend that more patients per dose level are enrolled in this type of phase I study.

In conclusion, the present study demonstrated that the combined modality of four cycles of CPT-11/cisplatin therapy with concurrent split-course TRT of 60 Gy was tolerable, and the recommended doses of CPT-11 (days 1, 8, 15)/cisplatin (day 1) were 40/60 mg/m^2. Based on the present results, a phase II trial is now ongoing for LD-SCLC.

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