Case Report

Phase II Study of Cisplatin Combined to Irinotecan Administered Alternatingly with Docetaxel in Advanced Non-Small Cell Lung Cancer

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Objective: *To assess the activity and toxicity of cisplatin and irinotecan alternating with docetaxel in patients with advanced non-small cell lung cancer (NSCLC).*
Material and Method: *Eligibility included chemo-naïve stage IIIB with malignant effusion and stage IV NSCLC patients with measurable disease and a good performance status. Twenty-four patients were enrolled into the present study. There were 19 males and 5 females with a median age of 58.5 years and the median performance status was 1. Ninety-six percent had stage IV disease. These patients received cisplatin at 80 mg/m^2 and irinotecan at 200 mg/m^2 on day 1, followed by docetaxel at 75 mg/m^2 on day 22, in 6-week cycle for a maximum of 3 cycles.*
Results: *Eight out of twenty-two evaluable patients obtained a partial response (36%). The median time to tumor progression was 6 months. The median survival time and 1-year survival rate were 10.4 months and 45% respectively. The most frequent severe toxicities were neutropenia, anemia, and diarrhea. Febrile neutropenia occurred in four patients (16%), and was the cause of treatment-related deaths in two (8%). Other non-hematologic toxicities were mild including nausea, vomiting, and skin rash.*
Conclusion: *Alternating cisplatin and irinotecan with docetaxel, as used in the present study was feasible and demonstrated encouraging efficacy in patients with non-small cell lung cancer. However, this approach appears to be more toxic, especially in myelosuppression, than in previous reports of the sequential use of the similar agents.*

Keywords: *Phase II study, Cisplatin, Irinotecan, Docetaxel, Non-small cell lung cancer*

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Lung cancer is the leading cause of malignancy related-death worldwide. Combination platinum-based chemotherapy has been demonstrated superior to best supportive care alone in terms of quality of life and survival in the treatment of patients with advanced non-small cell lung cancer (NSCLC)[1]. During the past decade, several new chemotherapeutic agents showing the activity in NSCLC have been developed. Among these are the taxanes (paclitaxel and docetaxel), vinorelbine, gemcitabine, and topoisomerase I inhibitors-Irinotecan (CPT-11). The combination of these new drugs with either cisplatin or carboplatin is the current cornerstone in the treatment of advanced NSCLC. In direct comparison, several of the new doublet regimens have shown similar efficacy, although they may differ in the toxicity profiles[2].

Irinotecan (CPT-11) is a topoisomerase I inhibitor that has shown a single agent activity in NSCLC[3]. In a pivotal phase III trial by Japanese investigators, the CPT-11 and cisplatin combination demonstrated a significant survival advantage when compared with cisplatin and vindesine in the treatment of patients with

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advanced stage IV NSCLC[4]. The median survival time was 50 weeks for patients who received CPT-11 and cisplatin and 36.4 weeks for those given cisplatin and vindesine (p = 0.004). Based on these results, the CPT-11 and cisplatin combination is considered one of the active first-line regimens in the treatment of NSCLC.

Among new chemotherapy that has undergone clinical development over the past decade, docetaxel is one the most extensively tested single agents in previously treated NSCLC, and it has consistently demonstrated activity in this setting. Two phase III trials comparing docetaxel to either vinorelbine or ifosfamide, or best supportive care, confirmed a survival benefit for docetaxel at a dose of 75 mg/m^2, given every 3 weeks to patients with previously treated NSCLC[5,6].

These findings suggest that currently available first line regimens such as CPT-11 and cisplatin could be combined with drugs that have activity in a second line therapy setting such as docetaxel, might be non-cross resistant and may result in increased response rates and median survival times in patients with previously untreated advanced stage NSCLC[7]. In order to exploit this concept, the authors conducted a single institution, phase II study using the convenient 3-week schedule of CPT-11 and cisplatin administered alternately with docetaxel, in patients with advanced chemotherapy na□ve NSCLC.

Material and Method

Patient selection

Patients with histologically or cytologically confirmed stage IIIB (caused by malignant pleural effusion only) and stage IV NSCLC were eligible. Additional eligibility criteria included age between 18 and 75 years, a World Health Organization (WHO) performance status (PS) of 0 or 1, measurable or assessable disease, no previous chemotherapy, and adequate following organ functions: white blood cell (WBC) count more than 4000/μL, platelet count more than 100,000/μL, hemoglobin more than 9.5 g/dL, serum bilirubin less than 1.5 mg/dL, serum AST/ALT less than twice the normal upper limit and creatinine clearance more than 40 ml/min. Previous radiotherapy was allowed if an interval of at least 4 weeks had elapsed, and the radiotherapy field did not include all measurable lesions used as a target lesion. Patients with brain metastases, who were treated with radiotherapy resulting stable condition without medication (e.g. corticosteroids), and asymptomatic were also eligible. Patients were required to provide written informed consent approved by the institution ethics committee before study entry.

Treatment protocol

Irinotecan (CPT-11) 200 mg/m^2 in 250 ml of normal saline was infused intravenously within 60-min, followed by cisplatin 80 mg/m^2 in 100 ml of normal saline intravenous infusion over a one hour period on day 1 then docetaxel 75 mg/m^2 was infused on day 22, in 6-week cycles for a maximum of 3 cycles. Patients were given pretreatment intravenous hydration of at least 1,000 ml over a 2 to 3 hour period before cisplatin administration, and they received mannitol diuresis and post treatment hydration. Appropriate antiemetic regimens were given before and after the administration of CPT-11 and cisplatin (e.g. ondansetron/dexamethasone with or without lorazepam). The next course of chemotherapy was delayed for one week if the neutrophil count was less than 1500/μL and/or platelet count less than 100,000/μL and/or diarrhea was not recovered to less than grade 2 on day 22 or day 1 of the next cycle. Patients who required more than 2 weeks treatment delay were withdrawn from the present study. If febrile neutropenia (or grade 4 neutropenia) occurred during the previous cycle, a 20% dose reduction of both CPT-11 and docetaxel was administered for the subsequent cycle. Patients who experienced more than grade 3 diarrhea, had their CPT-11 doses reduced by 20% in subsequent cycles. If the serum creatinine concentration was increased more than 1.5 and less than 3 times the normal institution upper limit, the dose of cisplatin was reduced to 60 mg/m^2 for the subsequent cycle. Only one dose reduction was allowed for all agents in the present study.

Cholinergic symptoms occurred during or within one hour after administering CPT-11 were treated with atropine. All patients were instructed to take 2 mg of loperamide every 2 hours as a therapy for CPT-11 induced diarrhea to start immediately after the first episode until the diarrhea had ceased for at least 12 hours. Routine use of hematopoietic growth factors was not allowed. It could be used as needed according to the published guidelines[8].

Patients were withdrawn from the present study if the disease progressed, the experienced grade 4 neutropenia or grade 4 diarrhea in spite of a 20% dosage reduction which required treatment delay for more than 2 weeks, or if the patients refused to continue the treatment protocol regardless of the cause.

Baseline and follow-up assessments

At study entry, the following investigations

were performed: complete history and physical examination, complete blood count and differential count and blood chemistry profile, and baseline tumor measurement. Before each chemotherapy administration, the following assessments were performed: medical history taken with toxicity assessment, physical examination, body weight, performance status, complete blood count and differential count and blood chemistry profile. Toxicities were graded according to the NCIC CTG Expanded Common Toxicity Criteria. Tumor response was assessed according to the WHO criteria[9] including a CT scan or radiologic and ultrasound evaluation of the lesions after the second cycle of chemotherapy, and 3 weeks after completion of the third cycle of chemotherapy.

Statistical analysis

The primary goal of the study was to observe the objective response rate. The phase II study was conducted using the two-stage design of Simon[10]. Twenty patients were treated, and if two or fewer responses were observed, accrual was terminated. This ensured that the 95% confidence interval (CI) would show the combination response rate of < 30%. Time to progression was calculated from the study entry until the day of first evidence of disease progression. Survival was calculated from the start of treatment to death or the last follow-up evaluation. Survival curves were drawn using Kaplan-Meier methods.

Results

Patients' characteristics

Between February 2001 and August 2002, 24 patients were entered into the present study. The characteristics of the patients are listed in Table 1. The median age was 58.5 years, ranging from 39 to 67. There was a predominance of male patients (79%) in the present study. One patient (4%) was in stage IIIB, whereas 23 patients (96%) had stage IV disease. Four patients (16%) had an ECOG PS of 0, and 20 patients (84%) had an ECOG PS of 1. Squamous cell carcinoma and adenocarcinoma accounted for 63% of all histologies.

Treatment protocol

Sixty-three cycles of chemotherapy was administered to these 24 patients. The median number of cycles per patient was 3 (range 1-3 cycles). Eighteen patients (75%) received the planned 3 cycles of therapy. Four patients (16%) discontinued therapy after 2 cycles of chemotherapy. The reasons for treatment being discontinued were progression of disease in all these patients, except two (8%) who received only the first course of the treatment cycle and experienced neutropenic fever with sepsis, which resulted in treatment related death. No other patients discontinued treatment due to adverse events.

Toxicity

The major toxicity of this regimen was myelosuppression (Table 2). Grade 3 or 4 neutropenia occurred following administration of cisplatin with irinotecan and docetaxel in 42% and 9% respectively. Four patients (16%) developed febrile neutropenia. Grade 3 anemia occurred following administration of cisplatin with irinotecan and docetaxel in 13% and 9% respectively. There was no episode of grade 3 or 4 thrombocytopenia or bleeding tendency in the present study.

Grade 4 diarrhea induced by CPT-11 occurred in one patient, who also developed grade 4 neutropenia and infections, which subsequently resulted in treatment-related death. Apart from this patient, the incidence of diarrhea induced by CPT-11 was generally grade 1 or 2, which occurred in 14 patients (58%). Other non-hematological toxicities were generally mild including nausea, vomiting, neuropathy and skin rash. Serum transminase and creatinine elevation was rarely observed.

Response and survival

Among 22 assessable patients, who received at least 1 cycle of chemotherapy, there were no complete and eight partial responses, for an overall response rate of 36%. Seven patients (32%) experienced stable disease and another seven patients (32%) had pro-

Table 1. Patient characteristics

No. of patients entered	24
Male	19 (79%)
Female	5 (21%)
Median age, Years (Range)	58.5 (39-67)
Performance status	
0	4 (16%)
1	20 (84%)
Histology	
Adenocarcinoma	11 (46%)
Squamous cell carcinoma	6 (25%)
Unclassified NSCLC	7 (29%)
Stage	
IIIB (pleural effusion)	1 (4%)
IV	23 (96%)

Table 2. Major toxicity

	Irinotecan with cisplatin n = 24				Docetaxel n = 22			
WHO Toxicity Grade	1	2	3	4	1	2	3	4
Anemia	8	11	3	0	5	12	2	0
Neutropenia	3	0	4	6	4	7	1	1
Leukopenia	5	5	1	1	11	1	1	0
Thrombocytopenia	0	0	0	0	0	0	0	0
Nausea/vomiting	5	11	0	0	4	2	0	0
Diarrhea	5	6	0	1	1	0	0	0
Skin rash	2	0	0	0	2	3	0	0
Neuropathy	0	0	0	0	3	0	0	0
Creatinine	2	0	0	0	0	0	0	0
AST/ALT	2	0	0	0	0	0	0	0

gressive disease. The median time to tumor progression was 6 months (range, 2.6-9).

With a minimum follow up duration of 15 months, the median survival time was 10.4 months (range, 0.3-24) and the 1-year survival rate was 45%. The survival curve is shown in Fig. 1.

Discussion

The present study demonstrated the feasibility of an alternating chemotherapy strategy in NSCLC. Its alternating therapy using a 3-week schedule of CPT-11 and cisplatin with docetaxel resulted in a response rate of 36%, median survival of 10.4 months and 1-year survival rate of 45% in patients with advanced stage NSCLC. The major toxicities encountered in this regimen were myelosuppression and diarrhea, which resulted in two treatment-related deaths.

Over the past few years, a number of new drugs have demonstrated activity in NSCLC. For the second-line setting, docetaxel is emerging as one of the most tested drugs, which consistently demonstrated activity in this disease[5,6]. Among several approaches

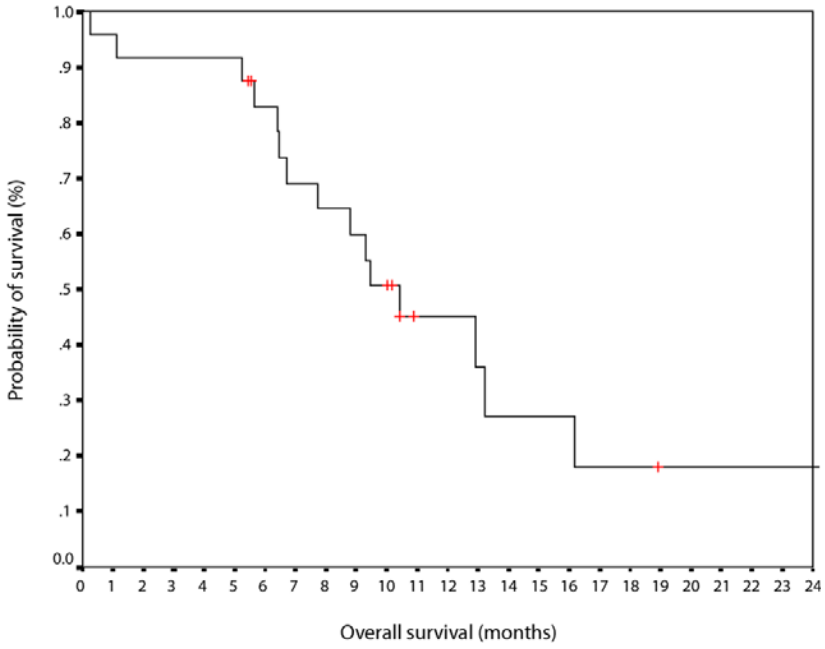

Fig. 1 Overall survival

to improve treatment efficacy, combinations of chemotherapy regimens, in which the drugs are administered concurrently as doublets or triplets, are commonly used. To date, none of these drugs has been demonstrated as superior to doublets platinum-based chemotherapy[2,11,12]. Other treatment strategies, which have the theoretical advantage of increasing efficacy, are administration of chemotherapeutic agents in sequential or alternating fashion before the emergence of clinical resistance[7,14]. These approaches could allow for the use of multiple agents, whose toxicity would prevent their concomitant administration and the advantage of eliminating cumulative or additive toxicity, permitting full delivery of each individual active drug or regimen. For sequential therapy, investigators from the South West Oncology Group (SWOG) reported results of a randomized phase II trial using carboplatin/gemcitabine followed by paclitaxel or cisplatin/vinorelbine followed by docetaxel in advanced NSCLC[19]. The present study demonstrated the feasibility of both sequential regimens, and the median and 1-year survival rates were modestly longer than those in previous trials of doublets combination in this population. Alternating therapy was tested in the present study by the administration of a current active first-line chemotherapeutic regimen alternating with a drug that has activity in the second line therapy setting in patients with advanced NSCLC. The authors chose the single dose every 3-week schedule of CPT-11 and cisplatin, based on the phase I study of this convenient schedule by de Jonge et al[14]. After this study was designed, several larger studies of variety combination schedules of CPT-11 and cisplatin have been reported[15-18]. These included weekly schedules of CPT-11 and/or cisplatin or a single 3-week schedule of both drugs, as in the present study. Myelosuppression was the major toxicity in all studies, with the reported incidence of febrile neutropenia ranging from 6% to 14% and toxic death from 0 to 2%. The incidence of febrile neutropenia (16%) and toxic death (8%) was higher in the present study compared to those reported in the other trials. In the present study, the 1-year survival of 45% was observed in patients with majority stage IV NSCLC. This result is compatible with the authors' hypothesis, that alternating chemotherapy may result in increased activity in this high-risk population. However, the potential benefits of this approach without prophylactic administration of G-CSF are offset by observed substantial hematological toxicity.

Findings from several trials, as outlined above, indicate that a plateau in efficacy has been reached with currently available chemotherapeutic regimens in a variety of schedules and combinations. The recent discovery of novel cellular targeted agents, such as epidermal growth factor receptor tyrosine kinase inhibitors, have demonstrated activity in pretreated patients with NSCLC and appeared to have less and non-overlapping toxicity to chemotherapy[20-22]. The future direction will continue to evaluate the optimal strategy of incorporating these novel agents with chemotherapy.

In conclusion, the present 3-week schedule of CPT-11 and cisplatin alternating with docetaxel is feasible and active in the treatment of advanced NSCLC. An alternating chemotherapy schedule appears to be more toxic, especially in myelosuppression, than in previous reports of the sequential use of similar agents. The authors do not intend to develop into approach any further.

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การศึกษา phase II เพื่อประเมินประสิทธิภาพของการใช้ยาเคมีบำบัด cisplatin ร่วมกับ irinotecan สลับกับ docetaxel ในผู้ป่วยมะเร็งปอดชนิด non-small cell

ชัยยุทธ เจริญธรรม, สุมิตรา ทองประเสริฐ, บุสยามาส ชีวสกุลยง, จันทิมา เอื้อตรงจิตร, ศิริกุล ศรฤทธิ์ชิงชัย, สุทธิรักษ์ มูลประการ

วัตถุประสงค์: *เพื่อประเมินประสิทธิภาพและผลข้างเคียงของการใช้ยาเคมีบำบัด cisplatin ร่วมกับ irinotecan สลับกับ docetaxel ในผู้ป่วยมะเร็งปอดชนิด non-small cell*

วัสดุและวิธีการ: *เกณฑ์การคัดเลือกได้แก่ผู้ป่วยมะเร็งปอดชนิด non-small cell ระยะ IIIB-IV ที่มีสุขภาพดี และมีรอยโรคที่วัดขนาดได้ มีผู้ป่วยจำนวน 24 รายเข้ารับการรักษาแบ่งเป็นชาย 19 รายและหญิง 5 ราย อายุเฉลี่ย 58.5 ปี และค่าเฉลี่ยของ performance status เท่ากับ 1 ผู้ป่วยร้อยละ 96 เป็นโรคระยะที่ IV ผู้ป่วยจะได้รับ cisplatin ขนาด 80 มิลลิกรัมต่อ ตารางเมตรร่วมกับ irinotecan ขนาด 200 มิลลิกรัมต่อตารางเมตร ในวันที่ 1 สลับกับยา docetaxel ขนาด 75 มิลลิกรัมต่อ ตารางเมตรให้วันที่ 22 โดยใช้ซ้ำทุก 6 สัปดาห์ไม่เกิน 3 รอบ*

ผลการศึกษา: *ผู้ป่วย 8 รายจาก 22 รายที่ประเมินผลการรักษาได้มีผลการตอบสนองที่ไม่สมบรูณ์คิดเป็นร้อยละ 36 ระยะเวลาโดยเฉลี่ยจากการรักษาจนมีโรคกำเริบ 6 เดือน ค่าเฉลี่ยของการรอดชีวิตและอัตราการรอดชีวิตที่เวลา 1 ปี เท่ากับ 10.4 เดือนและร้อยละ 45 ผลข้างเคียงที่รุนแรงที่พบได้บ่อยที่สุดได้แก่ เม็ดเลือดขาวต่ำ ซีดและท้องร่วง มีผู้ป่วย 4 รายที่มี febrile neutropenia คิดเป็นร้อยละ 16 และเสียชีวิตจากเหตุดังกล่าว 2 ราย คิดเป็นร้อยละ 8 ผลข้างเคียงอื่น ๆ ที่พบไม่รุนแรง ได้แก่ คลื่นไส้ อาเจียน และผื่น*

สรุป: *การใช้ cisplatin ร่วมกับ irinotecan สลับกับ docetaxel มีประสิทธิภาพในการรักษามะเร็งปอดชนิด non-small cell แต่ผลข้างเคียงที่กดไขกระดูกพบได้สูงกว่าการใช้ยาชนิดเดียวกันเป็นลำดับทีละสูตรตามแบบที่เคยมีรายงานมาก่อน*