Lung cancer is the leading cause of cancer death in Taiwan and throughout the world. The majority of non-small cell lung cancer (NSCLC) patients develop metastatic disease in their disease course; thus, systemic chemotherapy plays an important role. The new chemotherapeutic drugs (vinorelbine, taxanes, and gemcitabine) and their combinations with cisplatin, have shown better response rates and survival when compared with conventional standard regimens. 1,4 Cisplatin-based chemotherapy regimens have shown to prolong survival, relieve symptoms, and improve the quality of life in chemonaive NSCLC patients in a good performance status. 1,2,5,6 How ever, the role of cisplatin in the second-line treatment of NSCLC is less clear. 7,8 The efficacy of vinorelbine treatment in the second-line setting for NSCLC has been disappointing. 19 How ever, a recent small phase II study showed the effectiveness of vinorelbine plus cisplatin treatment in patients who have failed previous chemotherapy.

**Background.** We conducted a phase II study of vinorelbine and cisplatin chemotherapy in non-small cell lung cancer (NSCLC) patients who had failed previous chemotherapy, to assess the response and toxicity of this combination chemotherapy.

**Methods.** Twenty-two patients were enrolled from September 1999 to March 2001. The median age was 70 years. All patients had a performance status of 2. Vinorelbine was administered on days 1, 8 and 15, at a dose of 20 mg/m²; and cisplatin was given on day 1 at a dose of 50 mg/m², every 4 weeks.

**Results.** Sixty-eight cycles of treatment were given, with a median of 3 cycles. All patients were evaluable for toxicity profile, and 21 patients were evaluable for response rate. The major toxicities were myelosuppression. Grade 3 or 4 neutropenia occurred in 40.9% of the patients, and grade 3 or 4 anemia occurred in 13.6% of the patients during treatment. Other toxicities were few and mild in severity. After 2 cycles of treatment, 2 of 21 patients (9.5%) had a partial response (95% confidence interval 0%-22%). The median time of disease progression was 3.7 months, the median survival was 7.6 months, and the one-year survival was 12.3%. Median survival was 8.7 and 4.9 months in those patients receiving this treatment as second-line and ≥ third-line chemotherapy, respectively.

**Conclusions.** Vinorelbine and cisplatin salvage chemotherapy produced a modest anti-tumor response, a mild toxicity profile, and reasonable survival in our elderly NSCLC patients with a poor performance status. This regimen deserves further study in elderly NSCLC patients who have failed previous chemotherapy.

Accepted: January 14, 2003.

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Given the proven efficacy of vinorelbine and cisplatin in the first-line treatment, there exists a clear rationale for the combination of these two drugs in salvage chemotherapy against NSCLC, if the patient has not received the regimen before. We designed the present study, combining these two drugs, to determine their tumor response rate and safety profile when used as salvage chemotherapy for NSCLC patients who have failed previous chemotherapy, especially those who have not received platinum (cisplatin, carboplatin) treatment before.

**METHODS**

Patients with NSCLC who had failed previous chemotherapy were enrolled into the study after giving informed consent. Eligibility criteria were: a histological diagnosis of stage IIIb or IV NSCLC; a performance status of 0 to 2 on the Zubrod scale; clinically measurable disease; no previous radiotherapy on measurable lesion(s); adequate bone marrow reserve with a WBC count ≥ 4000/mm³, platelets ≥ 100000/mm³, and hemoglobin ≥ 10 g/dL; no vinorelbine or cisplatin treatment within three months before entering the study; and no evidence of disease progression during previous vinorelbine or cisplatin treatment if they had received the study drug before. Exclusion criteria were: inadequate liver function (bilirubin > 1.5 times normal range, ALT and AST > 3 times normal); inadequate renal function with creatinine > 2.0 mg/dL; and neurologic conditions which could interfere with the evaluation of neurologic toxicity. Patients with brain metastases were eligible for the study if they were neurologically stable after palliative brain irradiation.

The treatment consisted of cisplatin 50 mg/m² in two静脉注射 (IV) 60 min utes on day 1 and vinorelbine 20 mg/m² IV for 8-10 min utes on days 1, 8, and 15 of every 4 weeks. Adequate hydration with half saline (2000 mL) was given on day 1 before and during chemotherapy. Granisetron and dexamethasone were given on day 1 before chemotherapy as antiemetic prophylaxes. Dexamethasone and metoclopramide were given on days 8 and 15 before chemotherapy. A complete blood cell count was done within 24 hours before chemotherapy. Serum biochemistry studies were performed before every course of chemotherapy, and during the course if clinically indicated. Study drug-related adverse events and toxicities also were recorded according to established Eastern Cooperative Oncology Group (ECOG) criteria.  

With regard to dose modification on days 8 and 15, the dose of vinorelbine was reduced by 50% if the absolute neutrophil count (ANC) was from 1.5 to 1.0 × 10⁹/L and/or platelet count 99 to 75 × 10⁹/L on the day of the scheduled chemotherapy. Treatment was omitted if the ANC was less than 1.0 × 10⁹/L or the platelet count less than 75 × 10⁹/L. For dose adjustment after the subsequent cycle, a 25% reduction in cisplatin and vinorelbine was instituted when the patient suffered from grade 4 neutropenia or thrombocytopenia. Subsequent dose escalation to the original dose level was allowed provided that the patient tolerated the doses given at the 75% level. For grade 3 non-hematological toxicities, vinorelbine and cisplatin were reduced to the 75% level, both during the cycle and for subsequent cycles, and delayed one week or omitted in cases of grade 4 toxicity, excluding nausea/vomiting and alopecia.

Baseline evaluations included a documentation of the patient’s history, a physical examination, and a performance score. A complete blood cell count, urinalysis, serum biochemistry profile, ECG, chest roentgenography, whole body bone scan, brain CT scan, and chest CT scan were also performed.

The response was evaluated after the first two courses of chemotherapy, and every 2 courses thereafter. Types of response were also assessed according to established ECOG criteria.  

Patients were considered assessable for response if they had completed at least two courses of chemotherapy. Responding patients and those with stable disease continued therapy until the disease progressed or 6 courses of treatment were completed. Time to disease progression was calculated from the date of entering the study to the date of disease progression. Length of survival was measured from the date of the first injection of the study drugs to the date of death or last follow-up. For statistical analysis, the Kaplan-Meier method with a log-rank test was used for single-variate survival analysis. The
SPSS statistical program was used.

RESULTS

Between September 1999 and March 2001, twenty-two patients were enrolled into this study. The median age was 70 years, with a range of 46 to 79 years (54.5% of the patients were aged 70 or more). The performance status was 2 in all patients. Nineteen patients had been previously treated with taxane-based combination chemotherapy (paclitaxel in 14, docetaxel in 5). Five patients had received cisplatin-containing chemotherapy before, and one patient carboplatin-containing treatment. Three patients had been treated with vinorelbine-containing regimens. Vinorelbine plus cisplatin was given as the second-line chemotherapy in 17 patients, as the third-line chemotherapy in 3 patients, and as the fourth-line in the remaining 2 patients. (Table 1) All were assessable for toxicity profile and 21 patients were evaluable for treatment response.

A total of 68 cycles of treatment were given to the patients. With the exception of one patient who refused, for no specific reason, further treatment after one cycle, all patients received at least 2 cycles of treatment. The mean and median number of cycles per patient was 3.1 and 3, respectively. The scheduled dose intensity of vinorelbine and cisplatin was 15 and 12.5 mg/m²/week, respectively. The actual dose given was 13.5 and 12.1 mg/m²/week, respectively. After two cycles of treatment, two of 21 evaluable patients achieved a partial response with a response rate of 9.5% (95% confidence interval 0% - 22%). Stable disease was found in 13 patients (61.9%), and progressive disease was documented in the remaining 6 (28.6%). A partial response was found in only the two patients who had previously been treated with gemcitabine plus paclitaxel and received the present treatment as second-line therapy. No partial or complete response could be found in patients previously treated with platinum-, vinorelbine-, or docetaxel-containing regimens. The median time to disease progression was 3.7 months. Median survival was 7.6 months, and one-year survival was 12.3% (Fig. 1). Median survival was 8.7 months in 17 patients receiving the study drugs as second-line treatment, and 4.9 months in 5 patients taking the drugs as ≥ third-line treatment (p = 0.065). Median survival was 8.7 months for those 13 patients who had undergone paclitaxel plus gemcitabine treatment before, and 4.9 months for 9 patients who had not received paclitaxel plus gemcitabine treatment before (p = 0.441). Median survival was 9.6 months for those 16 patients who had not received cisplatin or carboplatin before, and 3.2 months for the 6 patients who had taken cisplatin or carboplatin before (p = 0.013). Cox-regression for multivariable analysis, including second-line vs ≥ third-line treatment, previous treatment with paclitaxel plus gemcitabine or not, and previous treatment with plat-

![Fig. 1. The Kaplan-Meier survival curve of 22 non-small cell lung cancer patients treated with vinorelbine and cisplatin. Median survival was 7.6 months in all patients.](image-url)
num drugs (cisplatin or carboplatin) or not, showed that only the previous treatment with platinum drugs or not had prognostic significance \( (p = 0.022) \).

All patients enrolled into the study were eligible for a toxicity evaluation. The main toxicities were hematological. The incidence of ECOG grade 3 or 4 hematological toxicity per patient was leukopenia 22.7%, neutropenia 40.9%, and anemia 13.6%; there was no grade 3 or 4 thrombocytopenia. Febrile neutropenia occurred in 1 patient whose cov ered an event fully. Two patients suffered from grade 3 or 4 nausea/vomiting. Other non-hematologic toxicities were few and mild; grade 3 or 4 toxicities in cluded 2 with grade 3 anorexia and 4 with grade 3 fatigue. No toxic death occurred in this study. Twelve patients (54.5%) were admitted with a total of 57 units of packed red blood cells transfusion.

Concerning the quality of life, seven of 22 patients showed an improvement in symptoms (pain, hemoptysis, or dyspnea), and the overall subjective feeling of well-being during the treat ment course was better than the patients’ pre-chemotherapy status. Eleven patients showed no obvious change in their daily social and physical activities. The remaining patients had a sensation of weakness or anorexia that interfered with their normal daily activities for days after the injections.

**DISCUSSION**

The options available to patients with advanced NSCLC resistant or refractory to the first-line chemotherapy are very limited. It is recommended that patients with good performance for mance, who fail prior chemotherapy and are still willing to undergo further chemotherapy, enter a well-designed second-line chemotherapy study. However, it is still controversial if elderly patients and those patients whose performance for mance status is not so good deserve a clinical trial.

The recommended vinorelbine dosage is 25-30 mg/m²/week, when in combination with cisplatin for the treatment of NSCLC in chemotherapy-naive patients. However, in view that the majority of our patients were elderly, and that most of them had a poor performance status, the scheduled vinorelbine dose age was only 15 mg/m²/week from the beginning of the study, and the scheduled cisplatin dose age was only 12.5 mg/m²/week. The actual dose of vinorelbine given was only 13.5 mg/m²/week, and the incidence of grade 3 or 4 neutropenia per patient was rel a tively high, up to 40.9%. So, this dose in ten sity should be considered adequate for our patient population, in which more than half were older than 70, and all had a per for mance status of 2. Our study was similar to that of other studies \( (n = 17) \). The median survival of our 22 patients was 7.6 months, in contrast to 8.2 months in their study. Nevertheless, the median survival was 8.7 months in the present study when only the patients having the previous treatment as the second-line alternative \( (n = 7) \) were taken into account. Me dian survival was also 8.7 months in our 13 patients who had previously received paclitaxel plus gemcitabine as their first-line treatment, and took this as a second-line treatment.

The response rate in the present study was lower than that in our previous reports of salvage chemotherapy with tamoxifen, ifosfamide, epirubicin, and cisplatin (TIEP treatment, 20% response rate, 95% confidence interval 4.3% - 35.7%); or docetaxel plus gemcitabine (DG treatment, 36.1% response rate, 95% confidence interval 20.3% - 51.9%). Time to disease progression was shorter in this study (3.7 months) as compared with these two studies (4.9 and 3.8 months, respectively). How ever, median survival (7.6 months) was similar to that of the TIEP treatment (7.7 months), and slightly longer than that of the DG treatment (6.9 months). The median survival for those who took study drugs as ≥ third-line treat-
ment was the same (4.9 months) in this and in the DG study. There fore, the median time to dis ease pro gression was around 4 months and the median sur vival was around 7.5 months in our Chinese NSCLC patients who were able to enter the clinical trial for sal vage che mo ther apy after they failed pri or che mo ther apy. Anoth er im por tant finding is the ab sence of corre la tion be tween the re sponse rate and survival in our patients. In addition, vinorelbine plus cisplatin was much lower in cost than the DG treat ment, but was sim i lar to the TIEP treat ment. Furthermore, survival was significantly better in those pa tients who had not taken plat i num drugs be fore, and who re ceived vinorelbine plus cisplatin as sal vage che mo ther apy. So, the phy si cian could con sider vinorelbine plus cisplatin when the pa tient has not had cisplatin as pre vi ous che mo ther apy; and con sider docetaxel alone, or docetaxel-based (such as DG) or TIEP treat ment when the pa tient has pre vi ously been treated with cisplatin-based che mo ther apy.

While all the pa tients in the pres ent study had a per for mance sta tus of 2, and more than half of the pa tients were aged 70 or more, they were able to toler ate this treat ment (rel a tively low dose vinorelbine and cisplatin) without obvious toxicity, and had reason able survival and qual ity of life. This find ing is quite en cour ag ing, be cause most pre vi ous sug ges tions of a sec ond-line che mo ther apy have been con fined to pa tients with a per for mance sta tus of 0 or 1. How ever, fur ther study is needed before sugges tion of this regi men to use in el derly NSCLC pa tients be cause of the lim ited num ber of el derly NSCLC pa tients in the pres ent study.

In sum mary, vinorelbine plus cisplatin is an ef fec tive and safe sal vage reg i men in NSCLC pa tients who have failed pri mary che mo ther apy, es pe cially in those who have never re ceived plat i num-based treat ment be fore. This regi men des erves fur ther study in el derly or poor per for mance sta tus NSCLC pa tients who have failed pre vi ous che mo ther apy.

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