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ORIGINAL ARTICLE

Irinotecan and oxaliplatin combination as the first-line treatment for patients with advanced non-small cell lung cancer

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Abstract
Background We conducted a prospective phase II trial of IrOx in patients with advanced non-small cell lung cancer to evaluate the efficacy and toxicity.
Patients and methods Patients with histologically or cytologically proven non-small cell lung cancer (NSCLC), aged ≥18 years, Eastern Cooperative Oncology Group performance status 0–1, at stage IIIB (pleural effusion)/IV or with recurrent disease not suitable for primary surgical treatment, with no palliative chemotherapy or radiotherapy to the chest or immunotherapy or biologic therapy, the presence of measurable disease by RECIST, and who had given signed written informed consent, were eligible. Treatment consisted of irinotecan 65 mg/m^2 on days 1 and 8 and oxaliplatin 130 mg/m^2 on day 1, repeated every 3 weeks.
Results A total of 18 patients were enrolled in June and August 2007, the median age was 59 years (47–73). In total, 71 cycles were administered with a median of 4 cycles per patient (range, 1–6 cycles) and 18 patients were evaluable for treatment response. An independent review of tumor responses gave an overall response rate of 27.7% (CR: 0, PR: 5/18; 95% CI, 7–48.4%) by intent-to-treat analysis. The median overall survival of all patients was 14 months and the median time-to-progression was 4.2 months (95% CI, 1.959–6.441). The most common grade 3/4 toxicities were diarrhea (7% of all cycles) and neutropenia (5.6% of all cycles). Grade 3 peripheral neuropathy occurred in one patient and one patient died due to sepsis.
Conclusion This study suggests that IrOx combination therapy has moderate activity with a tolerable toxicity profile. However, it was not warranted to evaluate further this regimen as first-line treatment for patients with advanced or metastatic NSCLC using the current dosages and schedule.

Keywords Irinotecan · Oxaliplatin · NSCLC · Chemotherapy · First-line

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Introduction

Lung cancer is the leading cause of cancer death worldwide, including in Korea [1, 2, 14]. More than 80% of lung cancer patients are diagnosed with non-small cell lung cancer (NSCLC) and the majority present with advanced inoperable disease. Several meta-analyses have revealed that platinum-based combination chemotherapy offers symptom improvement and an absolute 1-year survival benefit of 10%. Therefore, platinum doublets are considered the standard treatment for advanced NSCLC [22]. However, several randomized phase III trials comparing different platinum combinations have failed to demonstrate a survival advantage [21, 28].

Oxaliplatin, an alkylating agent, inhibits DNA replication by forming DNA adducts between two adjacent guanines or guanine and adenine molecules. It showed a survival benefit in patients with colorectal cancer and NSCLC [2, 6, 11, 24, 26]. Oxaliplatin has a more manageable toxicity profile than cisplatin, with no renal toxicity and a lower incidence of hematological and gastrointestinal

toxicities. It lacks the nephrotoxicity of cisplatin and causes less myelotoxicity than carboplatin, the leading cisplatin analog, and it may be active in cisplatin- and carboplatin-resistant tumors [4, 25]. A phase II study of oxaliplatin plus pemetrexed (oxaliplatin 120 mg/m^2, pemetrexed 500 mg/m^2, every 3 weeks) in 41 NSCLC patients yielded a response rate of 26.8%, with manageable toxicity. [26] Another phase II study of oxaliplatin plus docetaxel (oxaliplatin 130 mg/m^2, docetaxel 70 mg/m^2, every 3 weeks) in 29 NSCLC patients also indicated promising activity, with a response rate of 37% [24].

Irinotecan (CPT-11), a plant alkaloid isolated from *Camptotheca acuminate* (family Nyssaceae), is a camptothecin analogue with strong antitumor activity through inhibition of topoisomerase I. It is converted into SN-38 by the cytochrome CYP3A4, and SN-38 is further metabolized through conjugation by uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1) to give SN-38-glucuronide. SN-38 glucuronidation is associated with not only severe irinotecan-related toxicity, but also excellent clinical efficacy in lung cancer [13]. In the phase II trial of irinotecan monotherapy for patients with untreated advanced NSCLC, the response rate was 31.9% and the median survival time was 42 weeks [9]. A randomized phase III trial of cisplatin plus irinotecan combination comparing other platinum doublets have demonstrated equivalent efficacy, with a response rate of 31%, median survival of 13.9 months, and a 1-year survival rate of 59.2% [21]. Preclinical studies have reported synergistic anti-tumor activities between irinotecan and oxaliplatin in several tumor cell lines [12]. In an attempt to develop a more active and efficacious chemotherapy regimen, two newer agents, irinotecan and oxaliplatin, were combined with or without 5-FU and leucovorin in phase I trials, and showed a safe toxicity profile in patients with advanced solid tumors [34].

On the basis of these encouraging results, we conducted a phase II study in order to assess the efficacy and safety of Irinotecan and Oxaliplatin (IrOx) as front-line chemotherapy in patients with advanced or metastatic NSCLC. We also examined the association between the UGT1A1 polymorphisms and the toxicity of irinotecan.

Patients and methods

Patient eligibility

Eligible patients were required to have histologically or cytologically confirmed stage IIIB (wet IIIB)/IV or recurrent disease not suitable for primary surgical treatment of NSCLC, at least one measurable lesion according to the response evaluation criteria in solid tumors (RECIST) criteria, no palliative chemotherapy, radiotherapy, immunotherapy, or biologic therapy, be aged ≥18 years, an Eastern Cooperative Oncology Group (ECOG) performance status less than or equal to 1, adequate hematologic parameters (hemoglobin ≥9.0 g/dl, absolute neutrophil count ≥1500 per μl; platelet count ≥100,000 per μl), renal function (creatinine clearance by the Cockroft formula ≥60 ml/min or creatinine ≤1.5 mg/dl), and liver parameters (aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5 times the upper limits of normal (ULN) and total bilirubin <1.5 × ULN, except with bone or liver metastasis). Patients with symptomatic metastasis to the central nervous system, uncontrolled or severe cardiovascular disease, including MI within 6 months of enrolment, New York Heart Association Class III or IV heart failure, uncontrolled angina, clinically significant pericardial disease, cardiac amyloidosis, acute severe infection requiring antibiotic therapy, a prior history of another malignancy within 5 years of study entry, except for basal cell carcinoma of the skin or carcinoma in situ of the uterine cervix, pregnancy or breast-feeding, previous renal transplantation, uncontrolled diabetes mellitus, or receipt of extensive radiation therapy within 4 weeks, were excluded from the study. All participants provided written informed consent before they entered the study, which was approved by the institutional review board.

Treatment

Patients received oxaliplatin 130 mg/m^2 diluted in 150 ml normal saline as a 2-h intravenous infusion on day 1 followed by irinotecan 65 mg/m^2 diluted in 500 ml 5% dextrose as a 60-min infusion on day 1 and day 8. Treatment cycles were repeated every 3 weeks until disease progression, unacceptable toxicity, patient refusal, or for a maximum of 6 cycles. For emesis prophylaxis, 5-HT3 antagonists were given before chemotherapy. Atropine 0.25 mg was administered subcutaneously for prophylaxis against the cholinergic syndrome. Prophylactic granulocyte colony-stimulating factor was not recommended for neutropenia.

Administration of irinotecan or oxaliplatin was delayed if there were non-hematologic toxicities of the National Cancer Institute Common Toxicity Criteria (NCI-CTC) grade 3 or greater, neutropenia of less than 1,500 per μl, or thrombocytopenia of less than 100,000 per μl. If the neutrophil count was greater than 1,500 per μl and the platelet count greater than 100,000 per μl after a one-week delay, chemotherapy was administered without dose reduction. If the neutrophil count was less than 1,500 per μl or the platelet count less than 100,000 per μl after a one-week delay, chemotherapy was delayed for an additional week. If patients required a delay of longer

than 2 weeks for recovery, patients went off the study protocol. The dose of irinotecan or oxaliplatin was reduced by 25% of the previous dose in cases of toxicities of NCI-CTC grade 3 or greater, diarrhea or mucositis, febrile neutropenia, or hemorrhagic complications due to thrombocytopenia.

UGT1A1 genotyping analysis

Genomic DNA was extracted from paraffin sections, using the QIAamp DNA Mini Kit (Qiagen, Hilden, Germany). DNAs were amplified in 20 μl reaction solution containing 2 μl 10× buffer (Roche, Mannheim, Germany), 1.7–2.5 mmol/l of $MgCl_2$, 0.3 μM of each primer pair, 250 μM of deoxynucleotide triphosphates, and 2.5 units of DNA polymerase (Roche). Amplification were performed using a 15-min initial denaturation at 95°C; followed by 32 cycles of 45 s at 94°C, 45 s at 58°C, and 45 s at 72°C, with a 10-min final extension step at 72°C.

DNA templates were processed for the DNA sequencing reaction using the ABI-PRISM BigDye Terminator version 3.1 (Applied Biosystems, Foster, CA) with both forward and reverse sequence-specific primers. Sequences were analyzed using Sequencer 3.1.1. software (Applied Biosystems) to compare variations.

Efficacy assessment

The primary objective of the study was to assess the response rate. The secondary objectives were to assess toxicity, overall survival (OS), time to progression (TTP), and the influence of UGT1A1 polymorphisms on the toxicity of irinotecan. Pretreatment evaluation included history and physical examination, complete blood cell count with differentials, chemistry, serum CEA, LDH, chest X-ray, computed tomography (CT) scan of chest, and magnetic resonance imaging (MRI) of the brain or whole body bone scans when clinical signs suggested. During treatment, history taking, physical examination including toxicity assessment, complete blood cell count, and chemistry were performed every 3 weeks, before each cycle. Appropriate imaging studies including chest CT scans were performed every 2 cycles to evaluate treatment response, or sooner if needed for documentation of disease progression. Responses were classified according to the RECIST criteria. Tumor measurements were independently reviewed by a radiologist and an oncologist who were blinded from the tumor assessments performed by the investigators.

Patients who received at least one cycle of treatment were considered assessable for toxicity. TTP was calculated from the first day of treatment to the date on which disease progression was first documented, or the last follow-up. OS was calculated from the first day of treatment to the date of death or the last follow-up. Toxicity was monitored according to the NCI-CTC version 3.0.

Statistical considerations

According to a Simon's two-stage phase II minimax design [29], a sample size of 37 was required to accept the alternative hypothesis that the true response rate is greater than 40% with 80% power, and to reject the null hypothesis that the response rate is less than 20% with 5% significance. At least 18 patients were enrolled in the first stage; if there were fewer than 5 responses out of the initial 18 patients, early termination of the study was required. Considering a 10% drop-out rate, it was planned to recruit 37 patients for this study.

Descriptive statistics were reported as proportions and medians. Kaplan–Meier estimates were used in the analysis of the time-to-event variables and the 95% confidence interval (CI) for the median time to event was computed.

Results

Patient characteristics

Eighteen patients were enrolled from June 2007 to August 2007. Their baseline characteristics are listed in Table 1. There were 16 men and 2 women. The median age was 59 years (range, 47–73 years). All patients had a histologically or cytologically proven NSCLC. One patient had two histological types (adenocarcinoma and squamous cell carcinoma), and one patient received adjuvant chemotherapy. All patients had a performance status ≤ 1.

Treatment and drug delivery

In total, 71 cycles were administered, with a median of 4 cycles per patient (range, 1–6 cycles). The relative dose intensities of the delivered regimens were 92% for irinotecan and, 94% for oxaliplatin (Table 2).

Response

All patients were assessable for response. There were no complete responses (CRs), and 5 partial responses (PRs), which were confirmed at least 4 weeks later. Main characteristic of responding patients are in Table 3. The overall response rate was 27.7% (95% CI, 7% to 48.4%) by intent-to-treat analysis. Fifty percent (9/18) of patients had stable disease (SD). Thirteen patients received second-line therapy after discontinuation of the study. Among them, 14 patients received systemic chemotherapy (gemcitabine plus cisplatin or paclitaxel plus cisplatin) and 5 patients received palliative radiation therapy.

Table 1 Patient characteristics

	No. of patients	%
Patients	18	100
Age, years		
Median	59	
Range	47–73	
Sex		
Male	16	88.9
Female	2	11.1
Performance		
ECOG, 0–1	18	100
ECOG, ≥2	0	0
Prior treatment		
Operation	7	38.9
Radiotherapy	0	0
Chemotherapy	1	5.6
None	11	61.1
Stage IIIB/IV/recur	2/14/2	11.1/77.8/11.1
Histology		
Adenocarcinoma	11	61.1
Bronchioalveolar cell carcinoma	0	0
Squamous cell carcinoma	5	27.8
Large cell carcinoma	1	5.6
Unspecified NSCLC	2	11.1
Metastatic sites		
Lung	5	27.8
CNS	4	22.2
Bone	4	22.2
Pleura/pleura effusion	2	11.1
Lymph node	1	5.6
Adrenal	0	0
Other organs	3	16.7
No. of organs		
0	3	16.7
1	11	61.1
≥ 2	4	22.2

ECOG Eastern Cooperative Oncology Group

Table 2 Number of chemotherapy cycles and delivered actual dose

	Irinotecan	Oxaliplatin
Number of dose reduction	18/71	15/71
Median relative doses	40 mg/m^2/week	41 mg/m^2/week
Dose intensity	92%	94%

Survival

All patients were included in the survival analysis. With a median follow-up of 15.8 months (range 14.5–16.9), median TTP was 4.2 months (95% CI, 1.959–6.441) (Fig. 1) and the median OS was 14 months (Fig. 2).

Table 3 Responding patient characteristics

	No. of patients	%
Patients	5	
Age, years		
Median	63	
Range	52–68	
Sex		
Male	5	100
Female	0	0
Stage IIIB/IV/recur	1/4/0	20/80/0
Histology		
Adenocarcinoma	3	60
Bronchioalveolar cell carcinoma	0	0
Squamous cell carcinoma	1	20
Large cell carcinoma	0	
Unspecified NSCLC	1	20
Metastatic sites		
Lung	1	20
CNS	2	40
Bone	0	0
Pleura/pleura effusion	2	40
Lymph node	0	0
Adrenal	0	0
Other organs	1	20
No. of organs		
0	1	20
1	2	40
≥2	2	40

Toxicities

All patients were assessable for safety. Toxicities observed during the study are listed in Table 4. The most common adverse events were diarrhea and neutropenia. During the course of therapy, 17% of patients ($n = 3$) had grade 3/4 neutropenia and 6% ($n = 1$) for grade 1/2 neutropenia. One patient died due to sepsis. Non-hematologic toxicities of grade 3/4 occurred in less than 10% of cycles. Grade 3/4 diarrhea occurred in 22.2% ($n = 4$) of patients. Five (27.8%) patients required dose reductions of at least one drug due to grade 3/4 toxicities, and four (22.2%) patients had delays of more than 1 week because of non-hematologic toxicities. No patient was discontinued from the study due to toxicities.

Association of UGT1A1 genotypes with tumor response or toxicity

Of the 18 patients enrolled, 14 had samples available for the analysis of their UGT1A1 genotype. No patient had the homozygous UGT1A1*6, UGT1A1*28 or UGT1A1*60

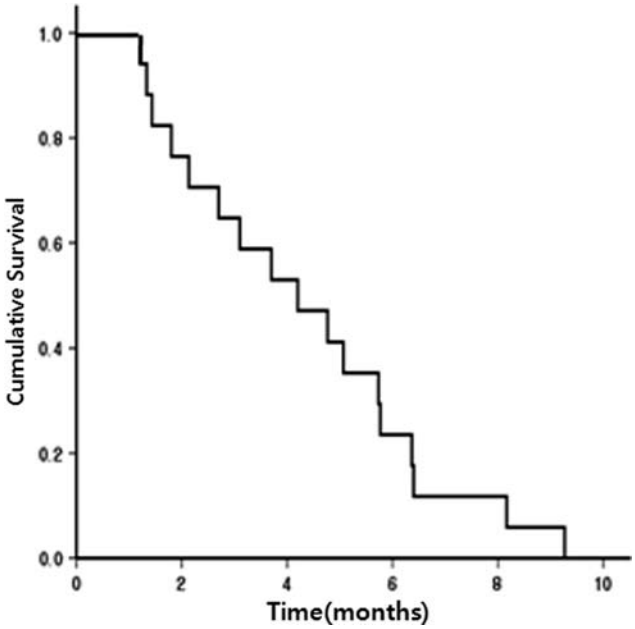

Fig. 1 Time to progression (TTP) of all patients

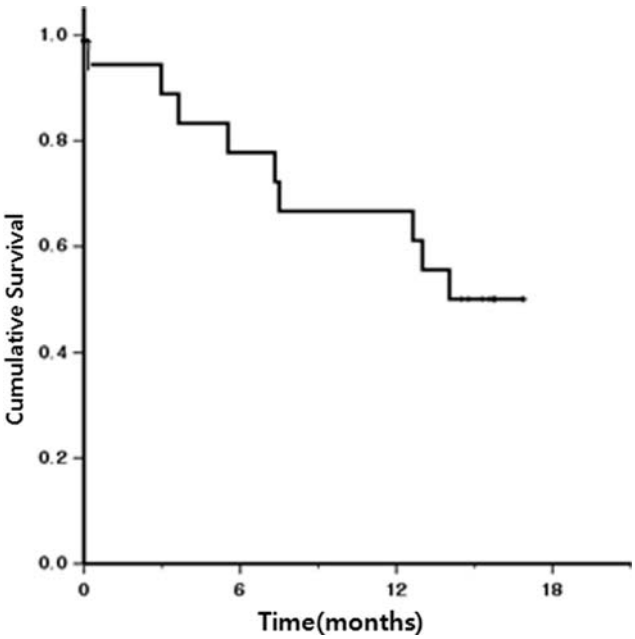

Fig. 2 Overall survival (OS) of all patients

genotypes (Table 5) and we could not find a statistically significant relationship between tumor response or toxicity and genotype.

Discussion

To the best of our knowledge, this is the first report of a combination of irinotecan combined with oxaliplatin in patients with advanced NSCLC. The overall response rate was 27.7%, the median TTP was 4.2 months, and the median OS was 14 months.

The ECOG 1594 study, which compared three different third-generation chemotherapeutic agents,—gemcitabine, docetaxel, and paclitaxel combined with platinum, cisplatin or carboplatin,—failed to show a survival advantage, with a median survival of 7.9 months and 1-year survival of 33% [28]. A Randomized phase III study conducted in Japan, comparing cisplatin plus irinotecan (IP) versus carboplatin plus paclitaxel (TC), cisplatin plus gemcitabine (GP), and cisplatin plus vinorelbine (NP) for advanced NSCLC also showed no difference in response rate or OS. However, irinotecan plus cisplatin combination chemotherapy produced a response rate of 31.0% and a 13.9 month median survival [21].

Oxaliplatin was employed as a single agent in poor-prognosis NSCLC patients [19], and oxaliplatin and third-generation drugs combinations have been investigated in 18 trials so far. Oxaliplatin plus taxane doublets showed an overall response rate of 34–48% and a median overall survival of 7.9–10.9 months. The combination of oxaliplatin–gemcitabine achieved overall response rates ranging from 13 to 36%, with median OS ranging from 6.5 to 11.3 months [5].

One possible explanation for the low response rate in this study might be the use of low-dose irinotecan. Other investigators have tested high-dose irinotecan (total dose 150–180 mg/m^2 every 4 weeks or 200–210 mg/m^2 every 3 weeks) [3, 7, 8, 10, 15–17, 20, 23, 30]. Negoro et al. examined irinotecan combined with cisplatin in 133 advanced NSCLC patients [20]. Irinotecan was given intravenously on days 1, 8, and 15 at a dose of 60 mg/m^2, and cisplatin was given intravenously on day 1 at a dose of 80 mg/m^2 every 4 weeks. The overall response rate was 43.7%, and 1-year survival was 47%. Giancarlo et al. [23] studied 42 advanced NSCLC patients treated with irinotecan (200 mg/m^2) and carboplatin (AUC 5) every 3 weeks. Six patients achieved PRs (14% of the total), whereas 19 (45%) had SDs and median OS was 11.7 months (95% CI, 8.4–13.2).

The second possible reason for the lack of response and poor survival is the high proportion of male subjects enrolled (88.9%). It has been reported that there are differences in the biology, natural history, and response to therapy between men and women with lung cancer. Moreover, sex differences in survival among treated patients may be related to better responses to the treatment among women and not to differences in tumor biology [31, 33]. All of the male patients in this study were smokers, who are considered poor responders to epidermal growth factor receptor tyrosine kinase inhibitors and pemetrexed [27].

Finally, a lack of antitumor activity of oxaliplatin might be considered in the treatment of advanced NSCLC.

Table 4 Toxicity profiles

Toxicity	Per cycle ($N = 71$)		Per patient ($N = 18$)	
	NCI-CTC grade (%)		NCI-CTC grade (%)	
	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4
Hematologic toxicities				
Neutropenia	3 (4.2)	4 (5.6)	1 (5.6)	3 (16.7)
Thrombocytopenia	1 (1.4)	–	–	–
Anemia	1 (1.4)	–	–	
Non-hematologic toxicities				
Nausea/vomiting	3 (4.2)	–	1 (5.6)	1 (5.6)
Peripheral neuropathy	1 (1.4)	1 (1.4)	1 (5.6)	1 (5.6)
Diarrhea	10 (14)	5 (7)	4 (22.2)	4 (22.2)
Alopecia	–	–	–	–

NCI-CTC National Cancer Institute Common Toxicity Criteria

Table 5 Association of UGT1A1 Genotypes with tumor response and toxicity

	Tumor response		G3/4 diarrhea		G3/4 neutropenia	
	No. of responder	*P*	No.	*P*	No.	*P*
UGT1A1*60						
−/−	1/6	0.301	1/6	0.580	1/6	1
−/+	4/8		3/8		2/8	
+/+	0		0			
UGT1A1*28						
6/6	3/9	1	1/9	0.095	2/9	1
7/6	2/5		3/5		1/5	
UGT1A1*6						
−/− and −/+	5/14		4/14		3/14	
+/+	0		0		0	

UGT1A1 Uridine diphosphate glucuronosyltransferase 1A1

P Fisher's exact test for all genotypes

Although a number of phase II studies with oxaliplatin-containing doublets showed relatively high response rates [5], a recent randomized phase III trial evaluating the gemcitabine/oxaliplatin doublet versus taxol/carboplatin showed a response rate of only 15.2% for the oxaliplatin-based chemotherapy and failed to indicate any significant improvement in the treatment of NSCLC [32]. McLaren et al. also reported a lack of antitumor activity with oxaliplatin and gemcitabine in advanced NSCLC, which is consistent with our result [18]. Although response rates were reached target level (27.7%, 5/18), due to the low level of efficacy, further investigation of IrOx regimens at this dose and schedule was not warranted, and it was decided to close the study at the first stage, with 18 patients enrolled.

However, the IrOx regimen demonstrated tolerable toxicity profile in this trial. The incidence of grade 3/4 neutropenia was 17% ($n = 3$), which was usually short lasting and rarely complicated by neutropenic fever (1.2% of all cycles), although one (5.6%) patient did died due to sepsis. The frequency of grade 3/4 diarrhea was 7% of all cycles and 22.2% of all patients. Significant (grade 3/4) neurotoxicity was rare ($n = 1$).

Given that UGT1A1*6 might be useful for predicting the tumor response and survival outcome of Korean patients with NSCLC treated with irinotecan-based chemotherapy, we also investigated UGT1A1 polymorphisms related to irinotecan [13]. In the 14 samples available, we did not find any subject homozygous UGT1A1*6 or homozygous UGT1A1*28. However, a definitive conclusion could not be drawn due to the small numbers of samples.

In conclusion, the lack of significant antitumor activity despite a favorable safety profile, suggests that continuing clinical trials with IrOx regimen as the first-line treatment at the studied dose and schedule in advanced NSCLC is not warranted. Nevertheless, because this less toxic regimen may be helpful in patients in whom cisplatin treatment may not be feasible, further studies with different doses and schedules are warranted.

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