Phase II Study of a Biweekly Regimen of Vinorelbine and Cisplatin in Advanced Non-small Cell Lung Cancer

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Background: Many novel agents, including vinorelbine, gemcitabine, paclitaxel and docetaxel, have been administrated in combination with cisplatin to patients with advanced non-small cell lung cancer (NSCLC). Of these drugs, vinorelbine is reported to have a high response rate and acceptable toxicity level. In an attempt to increase treatment activity, a biweekly regimen using vinorelbine and cisplatin was designed.

Methods: From March 2001 to July 2003, 43 patients with NSCLC, who met the selection criteria, were enrolled. Of the 43 patients, 28 were male and 15 were female. All of them had their diagnosis confirmed histologically and were in an advanced stage, i.e., stage IIIB with pleural effusion or stage IV. Vinorelbine 30 or 35 mg/m^2 and cisplatin 50 mg/m^2 were given intravenously every 2 weeks.

Results: Of the 43 assessable patients, 11 achieved a Partial Response (PR) and 13 had a Stable Disease (SD). Overall response was 25.6% (95% CI 12.0%-39.2%). Median survival was 9.0 months (95% CI: 6.2-11.8) and the 1-year survival rate was 32.6%. Median time to disease progression was 3.9 months (95% CI 2.4-5.4 months). The major hematological toxicity was neutropenia. Seven patients (16.3%) developed grade 3 neutropenia and 17 patients (39.5%) developed grade 4 neutropenia. Eight patients developed febrile neutropenia, 4 patients had confirmed sepsis, 2 of which died due to sepsis. One patient had grade 3 thrombocytopenia. Six patients (7%) developed severe anemia. Ten patients (23.3%) had grade 3/4 nausea and vomiting. Only 2 patients developed grade 3 neuropathy.

Conclusions: This biweekly regimen of vinorelbine and cisplatin is effective against advanced NSCLC. Due to the high incidence of neutropenia, this regimen did not improve therapeutic efficacy and its dose intensity is less than that of a conventional schedule.

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Key words: non-small cell lung cancer, chemotherapy, vinorelbine, cisplatin

Lung cancer continues to be the leading cause of cancer-related deaths in Taiwan and throughout the world.[1,2] At the time of initial diagnosis, the majority of patients with non-small cell lung cancer

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(NSCLC) present with distant metastasis or locally advanced unresectable tumors. Prognosis for these patients is typically poor. Therapeutic goals are prolonging life and symptom palliation. Meta-analysis demonstrates that a cisplatin-based chemotherapy may reduce the risk of death by 27%, increase the 1-year survival rate by 10% and increase median survival by up to 1.5 months for patients with advanced NSCLC.[3] The use of cisplatin is also an independent prognostic factor improving survival.[4] Several new cytotoxic agents for NSCLC, including taxanes, gemcitabine and vinorelbine, have been introduced during the past decade. Current practice for treating patients with metastatic lung cancer includes the addition of a platinum agent, such as cisplatin or carboplatin, to these new cytotoxic agents but no combination has been found to be superior to others.[5,6] Vinorelbine is a semi-synthetic vinca alkaloid that acts as an inhibitor of tubulin polymerization. Single vinorelbine has been shown to achieve a response, prolong the median survival and improve the quality of life of advanced NSCLC patients.[7,8] Chemotherapy with vinorelbine plus cisplatin has demonstrated better improvements in response rates (26%-30%), 1-year survival (from 35% to 45%) and median survival when compared with single vinorelbine and vindesin plus cisplatin.[9] A combination of vinorelbine and cisplatin has been employed for treating NSCLC patients, achieving a median survival of 8 to 9.2 months.[9-12] A different drug schedule can probably deliver the same or a higher cumulative dose, achieving a higher dose intensity.[13] In an attempt to increase treatment activity, a biweekly schedule using vinorelbine and cisplatin was designed. This prospective study evaluates the efficacy and safety of this proposed regimen.

METHODS

Eligibility criteria and pretreatment evaluation

Patients with histologically confirmed NSCLC stage IIIB or IV, who met the following eligibility criteria, were enrolled. Patients were required to have complete medical history records, a physical examination, complete blood cell count, biochemical analysis profile, chest radiographs, computed tomographic (CT) scan of the thorax and a whole-body radionuclide bone scan. Eligibility criteria included a performance status scale (ECOG) of 0 to 2, a life expectancy in excess of 12 weeks, no prior chemotherapy or radiotherapy for the assessable lung tumor, at least a bidimensionally measured lesion, a granulocyte count ≥ 1,500/μL, a platelet count ≥ 100,000/μL, a hemoglobin level ≥ 10 g/dl, a serum creatinine level ≤ 1.6 mg/dl, a serum bilirubin level ≤ 1.5 times the upper normal limit, no history of other malignancies, no severe concomitant disease and no brain metastasis. Informed consent was obtained verbally from each patient prior to enrollment.

Treatment regimens and dose modification

Vinorelbine at a dose of 30 or 35 mg/m^2 and cisplatin at a dose of 50 mg/m^2 were given every 2 weeks. Parenteral administration of 5-hydroxytryptamine (5-HT3) receptor antagonists plus corticosteroids preceded cisplatin infusion. Treatment discontinuation occurred if there was disease progression or unacceptable side effects. The responding patients were given a maximum of 12 cycles. Treatment with vinorelbine and cisplatin was delayed until the patient recovered if the granulocyte count was ≤ 1,000/μL and/or the platelet count was ≤ 50,000/μL. Granulocyte-colony stimulating factor (G-CSF) was allowed in the presence of neutropenic fever. Dose intensity was calculated as the ratio between total dose and total time.

Response and toxicity evaluation

Treatment response was recorded according to World Health Organization (WHO) criteria for assessing chemotherapy efficacy. A complete response was defined as the complete disappearance of all evidence of tumor. Partial response (PR) was defined as a ≥ 50% reduction in the sum of the products from the two largest perpendicular diameters of all measured lesions for at least 4 weeks. Stable disease (SD) was defined as a decrease of less than 50% or an increase of less than 25% in well-outlined lesions without the appearance of any new lesion. Progressive disease was defined as a greater than 25% increase of the sum of the cross-sectional areas of all lesions or the development of new lesions. Toxicity was evaluated using the WHO toxicity grading scale. All patients had a chest X-ray every 2 cycles of chemotherapy. Chest CT was performed every 4 cycles of chemotherapy. One chest physician and one radiologist evaluated the tumor responses

independently. After completing 12 treatment cycles, a complete physical examination and chest X-ray were done at least every 3 months, and a chest CT was performed when any abnormality was observed on the X-ray film. Brain CT or bone scan were done when a patient had symptoms of brain or bone metastasis.

Statistical methods and designs

According to Simon's two-stage optimal design, we chose the lower activity (p0) of 0.20 and target activity level (p1) of 0.40. At least 37 assessable patients were needed to guarantee 80% power under a α-level of 5%. Time to disease progression was calculated from date of initial treatment until date of disease progression. Response duration was assessed from date of response until date of disease progression. Overall survival was estimated using the Kaplan-Meier method.

RESULTS

Patients' characteristics

Between March 2001 and July 2003, 43 patients with NSCLC were enrolled in this study. Table 1 lists the patients' characteristics. Median age of the 43 patients was 62 years (range 34-74 years); 65.1% (28/43) were male and 34.9% (15/43) were female. Adenocarcinoma was the most common histology subtype accounting for 58.1% of patients. Patients with stage IV disease accounted for 72% of patients.

Table 1. Characteristics of Enrolled Patients

Characteristics		N (%)
Gender	Male	28 (65.1)
	Female	15 (34.9)
Age	Median	62
	Range	34-74
Stage	IIIB	12 (28.0)
	IV	31 (72.0)
Histological types	Squamous cell carcinoma	14 (32.6)
	Adenocarcinoma	25 (58.1)
	Other	4 (9.3)
Performance score	1	21 (48.8)
	2	22 (51.2)
Response	Progressive disease	19 (44.2%)
	Stable disease	13 (30.2%)
	Partial response	11 (25.6%)

Response and survival

Of the 43 assessable patients, 11 achieved a PR and 13 had an SD. The overall response was 25.6% (95% CI: 12.0%-39.2%). Survival data were analyzed in July 2005. Overall, 1 patient had no disease progression and 6 patients were still alive. Median survival was 9.0 months (95% CI: 6.2-11.8 months) and the 1-year survival rate was 32.6%. Response duration was 8.4 months (95% CI: 0.5-16.3 months). Median time to disease progression for all patients was 3.9 months (95% CI: 2.4-5.4 months). Fig. 1 presents the Kaplan-Meier curve for survival.

Delivered dose intensity

Twenty-six patients received vinorelbine 30 mg/m^2 every 2 weeks and 17 received vinorelbine 35 mg/m^2. In total, 311 chemotherapy cycles were administered to these patients. The median number of cycles administered was 4 (range 1-12 cycles). Treatment was delayed in 71 cycles (22.8%) due to leukopenia. Median delivered dose intensity of vinorelbine and cisplatin was 14.7 mg/m^2/week and 22.2 mg/m^2/week, respectively.

Toxicity

Tables 2 and 3 show the hematological and non-hematological toxicities of the treatment regimen. The major hematological toxicity was neutropenia. Grade 3 and 4 neutropenia was reported in 7 (16.3%) patients and 17 (39.5%) patients, respectively. Eight patients developed febrile neutropenia, 4 patients had confirmed sepsis, 2 of whom died due to sepsis. One

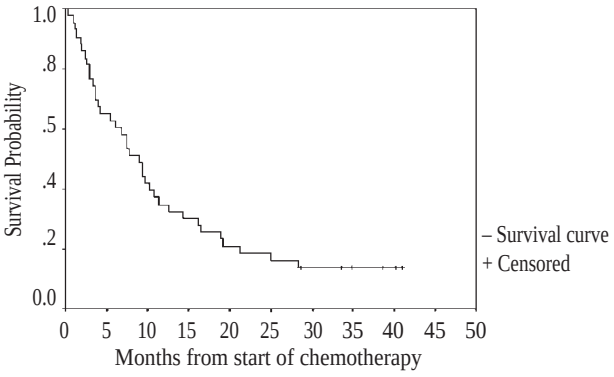

Fig. 1 Kaplan-Meier curve for survival.

Table 2. Hematological Toxicity

	WHO Toxicity grade							
	1		2		3		4	
	No	%	No	%	No	%	No	%
Hemoglobin	14	32.6	16	37.2	4	9.3	2	4.7
Granulocyte	4	9.3	6	14.0	7	16.3	17	39.5
Platelets	7	16.3	0	0	1	2.3	0	0

Abbreviation: WHO: world health organization

Table 3. Non-hematological Toxicity

	WHO Toxicity grade							
	1		2		3		4	
	No	%	No	%	No	%	No	%
Hepatic	5	11.6	1	2.3	0	0	0	0
Renal	5	11.6	0	0	1	2.3	0	0
Constipation	1	2.3	1	2.3	0	0	0	0
Diarrhea	6	14.0	1	2.3	0	0	0	0
Nausea/Vomiting	7	16.3	13	30.2	8	18.6	2	4.7
Skin rash	4	9.3	1	2.3	0	0	0	0
Neuropathy	9	20.9	4	9.3	2	4.7	0	0
Mucositis	4	9.3	2	4.7	1	2.3	0	0
Myalgia	1	2.3	2	4.7	1	2.3	0	0
Fatigue	8	18.6	16	37.2	11	25.6	0	0

Abbreviation: WHO: world health organization

patient had grade 3 thrombocytopenia. Six patients (7%) developed severe anemia. Ten patients (23.3%) had grade 3/4 nausea and vomiting. Hepatic and renal impairment was mild. Only 2 patients developed grade 3 neuropathy.

DISCUSSION

The overall response rate of this study was only 25.6% (95% CI: 12.0%-39.2%); the median survival of 9 months is comparable with that obtained by a previous report.[9-12] Median delivered vinorelbine dose intensity of this biweekly regimen was only 14.7 mg/m^2/week. Too many treatment delays were the principal cause of the low vinorelbine dose intensity. Treatment was delayed in 71 cycles (22.8%) because of leucopenia, which may be due to day 15 being just over the rapid recovery of bone marrow element. This may cause the low response rate, although there is no evidence to prove that higher delivered dose intensities of vinorelbine correlate with better treatment response. Better response does not always equate to better patient survival. Grade 3/4 neutropenia was observed in 24 (55.8%) patients. Two patients died due to sepsis. Grades 3 and 4 nausea/vomiting occurred in 23.3% of our patients.

Different vinorelbine scheduling results in a different dose intensity and response rate. Perng et al. administered vinorelbine 30 mg/m^2 on days 1 and 5 of a 21-day cycle, and cisplatin 100 mg/m^2 on day 1, achieving a response rate of 50%, 1-year survival rate of 54% and a median survival of 13 months. In that report, the dose intensity was 16.9 mg/m^2/week.[14] The authors of this study previously conducted a randomized phase II study comparing vinorelbine plus cisplatin with gemcitabine plus cisplatin for patients with advanced NSCLC. The vinorelbine and cisplatin arm, in which 34 patients received vinorelbine 20 mg/m^2 on days 1, 8 and 15 in a 28-day cycle, and cisplatin 80 mg/m^2 on day 15, achieved a response rate of 26%, 1-year survival rate of 54% and a median survival of 13 months. The median delivered dose intensity of vinorelbine was 14.3 mg/m^2/week.[15]

To the best of our knowledge, there are only a few published phase II studies using a biweekly schedule for patients with NSCLC. Lopez-Vivanco et al. treated patients with gemcitabine 2,500 mg/m^2 and cisplatin 50 mg/m^2 biweekly, and a partial response rate of 38.8% was achieved; the median survival was 48 weeks.[16] Only 3 episodes of grade 3/4 neutropenia were noted. In the paper by Ichiki et al. patients were treated with a biweekly schedule of paclitaxel 140 mg/m^2 plus carboplatin at an area under the curve (AUC) of 3.[17] The overall response rate was 35.1%; the median survival was 51 weeks. Grade 3/4 neutropenia was found in 50.0% of the patients. Galetta et al. treated patients with docetaxel 50 mg/m^2 plus gemcitabine 2,000 mg/m^2 every 2 weeks.[18] A response rate of 38.3% was achieved, with a median survival of 10.5 months. Grade 3/4 neutropenia was 17%. In our present report, grade 3/4 neutropenia affected 24 (55.8%) patients. The toxicity of neutropenia is higher than these reports.

A phase III randomized trial by Gebbia et al. suggested that scheduling vinorelbine on days 1 and 8 every 3 weeks preserved dose intensity and reduced associated side effects.[19] This schedule is also effective and decreased the incidence of leucopenia, therapy omissions and discontinuation. A Japanese trial with NSCLC patients by Hotta et al. showed that the maximum tolerated dose (MTD) and recommended dose for vinorelbine weekly in a 21-day cycle are 35 and 30 mg/m^2, respectively.[20]

In conclusion, this biweekly regimen of vinorelbine and cisplatin is effective against advanced NSCLC; however, it results in considerable toxicity. Due to the high incidence of neutropenia, this regiment did not improve therapeutic efficacy and its dose intensity is less than that of a conventional schedule.

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每兩週一次溫諾平加上順鉑的化學治療配方對末期非小細胞肺癌病人的第二期研究

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背 景： 許多以新一代抗癌藥物爲主合併順鉑的不同的化療配方，被使用於末期非小細胞肺癌病人身上。本研究以每兩週一次溫諾平加上順鉑的化學治療配方對末期非小細胞肺癌病人評估療效以及毒性。

方 法： 從 2001 年 3 月到 2003 年 7 月，43 位末期非小細胞肺癌病人。接受溫諾平 30 或 35 mg/m^2 加上順鉑 50 mg/m^2 每兩週一次的化學治療。

結 果： 本研究配方的化學治療反應率爲 25.6%，平均存活時間爲 9 個月，一年存活率爲 32.6%。主要血液方面的副作用爲白血球低下，七個病人有第三級白血球低下毒性，十七個病人有第四級白血球低下毒性。四個病人罹患敗血症而兩個病人因而死亡。

結 論： 本研究配方較低的化學治療反應率，可能導因於白血球低下出現機會過高致使藥物劑量偏低，但平均存活時間與其他研究類似。

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關鍵詞：非小細胞肺癌，化學治療，溫諾平，順鉑

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