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ORIGINAL ARTICLE

Phase I study of vinorelbine and irinotecan in previously untreated patients with advanced non-small cell lung cancer

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Abstract
Introduction Vinorelbine alone and irinotecan alone have been shown to have efficacy against non-small cell lung cancer (NSCLC); each drug has different mechanisms of action. A phase I study using a combination of vinorelbine and irinotecan as first-line treatment for advanced NSCLC was done to determine the maximum tolerated dose (MTD) and the dose-limiting toxicity (DLT).
Methods Previously untreated patients (≤75 years old) with Stage IIIB or IV NSCLC were enrolled. Based on a 4-week cycle, vinorelbine was given on days 1 and 8, and irinotecan was given on days 1, 8, and 15 intravenously. To prevent an injection site reaction to vinorelbine, the site was treated with topical clobetasol ointment, and the patients were given intravenous dexamethasone prior to vinorelbine treatment. DLT was defined as grade 4 neutropenia lasting ≥4 days or febrile neutropenia, grade 4 thrombocytopenia, ≥grade 3 non-hematological toxicities, or the need to cancel drug administration on both days 8 and 15.
Results A total of 23 patients were enrolled. DLT was observed in 1 of 6 patients at level 3 (20 mg/m^2 vinorelbine, 50 mg/m^2 irinotecan), in 2 of 3 at level 4 (25 mg/m^2, 50 mg/m^2), and in 2 of 5 at modified level 4 (20, 60 mg/m^2). Level 4 and modified level 4 were considered to be the MTD; dose level 3 was therefore recommended. DLTs included liver dysfunction, pneumonitis, colitis, and arrhythmia. Injection site reactions were mild. Hematological and non-hematological toxicities were mild and easily controlled.
Conclusion Use of 20 mg/m^2 vinorelbine on days 1 and 8 followed by 50 mg/m^2 irinotecan on days 1, 8, and 15 every 4 weeks warrants a phase II study.

Keywords Non-small cell lung cancer · Chemotherapy · Vinorelbine · Irinotecan · Phlebitis · Clobetasol ointment

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Introduction

Non-small cell lung cancer (NSCLC) is a relatively chemoresistant cancer; several chemotherapeutic agents and various treatment strategies have been investigated. Cisplatin has been considered to be a key drug in the treatment of advanced NSCLC [1]. In fact, platinum-based chemotherapy regimens are the most extensively studied treatments for advanced NSCLC. Recently, several new active agents for NSCLC have been introduced, including

gemcitabine, paclitaxel, docetaxel, vinorelbine, and irinotecan [2]. In several randomized phase III trials, combination chemotherapy with cisplatin and one of the new drugs has produced results that are superior to the older combinations [3, 4]. However, cisplatin-containing regimens must be avoided in certain patients, such as those with renal or cardiac diseases, due to the risk of nephrotoxicity, peripheral neuropathy, and emesis, as well as the need to pretreat the patient with massive hydration [5]. Carboplatin is considered to be an alternative to cisplatin; it has lower rates of emesis, neurotoxicity, and nephrotoxicity. However, a recent meta-analysis suggested that combination chemotherapy that included cisplatin and a new agent provided an 11% longer survival than carboplatin with the same agents [6]. Several phase III trials suggest that non-platinum doublets may be equivalent to platinum doublets in terms of efficacy, and that they have comparable toxicities [4]. Therefore, non-platinum doublets may offer an alternative treatment in advanced NSCLC patients. The non-platinum doublets that were previously examined in phase III studies were primarily gemcitabine and vinorelbine, as well as gemcitabine and a taxane. There are no phase III studies dealing with non-platinum doublets that include irinotecan.

Irinotecan is a semi-synthetic, water-soluble camptothecin analog [7]. The active metabolite SN-38 inhibits topoisomerase-I activity by stabilizing the topoisomerase I-DNA cleavable complex [8]. In chemotherapy-naïve, advanced NSCLC patients, irinotecan given as a single agent has a response rate of approximately 30% [9]. On the other hand, vinorelbine is a semi-synthetic vinca alkaloid that inhibits the assembly of tubulins, which leads to mitotic arrest at metaphase [10–12]. Used as a single agent, vinorelbine has a response rate ranging from 8 to 37% in previously untreated, advanced NSCLC patients [13].

In a preclinical study, the combination of vinorelbine and irinotecan showed additive antiproliferative effects in NSCLC cell lines [14]. Vinorelbine and irinotecan have different mechanisms of action, and their toxicity profiles do not overlap. Two pilot studies have reported that the combination of vinorelbine and irinotecan has modest activity as a second-line treatment in advanced NSCLC patients. However, to the best of our knowledge, no reports have examined the efficacy of vinorelbine and irinotecan in chemotherapy-naïve, advanced NSCLC patients. Toxicities are known to be more severe in patients receiving second line treatment than in those receiving first line treatment. Two phase III studies of second line treatment with docetaxel reported that patients showed more severe toxicities, and that the dosage of docetaxel had to be reduced from 100 to 75 mg/m^2 during the trials. Furthermore, two previous studies that evaluated the combination of vinorelbine and irinotecan as second line therapy were not conducted as dose-escalation studies [15–18]. Thus, the present phase I study of combination chemotherapy with vinorelbine and irinotecan in previously untreated, advanced NSCLC patients was done. The present study was designed to determine the dose-limiting toxicities (DLTs), the maximal tolerated dose (MTD) of the combination, and the recommended dose for a subsequent phase II study.

Methods

Eligibility

Written informed consent was obtained from all patients prior to treatment. The protocol and informed consent procedures were reviewed and approved by the Institutional Review Board of each participating institute. Eligibility criteria were as follows: histologically or cytologically confirmed NSCLC; stage IIIB or IV disease; no prior chemo- or radiotherapy; no massive pleural effusion or ascites; age ≤75 years; Eastern Cooperative Oncology Group performance status 0–1; life expectancy of at least 12 weeks; adequate bone marrow function (leukocyte count ≥4,000/μl, platelet count ≥100,000/μl, and hemoglobin level ≥10.0 g/dl); serum bilirubin levels below the upper limit of normal; alanine aminotransferase (AST) and aspartate aminotransferase (ALT) levels <2 times the upper limit of normal; and serum creatinine below the upper limit of normal. The major exclusion criteria were: superior vena cava syndrome; symptomatic central nervous system metastasis; concomitant malignancies; major surgery, cytotoxic chemo- or radiotherapy within the previous 4 weeks; clinically significant cardiac diseases; infectious diseases; watery diarrhea; paralytic ileus; and intestinal obstruction. Pregnant or breast-feeding women were also excluded.

Treatment and dose escalation

Every 4 weeks, vinorelbine was given on days 1 and 8 by a 15-min peripheral intravenous infusion, and irinotecan was given on days 1, 8, and 15 by a 90-min peripheral intravenous infusion. This schedule was determined based on the standard cisplatin combination regimen with vinorelbine or irinotecan that is used in Japan: cisplatin is given on day 1, and vinorelbine is given on days 1 and 8 every 3 weeks; or cisplatin is given on day 1, and irinotecan is given on days 1, 8, and 15 every 4 weeks [19]. If a patient had a leukocyte count <3,000/μl, a platelet count <100,000/μl, or grade 2 or worse diarrhea on either day 8 or 15, the treatment scheduled for that day was not given. The treatment protocol was repeated every 4 weeks, until the patient refused treatment or showed progressive disease. The next cycle started after the leukocyte and platelet counts reached at least >3,000

Table 1 Dose-escalation scheme and results

Dose level	Vinorelbine (mg/m^2)	Irinotecan (mg/m^2)	Total no. of patients	Delivered doses / Planned dose (%)	Dose limiting toxicities in 1st cycle (No. of patients)	No. of responders PR/SD/PD
1	15	40	3	14/15 (93.3)		1/2/0
2	20	40	6	45/57 (78.9)	Day 8 skip (1)	2/4/0
3	20	50	6	39/45 (86.7)	Grade 3 elevation of AST, ALT (1)	2/2/2
4	25	50	3	5/9 (55.5)	Grade 3 colitis (1), Grade 3 pneumonitis (1)	0/1/2
4′	20	60	5	18/27 (66.7)	Day 8 skip (1) Grade 4 arrhythmia (1)	0/3/2

and 100,000/μl, respectively. Doses were not escalated in individual patients.

To prevent injection site reactions and phlebitis caused by vinorelbine, topical clobetasol ointment was applied to the skin along the vein into which the anti-cancer drugs were injected; 8 mg dexamethasone diluted in 100 ml of physiological saline was also injected into the vein before treatment. Using the same line, vinorelbine diluted in 50 ml of physiological saline was infused over 15 min, followed by a 90-min infusion of irinotecan diluted in 250 ml of 5% dextrose. The starting doses for vinorelbine and irinotecan were 15 and 40 mg/m^2, respectively. The dose levels were increased as shown in Table 1.

Toxicities were assessed according to the US National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 2.0 [20]. In the present study, dose-limiting toxicity (DLT) was defined as: grade 4 hematological toxicities lasting 4 days or more; grade 4 febrile neutropenia; grade 3 or worse non-hematological toxicities except for nausea, vomiting, anorexia, fever, and alopecia; the need to withhold both vinorelbine/irinotecan on day 8 and irinotecan on day 15; and failure to start the second cycle until day 36. To assess the dose increases for vinorelbine and irinotecan, at least 3 patients were enrolled at each dose level, and the dose was increased to the next level if none of the patients had DLT. If 2 of 3 patients had DLT, then this dose level was defined as the maximum-tolerated dose (MTD). If 1 of 3 patients had DLT, then 3 additional patients were treated at the same level; if none of these additional patients had DLT, then the dose was increased to the next level. When 1 or more of the 3 additional patients had DLT, then this dose level was defined as the MTD. The recommended dose for phase II study was the dose given immediately before the MTD. If the MTD was not reached at level 4, then the level 4 dose became the recommended dose.

When grade 3 or worse leukocytopenia/neutropenia occurred, recombinant human granulocyte-colony stimulating factor (rhG-CSF) could be given. Prior to treatment, all patients received prophylactic anti-emetic therapy with a type-3 serotonin receptor antagonist.

Assessment of treatment

Tumor staging was based on the patient's medical history, physical examination, chest radiography, bone scintigraphy, computed tomography of the chest and abdomen, computed tomography or magnetic resonance imaging of the brain, and bronchoscopy. Prior to the first course of therapy, complete blood cell counts, urinalysis, and biochemistry tests were done to assess renal and hepatic function. During the study period, complete blood cell counts and biochemistry tests were repeated at least once weekly, whereas other investigations were repeated as needed to evaluate marker lesions. Indeed, complete blood cell counts and biochemistry tests were repeated more than twice a week in all patients during the first and second cycles of chemotherapy. After completion of chemotherapy, all of the tests done during the initial work-up were repeated to restage each patient.

The response was evaluated according to the response evaluation criteria in solid tumors (RECIST) [21]. In brief, complete response (CR) was defined as the disappearance of all known disease. Partial response (PR) was defined as a 30% reduction from baseline in the sum of the longest diameters of the target lesions and a lack of disease progression in non-target lesions. Progressive disease (PD) was defined as the development of any new lesions or an increase of 20% in the sum of the longest diameters of the target lesions. Patients with stable disease (SD) did not meet the criteria for PR or PD.

Survival curves were estimated using the Kaplan-Meier method, and results are reported with a 95% confidence interval (95% CI). Analysis was conducted using StatView version 5.0 software (SAS institute, Cary, NC, USA).

Results

Determination of MTD

A total of 23 patients, including 15 males and 8 females, were enrolled in this trial between February 2001 and

Table 2 Patient characteristics

Characteristics	No. of patients
Gender	
Male	15
Female	8
Age (years)	
Median	66
Range	41–75
ECOG performance status	
0	6
1	17
Histological type	
Adenocarcinoma	12
Squamous cell carcinoma	8
Others	3
Clinical stage	
IIIB	4
IV	19

December 2002; all of them received chemotherapy (Table 2). The patients' median age was 66 years. Nineteen patients had stage IV disease, and the others had stage IIIB disease. This study used five dose levels and included a total of 51 cycles. One cycle was given to six patients (26.1%), two cycles to ten patients (43.5%), three cycles to three patients (13.0%), and four cycles to four patients (17.4%).

As shown in Table 1, one of three level 2 patients experienced DLT (both days 8 and 15 canceled), and the three additional level 2 patients had no DLT. At level 3, 1 of 3 patients experienced DLT (grade 3 AST and ALT elevation), and the three additional level 3 patients had no DLT. At level 4, 2 of the 3 patients developed DLT (grade 3 colitis and grade 3 pneumonitis). Thus, the level 4 dosage (25 mg/m^2 vinorelbine and 60 mg/m^2 irinotecan) was considered to be the MTD. To precisely evaluate toxicities and safety at the recommended dose level, the dose of vinorelbine was reduced from 25 to 20 mg/m^2, and additional patients were treated with the modified level 4 dosage. At modified level 4, 1 of 3 patients experienced DLT (both days 8 and 15 canceled), and 1 of the 2 additional modified level 4 patients experienced DLT (grade 4 arrhythmia). The modified level 4 dosage, as well as the initial level 4 dosage, was considered to be the MTD. Therefore, level 3 was determined to be the recommended dose for this regimen (Table 1).

Toxicities

All 23 patients were fully assessable for toxicity. The hematological toxicities during the first cycle are shown in Table 3. Neutropenia was the major hematological toxicity. Grade 3 or worse neutropenia occurred in 12 of 23 patients (52.2%), but no patient had severe neutropenia. One level 4 patient and 2 modified level 4 patients had grade 3 febrile neutropenia, but all of these patients recovered within a week after treatment with antibiotics and rhG-CSF. Thrombocytopenia and anemia were rarely observed, and no patients required a blood transfusion. All of the hematological toxicities that occurred during the total of 51 cycles that were given were easily controlled (Table 4).

Non-hematological toxicities that occurred during the first cycle are listed in Table 5. One level 3 patient had grade 3 AST and ALT elevation, but the AST and ALT

Table 3 Hematological toxicities that occurred during the first cycle (n = 23)

Dose level	No. of patients	Anemia	Leukopenia	Neutropenia	Febrile neutropenia	Thrombocytopenia
		G Grade				
		G2/G3/G4	G2/G3/G4	G2/G3/G4	G2/G3/G4	G2/G3/G4
1	3	2/0/0	0/1/0	1/0/1	0/0/0	0/0/0
2	6	0/0/0	4/0/0	3/1/0	0/0/0	0/0/0
3	6	1/0/0	1/0/0	1/2/0	0/0/0	0/0/0
4	3	0/0/0	1/2/0	0/0/3	0/1/0	0/0/0
4′	5	0/0/0	2/2/0	0/4/1	0/2/0	0/0/0

Table 4 Hematological toxicities that occurred during all cycles (n = 23)

Dose level	No. of patients	Anemia	Leukopenia	Neutropenia	Febrile neutropenia	Thrombocytopenia
		G grade				
		G2/G3/G4	G2/G3/G4	G2/G3/G4	G2/G3/G4	G2/G3/G4
1	3	4/0/0	0/1/0	3/0/1	0/0/0	0/0/0
2	6	2/0/0	7/0/0	3/4/0	0/1/0	0/0/0
3	6	2/1/0	2/0/0	2/3/0	0/0/0	0/0/0
4	3	0/0/0	1/2/0	0/0/3	0/1/0	0/0/0
4′	5	0/0/0	6/2/0	1/6/2	0/2/0	0/0/0

Table 5 Non-hematological toxicities that occurred during the first cycle ($n = 23$)

Dose level	No. of patients	Nausea/vomiting G2/G3/G4	Diarrhea G2/G3/G4	Phlebitis G2/G3/G4	AST/ALT G2/G3/G4	Pneumonitis G2/G3/G4	Arrhythmia G2/G3/G4	Colitis G2/G3/G4
1	3	0/0/0	0/0/0	0/0/0	0/0/0	0/0/0	0/0/0	0/0/0
2	6	0/0/0	0/0/0	0/0/0	0/0/0	1/0/0	0/0/0	0/0/0
3	6	0/1/0	2/0/0	1/0/0	0/1/0	0/0/0	0/0/0	0/1/0
4	3	0/0/0	2/0/0	0/0/0	0/0/0	0/1/0	0/0/0	0/0/0
4′	5	1/0/0	1/0/0	1/0/0	1/0/0	0/0/0	0/0/1	0/0/0

G Grade

levels normalized within 7 days without requiring treatment. Another level 3 patient developed grade 3 nausea that disappeared within 24 h with conventional anti-emetic treatment. One level 4 patient had grade 3 pneumonitis, which improved with treatment including oxygen inhalation and oral prednisolone. Another level 4 patient had grade 3 colitis; this patient was treated with antibiotics and parenteral nutritional support and recovered within a week. One modified level 4 patient had a grade 4 arrhythmia (ventricular tachycardia); the patient recovered immediately after defibrillation and the administration of lidocaine. In the total of 51 cycles that were given in the present study, colitis and arrhythmia were not observed in any of the other patients. Furthermore, non-hematological toxicities, including diarrhea, were mild and easily controlled. Grade 2 phlebitis was seen in only two patients (8.7%; 95% CI, 1.1–28.0%). Other non-hematological toxicities were grade 2 nausea, grade 2 dyspnea, grade 3 infection, and grade 3 pneumonitis, which occurred in one patient each; all of these non-hematological toxicities were controllable.

Compliance with treatment was relatively good, and there was no cumulative toxicity with subsequent courses (Table 1). For the total of 51 cycles, 102 doses of vinorelbine and 153 doses of irinotecan were planned; 96 (94.1%) doses of vinorelbine and 110 (72.5%) doses of irinotecan were actually given. The relative dose intensities are summarized in Table 1. At the recommended level 3 dose, the relative dose intensities were 100% for vinorelbine and 86.7% for irinotecan.

Clinical response and survival

Although the current study was a phase I study, response and survival were determined for reference purposes. All 23 patients were assessable for response (Table 1). Five patients showed PR, for a response rate of 21.7% (95% CI, 7.5–43.7%); 12 patients had SD, and 6 had PD. The disease control rate including SD was 73.9% (95% CI, 51.6–89.8%).

Among the 23 patients, 16 patients received subsequent systemic chemotherapy regimens after recurrence, including platinum-based regimens in 10 patients and platinum-based regimens with gefitinib in 6 patients. All 23 patients died due to disease progression, and final follow-up of the survival data was completed in December 2006. Median progression-free survival was 3.0 months (95% CI, 2.7–3.3 months). Median overall survival was 11.8 months (95% CI, 8.5–15.1 months), the 1-year overall survival rate was 47.8% (95% CI, 27.4–68.2%), and the 3-year overall survival rate was 17.4% (95% CI, 2.0–32.8%).

Discussion

Based on the results of the current study, 20 mg/m^2 vinorelbine on days 1 and 8, followed by 50 mg/m^2 irinotecan on days 1, 8, and 15 given in a 4-week cycle is the recommended dosage regimen for patients with advanced NSCLC. With this regimen, the hematological and non-hematological toxicities were tolerable. To the best of our knowledge, this is the first report that has evaluated the safety and determined the recommended dose of vinorelbine and irinotecan in previously untreated, NSCLC patients.

The recommended dose identified in the current study is relatively low compared to the dose of the same agents used as second line treatment. Pectasides et al. [22] studied refractory NSCLC patients treated with 150 mg/m^2 irinotecan and 25 mg/m^2 vinorelbine on days 1 and 15, every 4 weeks. Gonzalez et al. [23] studied refractory NSCLC patients treated with 300 mg/m^2 irinotecan on day 1 and 25 mg/m^2 vinorelbine on days 1 and 14, every 4 weeks. However, these previous studies were not dose-escalation studies. Furthermore, patients in these studies were younger than those in the current study (median age, 57–58 vs. 66 years). Since lung cancer occurs mainly in the elderly, the dosages of vinorelbine and irinotecan used in the previous studies may be too high for most NSCLC patients, even as first line treatment.

In the present study, the response rate was 21.7% (95% CI, 7.5–43.7%), which was not as high as expected; however, the present study was a phase I study. Nevertheless, the median progression-free survival was 3.0 months, and the median overall survival was 11.8 months, which is

comparable to cisplatin-containing regimens. At present, the standard chemotherapy for previously untreated, advanced NSCLC patients consists of cisplatin-containing regimens [4]. However, all patients with advanced NSCLC do not benefit clinically from platinum-based chemotherapy. It is important to identify the optimal patient population in whom non-platinum regimens should be used. Several investigators have reported that the expression of excision repair cross-complementation group 1 (ERCC1) mRNA confers resistance to platinum agents in NSCLC [24, 25]. A recent study has also shown that patients with ERCC1-positive NSCLC do not appear to benefit from adjuvant cisplatin-based chemotherapy [26]. These findings suggest that non-platinum regimens may be preferable in certain patients with ERCC1-positive tumors. In addition, it is not known whether the increase in toxicity of cisplatin-based regimens is counterbalanced by the small survival benefit in patients with advanced metastatic NSCLC. Cisplatin-based regimens must be avoided in patients with renal or cardiac dysfunction. Thus, non-platinum regimens can be selected for NSCLC patients expressing platinum-resistant mechanisms, or for those who cannot tolerate platinum due to renal or cardiac diseases.

As with other vinca alkaloids, an injection site reaction is a common adverse event with vinorelbine. In a previous report, as many as 26% of patients treated with vinorelbine developed injection site reactions, including erythema, increased warmth, pain, venous discoloration, and phlebitis [10]. Recently, Yoh et al. [27, 28] also reported that 28–31% of patients treated with vinorelbine developed venous irritation. Several methods, including pretreatment with intravenous defibrotide or cimetidine, have been reported to prevent injection site reactions related to vinorelbine administration [29–31]. In a retrospective study, 2- or 3-min intravenous bolus injections of vinorelbine reduced the incidence of phlebitis [32]. However, when vinorelbine leaks out after a bolus injection, the skin ulceration that results is a serious issue. Thus, in the present study, in order to prevent injection site reactions, topical clobetasol ointment was applied to the skin upstream of the vinorelbine injection site, and intravenous dexamethasone was given prior to vinorelbine treatment. As shown in Table 5, only two patients had grade 2 phlebitis (injection site pain) even though a peripheral vein was used. Topical and intravenous steroid pretreatment may be effective for preventing injection site reactions occurring as a result of vinorelbine administration.

In conclusion, based on the present study's results, the combined use of 20 mg/m^2 vinorelbine on days 1 and 8, followed by 50 mg/m^2 irinotecan on days 1, 8, and 15 in a 4-week cycle warrants a phase II study involving advanced NSCLC patients, especially those who cannot tolerate cisplatin.

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