Scheduled administration of low dose irinotecan before gemcitabine in the second line therapy of non-small cell lung cancer: a phase II study

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We had previously demonstrated that low dose irinotecan (CPT-11) leads to increased accumulation of cells in S-phase and shows a therapeutic synergy with S-phase specific chemotherapy such as gemcitabine and 5-fluorouracil. In this phase II study, our objectives were to evaluate the tolerability and activity of low dose CPT-11 followed 24 h later by gemcitabine as second line therapy in patients with metastatic non-small cell lung cancer (NSCLC). CPT-11 (60 mg/m^2) was administered 24 h before gemcitabine (1000 mg/m^2) on days 1, 2, 8, and 9 every 3 weeks. Twenty-nine patients were evaluable for response. The median follow-up was 7.4 months. Partial response (PR) was seen in two (6.9, 95% confidence interval (CI): 0.009–0.228). PR and stable disease were seen in 22 patients (75.9, 95% CI: 0.564–0.897). The median survival time was 13.8 months (95% CI: 8.1–19.3). The median time to progression was 4.6 months (95% CI: 2.6–6.2). Thirty-eight patients were evaluable for toxicity. Neutropenia (grade 3 or 4) was observed in 27 patients (71%). Eight patients did not receive cycle 2 of therapy owing to prolonged neutropenia. No treatment-related deaths occurred. Scheduled administration of low dose CPT-11, 24 h before gemcitabine in the second line therapy of NSCLC yielded comparable disease control rates (PR and stable disease) when compared with other studies using the two chemotherapy drugs in the traditional sequence. However, this approach was associated with higher grade 3/4 neutropenia and is not recommended for further study in metastatic NSCLC. *Anti-Cancer Drugs* 19:749–752 © 2008 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Introduction

Non-small cell lung cancer (NSCLC) is a deadly disease affecting over 160 000 patients in the United States each year with about 120 000 annual deaths [1]. Double-agent chemotherapy is the standard of care for first line treatment of patients with advanced NSCLC. It produces response rates of approximately 20%, a median overall survival (OS) of 8 months, and a 1-year survival rate of 33% [2]. More recently, studies have been published combining platinum doublets and bevacizumab, an antiangiogenic agent. These studies report higher response rates (28–41%) as well as a greater median OS (12.5 months) [3] and progression-free survival [4]. Despite these improvements, there is a high rate of recurrence after initial therapy, calling for second line options. The NCCN guidelines recommend docetaxel, pemetrexed, or erlotinib in the second line setting (*www.nccn.org*). The response rates to the aforementioned drugs in this setting is low (about 10%) with a median survival of about 8 months [5]. The toxicity profile of these drugs varies with docetaxel causing more myelosuppression than pemetrexed [5]. In reported studies of single-agent gemcitabine in the second line therapy for NSCLC, the response rates were from 7 to 21% [6,7]. We have previously shown both in animal models as well as in phase I studies that low dose CPT-11 increases the number of cells in S-phase [8]. The present phase II study was undertaken to evaluate the efficacy and toxicity of low dose CPT-11 followed 24 h later by gemcitabine in previously treated patients with metastatic NSCLC, who had failed chemotherapy with a platinum-containing doublet.

Patients and methods

Patients were required to have histologically or cytologically documented metastatic NSCLC that had progressed during or after one platinum-based chemotherapy regimen that did not include gemcitabine as the second drug. Patients had to be at least 4 weeks from the previous therapy and to have no on-going toxicity greater than grade 1. Other criteria included: measurable disease, life expectancy of at least 12 weeks, Eastern

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Cooperative Oncology Group performance status, (ECOG PS) score, 0, 1, adequate bone marrow reserve (as defined by absolute neutrophil count $>2000/\mu l$, platelet count $>100\,000/\mu l$) adequate hepatic and renal function (defined as serum creatinine <2 mg/dl, aspartate aminotransferase and alanine aminotransferase $1.5\times$ upper limit normal and bilirubin <1.5 mg/dl). Exclusion criteria included active infections, and preexisting toxicities related to prior chemotherapy $\geq$ grade 2. Patients with brain metastasis had to have been treated with radiation and 4 weeks must have elapsed since whole brain radiation or 2 weeks since γ-knife treatments. Palliative radiation had to be 2 weeks before starting therapy. Written informed consent was obtained from every patient. Patients were considered evaluable for response only if they had completed two cycles of the chemotherapy. This study was approved by the Roswell Park Cancer Institute Institutional Review Board.

Treatment

CPT-11 was administered at 60 mg/m^2 over 30 min followed 24 h later by gemcitabine 1000 mg/m^2 over 30 min on days 1, 2, 8, and 9 every 3 weeks. No routine premedications were used. Patients who experienced grade 4 leucopenia, neutropenia or thrombocytopenia, or grade 2 or higher liver dysfunction received reduced doses of both drugs (25% lower) for the next cycle. If more than two dose reductions were required or if there was a delay of ≥ 14 days because of grade 3/4 neutropenia, the patients were taken off study. The National Cancer Institute Common Terminology Criteria for adverse events version 3.0 was used for this study. If nonhematological toxicities greater than grade 3 occurred, the patients were taken off study.

Evaluation of response and toxicity

Pretreatment evaluation included complete medical history, physical examination, complete blood count, serum biochemistry, chest and abdomen computed tomography (CT) scans, and brain MRI. Complete blood counts and chemistry profile were obtained weekly during this study. Responses and toxicity were evaluated on the basis of tumor images on CT scans, laboratory data, patient symptoms, and signs at baseline and after administration of study drugs. CT scans were obtained every two cycles. Responses were assessed using the Response Evaluation Criteria in Solid Tumors criteria. Patients were withdrawn from study for progression of disease, withdrawal of consent, or if they required more than two dose reductions or had a dose delay of >14 days because of toxicity.

Statistics

An exact one-stage design was used. Response rates are generally reported to be less than 10% for a second line therapy [5,9]. The study was designed to determine if the objective response rate [complete response (CR), partial response (PR)] would be greater than 10% in patients receiving the study treatments. If the number of patients responding was greater than or equal to seven of 30, then it would be concluded that the study treatment improved the objective response rate compared with that with standard care. The upper bound on the type I error was 0.05. The lower bound of the statistical power was 0.80 if the true objective response rate was 28.7%. The number of evaluable patients (those who received at least two cycles) required was 30. Secondary endpoints were progression-free survival and overall survival (OS). OS and time to progression were measured from the start of treatment up to the time of death or up to the last follow-up clinical assessment. Survival curves were constructed using the Kaplan–Meier method [10]. Ninety-five percent confidence intervals (CIs) for the proportion were calculated using the exact method.

Results

To be evaluable for response and survival, patients had to receive two full cycles. The study called for patients who did not receive two full cycles to be replaced. All patients were evaluated for toxicity. Thirty-eight patients were enrolled in this study. One patient rescinded consent after cycle 1. One patient progressed after cycle 1. Two patients had a decline in PS after cycle 1. Five patients could not undergo cycle 2 because of prolonged neutropenia that did not recover by day 21 to begin cycle 2. One of these five patients received day 8 but not day 9 (this patient was not considered evaluable once the study closed). Hence, we report our results in 29 evaluable patients. Accordingly, the statistical tests were based on a sample size of 29. With this sample size, the critical value to test the objective response remains the same as for 30 patients, whereas the study power (0.77) is slightly smaller than 0.80. Patient characteristics are listed in Table 1. All 29 evaluable patients had received prior platinum-based doublet chemotherapy. The second drug was paclitaxel in all but six patients. The median recurrence time after the first chemotherapy was 5 months (range: 1–18). Of the 29 patients, two (7%) exhibited a PR and 20 exhibited stable disease (SD) (69%). The median number of cycles received was four (range 2–8). Nineteen patients (65%) required a dose reduction for neutropenia or thrombocytopenia. Seven patients had progressive disease (PD). The overall median survival was 13.8 months (95% CI: 8.1–19.3) (Fig. 1). The 1-year survival rate was 53% (95% CI: 27–79). The median time to progression was 4.6 months (95% CI: 2.6–6.2). The median follow-up was 7.4 months.

Toxicities

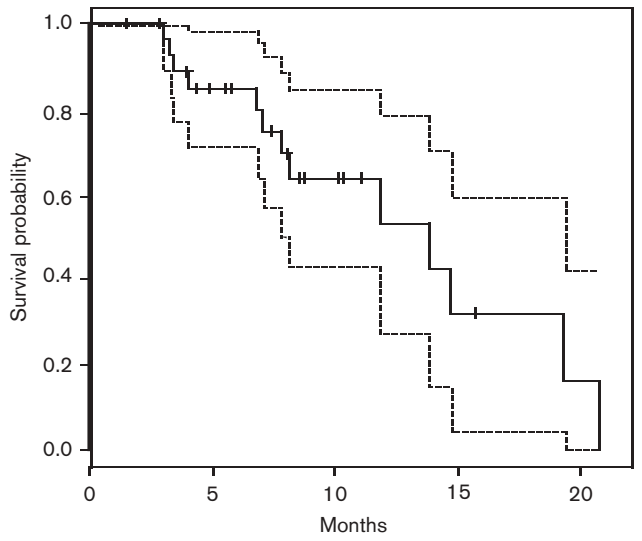
Toxicities are reported for 38 patients (Table 2). Hematological toxicities included neutropenia and

Table 1 Evaluable patient characteristics

Characteristics ($n=29$)	No. of patients (%)
Sex	
Male/female	19/10
Age (years)	
Median (range)	63 (38–80)
Performance status (ECOG)	
0	16 (55.2)
1	13 (44.8)
Histology	
Squamous cell carcinoma	3 (10.3)
Adenocarcinoma	14 (48.3)
Non-small cell carcinoma	12 (41.4)
Stage	
III	6 (20.7)
IV	23 (79.3)
Previous radiotherapy	
Yes	13 (44.8)
No	16 (55.2)
Previous surgery	
Yes	17 (58.6)
No	12 (41.4)
Previous drug	
Carboplatin	27 (93.1)
Cisplatin	2 (6.8)
Paclitaxel	23 (79.3)
Docetaxel	4 (13.8)
Bevacizumab	4 (13.8)

ECOG, Eastern Cooperative Oncology Group.

Fig. 1



Kaplan–Meier curve for overall survival in 29 evaluable patients. [dashed line: 95% confidence interval (CI)]. The median overall survival duration was 13.8 months (95% CI: 8.1–19.3).

thrombocytopenia. A high incidence of grades 3 and 4 neutropenia (71%) was found. Five patients had grade 3 neutropenia lasting more than 14 days; these patients did not receive cycle 2. Grade 3/4 anemia and thrombocytopenia occurred in 8 and 5%, respectively. Nonhematological toxicities included nausea (29%), vomiting (26%), fatigue (50%), and leg edema (13%). No treatment-related deaths occurred.

Table 2 Incidence of treatment-related toxicities (NCI-CTC, version 3.0)

Toxicity ($n=38$)	Grade 1	Grade 2	Grade 3	Grade 4
Hematological toxicities				
Leukopenia	2	9	12	5
Neutropenia	0	5	14	13
Anemia	7	13	2	1
Thrombocytopenia	8	2	2	0
Nonhematological toxicities				
ALT increased	10	1	1	0
AST increased	6	2	0	0
Alkaline phosphatase increased	3	0	0	0
Alopecia	1	0	0	0
Anorexia	2	0	0	2
Dehydration	0	2	0	0
Diarrhea	10	3	3	0
Fatigue	9	6	3	1
Fever	2	1	0	0
Hyperglycemia	0	1	0	0
Hypoalbuminemia	1	0	0	0
Hypokalemia	1	0	1	0
Hyponatremia	1	0	0	0
Hypotension	1	1	0	0
Infection	0	0	1	0
Myalgia	0	0	1	0
Nausea	10	0	1	0
Stomatitis	2	0	0	0
Swelling of legs	4	1	0	0
Tingling feet/hands	1	0	0	0
Vomiting	6	3	1	0

NCI-CTC, The National Cancer Institute Common Terminology Criteria for adverse events.

Discussion

As gemcitabine is an S-phase specific agent, its activity should increase with an increase in the number of cells in S-phase. Studies in the rat ward colorectal carcinoma model by one of us (Y.M.R.) demonstrated that giving low dose CPT-11, 24 h before the S-phase specific drug 5-fluorouracil (5-FU), increased the complete tumor regression rate from 62 to 95% [8]. It was further demonstrated, using the HCT-8 cell line in athymic nude mice, that the number of cells in S-phase at 24 h increased 148% over control after a dose of CPT-11 that was 50% of the maximally tolerated dose. A 100% complete tumor regression of HCT-8 was achieved in nude mice with CPT-11 preceding capecitabine, a 5-FU precursor [11]. These results led to two clinical studies, exploring the effect of CPT-11, given 24 h before 5-FU and before gemcitabine in advanced solid tumors [8]. Tumor biopsies were assayed for cyclin A before and 24 h after CPT-11. At a dose of 80 mg/m^2, the increase in cells positive for cyclin A was a median of 141% (range 95–200%, $n = 5$), G2 (by FACS) decreased in two patients, and increased in one ($n = 3$) indicating that it was highly unlikely that the increases in cyclin A positive cells seen were a result of blocking cells in G2. Clinically, the maximal tolerated dose was 60 mg/m^2 of CPT-11 followed by 1000 mg/m^2 of gemcitabine given 24 h later. A third study showed similar results in patients with breast cancer who, before and 24 h after CPT-11, underwent tumor biopsies

before starting capecitabine. In five patients the median increase in cyclin A index was 113% (range 12–160%). Patients had had one to seven prior regimens (median 3). Of seven patients evaluable for response, there was one PR, four SD, and two PD after one cycle of therapy [12]. These results, though preliminary, were indicative of activity of CPT-11 in increasing the number of cells in S-phase, 24 h after treatment, in a variety of solid tumors in humans, were suggestive of clinical benefit in heavily pretreated, 'phase I' patient populations, and were the rationale for the present phase II study. Single-agent gemcitabine is used not only to treat advanced NSCLC, but also has use in pancreatic, breast, and ovarian cancers [13–15]. Gemcitabine is fairly well tolerated with myelosuppression, fatigue, and leg edema being some of the toxicities [16]. This study attempted to improve the response rates of single-agent gemcitabine, as a second line chemotherapeutic agent in previously treated patients with metastatic NSCLC. Similar attempts at combining CPT-11 with gemcitabine have been made by others [17–20]. Three of these were phase I studies looking at escalating doses of CPT-11 with either fixed dose gemcitabine [17,18] or variable doses of gemcitabine [19]. Kosmas *et al.* [21] reported on a phase I/II study of escalating doses of both CPT-11 and gemcitabine. In all these studies, gemcitabine was administered immediately following CPT-11. The rates of PR and SD reported by Kosmas *et al.* (65%) are comparable to those seen in our study. However, our study saw greater grade 3/4 neutropenia (70%) in comparison to their's (18%). The median survival (13.8 months) in our study is better than that reported by Kosmas *et al.* (7 months), understanding that such a comparison in a study of small numbers may not be optimal. A more recent randomized phase II study comparing CPT-11/docetaxel or CPT-11/gemcitabine with or without celecoxib in second line treatment of NSCLC showed a response rate of 4% (PR) in the irinotecan/gemcitabine arm [21]. The rates of PR and SD seen in the present phase II study (where CPT-11 was administered 24 h before gemcitabine) are comparable to the aforementioned studies. Whereas there was an apparent increase in disease control, there were also several patients who exhibited grades 3 and 4 hematological toxicities, notably neutropenia, necessitating dose reductions and missed doses. It is possible that CPT-11 causes sensitization of the bone marrow to the subsequently administered gemcitabine, but we do not have proof of this.

The approach presented in this study has a solid scientific basis. However, there was no improvement in objective response rates when compared with other chemotherapy drugs administered in the second line setting in advanced NSCLC. Moreover, there was a significantly higher incidence of myelosuppression with this approach. Based on this, we do not recommend further study of this approach in this group of patients.

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