Multicenter, single-arm phase II study of modified carboplatin/ nab-paclitaxel in untreated performance status 2 patients with advanced non-small cell lung cancer: TORG1426

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Background: Currently, only a few treatment options exist for performance status (PS) 2 patients with advanced non-small cell lung cancer (NSCLC), whereas the carboplatin/nab-paclitaxel (CBDCA/nab-PTX) regimen is attracting attention as a standard of care for PS 0–1 patients because of its wide suitability and modest risk of peripheral neuropathy. However, the treatment dose and schedule should be optimized for PS 2 patients. Therefore, we planned a single-arm phase II study to characterize the efficacy and tolerability of our modified CBDCA/nab-PTX regimen for untreated PS 2 patients with advanced NSCLC.

Methods: Enrolled patients were treated with CBDCA (area under the curve 5 on day 1) plus nab-PTX (70 mg/m^2 on days 1, 8, and 15) every 4 weeks for up to six cycles. The primary endpoint was the progression-free survival (PFS) rate at 6 months. As exploratory analyses, the reasons for PS 2 (disease burden versus comorbidities/indeterminant) and the Charlson Comorbidity Index (CCI) were evaluated as efficacy indicators.

Results: This study was terminated early because of slow accrual. Seventeen patients [median age, 68 years (range, 50–73 years)] received a median of three cycles. The 6-month PFS rate, median PFS, and median overall survival were 20.8% [95% confidence interval (CI): 0–41.6], 3.0 months (95% CI: 1.7–4.3), and 9.5 months (95% CI: 5.0–14.0), respectively. Exploratory analyses suggested better overall survival in patients whose PS was not attributable to the disease burden (median, 9.5 *vs.* 7.2 months) or whose CCI was ≤3 (median, 15.5 *vs.* 7.2 months). Grade 3–4 adverse events occurred in 12 (71%) patients, and grade 5 pleural infection occurred in one (6%) patient. Meanwhile, only one (6%) patient each experienced grade 1 peripheral neuropathy and grade 2 interstitial pneumonitis.

Conclusions: No conclusion could be drawn from this study because of its early termination. However, our modified CBDCA/nab-PTX regimen might be useful for PS 2 patients who hesitate to use regimens other than nab-PTX, and particularly patients concerned about peripheral neuropathy or interstitial pneumonitis. The potential role of PS 2 and CCI as efficacy predictors for this regimen should be further examined.

Introduction

Non-small cell lung cancer (NSCLC) is the leading cause of cancer death worldwide (1). Although there have been major advances in the treatment of NSCLC in recent years, performance status (PS) remains an important consideration when selecting treatment options (2). Currently, platinum-based chemotherapy in combination with immune checkpoint inhibitors (ICIs) has become a standard of care for PS 0–1 patients, whereas platinum-based chemotherapy remains a standard of care for PS 2 patients (3-5). Although patients with poor PS (PS ≥2) account for 30–50% of those with advanced NSCLC in the clinic, they are typically underrepresented in clinical studies, possibly because of concerns about the tolerability associated with experimental treatment and reduced efficacy relative to patients with good PS (PS 0–1) (6-8). In fact, overall survival (OS) in PS 2 patients with advanced NSCLC has been demonstrated to be worse than that in PS 0–1 patients (9,10).

Nevertheless, some recent prospective studies as well as subset analyses from several historical studies, including ECOG 1594 and CALGB 9730, have demonstrated the benefit of first-line platinum-based chemotherapy in PS 2 patients with advanced NSCLC (9-20). Among these studies, combination therapy with carboplatin/pemetrexed (CBDCA/PEM) was linked to significantly improved survival for PS 2 patients with advanced non-squamous NSCLC on the basis of a phase III study (12). As a result, the CBDCA/PEM regimen has become a reliable treatment option in this patient population. However, such patients are often ineligible for this regimen because of the histology of squamous cell carcinoma, pre-existing interstitial pneumonitis, or impaired renal function (21-24). Therefore, given the limited utilities of this regimen, the establishment of other combination therapies is warranted in PS 2 patients with advanced NSCLC.

In a recent phase III study of PS 0–1 patients with advanced NSCLC (CA031 trial), the CBDCA/nab-paclitaxel (nab-PTX) regimen, tended to exhibit superior progression-free survival (PFS) and OS versus the CBDCA/

PTX regimen on the basis of better tolerability in elderly patients older than 70 years (25,26). Thus, the CBDCA/nab-PTX regimen could be a valid treatment option for PS 2 patients. However, the treatment schedule required modification 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 every 3 weeks in that phase III study (25). Therefore, because the modified CBDCA/PTX regimen [CBDCA AUC 6 on day 1 plus PTX 70 mg/m^2 on days 1, 8, and 15 every 4 weeks (q4w)] achieved higher efficacy with less toxicity than single-agent docetaxel in PS 0–1 patients older than 70 years with advanced NSCLC, we used this regimen as a reference for PS 2 patients (27). We further modified the dose of CBDCA to AUC 5 according to the aforementioned phase III study that successfully adopted AUC 5 in the CBDCA/PEM regimen in PS 2 patients with advanced NSCLC (12).

Thus, this phase II study was designed to characterize the efficacy and tolerability of the modified CBDCA/nab-PTX regimen (CBDCA AUC 5 on day 1 plus nab-PTX 70 mg/m^2 on days 1, 8, and 15 q4w) in untreated PS 2 patients with advanced NSCLC. We present the following article in accordance with the TREND reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/trc-22-2144/rc).

Methods

Study population

The key inclusion criteria for registration were as follows: age ≥20 and ≤74 years; histological or cytological diagnosis of NSCLC; stage IIIB or IV NSCLC according to the Union for International Cancer Control Staging Manual in Thoracic Oncology, 7th edition; presence of measurable lesion(s) defined in the Response Evaluation Criteria in Solid Tumor version 1.1.; Eastern Cooperative Oncology Group PS 2; preserved bone marrow and organ functions; and no prior anticancer chemotherapy.

The key exclusion criteria for the registration were

as follows: active brain metastases (continuous systemic administration of prednisone more than 10 mg daily); uncontrolled pleural effusion; and pre-existing peripheral neuropathy grade ≥1 according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

Study design

This multicenter, single-arm phase II study was conducted at seven sites in Japan. Enrolled PS 2 patients were treated with the modified CBDCA/nab-PTX regimen (CBDCA AUC 5 on day 1 plus nab-PTX 70 mg/m^2 on days 1, 8, and 15 q4w) up to six cycles. The primary endpoint was the PFS rate at 6 months. Secondary endpoints included PFS, OS, objective response rate (ORR), disease control rate (DCR), incidence of adverse events (AEs), and quality of life (QOL). As exploratory analyses, the reasons for a diagnosis of PS 2 (disease burden versus comorbidities/indeterminant) and the Charlson Comorbidity Index (CCI) were evaluated as potential predictors of therapeutic efficacy for this regimen.

Ethics

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethical Review Board for Medical and Health Research Involving Human Subjects at Teikyo University (No. 15-012). All enrolled patients provided written informed consent. This trial was registered with the University Hospital Medical Information Network clinical trial registry (No. UMIN000019458).

Study assessments

All patients who received ≥1 dose of study drugs were included in the study assessments. Tumor assessment via systemic computed tomography scan and brain magnetic resonance imaging was conducted every 6 weeks until treatment discontinuation, withdrawal of consent, or death. AEs were classified by the Medical Dictionary for Regulatory Activities, and severity was assessed according to CTCAE v4.0. The Functional Assessment of Cancer Therapy-Lung Cancer Subscale (FACT-LCS) as the QOL survey was assessed on day 1 of every cycle throughout the study. CCI was assessed before the start of cycle 1.

Statistical analyses

The expected 6-month PFS rate and its threshold [the lower limit of the 95% confidence interval (CI)] were assumed to be 50% and 30%, respectively, based on the results of previous studies of PS 2 patients with advanced NSCLC (9-20). The estimated power of this design was 80% with a type I error of 0.05, resulting in a target population of 35 patients.

PFS and OS were estimated using the Kaplan–Meier method. ORR was defined as the percentage of patients who had a complete or partial radiological response. DCR was defined as the percentage of patients who had a complete or partial response, or stable disease. Patients with available FACT-LCS data from baseline and ≥1 post-baseline visit were included in the QOL analyses. All scales were aligned so that a negative change from baseline indicated improvement. Data were analyzed using EZR software, version 1.36 (Saitama Medical Center, Jichi Medical University, Saitama, Japan), unless otherwise stated (28).

Results

Patients

Because of slower-than-planned accrual, enrollment was terminated early. In total, 17 patients were enrolled in this study from September 2015 to August 2018. Patient characteristics are listed in *Table 1*.

The median age was 68 years (range, 50–73 years), and 24% of patients were aged 70–73 years. Most patients were men (94%), had adenocarcinoma (59%), had stage IV cancer (94%), had a smoking history (100%), were epidermal growth factor receptor (EGFR) mutation-negative (70%), were anaplastic lymphoma kinase translocation-negative (65%), and had no brain metastasis (82%).

The reasons for a diagnosis of PS 2 were the disease burden (70%), comorbidities (12%), and indeterminant, meaning that the exact cause was difficult to clarify (18%). The median CCI was 3 (range, 1–7), and the score was linked to a variety of comorbidities, including chronic obstructive pulmonary disease and diabetes.

Patient flow

Patient flow is summarized in *Figure 1*. Among all 17 enrolled patients, treatment discontinuation was observed

Table 1 Baseline patient characteristics

Variables	Value (N=17)
Age	
Median [range], years	68 [50–73]
50–69 years, n [%]	13 [76]
70–73 years, n [%]	4 [24]
Sex, n [%]	
Male	16 [94]
Female	1 [6]
Histology, n [%]	
Adenocarcinoma	10 [59]
Squamous cell carcinoma	6 [35]
Others	1 [6]
Stage, n [%]	
IIIB	1 [6]
IV	16 [94]
Smoking habit, n [%]	
Current/former	17 [100]
Never	0 [0]
EGFR mutation, n [%]	
Positive	2 [12]
Negative	12 [70]
Unknown	3 [18]
ALK translocation, n [%]	
Positive	0 [0]
Negative	11 [65]
Unknown	6 [35]
Brain metastasis, n [%]	
Positive	3 [18]
Negative	14 [82]
Reasons for a diagnosis of PS 2, n [%]	
Disease burden	12 [70]
Comorbidities	2 [12]
Indeterminant	3 [18]
CCI	
Median [range]	3 [1–7]
>3, n [%]	8 [47]
≤3, n [%]	9 [53]

Table 1 (*continued*)

Table 1 (*continued*)

Variables	Value (N=17)
Comorbidities associated with CCI, n [%]	
Myocardial infarction	1 [6]
Peripheral vascular disease	1 [6]
Cerebral vascular disease	1 [6]
Chronic obstructive pulmonary disease	3 [18]
Connective tissue disease	1 [6]
Mild liver disease	1 [6]
Diabetes	2 [12]
Hemiplegia	1 [6]

EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase; PS, performance status; CCI, Charlson Comorbidity Index.

in 13 patients (76%) during a median follow-up period of 7.3 months (range: 0.5–22.8 months). The reasons for treatment discontinuation were progressive disease in six patients (35%); AEs in 4 patients (24%), including grade 2 interstitial pneumonitis, grade 3 cerebral infarction, grade 4 lung infection, and grade 5 pleural infection in one patient (6%) each; and patient request in three patients (18%). Finally, four patients (24%) completed the protocol treatment.

Treatment exposure

Among 17 patients, the median treatment duration was three courses (range, 1–6). Five (29%) patients received only one cycle of treatment, whereas four (24%) patients completed six cycles. Dose delay, dose skipping, and dose reduction occurred in 10 (59%), 8 (47%), and 1 (6%) patient, respectively.

Efficacy

Tumor responses to the treatment are summarized in *Table 2*. The ORR and DCR were 17.4% (95% CI: 3.8–43.4) and 70.6% (95% CI: 44.0–89.7), respectively.

Kaplan–Meier curves of PFS and OS are presented in *Figure 2A,2B*, respectively. The 6-month PFS rate and median PFS were 20.8% (95% CI: 0–41.6) and 3.0 months (95% CI: 1.7–4.3), respectively, whereas median OS was 9.5 months (95% CI: 5.0–14.0).
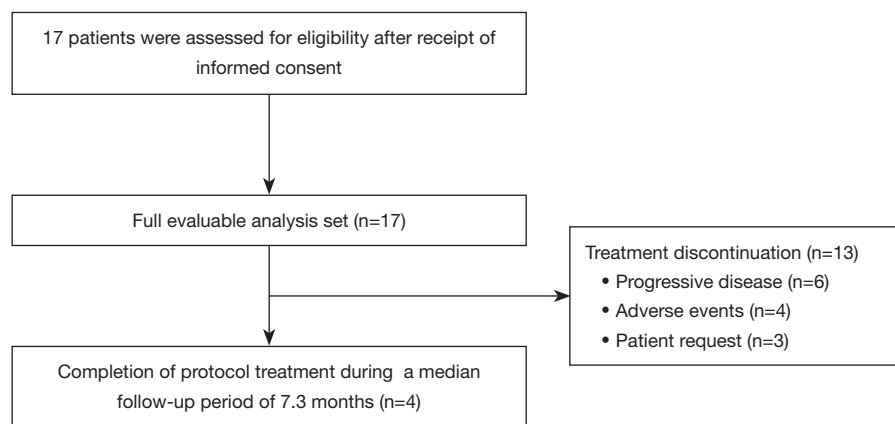
Figure 1 Patient flow in this phase II study of the modified carboplatin plus nab-paclitaxel regimen.

Table 2 Tumor responses to the treatment

Variables	Value (N=17)
Best overall response, n [%]	
Complete response	0 [0]
Partial response	3 [17]
Stable disease	9 [53]
Progressive disease	3 [17]
Could not be evaluated	2 [12]
Objective response rate	
No. of patients with responses	3
% of patients (95% CI)	17.4 (3.8–43.4)
Disease control rate	
No. of patients with responses	12
% of patients (95% CI)	70.6 (44.0–89.7)

CI, confidence interval.

When histology was classified into two categories [squamous cell carcinoma (n=6) and non-squamous cell carcinoma (n=11)], the ORR, median PFS, and median OS were 9%, 3.0 months, and 6.6 months, respectively, in the former group and 33%, 3.7 months, and 9.5 months, respectively, in the latter group.

The post-study treatment rate was 65% (11/17). Median PFS in 11 patients who received second-line chemotherapy was 4.5 months, whereas that in six patients who did not receive second-line treatment was 1.7 months. Similarly, median OS was 15.5 months in patients who received second-line chemotherapy, versus 3.2 months in those who did not receive second-line treatment. Statistical analyses were not performed because of the small sample size.

Therapeutic efficacy according to the reasons for a diagnosis of PS 2 or CCI

Therapeutic efficacy according to the reasons for a diagnosis of PS 2 or CCI is summarized in *Table 3*. Statistical analyses were not performed because of the small sample size.

The three aforementioned reasons for a diagnosis of PS 2 were combined into two categories [disease burden (n=12) and comorbidities/indeterminant (n=5)]. The ORR, median PFS, and median OS in the former group were 0%, 2.6 months, and 7.2 months, respectively, compared with 60%, 5.2 months, and 9.5 months, respectively, in the latter group.

Similarly, when CCI was classified into two categories [CCI >3 (n=8) and CCI ≤3 (n=9)], the ORR, median PFS, and median OS were 13%, 3.0 months, and 7.2 months, respectively, in the former group and 22%, 3.7 months, and 15.5 months, respectively, in the latter group.

Tolerability

A summary of grade 3–5 AEs is presented in *Table 4*. Among the 17 patients, grade 3 and 4 AEs occurred in 10 (59%) and 2 (12%) patients, respectively. Grade 5 pleural infection occurred in one (6%) patient, although the cause was determined to be unrelated to the study drugs by the Data and Safety Monitoring Committee. The most frequent grade 3–4 hematological AEs were anemia (18%) and neutropenia (18%), whereas the most frequent grade 3–4
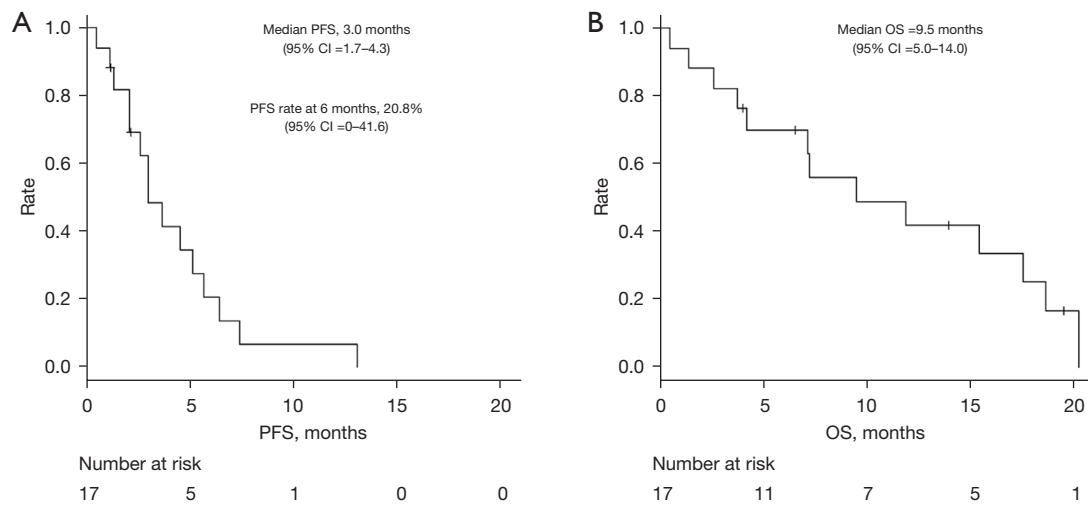
Figure 2 Kaplan–Meier curves of PFS (A) and OS (B) in performance status 2 patients with advanced non-small-cell lung cancer treated with the modified carboplatin plus nab-paclitaxel regimen. CI, confidence interval. PFS, progression-free survival; OS, overall survival.

Table 3 Therapeutic efficacy according to the reasons for a diagnosis of PS 2 or CCI

Efficacy variable	Reasons for a diagnosis of PS 2		CCI	
	Disease burden (n=12)	Comorbidities/indeterminant (n=5)	Score >3 (n=8)	Score ≤3 (n=9)
Objective response rate (%)	0	60	13	22
Median PFS (months)	2.6	5.2	3.0	3.7
Treatment discontinuation rate (%)[†]	33	40	50	22
Post-study treatment rate (%)	58	80	50	78
Median OS (months)	7.2	9.5	7.2	15.5

[†], not attributable to disease progression. PS, performance status; CCI, Charlson Comorbidity Index; PFS, progression-free survival; OS, overall survival.

non-hematological AEs were lung infection (24%), malaise (24%), and hypoalbuminemia (18%). Meanwhile, only one (6%) patient each developed grade 1 peripheral neuropathy and grade 2 interstitial pneumonitis, which were of special interest.

FACT-LCS

Mean changes in FACT-LCS from baseline during the treatment are presented in *Figure 3*. Among the 17 enrolled patients, FACT-LCS data were available for 11 (65%) patients, whereas these data were unavailable because of a lack of baseline data in one (6%) patient and unavailable post-baseline data in 5 (29%) patients. Among the 11 included patients, the symptom burden generally decreased,

and a trend toward FACT-LCS improvement was observed in cycles 2–6, although it did not reach a clinically meaningful level (i.e., mean change ≤–10 points). The mean maximum change from baseline at any point during the treatment was –4.9 points (standard deviation, 5.0).

Discussion

This phase II study suggested the potentially favorable efficacy and tolerability of the modified CBDCA/nab-PTX regimen (CBDCA AUC 5 on day 1 plus nab-PTX 70 mg/m^2 on days 1, 8, and 15 q4w) in untreated PS 2 patients with advanced NSCLC despite the failure to draw conclusions because of early termination. The ORR, 6-month PFS rate, median PFS, and median OS were 17.4% (95% CI:

Table 4 Summary of grade 3–5 adverse events

| Adverse events	Grade 1, n [%]	Grade 2, n [%]	Grade 3, n [%]	Grade 4, n [%]	Grade 5, n [%]	Grade 3–5, n [%]
Hematological						
Leukopenia	3 [18]	4 [24]	2 [12]	0 [0]	0 [0]	2 [12]
Neutropenia	2 [12]	3 [18]	2 [12]	1 [6]	0 [0]	3 [18]
Anemia	4 [24]	10 [59]	3 [18]	0 [0]	0 [0]	3 [18]
Thrombocytopenia	5 [29]	1 [6]	1 [6]	1 [6]	0 [0]	2 [12]
Non-hematological						
Lung infection	0 [0]	2 [12]	3 [18]	1 [6]	0 [0]	4 [24]
Malaise	1 [6]	2 [12]	4 [24]	0 [0]	0 [0]	4 [24]
Hypoalbuminemia	6 [35]	7 [41]	3 [18]	0 [0]	0 [0]	3 [18]
Hyponatremia	9 [53]	0 [0]	2 [12]	0 [0]	0 [0]	2 [12]
Anorexia	1 [6]	6 [35]	2 [12]	0 [0]	0 [0]	2 [12]
ALP elevation	5 [29]	2 [12]	1 [6]	0 [0]	0 [0]	1 [6]
Nausea	2 [12]	3 [18]	1 [6]	0 [0]	0 [0]	1 [6]
Arthralgia	0 [0]	0 [0]	1 [6]	0 [0]	0 [0]	1 [6]
Cerebral infarction	0 [0]	0 [0]	1 [6]	0 [0]	0 [0]	1 [6]
Febrile neutropenia	0 [0]	0 [0]	1 [6]	0 [0]	0 [0]	1 [6]
Pleural infection	0 [0]	0 [0]	0 [0]	0 [0]	1 [6]	1 [6]
Special interest						
Peripheral neuropathy	1 [6]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]
Interstitial pneumonitis	0 [0]	1 [6]	0 [0]	0 [0]	0 [0]	0 [0]

ALP, alkaline phosphatase.
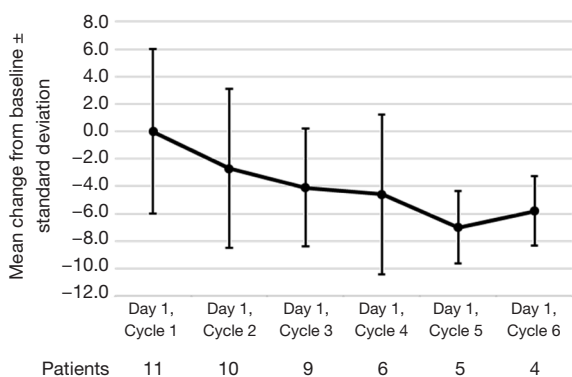
Figure 3 Mean changes in the FACT-LCS from baseline during treatment. FACT-LCS, Functional Assessment of Cancer Therapy-Lung Cancer Subscale.

3.8–43.4), 20.8% (95% CI: 0–41.6), 3.0 months (95% CI: 1.7–4.3), and 9.5 months (95% CI: 5.0–14.0), respectively. The frequencies of grade 3–4 AEs, grade 5 AEs, treatment discontinuation not attributable to disease progression, and post-study treatment were 71%, 6%, 35%, and 65%, respectively.

When comparing the results of our study with historical data of platinum-based chemotherapy in untreated PS 2 patients with advanced NSCLC, to our knowledge, there have been at most 10 prospective studies (11-20). Among these studies, separate comparisons of our study are shown in *Table 5* (versus other studies with CBDCA/nab-PTX) and *Table 6* (versus other studies with chemotherapy regimen other than CBDCA/nab-PTX). Comprehensively, the

Table 5 Comparison of present study with other studies using CBDCA/nab-PTX in untreated PS 2 patients with advanced NSCLC

Author	Study phase	Accrual	Regimen	n	ORR (%)	PFS rate at 6 months (%)	Median PFS (months)	Median OS (months)	Grade 3–4 AEs (%)	Grade 5 AEs (%)	Treatment discontinuation[†] (%)	Post-study treatment (%)
Nakasima (19)	II	Completed	Cb [6] + nab-PTX (100, day 1/8), q3w	27	44	28[‡]	5.2	14.0	73	0	19	63
Gajra (20)	II	Suspended	Cb [5] + nab-PTX (100, day 1/8), q3w	40	30	33	4.4	7.7	75	3	48	—
Our study	II	Suspended	Cb [5] + nab-PTX (70, day 1/8/15), q4w	17	17	21	3.0	9.5	71	6	41	65

[†], not attributable to disease progression; [‡], estimated according to the Kaplan–Meier curve in the original article. PS, performance status; NSCLC, non-small-cell lung cancer; ORR, objective response rate; PFS, progression-free survival; OS, overall survival; AE, adverse event; Cb, carboplatin; PTX, paclitaxel; q3w, every 3 weeks; q4w, every 4 weeks.

results of the present study appear to show modest efficacy in the former group and comparable efficacy in the latter group.

Thus, our study is the 11th prospective study of any regimen and the third prospective study of the nab-PTX-based regimen, providing an expanded treatment option for PS 2 patients with advanced NSCLC. As a characteristic of each regimen, the indication for PEM-based regimens is often restricted by the histology of squamous cell carcinoma, pre-existing interstitial pneumonitis, and impaired renal function (21-24). Similarly, the indication for gemcitabine (GEM)-based regimens is especially restricted by the pre-existing interstitial pneumonitis (23,29). However, PTX-based regimens are less likely to be restricted by these factors despite the high incidence of peripheral neuropathy (23,30). With the advent of nab-PTX-based regimens, the incidence of this unpleasant AE has been reduced to some extent. In the CA031 study, the frequencies of all-grade peripheral neuropathy for PTX-based and nab-PTX-based regimens were 62% and 37%, respectively (25,26). Furthermore, among three nab-PTX-based regimens presented in *Table 5*, the frequencies of all-grade peripheral neuropathy reported by Nakashima *et al.*, Gajra *et al.*, and our study were 30%, 16%, and 6%, respectively, although the frequencies of grade 3–4 AEs and grade 5 AEs were comparable across the studies (19,20). Therefore, our regimen might be useful for PS 2 patients who have pre-existing comorbidities, including interstitial pneumonitis and impaired renal function, and those who wish to avoid peripheral neuropathy. In fact, our modified CBDCA/nab-PTX regimen did not negatively affect QOL

as assessed by FACT-LCS.

In contrast, when comparing the results of our study with historical data of immunotherapy, to our knowledge, there has been one prospective study in PS 2 patients with advanced NSCLC (PePS2) (31). This study included both untreated (n=24) and pre-treated (n=36) patients. When treated with pembrolizumab monotherapy, the ORR, median PFS, and median OS were 27%, 4.4 months, and 9.8 months, respectively, whereas the frequencies of grade 3–4 AEs, grade 5 AEs, and treatment discontinuation not attributable to disease progression were 15%, 0%, and 10%, respectively. Furthermore, in patients with a PD-L1 ≥50% status (n=15), the ORR, median PFS, and median OS were 47%, 12.6 months, and 14.6 months, respectively. Therefore, the results of the PePS2 study seem more favorable than those of our study in terms of the efficacy and tolerability. However, major limitation of the PePS2 study is the small sample size and the absence of a control arm. Recently, the results of a randomized phase III study of nivolumab/ipilimumab versus carboplatin-based doublet in untreated PS 2 patients with advanced NSCLC (eNErgy) were presented (32). This study included both PS 2 (n=79) and elderly (n=137) patients. Among them, the median OS of 2.9 months in PS 2 patients treated with nivolumab/ipilimumab seemed unfavorable compared with that of 6.1 months in those treated with carboplatin-based doublet despite no statistically significant difference. Furthermore, recent retrospective analysis of untreated PS 2 patients with advanced NSCLC and a PD-L1 ≥50% status (n=56) demonstrated the median PFS of 2.6 months and the median OS of 7.8 months when treated with

Table 6 Comparison of present study with other studies using chemotherapy regimen other than CBDCA/nab-PTX in untreated PS 2 patients with advanced NSCLC

Author	Study phase	Accrual	Regimen	n	ORR (%)	PFS rate at 6 months (%)	Median PFS (months)	Median OS (months)	Grade 3–4 AEs (%)	Grade 5 AEs (%)	Treatment discontinuation[†] (%)	Post-study treatment (%)
Any regimen												
Sweeney (11)	II	Suspended	Cis/PTX, Cb/ PTX, Cis/ GEM, Cis/DTX	64	14	—	1.7	4.1	75	7	—	—
PEM-based regimens												
Zukin (12)	III	Completed	Cb [5] + PEM (500, day 1), q3w	103	24	49	5.8	9.3	—	4	—	35
GEM-based regimens												
Kosmidis (13)	II	Completed	Cb [3] + GEM (1,250, day 1/14), q4w	43	14	—	4.1	6.7	—	2	26	—
Reynolds (14)	III	Suspended	Cb [5] + GEM (1,000, day 1/8), q3w	85	21	38[‡]	3.8	6.7	—	0	32	—
Morabito (15)	III	Suspended	Cis [60] + GEM (1,000, day 1/8), q3w	28	18	34[‡]	3.3	5.9	—	0	7	25
PTX-based regimens												
Langer (16)	II	Completed	Cis [60] + GEM (1,000, day 1/8), q3w	47	23	32[‡]	3.0	6.9	80	0	39	—
			Cb [6] + PTX (200, day 1), q3w	51	14	28[‡]	3.5	6.2	80	2	33	—
Lilenbaum (17)	II	Completed	Cb [6] + PTX (200, day 1), q3w	51	12	16[‡]	3.5	9.7	35	4	24	57
Langer (18)	III	Completed	Cb [6] + PTX (225, day 1), q3w	201	37	—	4.6	8.0	—	5	30	50
Present nab-PTX-based regimen												
Our study	II	Suspended	Cb [5] + nab-PTX (70, day 1/8/15), q4w	17	17	21	3.0	9.5	71	6	41	65

[†], not attributable to disease progression; [‡], estimated according to the Kaplan–Meier curve in original article. PS, performance status; NSCLC, non-small-cell lung cancer; ORR, objective response rate; PFS, progression-free survival; OS, overall survival; AE, adverse event; Cis, cisplatin; Cb, carboplatin; PTX, paclitaxel; GEM, gemcitabine; DTX, docetaxel; PEM, pemetrexed; q3w, every 3 weeks; q4w, every 4 weeks.

pembrolizumab monotherapy (33). Therefore, the issue of superiority between platinum-based chemotherapy and immunotherapy in untreated PS 2 patients with advanced NSCLC seems still controversial (4,5).

In the present study, there appeared to be a potential signal for better efficacy in patients whose PS was attributable to reasons other than the disease burden and whose CCI was ≤3 as presented in *Table 3*. To date, it is conceivable that chemotherapy can potentially exacerbate the clinical situation in PS 2 patients who are symptomatic because of comorbidities, whereas patients whose poor PS is attributable to the disease burden may actually benefit from treatment (16,34). Contrary to these expectations, in our study, the former group experienced a potential benefit from our regimen in terms of efficacy over the latter group, although statistical analyses were not performed because of the small sample size. Given the modest efficacy but low treatment discontinuation rate and high post-study treatment rate of our study relative to the reported prospective studies, the balance between the efficacy and tolerability of our modified CBDCA/nab-PTX regimen might be leaning toward tolerability, suggesting the suitability of this regimen for patients whose PS is attributable to comorbidities. Interestingly, a retrospective analysis of patients treated with pembrolizumab monotherapy demonstrated that patients with PS 2 because of comorbidities had significantly better median PFS (5.6 *vs.* 1.8 months) and median OS (11.8 *vs.* 2.8 months) than those with PS 2 because of the disease burden (35). To our knowledge, no prospective studies distinguished the treatment outcome between comorbidities and the disease burden as the cause of PS in the field of cytotoxic chemotherapy. Therefore, our prospective study would be also valuable from this point of view.

On the other hand, we need to deepen our awareness of the disease burden. The disease burden refers to the severity of lung cancer itself and to its impact on daily life. However, this index is conceptual and is largely determined by the subjective judgment of the physician. If we manage to determine it by the objective judgment, it would be an index that included not only tumor volume but also the intensity of tumor progression (T factor, site of metastasis, number of metastases, etc.). In our study, we unfortunately did not obtain the information on tumor volume and T factor, but we did obtain the information on site of metastasis and number of metastases. Thus, we explored the association of these factors with PS categories and ORR using Spearman's correlation coefficients, but no significant correlations were observed (data not shown). We also performed a similar exploratory analysis using the chi-square test after creating a two-way table, but again no significant difference was observed (data not shown). Therefore, although the small sample size may have affected these results, we believe that efforts should be made to further clarify this index.

For the significance of CCI, this method of classifying comorbidity is known as a valid system for estimating the risk of death from comorbid disease, where there are stepwise increases in the mortality risk with each increased level of the comorbidity index (36). In elderly patients with advanced NSCLC, CCI was correlated with both the treatment discontinuation rate and median OS in a phase III study comparing GEM/vinorelbine and vinorelbine alone (37). In that study, the treatment discontinuation rates of patients with CCI <3 and CCI ≥3 were 30% and 82%, respectively, whereas the median OS times of patients with CCI 0, 1–2, and ≥3 were 6.5, 4.8, and 3.7 months, respectively (37). Similarly, our study also suggested a potential signal for better efficacy among patients with CCI ≤3 than among those with CCI >3 regarding the treatment discontinuation rate and median OS, although statistical analyses were not performed because of the small sample size. Therefore, in addition to the reasons for a diagnosis of PS 2, CCI might have potential as a predictor of therapeutic efficacy for our modified CBDCA/nab-PTX regimen.

Finally, our study had several limitations. First, this was a small, single-arm phase II study that failed to draw a conclusion. Therefore, we have to interpret our results with caution, including those for therapeutic efficacy according to the reasons for a diagnosis of PS 2 or CCI. However, we believe these signals suggested in the present study are reasonable and precious. Therefore, a large-scale prospective study is needed to confirm our findings. Second, this study was terminated early because of slow accrual. Regarding the early suspension of our study, early termination occurred in four previous studies (*Tables 5,6*) because of toxicity in one phase II study and slow accrual in one phase II and two phase III studies, indicating the difficulty of conducting prospective studies in this patient population (11,14,15,20). Nonetheless, we must continue clinical studies to explore more treatment options for such patients. Third, the completion of this study suffered a significant delay owing to the slower-than-expected patient accrual rate; during this time period, the mainstream treatment options for advanced NSCLC have shifted towards ICI-based regimens (3). However, platinum-based chemotherapy remains a standard of care for PS 2 patients, and the efficacy

and tolerability of platinum-based chemotherapy with ICIs for PS 2 patients remains controversial (4,5). Furthermore, even if ICI monotherapy is used as the first-line treatment, our well-tolerated regimen could still be a treatment option for second-line treatment. Therefore, our modified CBDCA/nab-PTX regimen would play an important role even in the current era of ICI therapy. Fourth, we accepted the entry of EGFR mutation-positive status and anaplastic lymphoma kinase translocation-positive status although these had not been allowed in the 10 previous prospective studies of untreated PS 2 NSCLC (11-20). This is because we learned, during the planning of our study, that the completion of this type of study was not always satisfactory, and thus we anticipated that patient accrual would be difficult in our study as well. On the other hand, the primary endpoint of our study was the 6-month PFS rate. Therefore, we determined that this endpoint would not be affected by a driver gene mutation-positive status. As a result, two patients with EGFR mutation-positive status were enrolled in our study. One patient had PFS of 2.1 months based on the discontinuation of our regimen due to AEs, but had OS of 18.7 months, including 6.0 months of second-line treatment with EGFR inhibitor. The remaining patient also discontinued treatment due to AEs with PFS of 2.2 months, and requested the best supportive care for the subsequent treatment, resulting in OS of 7.3 months. Thus, the former patient may have achieved long-term OS based on the use of EGFR inhibitor, regardless of our regimen. This should be kept in mind when interpreting the median OS of our study. Fifth, we did not report how many patients were screened, how many exclusions occurred, and what their causes were in our study. Currently, patients with PS 2 are still underrepresented in clinical studies, possibly because the reasons for PS 2 are multifactorial. On the other hand, previous studies of patients with PS 2 have enrolled only those with preserved organ function who could receive cytotoxic chemotherapy. Therefore, this underrepresentation of patients with PS 2 in clinical studies leads to a data-free zone regarding their treatment. To address this issue, after clarifying the details of ineligibility, future clinical studies need to consider broader eligibility criteria to better reflect this population to obtain the best evidence for their treatment. In our study, enrollment was terminated early because of slower-than-planned accrual. Therefore, it was precisely in our study that we needed to identify the reasons for poor accrual of patients with PS 2. In the future, we would like to conduct another study to obtain such important data, by all means.

Conclusions

This phase II study failed to draw conclusions because of its early termination. However, our modified CBDCA/nab-PTX regimen might be useful for PS 2 patients who hesitate to receive PEM- or GEM-based regimens because of pre-existing comorbidities and desire to avoid PTX-based regimens because of peripheral neuropathy with an emphasis on tolerability. The potential roles of the reasons for a diagnosis of PS 2 and CCI as predictors of therapeutic efficacy for this regimen should be further examined.

Footnote

Reporting Checklist: The authors have completed the TREND reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-2144/rc

Data Sharing Statement: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-2144/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-2144/coif). NS obtained research grants from Eli Lilly, Chugai Pharmaceutical, Taiho Pharmaceutical, Pfizer, Ono Pharmaceutical, Nippon Kayaku, Takeda Pharmaceutical, and Boehringer Ingelheim and received speaking honoraria from Eli Lilly, AstraZeneca, MSD, Chugai Pharmaceutical, Taiho Pharmaceutical, Pfizer, Ono Pharmaceutical, Nippon Kayaku, Takeda Pharmaceutical, Daiichi Sankyo, Boehringer Ingelheim, and Bristol Myers Squibb. AB obtained research grants from Ono Pharmaceutical, AstraZeneca, Pfizer, Chugai Pharmaceutical, MSD, and AbbVie and received speaking honoraria from Ono Pharmaceutical, Bristol Myers Squibb, AstraZeneca, Pfizer, Chugai Pharmaceutical, Eli Lilly, and Merck Biopharma. YN obtained research grants from JSPS KAKENHI, Takeda Pharmaceutical and Bristol Myers Squibb and received speaking honoraria from Takeda Pharmaceutical, Bristol Myers Squibb, Ono Pharmaceutical,

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