A Randomized Study of Gemcitabine plus Cisplatin and Vinorelbine plus Cisplatin in Patients with Advanced Non-small-cell Lung Cancer

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Background: Gemcitabine plus cisplatin (GC) and vinorelbine plus cisplatin (VC) are active and well-tolerated regimens for the treatment of patients with advanced non-small-cell lung cancer (NSCLC). We conducted this study to compare the safety and efficacy of these regimens as front-line chemotherapy for patients with NSCLC.

Methods: Eligible patients were randomized to receive either gemcitabine (1000 mg/m^2) on days 1, 8, and 15 plus cisplatin (80 mg/m^2) on day 15 (arm GC), or vinorelbine (20 mg/m^2) on days 1, 8, and 15 plus cisplatin (80 mg/m^2) on day 15 (arm VC). Treatments were repeated every 28 days. The costs of treatment were retrieved from the Health Care Reporting System of Chang Gung Memorial Hospital at the time of final data analysis.

Results: Eighty-three patients (GC, n = 39; VC, n = 44) were enrolled in the study. Seventy-three patients were analyzed. Response rates were 38% and 31% and median survivals were 12.9 and 9.0 months for the 34 patients in the GC arm and 39 patients in the VC arm, respectively. One-year survival was 55.9% in the GC arm and 33.3% in the VC arm. There was no difference in the response rate (p = 0.622), progression free survival (p = 0.443) and median survival (p = 0.4197) between the two arms. Grade 3-4 toxicities were vomiting (GC: 16.3% vs VC: 36.3%), neutropenia (GC: 14.7% vs VC: 20%), and thrombocytopenia (GC: 8.68% vs VC: 5%). There was a significant increase in all-grade thrombocytopenia (p = 0.002) in the GC arm. The GC arm had higher total expenses than the VC arm (p = 0.020).

Conclusions: Both vinorelbine plus cisplatin and gemcitabine plus cisplatin yielded similar efficacies for NSCLC.

(Chang Gung Med J 2008;31:559-66)

Key words: non-small-cell lung cancer (NSCLC), gemcitabine, vinorelbine, cisplatin

Lung cancer is one of the most common malignancies in the world.[1] Non-small cell lung cancer (NSCLC) accounts for about 80% of these cases, with the five-year survival ranging from 10% to 15%

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Received: Jun. 26, 2007; Accepted: Jan. 30, 2008

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when all stages are taken into consideration. Preliminary diagnosis screens only 10% to 15% of the patients with eligibility for potentially curative surgery. Most patients with advanced and metastatic disease are treated palliatively. Single agents have an overall response rate of 11-19%.[2-4] Cisplatin is one of the most extensively studied agents used in the treatment of advanced NSCLC. A recent meta-analysis on more than 9,000 patients with NSCLC has shown a modest improvement in the overall survival rate when patients were randomized to receive cisplatin-based chemotherapy in comparison with non-cisplatin-based chemotherapy.[5] As a single agent in early phase II trials, gemcitabine produced a 13% to 19% response rate and a median survival of 8-9 months,[6-8] while vinorelbine exhibited a 14% to 16% response rate and median survival of 8 months.[9,10] Previous data showed that weekly administration of 1000 mg/m^2 gemcitabine in combination with 80 mg/m^2 cisplatin on day 15, followed by a one week break, was well-tolerated with a response rate of 41% and a 1-year survival rate of 59%.[11] Several phase II/III studies have shown that gemcitabine plus cisplatin (GC) and vinorelbine plus cisplatin (VC) were active in patients with advanced NSCLC.[3,4,11-13] Our study of the safety and efficacy of GC and VC administered to patients with advanced NSCLC is presented below.

METHODS

Patient eligibility

Patients eligible for this study had histologically confirmed stage IIIB or IV NSCLC. Patients were required to have a measurable disease, be older than 18 years old, and have an Eastern Cooperative Oncology Group (ECOG) performance status of 2 or better. Patients were allowed to receive prior palliative radiotherapy, if performed more than four weeks prior to enrollment in the study, on less than 30% of the marrow-bearing bones. Patients with asymptomatic brain metastasis were eligible provided that it was not the only disease site. Adequate baseline bone marrow and hepatic and renal function were required. Patients were ineligible if they had a history of prior or concomitant malignancy. Female patients could not be pregnant or lactating. Written informed consent was obtained from each patient before being enrolled in the study. The study was approved by the Ethics Committee of Chang Gung Memorial Hospital.

Treatment

From August, 1999 to November, 2000, 83 patients (GC, n = 39; VC, n = 44) were enrolled in the study. Thirty-four patients were randomized to receive gemcitabine (1000 mg/m^2) on days 1, 8 and 15, in combination with cisplatin (80 mg/m^2) on day 15, thus being categorized into the GC arm. The VC arm was comprised of the other 39 patients receiving vinorelbine (20 mg/m^2) on days 1, 8 and 15 while cisplatin (80 mg/m^2) was administered on day 15. Treatments were repeated every 28 days in both arms. No prophylactic granulocyte colony stimulating factor was administered.

Patients were scheduled to receive cisplatin at 80 mg/m^2, which was diluted with 500 ml normal saline and administered intravenously over three hours. Prehydration and posthydration using 2 liters of normal saline was done on the day of cisplatin infusion. Ondansetron, dexamethasone, and metoclopramide were used as prophylactic antiemetic medications.

Gemcitabine was administered at a dosage of 1000 mg/m^2 in 100 ml 5% dextrose and given over 30 minutes on days 1, 8 and 15. Vinorelbine was administered at a dosage of 20 mg/m^2 in 100 ml dextrose over 10 minutes on days 1, 8 and 15.

Treatments in both arms were repeated every 28 days or following recovery from hematological and non-hematological toxicity. Dose modification was based on the level of toxicity encountered following the previous treatment course and the laboratory data on the treatment day.

Dose modification

Patients underwent a weekly complete blood count (CBC), white blood cell (WBC) differentiation, and platelet count. The dosages of gemcitabine, vinorelbine and cisplatin were originally scheduled for reduction by 25% if the granulocyte count was between 1,000 and 1,500/μl and/or the platelet count was between 75,000 and 50,000/μl on the day of treatment, but this was later changed to a delay of one week before the next cycle of treatment. Granulocyte colony stimulating factor was permitted but not required if absolute neutrophil counts fell to less than 500/μl. Cisplatin was reduced by 25% if

serum creatinine levels were more than 1.5 mg/dl. Cisplatin was held if serum creatinine levels were more than 2.0 mg/dl. Gemcitabine and vinorelbine administration were delayed if bilirubin levels were > 2 mg/dl. Chemotherapy was delayed for a maximum of two weeks until recovery if the granulocyte count was < 1,000 /μl or the platelet count was < 50,000/μl.

In the absence of disease progression or intolerable toxicity, patients were to remain on the treatment protocol for a total of six cycles of treatment. Evidence of disease progression would lead to treatment discontinuation.

Pretreatment and follow-up studies

Before enrollment, all patients were required to have a physical examination, a chest radiograph, chest and upper abdominal computed tomographic (CT) scans, a bone scan, and complete blood tests. A brain CT or magnetic resonance imaging scan was only performed when brain metastasis was suspected. A physical examination, complete liver and renal function tests, and a chest radiograph were performed before each cycle. A chest and upper abdominal CT scan was performed for evaluation and confirmation of treatment response. Patients were reviewed monthly after protocol cessation.

Treatment evaluation

The objectives of this study were to evaluate the safety and efficacy of the two treatment arms. The unplanned comparison of the costs was made retrospectively. Responses were initially defined according to World Health Organization (WHO) criteria for measurable disease which was then revised to the criteria set by the Response Evaluation Criteria in Solid Tumors (RECIST) when RECIST was available. A complete response (CR) was defined by RECIST as the disappearance of all clinical evidence of an active tumor for a minimum of four weeks. A partial response (PR) was defined as a 30% or greater reduction in the sum of the longest diameters of all measurable lesions lasting for at least four weeks without the appearance of any new lesion and without progression at any disease site. Stable disease (SD) was defined as a decrease of less than 30% in the sum of the longest perpendicular diameters of all measurable sites or an increase of less than 20% change in the sums of the longest diameters without the appearance of any new site and without progression at any disease site. Progressive disease (PD) represented an increase of 20% in the diameters of the sum of all measurable lesions or the appearance of a new lesion.

For all patients who died, the survival duration was calculated from the date of randomization to the date of death. Otherwise, the patient was censored until the last day for which he or she was confirmed to be alive. Time to progression was calculated for all patients from the date of randomization until the date progressive disease was first reported. Each patient who received at least one dose of any study drug was considered assessable for safety. Drug safety was based on laboratory tests and clinical signs and symptoms experienced during the treatment period by the National Cancer Institute Common Toxicity Criteria (NCI CTC) version 2.0.

Cost evaluation

The costs of treatment were retrieved from the Health Care Reporting System of Chang Gung Memorial Hospital at the time of the final data analysis. The cost for each patient was calculated from first day of treatment until disease progression, including total expenses during the therapeutic course, total medication expenses during hospitalization, outpatient expenses, emergency expenses, and chemotherapeutic medication costs. Follow-up checks and second-line chemotherapy expenses were not included.

Statistical considerations

This study was designed to enroll a total of 80 patients. The primary hypothesis was that the response rates were equal in these two regimens and that the lower limit of the 95% confidence interval (CI) was higher than 20% for the response rates of the two arms. A 40% response rate would predict a 95% CI ranging from 21.3% to 56.8%. Kaplan-Meier estimates were used for the analysis of all time-to-event variables such as survival duration, time to progression, and duration of response. The response rates were compared using Fisher's exact test. Toxicity was evaluated by taking the worst reported event per patient into consideration. For each class of toxicity, treatment arms were compared using Fisher's exact test in the 2 x 2 table format for the occurrence of any level of toxicity and severe toxici-

ty. Survival duration and time-to-progression were computed by conducting a log-rank comparison. Costs were compared by applying the independent sample *t* test.

RESULTS

Patient characteristics

A total of 83 patients were enrolled at Chang Gung Memorial Hospital between August, 1999 and November, 2000 (Table 1). The median follow-up time was 27.6 months. Ten patients did not meet the eligibility criteria, four because of malignancy other than NSCLC, two because of incorrect staging, one because of a lack of adequate performance or bone marrow reserve, and three because of prior chemotherapy. Thirty-four patients were enrolled into the GC arm and thirty-nine were enrolled into the VC arm. There were seventy-three patients eligible for response evaluation, with characteristics listed in Table 1. The two groups were comparable with respect to sex, age, and ECOG performance status. Disease characteristics, including cell types and stages of the two treatment groups, were comparable.

Table 1. Patient Characteristics

	GC		VC	
	No	%	No	%
Eligible	34		39	
Gender				
Male	24	70.6	25	64
Female	10	29.4	14	36
Age				
Median	62.4		61.6	
Range	34~81		23~85	
Pathology				
Adenocarcinoma	22	64.7	24	61.5
Squamous cell carcinoma	8	23.5	13	33.3
Large cell carcinoma	4	11.8	2	5.1
Stage				
IIIb	9	26.5	14	35.9
IV	25	73.5	25	64.1
ECOG				
0	0	0	1	2.6
1	18	52.9	24	61.5
2	16	47.1	14	35.9
Cycle				
1	4	11.8	4	10.3
2	2	5.9	6	15.4
3	4	11.8	4	10.3
4	2	5.9	4	10.3
5	0	0	4	10.3
6	22	64.7	17	43.6
Mean	4.71		4.26	

Dosing

Of the 73 eligible patients, 160 courses of GC were administered to 34 patients, while 166 courses of VC were administered to 39 patients. The mean numbers of courses were 4.7 in the GC arm and 4.3 in the VC arm. The number of courses administered per patient did not differ significantly between the two arms ($p = 0.221$). In the GC arm, 60% of patients received the full-schedule chemotherapy doses without dose modification or delay, in comparison with the 34% in the VC arm. Compliance was insignificantly ($p = 0.062$) favorable for the GC arm.

Treatment response

Among the assessable patients, the overall response rates were 38% in the GC arm (13 of 34 patients; 95% confidence interval, 21% to 55%) and 31% in the VC arm (12 of 31 patients; 95% CI, 16% to 46%) (Table 2). The response rates for the two arms did not differ significantly ($p = 0.622$).

Time to progression and response duration

The median time to progression was 6.6 months (95% CI, 5.2 to 7.6 months) in the GC arm, while it was 5.3 months (95% CI, 4.7 to 8.5 months) in the VC arm. The difference in time to progression in the VC arm, when compared with the GC arm, was statistically insignificant ($p = 0.443$). Response durations were 4.57 (95% CI, 4.0 to 7.8) months and 4.1 (95% CI, 2.1 to 9.1) months in the GC and VC arms,

Table 2. Clinical Response

	GC (N = 34)			VC (N = 39)			*p* value
	N	%	95% CI	N	%	95% CI	
Complete response	0	0		0	0		
Partial response	13	38	(21-55)	12	31	(16-46)	0.622
Stable disease	10	29	(16-43)	12	31	(16-46)	0.795
Disease progression	11	33	(15-47)	15	38	(22-54)	0.698

respectively. No difference was observed in the response duration ($p = 0.461$).

One-year survival and overall survival

At the time of this analysis in August, 2003, 29 (85.3%) of the 34 patients in the GC arm and 33 (84.6%) of the 41 patients in the VC arm had died (Fig. 1). The median survival duration was 12.9 months in the GC arm versus 9.0 months in the VC arm ($p = 0.4197$ by log-rank test). The Kaplan-Meier estimate of the 1-year survival rates were 55.9% in the GC arm and 33.3% in the VC arm.

Cost evaluation

Mean total expenses were significantly ($p = 0.020$) higher in the GC arm ($277,318 NT dollars) than in the VC arm ($193,684 NT dollars) (Table 3). The GC arm had a higher level of outpatient expenses and chemotherapeutic agent fees. Gemcitabine ($163,802 NT dollars) was the major expense and its cost was significantly ($p < 0.001$) higher than that of vinorelbine ($64,811 NT dollars). There were no differences in the total admission fees, cisplatin fee, and emergency room visit costs.

Follow-up therapy

Patients whose disease conditions progressed during therapy or the follow-up period received second-line docetaxel chemotherapy. Twenty patients in the GC arm and 15 in the VC arm received second-line treatment. There was no significant difference in post-progression therapy between the two arms.

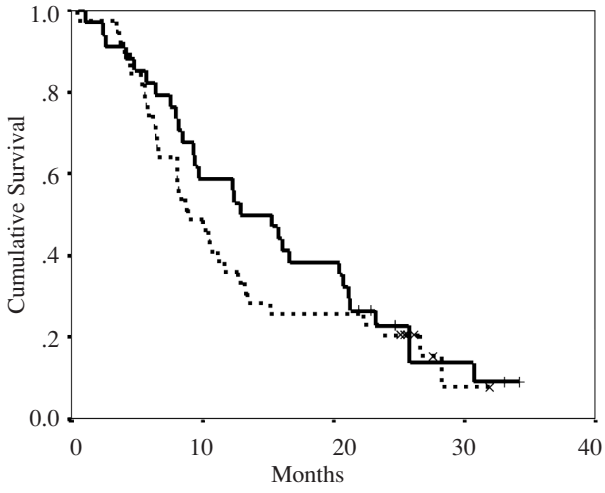

Fig. 1 Overall survival for GC (solid) and VC (dots). The median survival time was comparable in both arms ($p = 0.4197$ by log-rank test). The median survival was 12.9 months in the GC arm versus 9.0 months in the VC arm. The Kaplan-Meier estimate of the 1- year survival rates were 55.9% in the GC arm and 33.3% in the VC arm.

Table 3. Costs of Gemcitabine plus cisplatin and Vinorelbine plus cisplatin

	GC (N = 34)	VC (N = 39)	*p* value
	Mean ± SD	Mean ± SD	
Total expenses*	277318 ± 129636	193683 ± 95599	0.002
Admission†	102448 ± 80761	106702 ± 79400	0.821
Outpatient visits†	173394 ± 93386	84858 ± 47610	< 0.001
Emergency-room visits	1474 ± 3268	2123 ± 3322	0.404
Chemotherapy‡	175529 ± 76950	75667 ± 40113	< 0.001
Cisplatin	11727 ± 5231	10855 ± 5486	0.491

*: Cost in NT dollars; NT$35 equaled approximately 1 US dollar at the time of this study; †: All drug expenses included; ‡: Chemotherapy including gemcitabine, vinorelbine and cisplatin.

Toxicity

All eligible patients receiving at least one dose of therapy were considered in this analysis (34 patients in the GC arm and 39 patients in the VC arm) (Table 4). Thrombocytopenia was observed significantly more frequently in the GC arm than in the VC arm ($p = 0.002$). However, most of these were grade 1-2 (61.8% vs 23%). Grade 3-4 thrombocytopenia induced by the GC combination occurred in only 8.8% of patients. Grade 3-4 neutropenia was present in 14.7% and 20% of the patients in the GC and VC arms ($p = 0.530$), respectively. There was one death due to toxicity in the VC arm.

Table 5 lists the non-hematological toxicity associated with the GC and VC combinations. With the exception of asthenia and nausea/vomiting, the frequency of severe non-hematological adverse events was low in both study arms. Nausea and vomiting were the most frequently reported gastrointestinal side effects. Significantly more patients experienced vomiting in the VC arm than the GC arm ($p = 0.004$).

DISCUSSION

A previous report by the authors showed a 40.6% response rate and a median survival of 13.5

Table 4. Hematological Toxicity

	GC (N = 34)				VC (N = 39)				*p* value
	Grade 1/2	%	Grade 3/4	%	Grade 1/2	%	Grade 3/4	%	
Neutropenia	17	50	5	14.7	16	41	8	20	0.530
Thrombocytopenia	21	61.8	3	8.8	9	23	2	5	0.002
Anemia	25	73.6	9	25.7	28	72	8	20	0.111

Table 5. Non-hematological Toxicity

	GC (N = 34)		VC (N = 39)		*p* value
	Grade 1/2 (%)	Grade 3/4 (%)	Grade 1/2 (%)	Grade 3/4 (%)	
Vomiting	34.3	16.3	46.8	36.6	0.004
Mucositis	2.9	2.9	12.2	0	0.260
Diarrhea	5.7	0.0	17.1	2.4	0.239
Constipation	5.7	0.0	7.3	4.9	0.260
Fever	0.0	0.0	9.7	2.4	0.206
Skin	2.9	0.0	4.9	0	0.652
Neuropathy	14.3	2.9	17.1	0	0.141
Fatigue	22.8	5.6	26.8	24.4	0.037
Myalgia	8.6	2.9	14.6	2.4	0.443
Allergy	0.0	2.9	9.8	0	0.096
Edema	2.9	0.0	7.3	2.4	0.435
Alopecia	28.6	0.0	24.4	0	0.604
Renal	28.6	0.0	19.5	0	0.337
Liver	55.6	0.0	43.9	4.8	0.101

months for GC treatment of NSCLC, with a 1-year survival rate of 59%.[11] The survival curve for patients in the GC arm was practically superimposeable. Both the median and 1-year survival rates observed in the present study were also comparable with those reported by Abratt et al.[12] The overall response rate, time to progression, and median survival duration were similar to those of the Southern Italy group.[14]

In this study, there were no significant differences between GC and VC in terms of response rate, time to progression and median survival. A mathematical difference in the 1-year survival rate was noted between GC (55.9%) and VC (33.3%). However, this difference was not statistically significant. Failure to demonstrate statistical significance could be caused by true insignificance or an underpowered design.

Schiller et al. reported a randomization trial comparing four regimens that showed that paclitaxel in combination with carboplatin (PC) had a higher response rate than docetaxel with cisplatin and GC, but the GC arm had a longer time-to-disease progression (TTP).[15] Kelly et al. showed in a phase III randomization trial that PC was as efficacious as VC for the treatment of advanced non-small-cell lung cancer.[16] The TTP did not differ between PC and VC. In their study, PC was demonstrated to be less toxic and better tolerated but more expensive than VC. The present study also showed that VC was less tolerated than GC and that compliance was better with GC.

In general, the toxicity levels of the GC and VC regimens were manageable. Only one patient in the GC arm ceased treatment early because of toxicity. One patient in the VC arm died of neutropenic sepsis. Compliance was favorable for the GC arm. In general, both the high dosage of cisplatin given in a single day and the weekly administration of vinorelbine resulted in postponement of further treatment due to severe vomiting and neutropenia in the VC arm. The GC arm was noted to have an associated but mild throbocytopenia. There were no significant differences between arms in terms of grade 3-4 thrombocytopenia.

Chen et al. conducted a cost-effectiveness study of advanced NSCLC in Taiwan. Both the PC and paclitaxel with gemcitabine (PG) arms were more expensive than either the GC or VC arm.[17] The mean total costs of PC and PG were $382,442 and $455,484 NT dollars, respectively. The efficacies of the PC and PG were similar to the present study.

Targeted therapy has recently been demonstrated to be encouraging as the treatment for advanced NSCLC.[18,19] Gefitinib was shown to yield survival benefits only in East Asian populations.[20] This ethnic difference was not sufficiently significant for chemotherapy. Further studies comparing the effica-

cy of gefitinib or erlotinib with chemotherapy will then be warranted. On the basis of this randomized trial, GC and VC regimens are equally effective and safe for treatment of advanced NSCLC.

Acknowledgements

We would like to thank Ms. Li-Ying Ou for her typographical aid and assistance in the preparation of this manuscript.

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進展期非小細胞肺癌用健澤加順鉑或溫諾平加順鉑治療的隨機研究

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背 景： 健澤加順鉑與溫諾平加順鉑都是治療非小細胞肺癌時安全有效的用藥。本研究直接比較此兩種第一線用藥的安全性及療效。

方 法： 符合條件的患者隨機分配選擇下列兩種之一的療法：於每個療程的第 1、8、15 天注射 1000 毫克／平方米的健澤 (gemcitabine) (GC 組) 或 20 毫克／平方米的溫諾平 (vinorelbine) (VC 組)，兩組皆於療程的第 15 天注射 80 毫克／平方米的順鉑 (cis-platin)，療程每 28 天重複一次。醫療費用是在最後結果分析時由長庚醫院健保申報系統回溯取得。

結 果： 本研究全程共收案 83 位患者 (39 位 GC 組；44 位 VC 組)，可分析療效者共 73 位。腫瘤反應率及中位數存活期在 34 位 GC 組及 39 位 VC 組分別是 38% 比 31% 及 12.9 個月比 9 個月。一年存活率於 GC 組爲 55.9%；於 VC 組爲 33.3%。比較兩組的腫瘤反應率 ($p = 0.622$)，無惡化存活期 ($p = 0.443$) 及中位數存活期 ($p = 0.4197$) 顯示療效無顯著差異。第三、四級的副作用包括嘔吐 (GC 組 16.3% 比 VC 組 36.3%)、中性白血球降低 (GC 組 14.7% 比 VC 組 20%)、血小板減少 (GC 組 8.68% 比 VC 組 5%)。不分等級的血小板減少在 GC 組有顯著較多 ($p = 0.002$)。GC 組的醫療費用比 VC 組顯著較高 ($p = 0.020$)。

結 論： 健澤加順鉑或溫諾平加順鉑治療對非小細胞肺癌有相同的療效。

(長庚醫誌 2008;31:559-66)

關鍵詞： 非小細胞肺癌，健澤，溫諾平，順鉑

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受文日期：民國96年6月26日；接受刊載：民國97年1月30日
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