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Original Article

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The Efficacy and Safety of Platinum/Vinorelbine as More Than Second-Line Chemotherapy for Advanced Non-small Cell Lung Cancer

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Purpose

There is no regimen that is strongly recommended for more than second-line treatment. We investigated the efficacy and safety of platinum/vinorelbine as more than second-line treatment.

Materials and Methods

We selected patients with advanced non-small cell lung cancer (NSCLC) who received treatment with platinum/vinorelbine at Chungnam National University Hospital from August 2001 to December 2013. The primary end point was the response rate, and secondary end points were progression-free survival (PFS), overall survival (OS), and toxicity.

Results

Thirty-five patients were enrolled. Response rate was 22.9% (complete response, 0 patients [0%]; partial response, eight patients [22.9%]; stable disease, 10 patients [28.6%]; progressive disease, 14 patients [40.0%]). A significantly higher response rate was observed for patients who had responded to previous chemotherapy than for those who did not (34.8% [8/23] vs. 0% [0/12], p=0.020). The median PFS was 4 months (range, 1 to 21 months). Patients with adenocarcinoma and non-smokers had a significantly longer PFS than patients with non-adenocarcinoma and smokers (5 months vs. 2 months, p=0.007; 4.5 months vs. 2 months, p=0.046, respectively). The median OS was 10 months (range, 1 to 41 months). Patients with good performance status and non-smokers had a significantly longer OS than patients with poor performance status and smokers (14 months vs. 4 months, p=0.02; 18.5 months vs. 6 months, p=0.049, respectively). The main serious adverse event (grade 3 or 4) was neutropenia (15 events, 13.3%) in a total of 113 cycles.

Conclusion

Platinum/vinorelbine was effective as more than second-line chemotherapy, and the toxicity was tolerable, in patients with advanced NSCLC.

Key words
Non-small-cell lung carcinoma, Third-line treatment, Drug therapy

Introduction

Despite recent advances in treatment of non-small-cell lung cancer (NSCLC), almost all patients with metastatic or unresectable cases of NSCLC inevitably experience disease progression [1]. In addition, as supportive care of patients with advanced cancer is developing, an increasing number of patients with advanced NSCLC who are treated with chemotherapy eventually receive therapies beyond second-line chemotherapy [2].

There are several standard first-line therapies for patients with advanced NSCLC: platinum-based doublet combination chemotherapy, epidermal growth factor receptor (EGFR)

tyrosine kinase inhibitors in patients with an *EGFR* mutation, or crizotinib for anaplastic lymphoma kinase (ALK)–positive patients [3]. Second-line chemotherapy using single-agent docetaxel, pemetrexed, or erlotinib is acceptable for patients with advanced NSCLC, with adequate performance status, and in whom the disease has progressed during or after first-line therapy [4-7]. However, there are no regimens that are strongly recommended as a third or higher line of treatment. In general, agents which have not already been administered are recommended as third-line therapies for patients with good performance.

Platinum/vinorelbine was one of the regimens recommended as a front-line treatment; its survival data and response rates are equivalent to those of cisplatin/gemcitabine [8,9]. However, no data on the use of platinum/vinorelbine beyond their use as a second-line therapy have been reported. Therefore, the aim of this retrospective analysis was to investigate the efficacy and safety of platinum/vinorelbine as a third or higher line of treatment.

Materials and Methods

1. Eligibility

Eligible patients were aged ≥ 18 years with a histologically confirmed diagnosis of advanced NSCLC and had experienced disease progression after second-line treatment. Patients were required to have an Eastern Cooperative Oncology Group (ECOG) performance status of 0-2 and adequate bone marrow, renal, and liver functions (absolute neutrophil count ≥ 1,500/μL, platelet ≥ 100,000/μL, hemoglobin ≥ 9.0 g/dL, serum creatinine and bilirubin < 1.5-fold the upper limit of normal and aspartate aminotransferase and alanine aminotransferase < 3-fold the upper limit of normal). Patients were treated with platinum/vinorelbine as the third or higher line of treatment at Chungnam National University Hospital from August of 2001 to December of 2013.

The medical records of the enrolled patients were reviewed retrospectively. The following data were evaluated: performance status based on the ECOG performance scale, histology, previous chemotherapy regimens, clinical stage at the time of diagnosis, dose intensity of chemotherapeutic agents, and objective response rate and survival data. The study protocol was approved by the local institutional review board.

2. Treatment

Patients received cisplatin 60 mg/m^2 or carboplatin at an area under the curve of 5, on day 1, plus vinorelbine 25 mg/m^2 on days 1 and 8, every 3 weeks. Treatment was sustained up to 6 cycles but was discontinued in patients who developed progressive disease or unacceptable toxicity.

3. Endpoints

The primary endpoint of this study was to evaluate the overall response rate of platinum/vinorelbine; the secondary endpoints were disease control rate, progression-free survival (PFS), overall survival (OS), and toxicity. The best response to chemotherapy was classified according to the Response Evaluation Criteria in Solid Tumor Criteria ver. 1.1. The disease control rate was defined as the addition of an objective response and stable disease rates. PFS was the interval from the first day of each line of chemotherapy until documented progression or death from any cause and was censored on the date of the last follow-up visit for patients who were still alive and whose disease had not progressed. OS was measured from the first day of each line of chemotherapy until death or the final day of the follow-up period. Toxicity was assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events ver. 3.0.

4. Statistical analysis

Categorical variables were compared using chi-square tests, and logistic regression was used to evaluate the correlations. Survival was assessed using the Kaplan-Meier method, and survival rates were compared using the log-rank test. Multivariate analysis of the independent prognostic factors for survival was performed using the Cox proportional hazard regression model with a 95% confidence interval. A p-value of < 0.05 was regarded as significant. Statistical analyses were performed using the SPSS ver. 17.0 (SPSS Inc., Chicago, IL).

Results

1. Patient characteristics

A total of 35 patients with advanced NSCLC who were treated at Chungnam National University Hospital between August of 2001 and December of 2013 were enrolled. The median age of the enrolled patients was 63 years, and there were more males than females. The stage at initial diagnosis was mostly IIIB and IV. Six patients with stage I to IIIA disease upon their initial diagnosis were recurrent cases. Most patients had a favorable performance status (ECOG

Table 1. Patients' baseline characteristics (n=35)

Characteristic	No. (%)
Median age (range, yr)	63 (47-86)
Gender (male:female)	27:8
Initial stage	
I	2 (5.7)
II	2 (5.7)
III	8
IIIA	2 (5.7)
IIIB	6 (17.1)
IV	23 (65.7)
ECOG PS	
1	25 (71.4)
2	10 (28.6)
Histology	
Adenocarcinoma	21 (60.0)
Squamous cell carcinoma	12 (34.3)
Others	2 (5.7)
Smoking history	
Former and current	15 (42.9)
Never	20 (57.1)
Chemotherapy line	
Third-line	17 (48.6)
Fourth- or fifth-line	18 (51.4)
Previous chemotherapy regimens (total 92 regimens)	
Platinum+gemcitabine	32 (34.8)
Platinum+docetaxel	15 (16.3)
Platinum+pemetrexed	2 (2.1)
Pemetrexed alone	10 (10.9)
Docetaxel alone	10 (10.9)
Gefitinib	10 (10.9)
Others	13 (14.1)
Response rate to the prior platinum-containing regimens	
First-line	18 (51.4)
More than first-line	3 (8.6)
Median follow-up duration (range, mo)	7 (1-41)

ECOG PS, Eastern Cooperative Oncology Group performance status.

Table 2. Response rate (n=35)

Best response	No. (%)
Complete response	0
Partial response	8 (22.9)
Stable disease	13 (37.1)
Disease progression	14 (40.0)

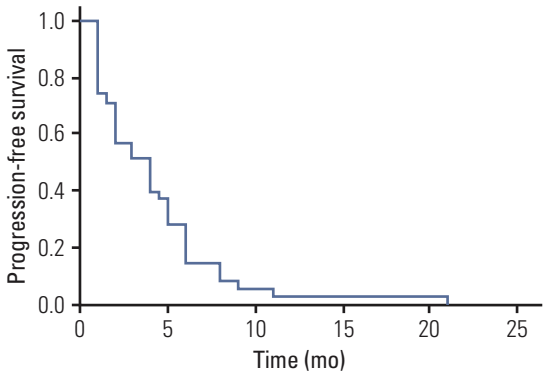

Fig. 1. Progression-free survival for patients who received platinum and vinorelbine as more than second-line chemotherapy (n=35).

performance scale, 0-2). Adenocarcinoma (60.0%) was the most common histological type of cancer, followed by squamous cell carcinoma (34.3%). Platinum/vinorelbine was administered to 17 patients as third-line chemotherapy and to 18 patients as fourth- or fifth-line chemotherapy. The median follow-up duration was 7 months (range, 1 to 41 months). The most common previously treated regimen was platinum/gemcitabine (34.8%) followed by platinum/docetaxel (16.3%). Twenty-one patients (18 patients at the first-line treatment; additional 3 patients at more than first-line treatment) had shown response to the prior platinum-containing regimens. The patients' characteristics are listed in Table 1.

2. Efficacy

There was no complete response. A partial response was observed in eight patients (response rate, 22.9%), and stable disease was observed in 13 patients (disease control rate, 60.0%) (Table 2). Statistically significant higher response rates were observed for patients who had shown a response to previous chemotherapy compared with patients who had not shown a response to previous chemotherapy (34.8% [8/23] vs. 0% [0/12], p=0.020). However, no statistically significant differences in response rates were observed according to age, histologic subtype, or treatment line. A significantly higher disease control rate was observed for patients with adenocarcinoma (76.2% [16/21] vs. 35.7% [5/14], p=0.017) and in females (100.0% [8/8] vs. 48.1% [13/27], p=0.009). However, no statistically significant differences in disease control rates were observed according to age, performance status, or treatment and responsiveness to previous chemotherapy treatments.

Table 3. Progression-free survival in univariate and multivariate analysis (n=35)

Variable	Median (95% CI)	p-value	
		Univariate	Multivariate
Age (yr)		0.090	-
< 65	2.0 (1.5-2.4)		
≥ 65	5.0 (3.1-6.8)		
Gender		0.116	-
Male	2.0 (1.4-2.5)		
Female	6.0 (4.8-7.2)		
Histology		0.007	0.117 (HR, 0.6; 95% CI, 0.4-1.1)
Adenocarcinoma	5.0 (3.5-6.4)		
Non-adenocarcinoma	2.0 (1.1-2.8)		
Stage		0.470	-
≤ IIIB	4.0 (2.3-5.6)		
IV	4.0 (0.6-5.3)		
ECOG PS		0.030	0.780 (HR, 0.8; 95% CI, 0.8-3.5)
0 or 1	4.5 (2.6-6.3)		
2 or 3	2.0 (0.8-3.1)		
Smoking history		0.046	0.144 (HR, 1.7; 95% CI, 0.8-3.5)
Never	4.5 (3.0-5.9)		
Former and current	2.0 (0.1-3.8)		
Treatment line		0.719	-
Third-line	2.0 (0.7-3.2)		
Fourth- and fifth-line	4.0 (2.6-5.3)		
Responsiveness for the previous treatment		0.358	-
Response	4.0 (1.0-6.9)		
No response	2.0 (0.0-4.1)		

CI, confidence interval; HR, hazard ratio; ECOG PS, Eastern Cooperative Oncology Group performance status.

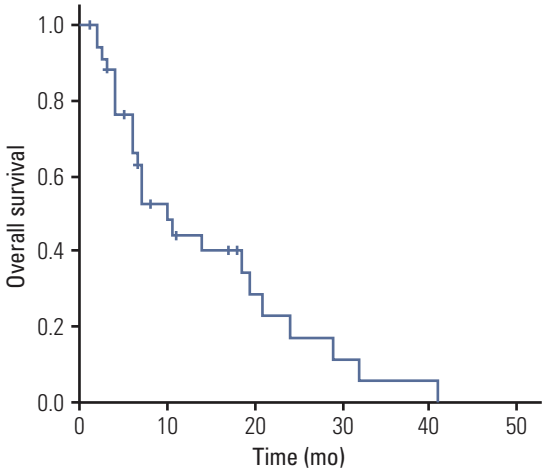

Fig. 2. Overall survival for patients who received platinum and vinorelbine as more than second-line chemotherapy (n=35).

3. Survival data

The median PFS was 4 months (95% CI, 2.1 to 5.8 months) (Fig. 1). In univariate analysis, patients with good performance status, those with histologically classified adenocarcinoma, and never-smokers had significantly longer PFS (Table 3). The median OS was 10 months (95% CI, 1.0 to 41.0 months) (Fig. 2). In univariate analysis, patients with good performance status, never-smokers, and those who had response over stable disease had significantly longer OS than patients with poor performance status, smokers, and those whose disease progressed after platinum/vinorelbine chemotherapy (Table 4). However, in multivariate analysis, there was no significant factor that influenced OS or PFS.

4. Toxicity

A total of 113 treatment cycles were administered. The median number of cycles per patient was 3 (range, 1 to 6). The mean dose intensity of the treatment regimen was 94.7% for both cisplatin and vinorelbine. The most common toxici-

Table 4. Overall survival in univariate and multivariate analysis (n=35)

Variable	Median (95% CI)	p-value	
		Univariate	Multivariate
Age (yr)		0.929	-
< 65	7.0 (1.9-12.0)		
≥ 65	14.0 (4.6-23.3)		
Gender		0.205	-
Male	7.0 (1.7-12.2)		
Female	18.5 (3.8-33.1)		
Histology		0.326	-
Adenocarcinoma	14.0 (1.5-26.4)		
Non-adenocarcinoma	6.5 (4.7-8.2)		
Stage		0.917	-
≤ IIIB	10.0 (0.0-21.8)		
IV	7.0 (1.8-12.1)		
ECOG PS		0.020	0.116 (HR, 0.4; 95% CI, 0.1-1.2)
0 or 1	14.0 (3.7-24.2)		
2 or 3	4.0 (1.7-6.2)		
Smoking history		0.049	0.339 (HR, 1.7; 95% CI, 0.6-4.8)
Never	18.5 (3.8-33.1)		
Former and current	6.0 (3.9-8.0)		
Treatment line		0.492	-
Third-line	7.0 (6.0-7.9)		
Fourth- and fifth-line	18.5 (2.7-34.2)		
Responsiveness for the previous treatment		0.774	-
Response	14.0 (0.9-27.0)		
No response	6.5 (5.1-7.8)		
Responsiveness for the current treatment		0.014	0.05 (HR, 0.4; 95% CI, 0.1-1.0)
Disease controlled	18.5 (4.9-32.0)		
Not controlled	4.0 (1.6-6.3)		

CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio.

ties were fatigue (41.6%) and peripheral neuropathy (24.8%); however, these side effects were tolerable. As shown in Table 5, other side effects included neutropenia, febrile neutropenia, anemia, thrombocytopenia, nausea/vomiting, and diarrhea; however, the incidences of these were low.

Table 5. Toxicities (n=113 cycles)

Grade	1	2	3	4
Neutropenia	-	3 (2.7)	6 (5.3)	9 (8.0)
Febrile neutropenia	-	-	-	3 (2.7)
Anemia	-	8 (7.1)	9 (8.0)	-
Thrombocytopenia	1 (1.0)	2 (1.8)	2 (1.8)	1 (1.0)
Mucositis	2 (1.8)	3 (2.7)	-	-
Nausea	2 (1.8)	7 (6.2)	3 (2.7)	-
Vomiting	1 (1.0)	3 (2.7)	4 (3.5)	-
Fatigue	6 (5.3)	47 (41.6)	-	2 (1.8)
Peripheral neuropathy	1 (1.0)	28 (24.8)	-	-
Constipation	-	3 (2.7)	-	-
Diarrhea	-	2 (1.8)	1 (1.0)	-

Values are presented as number (%).

Discussion

Due to recent advances in treatment of advanced NSCLC and supportive care, the patient population requiring subsequent chemotherapy is increasing [10,11]. Asahina et al. [1] reported that nearly 38% of patients with advanced NSCLC who received first-line chemotherapy went on to receive third-line chemotherapy, and the authors emphasized the need for randomized controlled trials for third-line treat-

ments. Girard et al. [2] reported that approximately 28% of patients received a third-line treatment; the authors suggested that patients who showed good performance statuses and had good disease control rates after their previous treatments may benefit from third-line treatment.

In this retrospective study, platinum/vinorelbine, when used as treatment regimen beyond second-line chemotherapy, was effective in patients with advanced NSCLC, and the toxicity was tolerable. Despite the availability of many new active agents for NSCLC, the reported response rates beyond second-line systemic therapy have generally been less than 20%. In the case of erlotinib as a third or fourth line of treatment in advanced NSCLC cases, the response rate was 8.9% in a randomized, controlled study [4]. In two other retrospective studies, the objective response rate was 10%-20%, and the OSs from third-line and fourth-line pemetrexed treatments were 11.0 and 13.0 months, respectively [12,13]. Single-agent vinorelbine as a third-line chemotherapy for advanced NSCLC had limited activity, as reported by Kanat et al. [14]; there was no partial response, and the median OS was approximately 3.5 months. However, in our study, the objective response rate of platinum/vinorelbine was 22.9%. Patients who had shown a response to prior therapy tended to have a good response, which was also similar to a report by Girard et al. [2], who demonstrated that the performance status and disease control after the first and second lines of treatment can be used as prognostic factors.

In our study, the survival data showed that the median PFS was 4 months, and that the median OS was 10 months. These findings are similar to the survival data for pemetrexed treatment beyond second-line therapy. Chang et al. [12] reported that the median PFS was 3.2 months, and the median OS was 11.6 months for third- and fourth-line pemetrexed treatments. Sun et al. [13] reported that the median PFS was 3.0 months and response rate was 12% for third-line pemetrexed treatment. We performed subgroup analyses for PFS and OS for evaluation of predictive factors for better outcome with platinum/vinorelbine therapy.

According to univariate analyses, the strong predictive factors were good performance status (ECOG performance scale, 0-1), never-smoker status, and responsiveness to the previous treatment. However, none of these factors maintained significance in multivariate analyses, which might be due to the small number of patients in this study. According to Sun et al. [13], good performance status was still a strong predictive factor in multivariate analysis.

And the toxicities of platinum/vinorelbine at more than second-line chemotherapy were quite tolerable. Compared to previous reports, the lower incidence of adverse events, particularly peripheral neuropathy, in this study might have arisen from the retrospective collection of the data [8,9]. Four cycles of platinum-based combination chemotherapy is usually used, thus the dose limit of cisplatin is not reached at first-line treatment. Therefore, we can use this platinum plus vinorelbine regimen as more than second-line chemotherapy in patients showing response to prior platinum containing regimen.

As a result of the increased understanding of the molecular pathogenesis of NSCLC and the introduction of new targeted agents, treatment of NSCLC has developed rapidly [15]. In particular, the presence of certain gene alterations (e.g., *EGFR* mutations or *ALK* gene rearrangement) affect decision-making for initial treatment. However, some studies have reported predictive biomarkers of the response to cytotoxic chemotherapy in NSCLC. Vinolas et al. [16] demonstrated that a single nucleotide polymorphism in the MDR1 gene was associated with chemosensitivity in patients treated with cisplatin plus vinorelbine. Therefore, there remains a need for identification of biomarkers for predicting the treatment outcome of platinum plus vinorelbine.

Conclusion

In conclusion, platinum plus vinorelbine may be a good therapeutic option as a third or higher line of treatment for advanced NSCLC, particularly in patients who responded to prior treatments and show a good performance status. In addition, more large prospective studies will be needed in order to confirm the efficacy and safety of platinum plus vinorelbine as a third or higher line of treatment.

Conflicts of Interest

Conflict of interest relevant to this article was not reported.

Acknowledgments

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