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ORIGINAL ARTICLE

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Phase II study of the combination of vinorelbine and cisplatin in advanced non-small-cell lung cancer

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Abstract *Purpose*: To evaluate the efficacy and safety of combination chemotherapy with cisplatin and vinorelbine for the treatment of previously untreated patients with advanced non-small-cell lung cancer (NSCLC). *Patients and methods*: Eligible patients were those with measurable NSCLC. They were treated with two or more cycles of a regimen consisting of vinorelbine 25 mg/m^2 on days 1 and 8 and cisplatin 80 mg/m^2 on day 1 every 3 weeks. *Results*: A total of 45 patients were enrolled. The response rate was 51.1% (23/45; 95% CI 35.8% to 66.3%). The median survival was 286 days with a 1-year survival rate of 40%. The median number of treatment cycles was 2. The major toxic effect was neutropenia of grade 3 or higher (84%). Nonhematological toxicities, including vomiting (62%), were mild (grade 2 or less). There were no treatment-related deaths. *Conclusion*: The high response rate and good tolerability proved this combination therapy to be a safe and effective treatment for advanced NSCLC.

Keywords Non-small-cell lung cancer · Vinorelbine · Cisplatin · Phase II study

Introduction

Vinorelbine ditartrate [1], a vinca alkaloid derivative, shows antitumor activity mainly by inhibiting microtubule polymerization in tumor cells just as other vinca alkaloid drugs do [2, 9]. Clinical studies of vinorelbine (VNR) have shown a good therapeutic outcome in non-small-cell lung cancer (NSCLC) and breast cancer, and a reduction in peripheral neuropathy that occurs frequently with vinca alkaloids [5, 7, 10, 12]. The combination of VNR and cisplatin (CDDP) (VP therapy) has shown a synergistic effect in vitro, while the main side effects are different between the drugs [4]. A phase I-II study has demonstrated efficacy of this combination in NSCLC [3]. VP therapy is considered a promising combination regimen for NSCLC on account of its higher response rate and longer survival compared with VNR or CDDP alone, or CDDP combined with vindesine [8, 17].

In clinical studies performed in Europe and the US, patient compliance rate was as low as 50% or less with regard to VNR when VP therapy, as VNR 25 mg/m^2 weekly and CDDP 80 mg/m^2 on day 1, was repeated every 4 weeks. This indicates the need to reconsider the dosing schedule of VNR [17]. Another dosing schedule for VP therapy (VNR 20 to 30 mg/m^2 on days 1 and 8 and CDDP 80 mg/m^2 on day 1 every 3 weeks) showed almost complete compliance and was found to be beneficial since the response rate was 28.3% to 56.7% and the survival 9.2 to 10.6 months [6, 13, 15, 17].

VP therapy is an effective regimen against advanced NSCLC. A multicenter joint phase III study is being planned in Japan to compare four regimens for advanced NSCLC: CDDP plus irinotecan used as a reference arm, CDDP plus VNR every 3 weeks, CDDP plus gemcitabine and carboplatin plus paclitaxel. A phase II study of VP therapy has not been conducted in Japan. We therefore carried out a phase II study of VNR 25 mg/m^2 on days 1 and 8 plus CDDP 80 mg/m^2 on day 1 given every 3 weeks in advanced NSCLC to evaluate the efficacy and safety of VP therapy.

Patients and methods

Patient selection

Patients eligible for the study were those admitted to our hospital between August 1999 and October 2001 who were histologically or

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cytologically diagnosed as having NSCLC and who were in clinical stage III or IV with unresectable disease, or in whom radiotherapy with curative intent was not possible, including those who had pleural effusion and dissemination, those with intrapulmonary metastasis within the ipsilateral lobe, those in whom the irradiation field exceeded one-half of one lung, those with metastasis to the contralateral hilar lymph nodes, and those with reduced lung function. None of the patients had received prior therapy. Other eligibility criteria included expected survival of 12 weeks, age ≤ 75 years, Eastern Cooperative Oncology Group performance score (PS) of 0–2, measurable lesions, adequate hematological function (WBC ≥4000/mm^3, platelet count ≥100,000/mm^3, hemoglobin ≥10 g/dl), renal function (serum creatinine ≤ 1.5 mg/dl, creatinine clearance ≥60 ml/min), and hepatic function (total serum bilirubin ≤ 1.5 mg/dl, serum GOT and serum GPT less than twice the upper limit of normal). Written informed consent was obtained from every patient with the statement that the patient was aware of the investigational nature of this treatment regimen. Pretreatment evaluation included medical history, physical examination, complete blood count, serum biochemical analyses, chest roentgenogram, electrocardiogram and urinalysis. All patients underwent radionuclide bone scan and computerized tomography of the brain, thorax, and abdomen.

Treatment

The anticancer drugs were administered via the intravenous route, VNR 25 mg/m^2 (Navelbine, Kyowa Hakko Kogyo) on days 1 and 8 and CDDP 80 mg/m^2 (Randa, Nippon Kayaku) on day 1. This combination therapy repeated every 3 weeks constituted a cycle of treatment. The minimal number of cycles to be evaluated was two. On day 8, the physician examined the patient and evaluated the development of adverse events, and if leukocytes had decreased to below 2000/mm^3, platelets had decreased to below 75,000/mm^3 or fever with infection had occurred, administration of VNR on that day was withheld at the discretion of the physician. To proceed with the second and subsequent cycles, patients were required to have a neutrophil count ≥1500/mm^3 and a platelet count ≥100,000/mm^3. Those patients receiving granulocyte colony-stimulating factor (G-CSF) were observed for 3 days after the final dose of G-CSF to ensure that their neutrophil count was 1500/mm^3 or more. Serum creatinine levels were required to be below the upper limit of normal and serum GOT/GPT levels below twice the upper limit of normal. In the presence of liver dysfunction due to apparent liver metastasis, however, serum GOT and GPT levels were required to be below three times the upper limit of normal. If fever occurred or if the PS advanced to grade 3 or worse, the subsequent cycle was postponed until the temperature fell below 38°C or until the PS returned to 2 or less. In the presence of grade 2 peripheral neuropathy dosing was temporarily postponed; with improvement to grade 1 or less treatment was cautiously resumed, but medication was discontinued if 6 weeks passed without any improvement. Peripheral neuropathy (including transient) grade 3 or higher required discontinuation of treatment. For the third and subsequent cycles, VNR or CDDP was decreased by 25% in accordance with the treatment-related adverse events observed during the preceding cycle. Steroid and HT_3-antagonist were administered to prevent nausea and vomiting.

Target population size and interim analysis

Simon's two-stage minimax design [16] was used to estimate the number of patients required for interim and final analyses at a threshold response rate (P_0) of 0.20, an expected response rate (P_1) of 0.40, $\alpha = 0.05$ and $\beta = 0.10$. If the interim analysis revealed 6 responding patients out of 24, recruitment would be continued until the target population size was achieved. The combination therapy was considered effective if 14 or more of 45 patients showed response in the final analysis.

Since an interim response rate of 48.1% (13/27) [11] was obtained, it was necessary to enroll up to 45 patients for the final analysis.

Evaluation of response and toxicity

Response and toxicity were evaluated on the basis of tumor images obtained by CT and other techniques, laboratory data and subjective/objective symptoms before, during and after administration of the study drugs and during the period from completion of treatment to the final analysis. Measurable disease parameters were determined every 4 weeks by various means such as computerized tomography. Evaluation was made in compliance with Response Evaluation Criteria in Solid Tumors (RECIST) guidelines [14] for antitumor activity and with NCI Common Toxicity Criteria version 2 for safety. The Institutional Ethical Review Committee gave approval to the study.

Results

Patient characteristics

Table 1 gives characteristics of the patients included. Their median age was 59.5 years (range 35 to 75 years). Male, PS 1 and adenocarcinoma predominated. There were 26 patients (58%) with stage IV disease and 19 (42%) with stage IIIB disease.

Treatments administered

The total number of cycles administered was 126 with a median of two per patient (ranging from one to four cycles; Table 2) and 43 patients received two cycles or more. In the two patients who received fewer than two cycles, treatment was discontinued because of CDDP-induced renal dysfunction in one and patient refusal in the other. Patients who completed two cycles or more accounted for 96% of patients (43/45). Except the two patients who received only one cycle, the every-3-week

Table 1 Patient characteristics

Eligible patients (*n*)	45
Age (years)	
Median	59.5
Range	35–75
Sex (*n*)	
Male	34
Female	11
Performance status (*n*)	
0	11
1	32
2	2
Histology (*n*)	
Adenocarcinoma	30
Squamous cell carcinoma	9
Other	6
Stage (*n*)	
IIIB	19
IV	26

Table 2 Efficacy of treatment ($n=45$)

No. of cycles	
Median	2.0
Range	1–4
Response	
Partial response	23
No change	21
Not evaluable	1
Response Rate (%)	51.1
95% CI (%)	35.8–66.3
1-year survival rate (%)	40

dosing schedule was adhered to by 88% of patients (38/43) in the second cycle, 68% (17/25) in the third and 92% (12/13) in the fourth, with a total of 83% (67/81). Only in two cycles was VNR withheld on day 8. The dose of VNR was reduced in 9% of dose administrations (22/250) and the does of CDDP was reduced in 8% (10/126). The planned dose intensities were 16.7 mg/m^2 per week for VNR and 26.7 mg/m^2 per week for CDDP while the actual dose intensities were 16.4 and 24.7 mg/m^2 per week, respectively. The median delivered dose intensity for CDDP (day 1) and VNR (days 1 and 8) of each course together was 90% or more (Table 3).

Efficacy of treatment

Of the 45 patients, 23 showed a partial response, 21 showed no change and 1 was not evaluable (Table 2). The response rate was 51.1% (23/45; 95% CI 35.8% to 66.3%; Table 2). The nonevaluable patient died of sudden hemoptysis on the 22nd day after the start of the second cycle (43rd day after the start of treatment) and could not be evaluated. Ten patients were alive at the time of this report. The time to progressive disease was 172 days and the median survival was 286 days (95% CI 248 to 404 days; Table 2). The 1-year survival rate was 40%.

Table 3 Median delivered dose intensity

	Median dose intensity (%)			
	Course 1	Course 2	Course 3	Course 4
CDDP	100	98.8	96	92.3
VNR				
Day 1	100	98.6	95.5	93.8
Day 8	97.8	98.6	95.5	93.8

Toxicities

Table 4 lists toxicities observed during the study. Hematological and blood biochemical reactions included a high incidence of leukopenia and neutropenia, i.e. leukopenia and neutropenia of grade 3 or higher occurred in 73% of patients (33/45) and 84% (38/45), respectively. Neutropenia-associated fever was limited to two patients. All neutropenic patients recovered upon treatment with G-CSF. Platelets decreased in 4% of patients (2/45). Creatinine was temporarily elevated in 15.6% (7/45).

Subjective and objective symptoms observed were of grade 2 or less and included vomiting in 77.8% of patients (35/45), hiccough in 33.3% (15/45), constipation in 40% (18/45), diarrhea in 22% (10/45), rash in 31.1% (14/45) and injection site reaction in 26.7% (12/45). All of these toxicities disappeared or improved with symptomatic treatment. There were no toxic deaths.

Discussion

As for the VP regimen for advanced NSCLC, the every-3-week dosing schedule has been tried in several medical facilities [6, 13, 15, 17]. Table 5 summarizes the clinical outcomes of every-3-week VP therapy reported in the literature and in this study. Response rates range from 28% to 57% and median survival is approximately 10 months. The results are similar among the studies.

In 96% of patients (43/45), two or more cycles of VP therapy were administered. The every-3-week dosing

Table 4 Toxicities ($n=45$)

Toxicity	Grade (Common Toxicity Criteria)				Grade 3/4 (%)
	1	2	3	4	
Leukopenia	4	3	25	8	33 (73%)
Neutropenia	2	2	13	25	38 (84%)
Anemia	12	3	1	4	5 (11%)
Thrombocytopenia	5	1	2	0	2 (4%)
Creatinine	5	2	0	0	–
Vomiting	29	6	0	0	–
Hiccough	15	0	0	0	–
Constipation	13	5	0	0	–
Diarrhea	9	1	0	0	–
Rash	10	4	0	0	–
Neuropathy	4	0	0	0	–
Injection site reaction	4	8	0	0	–
Alopecia	3	0	0	0	–

Table 5 Outcomes of studies of VP therapy (VNR days 1 and 8, CDDP day 1, every 3 weeks)

Reference	VNR (mg/m^2)	CDDP (mg/m^2)	Response	Median survival time (months)
4	25	80	28.3% (28/99)	9.2
10	25	80	56.7% (42/74)	10
11	20–25	80	46.7% (14/30)	10.6
1	30	80	36.2% (47/130)	–
Present study	25	80	51.1% (23/45)	9.6

schedule was adhered to in 85% of all cycles administered. In cycles in which noncompliance was seen, medication was postponed to the 4th to 5th week because, in most cases, the neutrophil count in the 3rd week failed to meet the criterion for going on to subsequent cycles. The planned dose intensity was almost attained since the actual dose intensity was 16.4 mg/m^2 per week for VNR and 24.7 mg/m^2 per week for CDDP, accounting for 98% and 93% of the planned values, respectively [13].

Most adverse reactions were hematological. In particular, leukopenia and neutropenia of grade 3 or worse occurred in 73% and 84% of 45 patients, respectively. Others have reported the incidence of leukopenia of grade 3 or worse to be 8% to 33% [6, 13, 17]. Although the difference in patient characteristics hinders simple comparison and analysis of these data, it can be said that leukopenia was more frequent in our study. The leukocyte count improved rapidly upon treatment with G-CSF. Nonhematological toxicities were mild and adverse reactions of grade 3 or higher were not noted.

The combination of VNR 25 mg/m^2 on days 1 and 8 and CDDP 80 mg/m^2 on day 1 was administered every 3 weeks to 45 patients with advanced NSCLC in this phase II study. The response rate was 51.1%; the main adverse effect was neutropenia. The high response rate and good tolerability indicate that this combination therapy is a safe and effective treatment for advanced NSCLC. Its usefulness will be further verified in phase III studies.

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