Cancer Chemother Pharmacol (2008) 61:503–508
DOI 10.1007/s00280-007-0496-6

ORIGINAL ARTICLE

Phase II trial of gemcitabine and irinotecan in previously treated patients with small-cell lung cancer

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Received: 4 January 2007 / Accepted: 5 April 2007 / Published online: 5 May 2007

Abstract
Purpose To investigate the activity of gemcitabine combined with irinotecan in patients with relapsed small cell lung cancer (SCLC).
Patients and methods SCLC patients who had experienced treatment failure with one prior chemotherapy were eligible. Patients were required to have a performance status of 0–2 and adequate organ function. Treatment consisted of gemcitabine (1,000 mg/m^2) and irinotecan (150 mg/m^2) on days 1 and 15 of a 28 day cycle.
Results Thirty-one patients were enrolled and 30 patients received protocol treatment (10 had refractory disease and 20 had sensitive disease). The median age was 64 years, and the median performance status was one. An objective response was obtained in 36.7% (95% CI: 17.3.1–56.0%) of the patients. The median overall survival time was 14.4 months, and the 1 year survival rate was 51%. The chief grade 3/4 toxicities included neutropenia (42%), thrombocytopenia (3%), diarrhea (9%), and liver dysfunction (3%). The only grade 4 toxicities were one case of grade 4 neutropenia (3.3%) and one case of grade 4 thrombocytopenia (3.3%).
Conclusion Gemcitabine plus irinotecan is an active regimen that seems to be well-tolerated by patients with previously treated SCLC.

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Keywords Gemcitabine · Irinotecan · Small cell lung cancer

Introduction

Small cell lung cancer (SCLC) accounts for 15–20% of all lung cancer [1]. Although SCLC is an exquisitely chemosensitive disease, it ultimately remains fatal for the great majority of patients. The combination of cisplatin and etoposide or cisplatin and irinotecan is considered to be standard first-line therapy in Japan [2]. Despite a high response rate to first-line chemotherapy (i.e., 70–85% PR) in patients with extensive disease, the duration of response is usually short, with a progression-free survival time of only 4–8 months.

No standard regimen has been developed for patients with SCLC who suffer a relapse after initial chemotherapy. Most patients are destined to relapse, and the prognosis after relapse is poor. Patients who relapse within 3 months of completing first-line therapy are commonly considered to have refractory disease, while patients who relapse more than 3 months after therapy are classified as having sensitive disease. Pawel et al. compared cyclophosphamide, Adriamycin, and vincristine (CAV) with single-agent topotecan in patients with sensitive relapse. This study showed an equivalent response rate and survival with single-agent topotecan, as well as superior quality-of-life and symptom control in the patients treated with topotecan [3]. Therefore, single-agent topotecan or the three-drug combination of CAV are the most common therapies for relapsed SCLC. However, response rates were modest in both arms at only 24.3 and 18.3% for topotecan and CAV, respectively, while median survival was only 25 weeks in each arm of the trial (3). Accordingly, new options are required for patients with relapse of SCLC.

Several new chemotherapy agents have shown activity in patients with previously untreated SCLC, including paclitaxel, docetaxel, irinotecan (CPT-11), vinorelbine, and gemcitabine, suggesting that these drugs are worthy of further investigation for relapsed SCLC [4].

Gemcitabine is metabolized intracellularly to produce its active metabolite gemcitabine diphosphate, which inhibits DNA polymerization. This antimetabolite has shown a broad spectrum of activity against a variety of solid tumors [5]. When used for previously untreated SCLC, gemcitabine achieved a response rate of 27% in 26 assessable patients [6]. Toxicity was moderate in this trial, with neutropenia in 18% of cycles and thrombocytopenia in less than 2%. In another trial of 42 patients with relapsed SCLC, gemcitabine achieved an overall response rate of 11.9% and a median survival time of 7.1 months [7].

Irinotecan is a camptothecin derivative that inhibits DNA topoisomerase I and shows strong activity against various tumors, including drug-resistant tumors [8]. The Japanese Cooperative Oncology Group compared the combination of cisplatin and irinotecan (PI) with cisplatin plus etoposide (PE) as first-line therapy for extensive SCLC (2). This trial showed that the PI arm did significantly better than the PE arm, with a median survival of 420 versus 300 days, respectively (2). When previously treated SCLC was targeted, irinotecan achieved a response rate of 47% in 17 patients with refractory or relapsed SCLC and the median survival time was 187 days [9].

Preclinical studies showed a synergistic interaction between gemicitabine and irinotecan [10, 11]. We recently conducted phase I and phase II studies of the combination of gemcitabine and CPT-11 for non-small cell lung cancer (NSCLC) using administration every 2 weeks. Those studies showed moderate activity against previously treated NSCLC and only minor toxicities were noted [12, 13].

On the basis of the activity of gemcitabine and irinotecan as single agents for untreated SCLC and the synergistic interaction of these drugs, as well as the need for new and better-tolerated treatments for relapsed SCLC in patients who experience failure of first-line regimens, we conducted a phase II trial to assess the activity of the combination of gemcitabine plus irinoctecan for previously treated SCLC. Patients with primary refractory SCLC and those with primary sensitive (but relapsed) SCLC were included in this trial.

Patients and methods

The primary objective of this phase II study was to evaluate the objective response rate achieved with a combination of gemcitabine plus irinotecan in SCLC patients for whom one prior chemotherapy regimen had failed. The secondary objectives were to evaluate the survival of patients with previously treated SCLC who received gemcitabine plus irinotecan as second-line therapy; to evaluate the toxicities of gemcitabine plus irinotecan as second-line therapy; and to determine whether there were response or survival differences between patients with primary refractory SCLC and those with relapse of primary sensitive SCLC. Primary refractory disease was defined on the basis of relapse during first-line chemotherapy or less than 3 months after the completion of initial chemotherapy, while sensitive disease was defined as relapse $\geq$3 months after the completion of first-line chemotherapy.

Eligible patients had histologically or cytologically proven SCLC and were between the ages of 20 and 74 years. Patients with either limited or extensive disease were eligible, provided that progression occurred after initial chemotherapy. This was defined as either a lack of response to first-line chemotherapy, progression after a partial response, or relapse after an initial complete response to first-line chemotherapy. Initial chemotherapy included cisplatin or carboplatin, and irinotecan-containing combination chemotherapy was also allowed. Patients were required to have at least one site of bidimensionally measurable disease. Patients were also required to have recovered completely from prior therapy, with no ongoing toxicity greater than grade 1. Prior radiotherapy was permitted, but measurable disease outside the radiation field or clearly progressive disease within it was required. Patients were required to have an ECOG performance status of 0–2 and adequate vital organ function, including the liver, kidneys, and bone marrow. The treatment protocol was approved by the investigational review board of the Cancer Institute Hospital, and all patients provided written informed consent.

The chemotherapy schedule included irinotecan at an initial dose of 150 mg/m^2 intravenously over 90 min and gemcitabine at an initial dose of 1,000 mg/m^2 intravenously over 30 min on days 1 and 15 of a 28 day cycle. The cycle was repeated in patients with acceptable toxicity and no evidence of disease progression. The dose levels and treatment schedule were modified to avoid severe adverse effects. During treatment, if grade 4 neutropenia or leukopenia lasted for longer than 3 days, or if neutropenic fever, grade 4 thrombocytopenia, grade 2 or worse peripheral neurotoxicity, grade 3 or 4 liver toxicity, or grade 3 or 4 diarrhea were observed, a reduced dose (125 mg/m^2) of CPT-11 and 1,000 mg/m^2 of gemcitabine were given during the following cycle. Patients requiring more than one dose reduction were removed from the study.

If a WBC count of less than 3.0×10^9/l, a platelet count of less than 75×10^9/l, grade 1 or worse diarrhea, fever higher than 38°C, or a performance status 3 or 4 were observed on the day of treatment day, further treatment was withheld until the patient recovered from the toxicity.

Patients who required a delay of more than 1 week were withdrawn from the study.

All patients underwent disease re-evaluation after the first cycle of chemotherapy and after every two subsequent cycles. Tumor response was assessed according to WHO criteria. Reassessment was generally performed by the same imaging method used to established baseline tumor measurements after every two cycles of therapy. Confirmation of response required a repeat imaging study at 4 weeks after the initial study that demonstrated a continuing tumor response. The time to tumor progression (time from the start of therapy to the first detection of progressive disease), and survival (time from the start of therapy to death) were determined. Time-to-event end-points were calculated by using the Kaplan-Meier method with appropriate censoring.

Simon's minimax two-stage phase II design [14] was used to allow early termination if the preliminary results indicated minimal efficacy. A response rate of 30% was deemed sufficient to warrant further investigation, whereas a response rate $\leq$10% was insufficient for continuation. This trial design called for 15 assessable patients to be enrolled in the first part. If one or more responses were observed among these initial patients, an additional ten assessable patients were intended to be entered. If five or more responses were observed among the total of 25 assessable patients, the treatment would be considered worthy of further consideration. If fewer than five responses were observed, this combination would not be considered for further testing. Assuming a dropout rate of 20%, a sample size of 30 patients provided an α error of 0.05 and β error of 0.2. The accuracy of estimating the objective response rate led to a maximum 95% confidence interval (CI) of 34.6%.

Results

In this phase II trial, a total of 31 patients were enrolled from 31 August 2002 to 1 May 2004 (stage 1), and from 1 October 2004 to 6 May 2006 (stage 2). One patient did not receive protocol treatment because of the rapid progression of liver metastasis, but the other 30 patients were assessable for toxicity.

One patient withdrew from the study after the first course of gemcitabine and irinotecan because of grade 2 interstitial pneumonia and one patient withdrew consent after 1.5 cycles of therapy. The response was analyzed in 30 patients who received at least one protocol treatment.

In this cohort, there were 24 male and 6 female patients (Table 1). Nine patients (30%) had received prior radiation.

Table 1 Characteristics of the refractory and sensitive patients

Characteristic	Refractory		Sensitive		Total	
	No. of patients	Percentage	No. of patients	Percentage	No. of patients	Percentage
Sex						
Male	8	80	16	80	24	80
Female	2	20	4	20	6	20
Age (range)	61 (52–71)		65 (51–74)		65 (51–74)	
Stage at diagnosis						
Limited disease	5	50	11	55	16	55.6
Extensive disease	5	50	9	45	14	44.4
Performance status						
0	5	50	6	31.6	11	36.7
1	5	50	10	52.6	16	53.3
2	0	0	3	15.8	31	10
Previous radiotherapy for lung cancer						
No	6	60	11	55	17	43.3
Yes	4	40	9	45	13	56.7
Chemotherapy regimen						
Cisplatin or carboplatin/etoposide	8	80	13	65	21	70
Cisplatin/irinotecan	2	20	4	20	6	20
Cisplatin/etoposide after cisplatin/irinotecan	0	0	3	15	3	10
Best response to prior chemotherapy						
Partial response	8	80	20	100	28	93.3
Stable disease	2	20	0	0	2	6.7

All 30 patients had received one prior chemotherapy regimen, including cisplatin or carboplatin/etoposide (66.7%), cisplatin/irinotecan (20%), or cisplatin/etoposide followed by cisplatin/irinotecan (13%). Ninety percent of the patients in this trial had shown a partial response to first-line chemotherapy. They had a good performance status, with 90% of the patients being categorized as 0 or 1. The median age was 65 years (range: 51–74 years).

The response to therapy was determined according to whether the patient had primary refractory disease or primary sensitive cancer that subsequently relapsed (Table 2). The partial response rate of refractory patients was 20% (95% CI: 15.2–24.8%), while the partial response rate was a much higher 45% (95% CI: 21.8–68.2%) for patients with relapse of sensitive disease, leading to an overall response rate of 36.7% (95% CI: 17.3–56.0%). No patient achieved a complete response.

The cut-off date for analysis was December 2006. The median follow-up time for patients who remained alive was 12.7 months (range: 8–21 months).

The median time to tumor progression was 3.0 months for the 28 assessable patients.

Overall survival of the patients treated in this study is shown in Fig. 1. The median overall survival time was 14.4 months for the 30 assessable patients, and the 1 year survival rate was 51%. Figure 2 shows the overall survival (Kaplan–Meier method) of the 10 patients with refractory disease and the 20 patients with relapse.

The median survival time of the patients with refractory disease was 7.4 months, compared with 14.4 months for patients who had relapse of sensitive disease. These survival times were not statistically different ($P = 0.32$).

Toxicities encountered during a total of 96 cycles are listed in Table 3. The primary problem was hematologic toxicity among the 30 patients assessed for toxicity. Grade 3/4 leucopenia occurred in two patients (6.6%), grade 3/4 neutropenia occurred in 12 patients (40%), and grade 3 anemia occurred in 1 patient (3.3%). Grade 3 diarrhea occurred in 3 patients (10%), grade 3 liver dysfunction occurred in 1 patient, and grade 2 pneumonitis was reported in 1 patient. This patient developed shortness of breath on day 15 of the first cycle and chest CT indicated interstitial pneumonia.

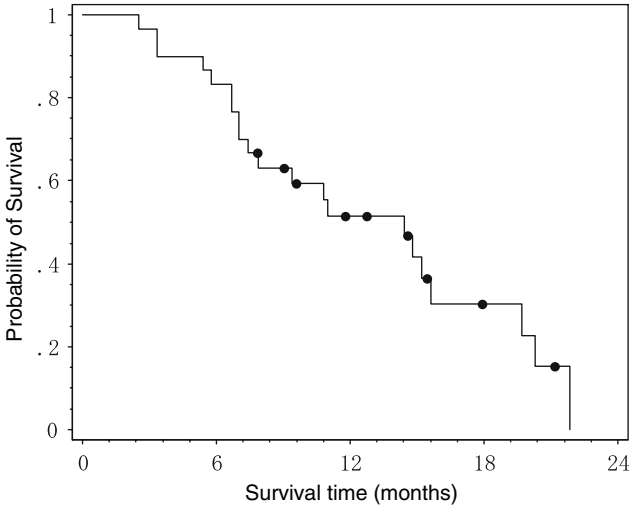

Fig. 1 Overall survival (Kaplan–Meier)

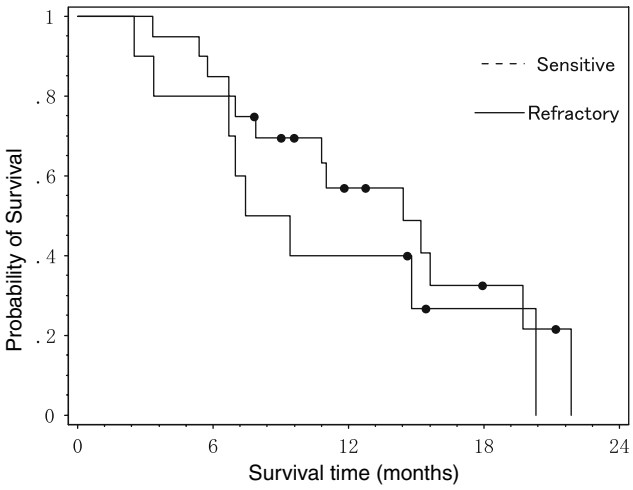

Fig. 2 Overall survival of patients with refractory disease or sensitive disease

She discontinued treatment and showed gradual improvement with corticosteroid therapy. The only grade 4 toxicities were one case of grade 4 neutropenia (3.3%), one of grade 4 thrombocytopenia (3.3%). Cerebral infarction occurred in one patient, who developed left hemiplegia on day 11 of the second cycle. Brain CT and MRI indicated

Table 2 Response

	Refractory ($n = 10$)		Sensitive ($n = 20$)		Total ($n = 30$)	
	No. of patients	Percentage	No. of patients	Percentage	No. of patients	Percentage
Complete response	0	0	0	0	0	0
Partial response	2	20	9	45	11	36.7
Stable disease	7	70	3	15	10	33.3
Progressive disease	1	10	6	30	7	23.3
Not evaluate	0	0	2	10	2	6.7

Table 3 Grade 3/4 toxicities in 30 assessable patients

	Grade 3	Percentage	Grade 4	Percentage
Leukopenia	2	6.7	0	0
Neutropenia	12	40	1	3.3
Thrombocytopenia	0	0	1	3.3
Anemia	1	3.3	0	0
Diarrhea	3	10	0	0
Nausea/vomiting	0	0	0	0
Abnormal liver function	1	3.3	0	0
Abnormal renal function	0	0	0	0

cerebral infarction, but toxicity of these medications could not be excluded.

There were no toxic deaths during this trial. Treatment was withheld on day 15 in 8 out of 30 patients, including 5 with neutropenia and 3 with diarrhea. Therefore, reduction of the irinotecan dose was needed in 8 (26.7%) of the 30 patients.

Discussion

In brief, this phase II trial demonstrated that a combination of gemcitabine plus irinotecan is a well-tolerated regimen causing few grade four toxicities in SCLC patients who have received prior first-line therapy. This study showed an overall response rate of 39% (95% CI: 18.1–60.5%), an overall median survival time of 14.4 months, and a 1 year survival rate of 51%. Although the activity of second-line treatments usually depends on tumor responsiveness to first-line therapy and there have been no active regimens for refractory disease, this combination seems to be active [the response rate was 20% (95% CI: 15.2–24.8%) for refractory disease and 45% (95% CI: 21.8–68.2%) for sensitive relapse].

The response and survival rates observed during this trial were very encouraging compared with single-agent topotecan or the three-drug combination of CAV, which are the commonest therapies for relapsed SCLC [3, 15]. Several new agents or new combination chemotherapy regimens for relapsed/refractory SCLC have been tested in small phase II studies, and high response rates (20–70%) have been reported [16–20], but the median survival time is almost the same as with topotecan or CAV. Therefore, it remains unclear which of the current options will achieve the optimal outcome for these patients.

Two other small studies of gemcitabine and irinotecan for relapsed SCLC were previously reported [21, 22]. The response rate was 10% in both studies and the median survival time was 5.8 and 4.5 months, respectively. Compared with our present results, these findings were not so impressive. In addition, a larger study of gemcitabine and irinotecan for relapsed SCLC was recently reported by Rocha Lima et al. [23] They treated 71 patients (35 with sensitive disease and 36 with refractory disease), and achieved response rates of 31% for relapse of sensitive disease and 11% for refractory disease, while the median survival time was 7.1 and 3.5 months, respectively [23].

Although these three studies and our study all targeted patients with relapsed SCLC, there were large differences in the response rates and survival between the other studies and ours. The reasons for these discrepancies are unclear, but a possible reason may be the different dosages and administration schedules (days 1 and 8 every 21 days vs. days 1 and 15 every 28 days).

Another possible reason may be differences of patient characteristics between these studies. In our study, all of patients had only received one prior regimens and 50% of the patients had limited disease at diagnosis and 70% of patients were receiving third-line chemotherapy for disease progression in our study. Third-line therapy may account for their long median survival.

A further possible reason may be pharmacogenomic differences between western patients and Japanese patients. Specifically, differences of UDP-glucuronosyltransferase polymorphism (*UGT1A1*), an enzyme that metabolizes irinotecan, are observed between these patient populations [24]. More or less extensive metabolism of irinotecan may result in differences of toxicity, compliance, and chemosensitivity. It is possible that irinotecan may be a better drug for Japanese patients. Indeed, two recent phase III studies comparing IP with EP showed different results between Japan and the United States [2, 25]. A Japanese phase III study show a significant difference of overall survival between the IP and EP regimens. On the other hand, there were no significant differences of the outcome between patients treated with IP or EP in the United States.

The response rate was superior in the patients with relapse of sensitive disease compared with the patients who had primary refractory disease (20 vs. 50%, respectively), but there was no significant difference. Perhaps investigation of a larger population would have shown that the response rate is significantly lower in patients with refractory disease. Survival was not significantly different between patients with refractory disease versus relapsed sensitive SCLC. It is likely that the failure to detect a difference between patients with refractory disease and relapsed sensitive disease was due to the small sample size in this particular trial.

Because of the good toxicity profile of this combination regimen in the present trial, it is reasonable to conclude that gemcitabine plus irinotecan can be considered as an option for second-line chemotherapy in patients with extensive SCLC. It may be difficult to justify a larger phase III

comparison with a standard agent such as topotecan because future efforts may be more appropriately focused on the integration of newer agents in this population.

In summary, gemcitabine plus irinotecan is an active regimen for SCLC patients who have received prior chemotherapy. Given the statistical design of this study, the 11 partial responses observed indicate that this combination is worth further consideration for such patients.

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