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Carboplatin Plus Nab-paclitaxel in Performance Status 2 Patients With Advanced Non-small-cell Lung Cancer

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Abstract. *Background/Aim: This phase I/II study aimed at assessing the efficacy of combination therapy with carboplatin (CBDCA) on day 1 and nab-paclitaxel (Nab-PTX) on days 1 and 8 of a 21-day cycle in performance status (PS) 2 patients with non-small-cell lung cancer (NSCLC). Patients and Methods: PS 2 patients with NSCLC were enrolled into a phase I study using a 3 + 3 design. Once the recommended phase II dose (RP2D) was established, the patients were enrolled into phase II. Results: Based on the phase I findings, the RP2D was determined as CBDCA area under the curve 6 mg/ml/min and Nab-PTX 100 mg/m^2. In the phase II part, 27 patients were evaluable. The overall response rate was 44%. The median progression-free survival and overall survival were 5.2 months and 14.0 months, respectively. There was no treatment-related death. Conclusion: CBDCA plus Nab-PTX therapy is a promising treatment strategy for PS 2 patients with NSCLC.*

Platinum combination chemotherapy is a standard treatment for patients with advanced non-small-cell lung cancer (NSCLC) and a good performance status (PS) (1). The recent development of less-toxic platinum combinations has broadened the indication to patients with a poor PS, such as an Eastern Cooperative Oncology Group (ECOG) PS of 2. For example, one study reported that the combination of carboplatin (CBDCA) plus pemetrexed therapy is more effective than pemetrexed alone among patients with advanced NSCLC and a PS of 2 (2). However, 4% treatment-related deaths in the CBDCA and pemetrexed therapy arm occurred in that study. Patients with a PS of 2 have increased risks of adverse events (3). Moreover, patients with NSCLC are often ineligible for pemetrexed because of having squamous cell carcinoma (Sq), interstitial pneumonia, or impaired renal function (4-6), and thus the standard treatment modality for NSCLC patients with PS 2 is yet to be established.

For patients with advanced NSCLC and PS 0 or 1, CBDCA plus nab-paclitaxel (Nab-PTX) yielded significantly higher overall response rates (ORR) and a non-significant 1-month improvement in median overall survival (OS) than CBDCA plus paclitaxel in a phase III study (CA031 study) (7). The subset analysis also demonstrated the safety and efficacy of CBDCA plus Nab-PTX in an elderly subgroup (8). CBDCA plus Nab-PTX treatment may be effective and tolerable for NSCLC patients with PS 2. However, the treatment schedule needed to be modified in most patients who received CBDCA area under the curve (AUC) 6 on day 1 plus Nab-PTX 100 mg/m^2 on days 1, 8, and 15 of a 21-day cycle in a phase III study (7).

Therefore, this phase I/II study aimed to assess the safety and efficacy of combination therapy with CBDCA on day 1 and Nab-PTX on days 1 and 8 of a 21-day cycle for advanced NSCLC patients with PS 2.

Patients and Methods

Patient selection. The eligibility criteria were 1) age 20 years or older; 2) histologically- or cytologically-confirmed cytotoxic

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chemotherapy-naive advanced (Stage IIIB, IV, postoperative recurrence, or recurrence after radiotherapy) NSCLC; 3) ECOG PS 2 (PS was assessed by more than 2 doctors); 4) evaluable lesions and adequate organ function; and 5) life expectancy of more than 12 weeks. All patients provided written informed consent.

Patients were excluded if they had 1) symptomatic brain metastasis; 2) interstitial pneumonia with usual interstitial pneumonia pattern on chest computed tomography; 3) uncontrolled pleural effusion, ascites or pericardial effusion; 4) received palliative radiotherapy within the past two weeks; 5) active concomitant malignancy; 6) severe complication; 7) positivity for hepatitis B surface antigen; 8) a history of previous severe drug allergy; 9) receiving continuous systemic administration of steroid; and 10) were pregnant or breastfeeding.

Study treatment. Patients received CBDCA on day 1 and Nab-PTX on days 1 and 8 every 21 days for 4-6 cycles. In the phase I trial, patients were enrolled in the dose escalation cohorts using a 3+3 design with a starting dose of CBDCA AUC 5 plus Nab-PTX 100 mg/m^2 (level 0 cohort). Dose-limiting toxicity (DLT) was assessed during cycle 1. DLT was considered to be any of the following adverse events: grade 4 (Common Terminology Criteria for Adverse Events ver. 4.0) neutropenia for ≥5 days, grade 3 or 4 febrile neutropenia, grade 4 thrombocytopenia, and grade 3 nonhematological toxicity for ≥5 days. Patients who did not receive Nab-PTX on day 8 for reasons other than DLT were excluded from the evaluation of DLT.

If more than 33% of patients receiving level 0 chemotherapy developed DLT, the dose was deescalated to CBDCA AUC 5 plus Nab-PTX 75 mg/m^2 (level -1 cohort). If less than 33% of patients receiving level 0 chemotherapy developed DLT, the dose was escalated to CBDCA AUC 6 plus Nab-PTX 100 mg/m^2 (level +1 cohort).

If more than 33% of patients receiving level -1 chemotherapy developed DLT, the RD could not be defined, and no phase II trial would be conducted. If less than 33% of patients receiving level -1 chemotherapy developed DLT, level -1 was considered to be the RD.

If more than 33% of patients receiving level +1 chemotherapy developed DLT, level 0 was considered to be the RD. If less than 33% of patients receiving level +1 chemotherapy developed DLT, level +1 was considered to be the RD.

In the phase II trial, patients received CBDCA plus nab-PTX treatment with the RD.

Ethics. This study complied with all the principles in the Declaration of Helsinki and has been approved by the institutional review board. All enrolled patients provided written informed consent. This trial was registered with the University Hospital Medical Information Network (UMIN) clinical trial registry (no. UMIN000014544).

Statistical analysis (Phase II). The primary endpoint of the phase II trial was progression-free survival (PFS). In a previous study, the median PFS was 2.9 months for the CBDCA plus PTX therapy for Japanese patients with NSCLC and PS 2 (9). Therefore, the PFS threshold of 3.0 months and an expected PFS of 6 months was set for the present study. To reach 10% (one-sided) significance and 80% statistical power, a minimum sample size of 24 patients was calculated to be required (10). Assuming a 10% exclusion rate, the planned sample size was 27 patients. Patients who were treated with RD in the phase I trial were included in the analysis of the phase II trial. All analyses were performed using JMP software (version 10.0; SAS Institute Inc., Cary, NC, USA).

Table I. *Patient characteristics*.

	Phase I trial N=10	Phase II trial N=27
Age, years		
Median (range)	70 (55-79)	69 (48-78)
Gender		
Male	5	17
Female	5	10
Stage		
IIIB	0	2
IV	8	21
Postoperative recurrence	2	3
Recurrence after radiotherapy	0	1
Histology		
Squamous cell carcinoma	2	5
Adenocarcinoma	8	20
Others	0	2
Mutation		
EGFR Exon20 insertion	2	3
EGFR Exon 18 G719X	0	1
Negative	8	23
Previous therapy		
Immune check point inhibitor	0	1
None	10	26
Comorbidity or previous illness		
Hypertension	2	5
Diabetes mellitus	3	7
Heart disease	2	5
Lung disease	3	4
Other cancer	2	4

Table II. *Treatment response in the phase II trial*.

	N=27
Complete response	0
Partial response	12
Stable disease	11
Progressive disease	4
Overall response rate (95%CI)	44% (28%-63%)
Disease control rate (95%CI)	85% (68%-94%)

Results

Patient characteristics. In total, 31 patients were enrolled from July 2014 through February 2018 in this study. The patient characteristics are listed in Table I. Ten patients were enrolled in the phase I trial. Twenty-seven patients, which included 6 patients from the phase I trial who were treated with the RD level, were enrolled in the phase II trial.

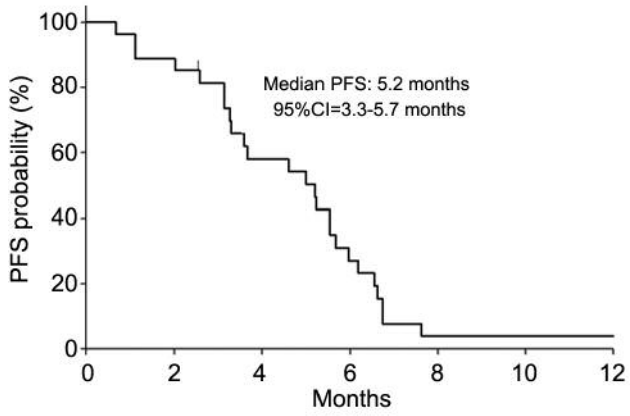

Figure 1. *Kaplan–Meier curve of progression-free survival (PFS).*

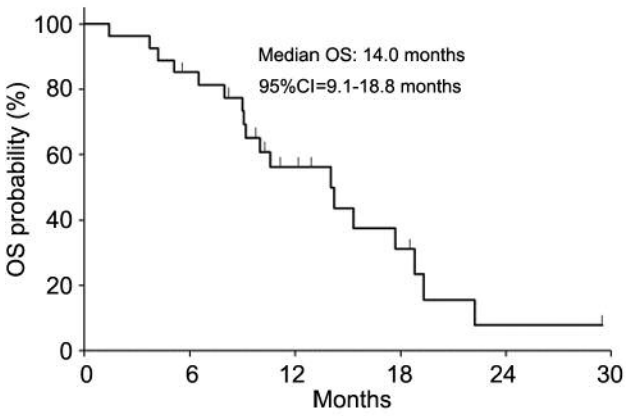

Figure 2. *Kaplan–Meier curve of overall survival (OS).*

The median age of the patients in the phase II trial was 69 years (range=48-78 years). Five patients had Sq NSCLC. Three patients had an *EGFR* exon 20 insertion, and 1 patient had an *EGFR* exon 18 G719X point mutation. One patient had been treated with immune checkpoint inhibitor.

Phase I. Four patients were enrolled in the level 0 cohort. One patient was excluded from evaluation of DLT because he could not receive Nab-PTX on day 8 due to elevated aspartate aminotransferase/ alanine aminotransferase (>100 IU/l). No DLT was observed in the three evaluable patients, and the dose was escalated to that of the level +1 cohort.

Three patients were enrolled in the level +1 cohort, and no DLT was observed. Three additional patients were enrolled in the same cohort, and no DLT was observed. The dose of level +1 cohort was chosen as the RD for phase II.

Phase II. Treatment delivery. The median number of chemotherapy cycles per patient was 4 (range=1-6 cycles). Eighteen of the 27 patients (67%) in phase II trial completed 4 chemotherapy cycles, and 9 patients (33%) did not complete the treatment plan. The major causes of discontinuation included disease progression (4 patients), worsening PS (3 patients), and patient's request (2 patients).

During the study treatment, 23 patients (85%) required treatment schedule modification. Twenty patients (74%) required extension of the next cycle of treatment, 12 patients (44%) required to skip Nab-PTX on day 8, and 10 patients (37%) required dose reduction.

The median CBDCA dose intensity was AUC 4.8/triweek (range=3.6-6 /triweek), and the relative CBDCA dose intensity was 80%. The median Nab-PTX dose intensity was 140 mg/m^2/triweek (range=81-200 mg/m^2/triweek), and the relative Nab-PTX dose intensity was 70%.

Efficacy. The objective tumor responses are summarized in Table II. The ORR was 44% (95% confidence interval (CI)=28%-63%), while the disease control rate was 85%. The ORRs in patients with Sq and non-Sq were 40% and 45%, respectively. The median PFS for all patients was 5.2 months (95%CI=3.3-5.7 months) (Figure 1). The median PFS in patients with Sq and non-Sq were 3.7 months and 5.2 months, respectively (p=0.78).

In the phase II trial, 17 patients (63%) received post-study treatment chemotherapy. Nine patients (33%) were treated with immune checkpoint inhibitor.

The median OS for all patients was 14.0 months (95%CI=9.1-18.8 months) (Figure 2). The median OS in patients with Sq and non-Sq were 9.0 months and 14.2 months, respectively (p=0.087).

The PS of 13 patients (48%) improved from 2 to a score of 1.

Adverse events. The adverse events experienced by patients during the treatment are shown in Table III. The incidence of grade 3 or 4 hematological adverse events was 73%. The incidence of grade 3 non-hematological adverse events was 37%, while none of the patients experienced grade 4 non-hematological adverse events. The most common grade 3 or 4 adverse events were neutropenia (60%), leukopenia (45%), anemia (30%), thrombocytopenia (22%), anorexia (15%), and fatigue (15%). Two patients experienced grade 3 febrile neutropenia. None of the patients experienced grade 5 adverse events.

Discussion

In the phase I trial, the RD for the phase II trial of CBDCA and Nab-PTX was determined to be CBDCA AUC 6 and

Table III. *Adverse events in the phase II trial.*

	All	Grade 1	Grade 2	Grade 3	Grade 4
Hematologic adverse events					
Anemia	26 (96%)	5 (19%)	13 (48%)	8 (30%)	0 (0%)
Leucopenia	24 (89%)	5 (19%)	7 (26%)	8 (30%)	4 (15%)
Neutropenia	23 (85%)	3 (11%)	4 (15%)	8 (30%)	8 (30%)
Thrombocytopenia	17 (63%)	5 (19%)	6 (22%)	6 (22%)	0 (0%)
Febrile neutropenia	2 (7%)	-	-	2 (7%)	0 (0%)
Nonhematologic adverse events					
Anorexia	19 (70%)	6 (22%)	9 (33%)	4 (15%)	0 (0%)
Fatigue	16 (59%)	6 (22%)	6 (22%)	4 (15%)	0 (0%)
Nausea	14 (52%)	7 (26%)	5 (19%)	2 (7%)	0 (0%)
Alopecia	14 (52%)	6 (22%)	8 (30%)	-	-
Diarrhea	8 (30%)	7 (26%)	0 (0%)	1 (4%)	0 (0%)
Sensory neuropathy	8 (30%)	7 (26%)	1 (4%)	0 (0%)	0 (0%)
Vomiting	6 (22%)	3 (11%)	3 (11%)	0 (0%)	0 (0%)
Infection	5 (19%)	-	3 (11%)	2 (7%)	0 (0%)

Data are presented as n (%).

Nab-PTX 100 mg/m^2. In the phase II trial, the median PFS of 5.2 months met the primary endpoint, and the lower limit of the 95%CI for the median PFS was 3.3 months, suggesting that CBDCA plus nab-PTX therapy may be effective for patients with NSCLC and PS 2. The median PFS of platinum combination therapy for NSCLC patients with PS 0-1 has been shown to be 4.0-6.3 months (4, 7, 11). Therefore, our result was comparable with the reported efficacy of platinum combination therapy for patients with PS 0-1. The ORR was 44% and is consistent with that of the CA031 study (7). The median OS was 14.0 months. In previous studies, the median OS of platinum combination therapy for NSCLC patients with PS 2 ranged from 4.7 months to 9.5 months (2, 9, 12-16). Therefore, CBDCA plus Nab-PTX may improve prognosis of NSCLC patients with PS 2.

In our study, patients received CBDCA on day 1 and Nab-PTX on days 1 and 8, every 21 days. No treatment-related deaths occurred. However, grade 3 or 4 adverse events were observed frequently, and most patients required modification of treatment schedule despite treatment without Nab-PTX on day 15. Okuma *et al.* conducted a phase II study to assess the efficacy and safety of the CA031 study regimen for elderly NSCLC patients (17). Their study was interrupted because of treatment-related deaths and serious adverse events. The modification of CBDCA plus Nab-PTX therapy should be considered for high-risk NSCLC patients. Gajra *et al.* reported the results of a phase II trial that evaluated the efficacy of CBDCA (AUC 5 day 1) plus nab-PTX (100 mg/m^2 days 1 and 8) combination induction and nab-PTX monotherapy (100 mg/m^2 days 1 and 8) maintenance treatment in patients with NSCLC and PS 2 (16). In that study, the ORR was 30%, and the median PFS was 4.4 months. Although, in our study, the patients did not receive maintenance therapy, the efficacy of treatment was comparable to that study. Moreover, the median OS (7.7 months) was short in that study. In our study, 63% of patients could receive post-study treatment chemotherapy. Treatment without maintenance therapy can cause reduction of treatment burden or facilitate induction of post-treatment chemotherapy. Our study treatment may be more reasonable for high-risk patients such as those with PS score of 2.

CBDCA plus pemetrexed therapy is reportedly effective among patients with advanced non-Sq NSCLC and PS 2 (2). Our study demonstrated the favorable efficacy of CBDCA plus Nab-PTX for non-Sq NSCLC (ORR: 45%; median PFS: 5.2 months; median OS: 14.2 months). The efficacy in patients with Sq was also favorable (ORR: 40%; median PFS: 3.7 months; median OS: 9.0 months). Relative to patients with non-Sq, patients with Sq had shorter PFS and OS. However, the results in Sq patients were comparable with those in previous reports (9, 12-16). Our study excluded patients who had interstitial pneumonia with a usual interstitial pneumonia pattern, while Usui *et al.* reported the safety of CBDCA plus Nab-PTX for NSCLC with interstitial pneumonia (18). CBDCA plus Nab-PTX may be feasible for patients who are ineligible for pemetrexed and may be a reasonable treatment option for NSCLC patients with PS 2.

The present study has several limitations. First, it was a small single-arm study. Second, patients with PS 2 were a heterogeneous population with variable ages, cancer condition, nutrition statuses, and comorbidities. Our study did not consider the reason of PS 2 and could not assess the efficacy and safety according to the reason of PS worsening.

Third, immunotherapies are becoming important first-line treatments for lung cancer (19). Although only one patient had been treated with immune checkpoint inhibitor before our study treatment, prior treatment with immune checkpoint inhibitor might be beneficial for the other patients. Further studies are needed to establish the optimal treatment modality for NSCLC patients with PS 2.

Recent studies have reported the efficacy of platinum combination chemotherapy plus immune checkpoint inhibitor (20-23). The combination of CBDCA, nab-PTX, and immune checkpoint inhibitor therapy has been shown to be effective for NSCLC patients with PS 0 or 1 (21, 23). The results of our study indicated that CBDCA plus Nab-PTX is tolerable for NSCLC patients with PS 2, and this finding is similar to that reported by Gajra *et al*. (16). A prospective study to verify the efficacy and safety of the combination of CBDCA, nab-PTX, and immune checkpoint inhibitor therapy for NSCLC patients with PS 2 is needed.

In conclusion, CBDCA plus Nab-PTX therapy demonstrates promising efficacy and safety for patients with advanced NSCLC and PS of 2.

Conflicts of Interest

Kazuhisa Nakashima, Haruyasu Murakami, and Hiroshige Yoshioka have received honoraria from Taiho Pharmaceutical Co., Ltd. Nobuyuki Yamamoto has received grants and honoraria from Taiho Pharmaceutical Co., Ltd. The other Authors declare no conflicts of interest.

Authors' Contributions:

Kazuhisa Nakashima: Corresponding Author. Creating the study protocol, recruitment of patients, and writing the manuscript; Hiroaki Akamatsu: Creating the study protocol, recruitment of patients, and reviewing the manuscript; Haruyasu Murakami: Creating the study protocol, recruitment of patients, and writing the manuscript; Takashi Niwa: Recruitment of patients and reviewing the manuscript; Yasuo Iwamoto: Recruitment of patients and reviewing the manuscript; Yuichi Ozawa: Recruitment of patients and reviewing the manuscript; Toshihide Yokoyama: Recruitment of patients and reviewing the manuscript; Hiroyasu Shoda: Recruitment of patients and reviewing the manuscript; Nobuyuki Yamamoto: Recruitment of patients and reviewing the manuscript; Hiroshige Yoshioka: Recruitment of patients and reviewing the manuscript; Ken Masuda: Recruitment of patients and reviewing the manuscript; Tateaki Naito: Recruitment of patients and reviewing the manuscript; Keita Mori: Primary biostatistician of this study. Creating the study protocol, statistical analysis, and reviewing the manuscript; Toshiaki Takahashi: Recruitment of patients and reviewing the manuscript.

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