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Phase I/II study of biweekly nab-paclitaxel in patients with platinum-pretreated non-small cell lung cancer: NJLCG1402

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Abstract

Background: NJLCG1402 was a phase I/II trial investigating biweekly nanoparticle albumin-bound paclitaxel (nab-PTX) in patients with advanced non-small cell lung cancer (NSCLC).

Methods: The study included patients aged ≥20 years with previously treated NSCLC. Nab-PTX (100–150 mg/m^2) was administered biweekly in a 28-day cycle. The phase I portion was performed to determine the recommended phase II dose of nab-PTX. In the phase II portion, the primary endpoint was the objective response rate. Secondary endpoints were disease control rate, progression-free survival, overall survival, and safety.

Results: A total of 15 patients received biweekly nab-PTX (100–150 mg/m^2) and 12 patients in phase II were treated with 150 mg/m^2. In the phase I portion, 150 mg/m^2 was determined as the recommended dose. Among those treated with 150 mg/m^2, the objective response rate was 22%, and the median progression-free and overall survival was 3.6 and 11.2 months, respectively. Adverse events grade ≥3 were observed in 39% of patients.

Conclusions: Biweekly nab-PTX monotherapy was well tolerated and exhibited favorable antitumor activity in patients with previously treated NSCLC.

KEYWORDS
nab-PTX monotherapy, non-small cell lung cancer, phase I/II trial

INTRODUCTION

Lung cancer remains the most commonly diagnosed cancer and a leading cause of cancer-related death globally.[1] Despite improvements in therapeutic modalities over the past few decades, such as the combination of immune-chemotherapy and targeted therapy, the survival benefit has been restricted to patients with advanced disease. Anticancer agents, such as docetaxel, pemetrexed, tegafur/gimeracil/oteracil (S-1 regimen), and immune checkpoint inhibitor monotherapy, are standard treatments for patients with previously treated non-small cell lung cancer (NSCLC).[2–8] Most advanced lung cancer patients receive several lines of chemotherapy and immunotherapy; however, few prospective trials to date have investigated the efficacy and safety of third- or later-line therapies.

Nanoparticle albumin-bound paclitaxel (nab-PTX) is a Cremophor EL-free, albumin-bound nanoparticle formulation of PTX that is easily soluble in saline.[9,10] Nab-PTX reduces the risk of anaphylaxes triggered by Cremophor EL compared with conventional PTX. In phase II and III trials, nab-PTX and carboplatin significantly increased the objective response rate

(ORR) in comparison with conventional PTX in patients with untreated advanced NSCLC.[11–15] Moreover, nab-PTX monotherapy showed antitumor activity against untreated advanced NSCLC in a phase I/II study.[16] However, its role as third-line or later-line chemotherapy for previously treated NSCLC has not been clarified. Furthermore, the optimal dose and schedule of nab-PTX monotherapy in previously treated patients with advanced NSCLC have not been established. Thus, investigating the optimal dose, schedule, efficacy, and safety of nab-PTX monotherapy for these populations is important to improve outcomes and optimize the use of nab-PTX in patients with NSCLC.

This phase I/II dose-finding study was conducted in collaboration with the North Japan Lung Cancer Study Group (NJLCG). Phase I results describe the biweekly nab-PTX maximum tolerated dose (MTD) and all adverse events to nab-PTX monotherapy in patients with previously treated advanced NSCLC.

METHODS

Patients

Stage IV or postoperative recurrent NSCLC patients who had received two or more chemotherapy regimens for advanced NSCLC were eligible for inclusion in this study. All patients had received prior platinum-based chemotherapy. Laboratory requirements for eligibility were absolute neutrophil count $\geq 1.5 \times 10^9$ cells/l, hemoglobin ≥9 g/dl, platelets count $\geq 100 \times 10^9$ cells/l, aspartate transferase and alanine transaminase ≤100 IU, total bilirubin ≤1.5 mg/dl, and creatinine ≤1.5 mg/dl. Patients previously treated with PTX or having peripheral neuropathy grade >2 were excluded. The Institutional Review Board of Tohoku University (Sendai, Japan; approval no.: 2014-2-116-1) approved the protocol and informed consent documents. All patients provided written informed consent and this trial is registered with UMIN-CTR (UMIN000014893).

Study design

This study was an open-label, multicenter, single-arm phase I/II trial for patients with platinum-pretreated NSCLC. The primary endpoints were the MTD to evaluate the tolerability of biweekly nab-PTX monotherapy in phase I of the trial, and the ORR of biweekly nab-PTX monotherapy in phase II of the trial. The ORR was evaluated only patients who were treated with the recommended dose (RD). Tumor response was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 in phase II of the trial. Secondary endpoints were safety in phase I, and progression-free survival (PFS), overall survival (OS), disease control rate, and safety in phase II. In phase I, three dose levels were planned (100, 125, and 150 mg/m^2) based on the previous phase I study.[16] Patients received nab-PTX on days 1 and 15 of a 28-day cycle at 100 mg/m^2 (level 1), 125 mg/m^2 (level 2), and 150 mg/m^2 (level 3) doses (Table 1). A dose-limiting toxicity (DLT) was defined as a treatment-related adverse event (AE) that occurred during the first cycle of treatment and led to treatment discontinuation, or met one of the following criteria: grade 4 uncomplicated neutropenia lasting ≥4 days, ≥grade 3 febrile neutropenia lasting ≥4 days, grade 4 thrombocytopenia, grade 3/4 non-hematological AE (excluding nausea, vomiting, appetite loss, fatigue, constipation, hyponatremia, hypokalemia, bodyweight loss, and infusion reaction), and day 15 dose skipped due to hematological toxicities. Three patients were enrolled at each dose level starting at dose 100 mg/m^2 (level 1). In the absence of DLT during cycle 1, three patients were enrolled at the next dose level (125 mg/m^2, level 2). If one DLT was observed, the dose level was expanded to six patients. If two DLTs were observed, the phase I trial was stopped as the toxicity threshold is exceeded. The RD for phase II was the highest dose level at which ≤1 of six patients experienced a DLT. The Safety Monitoring Committee was responsible for decisions on dose escalation, MTD, the RD for phase II, and study continuation.

TABLE 1 Dose escalation schedule

Level	Nab-PTX (mg/m^2)
0	75
1	100
2	125
3	150

Abbreviation: Nab-PTX, nanoparticle albumin-bound paclitaxel.

Treatment

Eligible patients received a 30-min intravenous infusion of nab-PTX at a dose of 100–150 mg/m^2 on days 1 and 15, every 28 days in phases I and II. If the administration of nab-PTX on day 15 was skipped, that week defined the week of treatment as rest. Treatment continued until progressive disease, development of an unacceptable AE, or withdrawal of consent, whichever occurred first. The use of granulocyte colony-stimulating factor as primary prophylaxis was not allowed during the study treatment. Dose reductions of nab-PTX (i.e., by 25 mg/m^2 to a minimum dose of 75 mg/m^2) due to toxicities (grade 4 uncomplicated neutropenia lasting ≥4 days, ≥grade 3 febrile neutropenia lasting ≥4 days, grade 4 thrombocytopenia, grade 3/4 non-hematologial AE, and grade 3/4 thrombocytopenia) were permitted. Concomitant treatment with radiotherapy or chemotherapy was not allowed during the trial. Toxicities were evaluated according to CTCAE version 4.0.

Statistical analysis

The efficacy of nab-PTX monotherapy was assessed by an independent review committee according to the RECIST

(version 1.1). Complete response (CR) and partial response (PR) required subsequent confirmation of response ≥4 weeks later. Radiographic assessments were performed at baseline, followed by every 4 weeks until PD. ORR was defined as the proportion of patients with CR plus those with PR. Disease control rate was defined as the proportion of patients with CR, PR, and stable disease maintained for ≥4 weeks. The median survival time and corresponding 95% confidence interval (CI) for PFS and OS were estimated using the Kaplan–Meier method. PFS and OS were defined as the time from registration until progression or death due to any cause, respectively.

Based on the results of previous reports, the threshold of the ORR (under the null hypothesis) and expected ORR (under the alternative hypothesis) was set at 5% and 15%, respectively.[17–20] It was estimated that a total sample size of at least 18 patients was needed in the phase II to allow a power of 70% at a one-sided significance level of 20% in this study. The primary endpoint was assessed in the full analysis set, which was defined as all patients who received at least one dose of nab-PTX and had efficacy data available at any timepoint post-baseline. Safety was assessed in patients who received at least one dose of nab-PTX. Statistical analysis was carried out using the SPSS version 22.0 (IBM Corp.) software. p-values <0.05 denoted statistically significant differences.

RESULTS

Phase I

Between October 2014 and October 2017, 15 patients were treated with 100–150 mg/m^2 of nab-PTX on days 1 and 15 of a 28-day cycle. Baseline characteristics of all patients in this study are summarized in Table 2. Three patients treated with the 100 mg/m^2 dose (level 1) had no DLT (Table 3). Six patients were treated with the 125 mg/m^2 dose (level 2) due to DLT; one patient experienced grade 3 rash during the first cycle of treatment. Six patients were also

TABLE 2 Patient characteristics

Characteristic	Number ($N = 27$)	Phase	
		Phase I ($N = 15$)	Phase II ($N = 18$)
Age (median), years	68	70	68
Age range, years	60–83	60–82	60–83
Sex			
Male	21 (78%)	11 (73%)	15 (83%)
Female	6 (22%)	4 (27%)	3 (17%)
Clinical stage			
IIIB	2 (8%)	2 (13%)	1 (6%)
IV	22 (81%)	11 (73%)	14 (78%)
Postoperative recurrence	3 (11%)	2 (13%)	3 (17%)
Histology			
Adenocarcinoma	22 (81%)	14 (93%)	14 (78%)
Squamous cell	5 (19%)	1 (7%)	4 (22%)
ECOG PS			
0	12 (44%)	7 (47%)	6 (33%)
1	15 (56%)	8 (53%)	12 (67%)
Driver mutation status			
EGFR	7 (26%)	6 (40%)	4 (22%)
ALK	1 (4%)	1 (7%)	1 (6%)
ROS-1	1 (4%)	1 (7%)	0
Wild	15 (55%)	6 (40%)	11 (61%)
Unknown	3 (11%)	1 (7%)	2 (11%)
Number of previous treatment regimen			
2	6 (22%)	6 (40%)	1 (6%)
3	14 (52%)	5 (33%)	12 (67%)
4	7 (26%)	4 (27%)	5 (28%)

Abbreviations: ALK, anaplastic lymphoma kinase; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EGFR, epidermal growth factor receptor; ROS-1, v-ros avian UR2 sarcoma virus oncogene homolog 1.

TABLE 3 Adverse events by dose level (phase I)

	100 mg/m^2 cohort ($N = 3$)				125 mg/m^2 cohort ($N = 6$)				150 mg/m^2 cohort ($N = 6$)			
	Grade				Grade				Grade			
	All	3	4	3/4	All	3	4	3/4	All	3	4	3/4
Hematological, N (%)												
Leukopenia	2	0	0	0	4	0	0	0	6	1	0	0
Neutropenia	2	0	0	0	3	0	0	0	3	1	1 (DLT)	0
Anemia	1	0	0	0	5	1	0	1	6	0	0	0
Thrombocytopenia	0	0	0	0	0	0	0	0	1	0	0	0
Febrile neutropenia	0	0	0	0	0	0	0	0	0	0	0	0
Nonhematological, N (%)												
Infection	0	0	0	0	0	0	0	0	1	0	0	0
Anorexia	1	0	0	0	1	0	0	0	2	0	0	0
Creatinin increased	0	0	0	0	0	0	0	0	1	0	0	0
Total bilirubin increased	0	0	0	0	0	0	0	0	2	0	0	0
Fatigue	0	0	0	0	1	0	0	0	0	0	0	0
Diarrhea	0	0	0	0	0	0	0	0	1	0	0	0
Alopecia	0	0	0	0	0	0	0	0	1	0	0	0
Peripheral sensory neuropathy	0	0	0	0	1	0	0	0	4	1	0	0
Arthralgia	0	0	0	0	0	0	0	0	2	0	0	0
Rash	0	0	0	0	1	1 (DLT)	0	1	0	0	0	0
Constipation	0	0	0	0	1	0	0	0	1	0	0	0

Abbreviation: DLT, dose-limiting toxicity.

TABLE 4 Objective tumor response ($N = 18$)

Tumor response	Number of patients (%)
Complete response	0
Partial response	4 (22.2)
Stable disease	9 (50.0)
Progressive disease	5 (27.8)
Objective response rate	22.2%
Disease control rate	72.2%

treated with the 150 mg/m^2 dose; one patient skipped the nab-PTX infusion due to grade 4 neutropenia on day 15 of the first cycle of treatment. Based on these results, the 150 mg/m^2 dose was expanded to six patients without DLT. Consequently, 150 mg/m^2 was selected as both the MTD and RD of nab-PTX. A total of 18 patients were enrolled in the phase II of the study.

Phase II

Patient characteristics

Between February 2016 and November 2018, 18 patients were treated with 150 mg/m^2 of nab-PTX on days 1 and 15 of a 28-day cycle. The baseline characteristics of these patients are listed in Table 2. The median age of the patients was 68 years (range: 60–83 years); the majority of patients were male (83%); 67% had Eastern Cooperative Oncology Group Performance Status 1; and 78% had adenocarcinoma. The median previous number of treatment regimens was three (range: 2–4), and 94% of patients were fourth-line or later. Four patients (22%) had epidermal growth factor receptor-activating mutation.

ORR and survival

The confirmed ORR to nab-PTX was 22.2% (4/18; 95% CI: 3.6%–40.9%; Table 4). The waterfall plot (Figure 1), in which the best unidimensional tumor response for each patient is plotted, shows a disease control rate (CR, PR, or stable disease) of 72.2% (13/18; 95% CI: 52.7%–91.7%). The confirmed ORR and disease control rate were 16.7% and 66.7% for fourth-line therapy, and 40.0% and 80.0% for fifth-line therapy, respectively. There was no significant difference between the treatment lines. The median PFS was 3.6 months (95% CI: 0–7.3 months) (Figure 2a); median OS was 11.2 months (95% CI: 4.6–17.7 months) (Figure 2b); and 1-year OS was 42%.

Data on treatment after protocol were available for all patients. Eight patients did not receive additional therapy (four patients remain alive without additional treatment). The remaining patients received one or two additional lines of chemotherapy and/or immunotherapy (median: one

FIGURE 1 The waterfall plot of patients with NSCLC treated in phase II of the study. Thirteen patients (72.2%) had some tumor shrinkage, including four partial responses (22.2%). NSCLC, non-small cell lung cancer; PD, progressive disease; PR, partial response; SD, stable disease

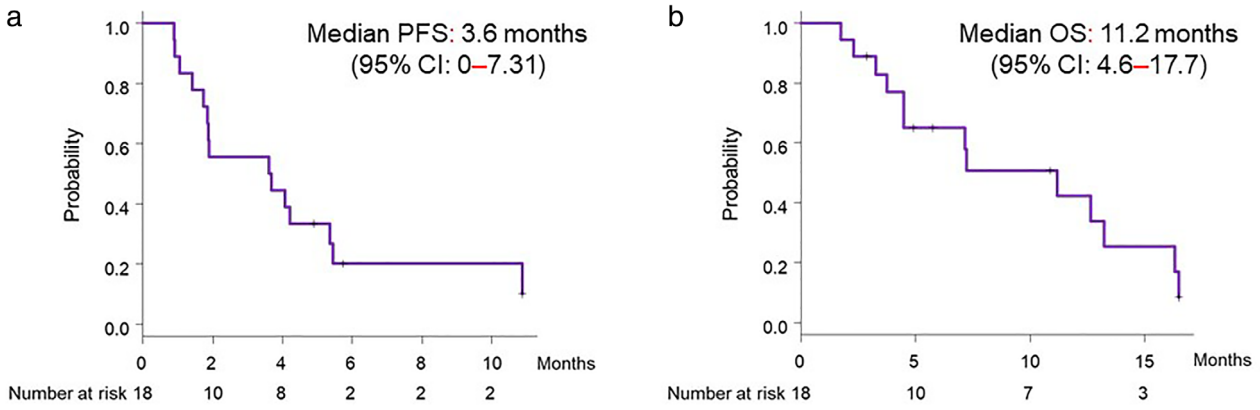

FIGURE 2 Kaplan–Meier curve of PFS (a) and OS (b) in phase II of the study. The median PFS and OS were 3.6 months (95% CI: 0–7.31 months) and 11.2 months (95% CI: 4.6–17.7 months), respectively. CI, confidence interval; PFS, progression-free survival

additional line of treatment). The most common treatment was immune checkpoint inhibitor monotherapy (five patients) and no patient received epidermal growth factor receptor tyrosine kinase inhibitor.

Toxicity

The median number of treatment cycles was four (range: 1–13). and median weekly dose intensity of nab-PTX was 75.0 mg/m^2/week (range, 37.5–75). Most patients (89%) did not require dose reduction, although five patients (28%) skipped nab-PTX infusion on day 15 due to hematological toxicity (one grade3, two grade 4) or peripheral neuropathy (one grade1, one grade 3). Patients who had peripheral neuropathy were able to continue the nab-PTX infusion after skipping event until disease progression. There was no treatment-related death observed in this study. The most frequent AEs in all patients are listed in Table 5. The most common grade 3/4 toxicities treated with 150 mg/m^2 were leukopenia (22%), neutropenia (22%), rash (6%), peripheral sensory neuropathy (6%), and febrile neutropenia (6%). Adverse events grade ≥ 3 were observed in 39% of patients. There was no significant difference in toxicity profile in each treatment line.

DISCUSSION

The role of nab-PTX monotherapy is not clarified on the efficacy and safety for the patients in third-line and later-line as shown in Table 6. This was the first phase I/II trial to evaluate the efficacy and safety of biweekly nab-PTX in patients with previously treated NSCLC. In the present study, most patients were fourth-line setting, and 150 mg/m^2 was determined as the RD for nab-PTX. The ORR was 22.2%, achieving the primary objective of the study; median PFS and OS were 3.6 and 11.2 months, respectively. The results obtained in this trial were similar to those of earlier studies in terms of ORR, PFS, and OS regardless of late-line setting (Table 6).[16,21–24] These data demonstrated that the nab-PTX monotherapy had antitumor activity for patients with advanced NSCLC, even in the later-line setting. Additionally, the biweekly dose modification schedule showed

TABLE 5 Adverse events in the 150 mg/m^2 cohort (phase II)

	All patients ($N = 27$)		150 mg/m^2 cohort ($N = 18$)	
	% (N)		% (N)	
Adverse event	**All grade**	**Grade 3/4**	**All grade**	**Grade 3/4**
Hematological				
Leukopenia	67 (18)	15 (4)	72 (13)	22 (4)
Neutropenia	52 (14)	15 (4)	56 (10)	22 (4)
Anemia	96 (26)	4 (1)	100 (18)	0
Thrombocytopenia	15 (4)	0	15 (4)	0
Febrile neutropenia	4 (1)	4 (1)	0	0
Nonhematological				
Febrile neutropenia	4 (1)	4 (1)	6 (1)	6 (1)
Infection	11 (3)	4 (1)	11 (2)	0
Anorexia	33 (9)	0	33 (6)	0
Creatinine increased	4 (1)	0	6 (1)	0
Total bilirubin increased	19 (5)	0	17 (3)	0
Fatigue	19 (5)	0	15 (4)	0
Diarrhea	4 (1)	0	6 (1)	0
Alopecia	11 (3)	0	17 (3)	0
Peripheral sensory neuropathy	30 (8)	4 (1)	39 (7)	6 (1)
Arthralgia	11 (3)	0	17 (3)	0
Rash	11 (3)	7 (2)	11 (2)	6 (1)
Constipation	11 (3)	0	11 (2)	0

TABLE 6 Efficacy and safety of nab-PTX monotherapy for advanced NSCLC

Study	Phase	Number of patients	Treatment line	Dose and schedule	Response rate (%)	Median PFS (month)	Median OS (month)	Median dose intensity (mg/m^2/week)	Peripheral neuropathy (grade 3/4)
Rizvi et al.[16]	1/2	40	First-line	Nab-PTX 125 mg/m^2 days 1, 8 and 15 each 28-day cycle	30	5	11	NA	15%
Anzai et al.[21]	2	32	Second-line	Nab-PTX 100 mg/m^2 days 1, 8 and 15 each 28-day cycle	28.1	5	10.9	57.8	6%
Hu et al.[22]	2	56	Second-line	Nab-PTX 100 mg/m^2 days 1, 8 and 15 each 28-day cycle	16.1	3.5	6.8	NA	NA
Sakata et al.[23]	2	41	Second-line	Nab-PTX 100 mg/m^2 days 1, 8 and 15 each 21-day cycle	31.7	4.9	13.1	89.1	5%
Xing et al.[24]	2	98	Second-line or later	Nab-PTX 130 mg/m^2 days 1 and 8 each 21-day cycle	22.4	4.3	11.7	NA	5%
Present study	1/2	18	Third-line or later	Nab-PTX 150 mg/m^2 days 1 and 15 each 28-day cycle	22.2	3.6	11.2	75.0	6%

Abbreviation: NA, not available.

the favorable efficacy of nab-PTX. The actual dose intensity in this study was comparable to previously reported weekly regimens (Table 6). Although all previous clinical trials of nab-PTX monotherapy were scheduled weekly, investigating the optimal schedule of nab-PTX has clinical benefit adapting the schedule to patients' and physicians' preference. The biweekly regimen is a suitable treatment option for heavily pretreated patients with advanced NSCLC in terms of reducing the visits for treatment.

The safety profile of biweekly nab-PTX monotherapy was consistent with that noted in previous reports.[16,21–24] There were no life-threatening severe AEs observed; AEs

were generally grade ≤3 and resolved without specific treatment. Importantly, the rate of peripheral neuropathy was the same or low in this study compared with previous reports[16,21–24] (Table 6). Thus, in our study, biweekly nab-PTX monotherapy (150 mg/m^2 on days 1 and 15 of a 28-day cycle) was beneficial to patients with advanced NSCLC and offered better tolerability with low occurrences of peripheral neuropathy.

Recently, a Japanese phase III trial comparing nab-paclitaxel with docetaxel monotherapy in patients with previously treated advanced NSCLC showed clinical benefit and safety of nab-PTX monotherapy.[25,26] Therefore, nab-PTX monotherapy may be a new alternative treatment option for patients with previously treated advanced NSCLC.

The present study had several limitations. First, this study used a small sample size, and for this reason, future studies will be required to evaluate the effectiveness of this modified regimen, though promising results were obvious in this study. Second, the present study lacked a quality-of-life (QoL) assessment. Most patients with advanced NSCLC do not have curative treatment options, and, therefore, the goal of therapy for such patients is a prolongation of survival without negatively impacting QoL. Lastly, we did not set a dose level higher than 150 mg/m^2 based on the result of previous phase I study.[16] As our study showed favorable tolerability, the dose of more than 150 mg/m^2 could be safely administered, thereby induce more clinical benefit.

In conclusion, our results show that biweekly nab-PTX monotherapy has modest activity and acceptable toxicity. This regimen may be a useful option in treating advanced NSCLC; it is recommended for individual patients owing to its good efficacy even in patients who have received multiple treatment courses. Further phase III studies are warranted to verify the efficacy of this modified regimen.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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