Phase II Trial of Vinorelbine and Cisplatin Chemotherapy in Advanced Non-Small Cell Lung Cancer

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Purpose: Platinum-based chemotherapy has conferred a modest but significant survival benefit and the introduction of newer drugs has led to achieve higher response rate in patients with advanced non-small cell lung cancer (NSCLC). We performed a phase II trial in order to evaluate the efficacy and toxicity of combination chemotherapy with vinorelbine (Navelbine) and cisplatin in advanced NSCLC.

Materials and Methods: Patients with previously untreated, unresectable stage IIIb or IV NSCLC with measurable lesion(s) were eligible for entry into the study. NP chemotherapy consisted of intravenous vinorelbine 25 mg/m², on day 1 and 8, and intravenous cisplatin 80 mg/m² on day 1; this cycle was repeated every three weeks.

Results: A total of 33 patients were enrolled in the study between July 1999 and Feb 2000. Of the 30 patients deemed eligible for analysis, thirteen patients

achieved a partial response and thirteen showed a stable disease. The overall response rate was 43.3%. The median duration of response was 5.7 months (95% CI: 2.8–8.5 months). The median time to progression was 7.6 months (95% CI: 5.5–9.7 months) and the overall median survival time was 15.1 months (95% CI: 9.8–20.4 months) in the intent-to-treat analysis. Chemotherapy-related grade 3 or 4 toxicities were anemia in 1.5%, leukopenia in 4.5%, nausea/vomiting in 2.3%, alopecia in 13.3%, and neurotoxicity in 3.3%.

Conclusion: The combination of vinorelbine and cisplatin chemotherapy seems to be active and fairly tolerable in patients with advanced NSCLC. (*Cancer Research and Treatment* 2001;33:373–376)

Key Words: Non-small cell lung cancer, Combination chemotherapy, Vinorelbine, Cisplatin

INTRODUCTION

Lung cancer is one of the most common malignancies worldwide. According to the National Statistical Office, the mortality from lung cancer in Korea has been rising progressively from 5.8 per 100,000 in 1983 to 22.1 per 100,000 in 1999. About 80% of lung cancers are of the non-small cell types and in most cases, non-small cell lung cancer (NSCLC) is unresectable at the time of diagnosis due to metastatic or locally advanced disease. For these patients, cisplatin-based chemotherapy has been the mainstay of treatment (1) and a large meta-analysis emphasized that combination chemotherapy conferred a modest survival benefit over best supportive care only (2).

Recently, the introduction of new active and less toxic drugs resulted in an improved response rate and rise in quality of life in patients with advanced NSCLC. Vinorelbine (Navelbine) is a semisynthetic vinka alkaloid that has been structurally modified to increase the therapeutic index and as a result, has been proven to be active in the management of NSCLC. Moreover, vinorelbine also improved the patient's quality of life (QOL), particularly in elderly patients with NSCLC (3). We previously performed a phase II trial in order to elucidate the activity and toxicity of vinorelbine and ifosfamide combination in patients with advanced NSCLC. The response rate was 32.4% and the duration of the response was 4.1 months. The overall survival rate was 9.5 months (4).

Based on non-overlapping toxicity and potential synergism, the vinorelbine and cisplatin combination has been widely tested in the last few years. Although the addition of vinorelbine to cisplatin has improved both response and QOL when compared to cisplatin alone, there is not yet clear evidence of a survival gain with this new regimen and the median survival time is still less than 1 year. In view of this, we conducted a phase II trial in order to evaluate the efficacy and toxicity of vinorelbine

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and cisplatin combination chemotherapy in Korean patients with advanced NSCLC.

MATERIALS AND METHODS

1) Patient eligibility and treatment

(1) **The criteria for eligibility were:** (1) histologically proven NSCLC, (2) previously untreated, (3) unresectable stage IIIB or IV (TNM staging, 1997), (4) ECOG performance status 0-2, (5) the presence of measurable lesion(s), and (6) adequate renal, hepatic and bone marrow functions.

Chemotherapy consisted of vinorelbine 25 mg/m², intravenously on day 1 and 8, and cisplatin 80 mg/m² intravenously on day 1, both of a 21-day cycle. To prevent vinorelbine-related phlebitis, vinorelbine was diluted with 50 ml of isotonic saline and infused over 10 minutes. Serotonin antagonist and lorazepam were routinely used for the control of emesis. Complete blood count, blood chemistry, and creatinine clearance were checked prior to each cycle.

All patients were required to comprehend and sign an informed consent form approved by the Institutional Review Board, Seoul National University Hospital.

2) Response and toxicity evaluation

Responses were assessed using modified WHO criteria. Chest radiographs and CT scan were performed every 3 cycles of chemotherapy in order to document response or disease progression. Chemotherapy was continued until disease progression or unacceptable toxicity. Salvage therapy was allowed based on a physician's decision in the case of no response. Toxicities were assessed using WHO criteria during every cycle of chemotherapy. Non-hematologic toxicities were also assessed by physical examination and systemic review.

RESULTS

1) Patient characteristics

A total of 33 patients were enrolled between July 1999 and Feb 2000. Twenty of 33 patients were male (60.6%) and the median age was 55.5 years (range: 34-70). The number of patients with stage IIIB and IV were 8 (24.3%) and 25 (75.7%), respectively. The performance state was grade 0-1 in 27 patients (81.8%) and grade 2 in 6 patients (18.2%). Histologic findings were adenocarcinoma in 24 patients (72.7%), squamous cell carcinoma in 8 (24.2%), and poorly differentiated carcinoma in 1 (3.0%).

Table 1. Response rate

Evaluable patients	30
Complete remission	0
Partial remission	13 (43.3%)
Stable disease	13 (43.3%)
Progressive disease	4 (13.3%)

2) Tumor response

A total of 133 cycles of chemotherapy were administered, with a mean 4.03 cycles per patient. The mean dose of vinorelbine was 14.9 mg/m²/week and that of cisplatin 25.0 mg/m²/week; calculated dose intensity for each drug was 89.4% and 93.7%, respectively.

Of the 33 patients, 3 patients were ineligible for the evaluation of tumor response due to early loss. Therefore, 30 patients were available for evaluation of responses (Table 1). There were no cases of complete remission and partial remissions were observed in 13 patients, scoring 43 percent of the overall response rate. No difference was found in response rate according to age, sex, histology, or stage. However, subset analysis showed that among the 22 patients with stage IV, the 11 patients with disease limited only to lung showed significantly higher response as compared with the remaining 11 patients with distant metastasis (Table 2). One responder with initially N3 nodes successfully underwent curative surgery after a total of

Fig. 1. Duration of remission of 13 partially responded patients, 1 patient underwent curative surgery and the median duration of the remission in remaining 12 patients was 5.7 months (95% confidence interval: 2.8-8.5 months).

Table 2. Response rate according to characteristics

Variable	Response	%	p-value
Age			
< 60 (n=17)	6	35.3%	0.31
> 60 (n=13)	7	53.8%	
Histology			
Adenoca. (n=22)	9	40.9%	0.78
Squamous cell (n=8)	4	50.0%	
Stage			
IIIB (n=8)	4	50.0%	0.8
IV (n=22)	9	40.9%	
Limited to lung (n=11)	7	63.6%	0.03
Distant (n=11)	2	18.2%	

3 cycles of chemotherapy and resulted in pathologic N1 disease. He has survived over 18 months without the evidence of disease recurrence.

The median duration of remission in the remaining 12 partially responded patients was 5.7 months (95% confidence interval (CI): 2.8–8.5 months) (Fig. 1). With a median follow-up of 18.1 months, the overall time to progression was 7.6 months (95% CI 5.5–9.7 months) (Fig. 2), and the overall survival time was 15.1 months (95% CI: 9.8–20.4 months) in the intent-to-treat analysis (Fig. 3). The median survival showed a tendency to be more prolonged in the responders than in the non-responders (18.1 months versus 13.2 months, $p=0.51$).

3) Toxicity

Toxicity was evaluable in all 30 response-evaluable patients. In general, toxicities appeared mild. Grade 3 or 4 hematologic toxicities were as follows: anemia in 2 out of 133 cycles (1.5%)

and leukopenia in 6 out of 133 cycles (4.5%). There was no grade 3 or 4 thrombocytopenia. Grade 3 or 4 non-hematologic toxicities were as follows: nausea/vomiting occurred in 3 out of 133 cycles (2.3%), alopecia in 4 out of 30 patients (13.3%), and neurotoxicity in only 1 out of 30 patients (3.3%). Vinorelbine-related phlebitis was not observed and no other significant toxicities were observed.

DISCUSSION

Until the early 1990s, regimens of cisplatin in combination with vindesine or etoposide were most commonly used in advanced NSCLC (1,2). More recently, newer agents, including taxanes, vinorelbine, gemcitabine, have become more widely used, and there is a trend indicating that regimens containing these newer agents show a higher response rate and better survival outcome than the older, “standard” regimen. However, there has been no documented survival advantage for one regimen over the others and the optimal chemotherapy regimen in this population remains elusive.

Vinorelbine is one of the new drugs that has been shown to be effective in non-small cell lung cancer. Its pharmacological behavior is essentially similar to that of the other vinca alkaloids, however it is more lipophilic than other vinca alkaloids. In fact, drug concentrations in the human lung have been demonstrated to be 300-fold greater than plasma levels and 3.4- to 13.8-fold higher than lung concentrations achieved with other vinca alkaloids. Neutropenia is the principal dose-limiting toxicity of vinorelbine, and the rate of neurotoxicity appears lower than other vinca alkaloid agents (5).

There have been some randomized trials evaluating the role of vinorelbine in non-small cell lung cancer. The SWOG trial by Wozniak and colleagues compared weekly vinorelbine plus cisplatin and cisplatin alone and reported significant improvement in progression-free survival (median, 2 months versus 4 months) and overall survival (median, 6 months versus 8 months; 1-year survival 20% versus 36%) (6). The European multicenter

Fig. 2. Time to progression with the median follow-up of 18.1 months, the overall time to progression was 7.6 months (95% CI 5.5–9.7 months).

Fig. 3. Overall survival. The overall survival of 33 patients was 15.1 months (95% CI: 9.8–20.4 months) in the intent-to-treat analysis (A). The median survival of responders and non-responders was 18.1 months and 13.2 months, respectively, and the difference was not significant ($p=0.51$) (B).

trial also demonstrated survival advantage favoring the vinorelbine and cisplatin method over vinorelbine alone and vindesine plus cisplatin. Vinorelbine was administered weekly and neutropenia was given more frequently than other variations (7). Given these findings, it is logical to conclude that vinorelbine plus cisplatin chemotherapy may be a better choice for advanced non-small cell lung cancer than the older, "standard" regimen.

There have been many trials with other new agents in combination with cisplatin or carboplatin, including paclitaxel. In a recent survey, paclitaxel plus carboplatin was found to be the most widely favored option for 1st line chemotherapy among medical oncologists in the United States (8). This is primarily due to the ease of administration on an outpatient basis. Recently, another SWOG trial compared paclitaxel plus carboplatin and vinorelbine plus cisplatin and concluded that both regimens provide "equally effective" palliation in an advanced non-small cell lung cancer, although they favored the paclitaxel plus carboplatin regimen due to its favorable toxicity profile and improved tolerability and compliance (9). Higher hematologic toxicity and nausea on the vinorelbine plus cisplatin arm lowered patient compliance with the treatment. To overcome this, a new schedule of vinorelbine plus cisplatin trial, modifying weekly vinorelbine into day 1 and day 5 of a 21-day cycle, was conducted. The response rate was 50%, the median duration of the response was 9 months and toxicities were mild (10).

Our study used a similar vinorelbine dose and schedule and showed a similar response rate, duration of remission and minimal toxicities. This low toxicity profile is probably attributed to the altered and reduced vinorelbine dose. There were two cases removed from the study during chemotherapy due to poor general condition, and 1 due to severe neutropenic fever that precluded further chemotherapy. Otherwise, there were only rare grade 3-4 toxicities, as mentioned above. This can be major advantage of the regimen over other relatively "toxic" ones.

In previous SWOG trials comparing paclitaxel plus carboplatin with vinorelbine plus cisplatin, the median survival and 2-year survival were similar between the two variations. However, the overall average cost of chemotherapy per patient was significantly different. The paclitaxel plus carboplatin arm costs about 10,000 dollars more than the vinorelbine plus cisplatin arm (43,522 versus 33,209 dollars). This was mainly due to the cost-difference of chemotherapeutic drugs (9). With a comparable therapeutic efficacy, relatively lower cost, and high tolerability as shown in these trials, vinorelbine plus cisplatin is considered a good therapeutic option for advanced non-small cell lung cancer. However, the efficacy of this modified regimen remains to be tested in randomized trial.

In our trial, a difference in the survival between chemotherapy responders and non-responders was observed, as mentioned above, despite being statistically not significant. This lack of statistical difference may be due to the small size of the study populations or the follow-on salvage chemotherapy. Salvage chemotherapy was done in 12 patients, 4 in the responder and 8 in the non-responder group. Commonly used regimens were paclitaxel plus carboplatin (in 3 patients), docetaxel (in 3 patients), paclitaxel plus cisplatin (in 2 patients), and other new drugs, alone or in combination.

CONCLUSIONS

Combination chemotherapy with vinorelbine and cisplatin is considered to be a good therapeutic option in terms of efficacy and toxicity in the management of patients with advanced NSCLC.

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