Efficacy and safety of nanoparticle albumin-bound paclitaxel monotherapy as second-line therapy of cytotoxic anticancer drugs in patients with advanced non-small cell lung cancer

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Abstract

Background: Nanoparticle albumin-bound paclitaxel (nab-PTX), which avoids toxicities associated with a vehicle used in solvent-based PTX, has already shown safety and efficacy in patients with non-small cell lung cancer (NSCLC).

Methods: A phase II study was performed to assess the safety and efficacy of nab-PTX monotherapy as second-line chemotherapy after cytotoxic anticancer drugs for previously treated advanced NSCLC. Thirty-two patients with advanced NSCLC who had previously undergone 1 regimen of cytotoxic anticancer drugs were enrolled. Nab-PTX was administered intravenously at a dose of 100 mg/m^2 on days 1, 8, and 15 of a 28-day cycle. The objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS), overall survival (OS), and toxicity profile were evaluated.

Results: The ORR was 28.1%, the DCR was 71.9%, median PFS was 3.9 months (95% confidence interval [CI] 2.7–5.1 months), and median OS was 10.9 months (95% CI 9.5–12.3 months). The mean relative dose intensity of nab-PTX was 77%. Grade 3 or 4 neutropenia, and grade 3 febrile neutropenia were observed in 11 and 1 of 32 patients, respectively. As nonhematologic toxicities, grade 3 peripheral sensory neuropathy and pneumonitis were each observed in 2 of 32 patients.

Conclusion: Nab-PTX is an active and well-tolerated regimen in patients with previously treated NSCLC.

Abbreviations: ALK = anaplastic lymphoma kinase, CBDCA = carboplatin, CR = complete response, DCR = disease control rate, DTX = docetaxel, EGFR = epidermal growth factor receptor, IrAEs = immune-related adverse events, nab-PTX = nanoparticle albumin-bound paclitaxel, NSCLC = non-small cell lung cancer, ORR = objective response rate, OS = overall survival, PD = progressive disease, PEM = pemetrexed, PFS = progression-free survival, PR = partial response, PS = performance status, RAM = ramucirumab, SD = stable disease, TKI = tyrosine kinase inhibitor.

Keywords: nab-paclitaxel, non-small cell lung cancer, previously treated patients, second-line chemotherapy

1. Introduction

Non-small cell lung cancer (NSCLC) is the most common form of lung cancer, accounting for more than 80% of all cases, with 60% to 70% of NSCLC cases being inoperable. Although platinum-based chemotherapy as first-line treatment for advanced NSCLC yields a survival benefit, its benefit is only modest.[1] Second-line treatment of a refractory or relapsed case after platinum-based combination therapy as first-line therapy is considered more difficult. In this setting, overall survival (OS) with combination therapy was not significantly prolonged compared with single-agent therapy.[2] The efficacy of second-line, single-agent docetaxel (DTX) was demonstrated in a trial in which 104 patients with advanced pretreated NSCLC were randomly assigned to DTX (100 mg/m^2 or 75 mg/m^2) or best supportive care.[3] In Japan, a lower dose (60 mg/m^2) of DTX has been recommended as a standard second-line therapy.[4] However, hematological toxicities are strong even in a lower dose of DTX. Despite the clinical activity, the use of DTX is limited by significant toxicities. Pemetrexed (PEM) is as active as DTX among patients with previously treated, nonsquamous advanced NSCLC, but it is not indicated for patients with squamous NSCLC because of its low efficacy. PEM should not be administered to patients with renal impairment (creatinine clearance less than 45 mL/min). Although there has been a phase II trial of paclitaxel (PTX) given as monotherapy for NSCLC,[5] randomized data regarding the efficacy of PTX in patients with pretreated NSCLC are lacking. Recently, nanoparticle albumin-bound PTX (nab-PTX), a solvent-free formulation of PTX, was introduced as a new anticancer drug for NSCLC, which avoids

toxicities associated with a vehicle used in solvent-based PTX (sb-PTX).

A cytotoxic agent, which is effective regardless of histologic subtype and has better toxic profiles, should be investigated as second or later treatment for NSCLC. Nab-PTX has already shown safety and efficacy in patients with breast cancer, pancreatic cancer, and NSCLC.[6–8] The dose of nab-PTX is not needed to be adjusted in patients with mild and moderate renal impairment. Based on these backgrounds, a phase II clinical trial was conducted to evaluate the efficacy and safety of nab-PTX as a second-line therapy for previously treated patients with advanced NSCLC.

2. Patients and methods

2.1. Patient eligibility

Eligible patients were required to have: histologically or cytologically proven unresectable advanced NSCLC; recurrent or refractory disease after 1 previous cytotoxic chemotherapy regimen; a performance status (PS) of 0 to 2 on the Eastern Cooperative Oncology Group; age $\geq$20 years; a life expectancy of 8 weeks or more; adequate bone marrow reserve (leukocyte count $\geq$3000/mm^3, absolute neutrophil count $\geq$1500/mm^3, platelet count $\geq$100,000/mm^3, and hemoglobin $\geq$9.0 g/dL); normal liver function (total serum bilirubin $\leq$1.5 mg/dL, aspartate transaminase and alanine transaminase $\leq$2.5 times the upper limit of the normal range), and normal renal function (serum creatinine $\leq$1.5 mg/dL); ECG findings within the normal range; and arterial oxygen pressure $\geq$60 mmHg or SpO$_2$ $\geq$90%.[9] Patients with concomitant malignancy, brain metastasis with clinical symptoms, active infectious diseases, active interstitial pneumonia, uncontrollable pleural or pericardial effusion, peripheral numbness worse than grade 2 of the Common Terminology Criteria for Adverse Events version 4.0 (CTCAE version 4.0),[10] or other serious medical problems were ineligible. Only 1 regimen using epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) or anaplastic lymphoma kinase (ALK) inhibitor was not counted as a previous chemotherapy regimen. The protocol and informed consent documents were approved by the Ethics Committee of the Faculty of Medical Sciences, University of Fukui, and the Institutional Review Board of Japanese Red Cross Fukui Hospital, and written informed consent was obtained from all patients who participated. This study was started on June 1, 2013 and closed on December 31, 2016. It was registered at UMIN-CTR (UMIN000010841).

2.2. Treatment schedule

Nab-PTX (Abraxane®, TAIHO Phamaceutical Co., Ltd., Tokyo, Japan) in 100 mL of normal saline was administered intravenously as a 30-minute infusion at a dose of 100 mg/m^2 on days 1, 8, and 15 of a 28-day cycle. Patients continued to receive the treatment until development of progressive disease (PD) or intolerance of treatment. Patients were required to have absolute neutrophil count $\geq$1500/mm^3 and platelet count $\geq$100,000/mm^3 without any nonhematologic toxicities of grade 3 or worse to start the next course. Granulocyte colony-stimulating factor was permitted as a therapeutic use for neutropenia, but not as prophylaxis. Dose reductions for toxicities were allowed with a reduction by 20 mg/m^2 to a minimum dose of 60 mg/m^2. Dose reductions were allowed for grade 3 or 4 thrombocytopenia, grade 4 neutropenia, or any grade 3 or 4 nonhematologic

toxicities. Adverse events were assessed according to the guideline of CTCAE version 4.0 published by the National Cancer Institute.[10]

2.3. Evaluation

Evaluations before treatment were a complete blood cell count, differential blood count, routine chemistry measurements, chest x-ray, chest computed tomographic (CT) scan, abdominal CT scan, whole-brain magnetic resonance imaging (MRI) or CT scan, and isotope bone scan or positron emission tomography with 2-deoxy-2-[fluorine-18] fluoro-D-glucose integrated with computed tomography (^{18}F-FDG PET/CT). We weekly measured complete blood cell count, differential blood count, and routine chemistry. Physical examination and toxicity assessment were also performed. The Response Evaluation Criteria in Solid Tumors were used to assess the response to nab-PTX.[11] Response based on target and nontarget lesions was defined as follows: complete response (CR), disappearance of all target and nontarget lesions and any pathological lymph nodes must have reduction in short axis to <10 mm; partial response (PR), at least 30% decrease in the sum of diameters of target lesions; PD, at least 20% increase in the sum of diameters of target lesions or the appearance of one or more new lesions; stable disease (SD), neither sufficient shrinkage to qualify for PR nor sufficient increase to quantify for PD. Toxicities were evaluated according to CTCAE version 4.0.[10]

2.4. Statistical analysis

Progression-free survival (PFS) was estimated from the start of chemotherapy to the first date of PD or death. OS was estimated from the start of treatment to the date of death. Time to event distributions were estimated using the Kaplan–Meier method, and 95% confidence intervals (CIs) were calculated. Probability values of <.05 indicated a significant difference. Fisher exact test was used to examine the association of 2 categorical variables.

The primary endpoints of this study were the objective response rate (ORR) and disease control rate (DCR). Secondary endpoints were OS, PFS, and toxicity profile. Assuming that an ORR of 22% would indicate potential usefulness in this study, whereas an ORR of 7% would be the lower limit of interest, with $\alpha = 0.05$ and $\beta = 0.2$, the estimated numbers of patients were 26. A goal of 30 patients was set. Statistical analysis was performed using Excel statistics software (Social Survey Research Information Co., Ltd., Tokyo, Japan) and SPSS software (IBM Japan, Tokyo, Japan).

3. Results

3.1. Patients' characteristics

Between June 2013 and October 2015, 32 patients (24 men, 8 women) were enrolled from 2 participating institutions— University of Fukui Hospital and Japanese Red Cross Fukui Hospital (Fukui, Japan). All patients were of Japanese heritage. Thirty-one patients came from Fukui prefecture and 1 patient came from another prefecture in Japan. The 32 patients were assessable for response, toxicity, and survival. The clinical characteristics of these patients are summarized in Table 1. The median age of the patients was 67.5 years (range 45–79 years). PS and histology of the patients were as follows: 8 patients with PS 0, 24 patients with PS 1; 25 patients with adenocarcinoma, 5

Table 1

Patient characteristics.

Characteristic	No. patients
Patients enrolled	32
Age, y	
Median	67.5
Range	45–79
Sex	
Male	24
Female	8
PS (ECOG)	
0	8
1	24
2	0
Histology	
Squamous cell carcinoma	5
Adenocarcinoma	25
Large cell carcinoma	1
Non-small cell carcinoma, NOS	1
Prior therapy	
Chemotherapy alone	30
Chemotherapy and chest radiation	1
Operation and chemotherapy	1

ECOG = Eastern Cooperative Oncology Group, NOS = not otherwise specified, PS = performance status.

patients with squamous cell carcinoma, 1 patient with large cell carcinoma, and 1 patient with non-small cell carcinoma, not otherwise specified (NSCC, NOS). Five patients with adenocarcinoma had EGFR mutations (deletion of exon 19 or L858R), and 1 patient with adenocarcinoma had ALK rearrangement. All patients had been previously treated with some form of platinum-containing (31 patients) or non-platinum-containing (1 patient) regimen of cytotoxic anticancer drugs. Any of the patients had not received a prior taxane. Five patients with EGFR mutations received gefitinib. Gefitinib was used as a first-line therapy in 3 of them and followed by a platinum-containing regimen. In 2 other patients, 1 platinum-containing regimen and maintenance therapy were performed before gefitinib. One patient with ALK rearrangement received alectinib after 1 platinum-containing regimen and maintenance therapy. One patient had chest radiation in addition to chemotherapy as an initial therapy, and another patient had an operation before first-line chemotherapy. All patients had 1 cytotoxic anticancer regimen before enrollment in this study. In all 32 patients, the median number of previous cytotoxic treatment cycles was 4 (range 2–8 cycles). Maintenance therapy, PEM, bevacizumab, or both of them, after platinum-containing regimens, was performed in 11 of 32 patients. The median number of treatment cycles of maintenance therapy was 4 (range 3–16 cycles).

3.2. Treatment delivery

In all patients enrolled in this study, nab-PTX was administered as a second-line regimen of cytotoxic anticancer drugs, excluding EGFR-TKI or ALK inhibitor treatment. Totally, 115 cycles of nab-PTX therapy were performed in 32 patients. The number of treatment cycles in each patient ranged from 1 to 9. The median number was 3. The median dose intensity of nab-PTX was 57.8 mg/m^2/wk, and the mean relative dose intensity was 77%. The protocol treatment was started in 2.3 to 39.1 months after the initial diagnosis of NSCLC. The median period from the diagnosis to the start of nab-PTX was

6.2 months. Two or more cycles of the treatment were delivered in 27 (84.4%) of 32 patients. In 5 (15.6%) patients, the nab-PTX therapy was terminated before the second treatment cycle because of PD. After the nab-PTX therapy, 24 (75%) patients received subsequent pharmacotherapy containing cytotoxic agents, EGFR-TKIs, bevacizumab, or nivolumab.

3.3. Response rate and survival analysis

Among the 32 assessable patients, 1 patient (3.1%) achieved CR, and 8 patients (25.0%) had PR. Fourteen patients (43.8%) had SD and 9 patients had PD. The ORR and DCR were 28.1% and 71.9%, respectively. The ORR was higher in female patients than in male patients, and it was higher in nonsquamous cell carcinoma than in squamous cell carcinoma, although these differences were not significant (Table 2).

Waterfall plots for best percentage change in target lesion diameter are shown in Fig. 1. Median PFS (mPFS) was 3.9 months (95% CI 2.7–5.1 months), and median OS (mOS) was 10.9 months (95% CI 9.5–12.3 months) (Fig. 2A, B).

3.4. Toxicity

The hematologic and nonhematologic toxicity profiles of all 32 patients are listed in Table 3. Grade 3 or 4 neutropenia, and grade 3 febrile neutropenia were observed in 11 (34.4%) patients and 1 (3.1%) patient, respectively. Grade 3 anemia was also observed in 3 (9.4%) patients. As nonhematologic toxicities, grade 3 peripheral sensory neuropathy, pneumonitis, and fatigue were observed in 2 (6.3%), 2 (6.3%), and 3 (9.4%) of the total 32 patients. Both cases of pneumonitis were severe, and 1 case needed steroid therapy. The drug-induced lymphocyte stimulation test of the latter case was negative.

4. Discussion

After the 1990s, several anticancer drugs containing PTX were introduced for treatment of NSCLC. Carboplatin (CBDCA) plus PTX has been 1 of the recommended regimens for the first-line treatment of advanced NSCLC without driver mutations. In a phase III trial that compared the efficacy and safety of nab-PTX plus CBDCA with sb-PTX plus CBDCA in advanced NSCLC, nab-PTX plus CBDCA demonstrated a significantly higher ORR and less grade 3 or more neuropathy, neutropenia, arthralgia, and myalgia than sb-PTX plus CBDCA.[8] In this trial, nab-PTX (100 mg/m^2) on days 1, 8, and 15 of a 21-day cycle in combination with CBDCA was efficacious. When this phase II trial of second-line nab-PTX therapy was planned, information on nab-PTX monotherapy for NSCLC was limited. In the phase I/II study for untreated NSCLC, the 125 mg/m^2 dose level of nab-PTX was determined to be the maximum tolerated dose, and 125 mg/m^2 administration on days 1, 8, and 15 of a 28-day cycle demonstrated an encouraging ORR (30%).[12] The treatment schedule for nab-PTX was determined to be 100 mg/m^2 on days 1, 8, and 15 of a 28-day cycle, because the approved dosage of nab-PTX for NSCLC by Japanese health insurance was 100 mg/m^2. Although nab-PTX plus CBDCA in the recommended first-line therapy was a 21-day cycle, the treatment schedule for nab-PTX monotherapy as a second-line treatment was determined to be a 28-day cycle according to the schedule for previously treated patients with melanoma.[13]

In the present study, the aim was to determine the efficacy and toxicity of nab-PTX monotherapy in previously treated NSCLC

Table 2

Response to nab-paclitaxel.

Enrolled patients (n = 32)			
Objective response rate (%)			28.1% (95% CI 6.9%–39.3%)
CR/PR/SD/PD			1/8/14/9
Disease control rate (%)			71.9% (95% CI 47.1%–83.7%)
No. of course			
Median			3
Range			1–9
Response			NSCLC (n = 32)

	No. of patients	No. of patients with response (%)	P
Total	32	9 (28.1%)	
Sex			
Male	24	6 (25.0%)	.655
Female	8	3 (37.5%)	
Histology			
Squamous cell carcinoma	5	0 (0%)	.288
Nonsquamous cell carcinoma	27	9 (33.3%)	
Adenocarcinoma	25	9 (36.0%)	
Adenocarcinoma with EGFR mutation	5	3 (60.0%)	
Adenocarcinoma with EML4-ALK fusion	1	0 (0%)	
Large cell carcinoma	1	0 (0%)	
NSCC, NOS	1	0 (0%)	

CI = confidence interval, CR = complete response, EGFR = epidermal growth factor receptor, EML4-ALK = echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase, NSCC, NOS = non-small cell carcinoma, not otherwise specified, PD = progressive disease, PR = partial response, SD = stable disease.

cases. The ORR was 28.1%, and mPFS and mOS were 3.9 and 10.9 months, respectively. The ORR was more than 22%, which was considered potentially useful in second-line chemotherapy on the basis of a previous DTX study performed in Japan.[4] In the evaluation of toxicities, peripheral neuropathy (grade 1–3) was observed in 43.8% of the patients. However, grade 3 or more was seen in 6.3%. Hematologic toxicities were also well-controlled by dose reduction. A second-line anticancer drug is required to preserve quality of life in addition to promising efficacy. Nab-PTX can be administered without premedication to prevent hypersensitivity reactions and it was acceptable from standpoint of peripheral neuropathy.

After this phase II trial was started, the results of some similar prospective studies that focused on nab-PTX as a second-line chemotherapy for NSCLC were published.[14–16] In the phase II study of second-line nab-PTX for NSCLC reported by a Chinese group, the treatment schedule was the same as in the present study. However, data on hematologic toxicities were not shown in that report.[14] In the study of the Kumamoto Thoracic Oncology Study Group (KTOSG), weekly nab-PTX was administered continuously at the same dose as in the present study (100 mg/m^2).[15] Although the intended dose intensity of the KTOSG study was greater than that of the present study (100 mg/m^2/wk vs 75 mg/m^2/wk), the ORR was similar to that of the present study (31.7% vs 28.1%). Actually, the median dose intensity in the KTOSG study was greater than in the present study (89.1 mg/m^2/wk vs 57.8 mg/m^2/wk). This may suggest that a dose intensity of nab-PTX of 75 mg/m^2/wk as a subsequent systemic therapy for previously treated patients with NSCLC is sufficient, and that further increasing the dose intensity of nab-PTX is not required. Because the mean relative dose intensity of nab-PTX in the present study was 77%, delay or dose reduction of administration may occur frequently in the actual clinical setting by increasing the dose intensity. A phase II trial by another Chinese group that increased the dose of nab-PTX, 150 mg/m^2 on days 1 and 8 of a 21-day cycle, did not increase the ORR in the same setting.[16] This also indicates that a dose intensity of more than 75 mg/m^2/wk does not always have an additive effect in subsequent nab-PTX therapy in previously treated patients with advanced NSCLC.

Recently, ramucirumab (RAM), a monoclonal antibody against the vascular endothelial growth factor (VEGF) receptor 2, was reported to improve OS when used with DTX in the second-line setting of NSCLC treatment.[17] Although can be administered to patients with squamous cell NSCLC, and also nonsquamous cell NSCLC, in contrast to the anti-VEGF monoclonal antibody, bevacizumab, it actually has increased adverse effects such as bleeding and hypertension. In particular, severe hematologic toxicity such as febrile neutropenia is a concern in Japanese patients, because febrile neutropenia was more common with RAM plus DTX (34.2%) than with DTX alone (19.8%) in the phase II study performed in Japan.[18] In KTOSG or the present trial using nab-PTX, grade 3 or 4 adverse events were observed much less than with RAM plus DTX or
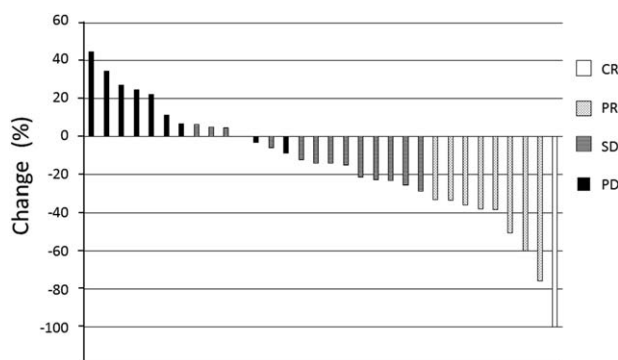

Figure 1. Waterfall plots for best percentage change in target lesion size are shown for all patients. The patterns of each bar indicate the level of response assessed by the response evaluation criteria in solid tumors.
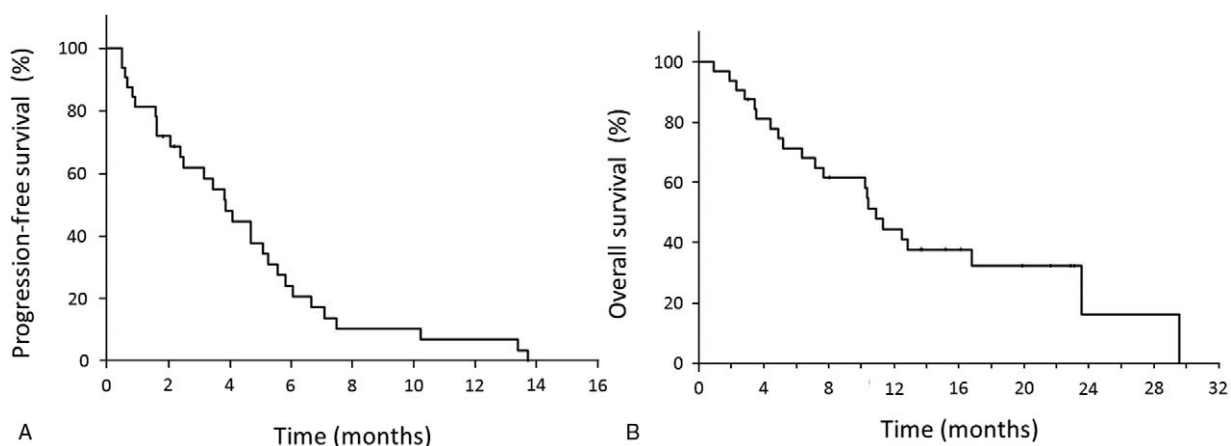
Figure 2. Kaplan–Meier curve for progression-free survival (A) and overall survival (B) in all patients. Tick marks indicate censored observations.

DTX alone, although the ORR with RAM plus DTX (28.9%) was similar to that with nab-PTX. Because the goal of treatment of advanced NSCLC is to minimize symptoms in addition to prolonging life, increased toxicities are a serious problem. Therefore, patients for whom the addition of RAM is beneficial in second-line therapy are limited, even if OS were to be extended.

Moreover, immune checkpoint inhibition, such as anti-programmed cell death 1 (PD-1) antibodies, has become an appropriate option for treating advanced NSCLC, especially when tumor cells are expressing PD-1 ligand 1 (PD-L1) well.[19] Nivolumab, an IgG4 monoclonal antibody against PD-1, significantly prolonged OS compared with DTX after platinum-based chemotherapy in both squamous and nonsquamous NSCLC in phase III trials.[20,21] Another anti-PD-1 monoclonal antibody, pembrolizumab, also prolonged OS compared with

DTX monotherapy when it was used as a second-line therapy after platinum-based chemotherapy, when at least 1% of tumor cells expressed PD-L1 that was positively stained with an anti-PD-L1 antibody (22C3).[22] These immunotherapies seem to be tolerable compared with cytotoxic anticancer drugs. However, they enhance immune responses and induce the immune-related adverse events (IrAEs) such as interstitial pneumonia, colitis, endocrine disorders, type 1 diabetes, myositis, myocarditis, myasthenia gravis, neurological disorders, uveitis, and skin disorders.[23] They can be cumbersome to manage since the IrAEs are different from adverse effects induced by traditional chemotherapy. It still remains obscure whether patients with pre-existing autoimmune diseases can be treated successfully with immune checkpoint inhibitors without exacerbating their autoimmune disorders.[24] The patients for whom immune

Table 3

Hematologic and nonhematologic toxicities.

| Toxicity | Patients (n = 32) | | | | | |
| | Grade | | | | ≥Grade 3 | |
	1	2	3	4	No.	%
Hematologic						
Neutropenia	1	5	4	7	11	34.4
Leukocytopenia	1	5	8	0	8	25
Thrombocytopenia	0	0	0	0	0	0
Anemia	3	4	3	0	3	9.4
Febrile neutropenia	0	0	1	0	1	3.1
Nonhematologic						
Peripheral sensory neuropathy	7	5	2	0	2	6.3
Myalgia	4	2	1	0	1	3.1
Arthralgia	3	3	0	0	0	0
Liver dysfunction	2	1	0	0	0	0
Nausea/anorexia	6	2	1	0	1	3.1
Diarrhea	0	0	0	0	0	0
Pneumonitis	0	0	2	0	2	6.3
Bronchial hemorrhage	0	1	0	0	0	0
Alopecia	4	5	0	0	0	0
Rash	0	0	0	0	0	0
Fever	3	0	0	0	0	0
Fatigue	0	0	3	0	3	9.4

checkpoint inhibition is effective are limited, and not all patients with NSCLC respond well to it. Therefore, cytotoxic anticancer drugs will play a significant role, and also immune checkpoint inhibitors in either first-line or subsequent therapy for patients with advanced NSCLC.

5. Conclusions

In conclusion, the results of the present study, and also other similar studies, indicate that nab-PTX is a candidate recommended cytotoxic anticancer drug in patients with previously treated NSCLC, and nab-PTX monotherapy is an active and well-tolerated regimen. NCCN guideline (Non-Small Cell Lung Cancer Version 8)[25] recommends DTX, PEM (except for squamous cell carcinoma), gemcitabine, or RAM plus DTX, and also immune checkpoint inhibitors as subsequent therapy after first-line systemic therapy in patients with advanced metastatic NSCLC when driver mutations are negative, PD-L1 expression is less than 50%, and their PS was 0 to 2. Nab-PTX may be added to another option in this situation. However, our study is an uncontrolled single-arm trial and the study number of patients is limited. We expect that the results of an ongoing randomized phase III trial comparing nab-PTX with DTX as a second-line chemotherapy for NSCLC may further clarify the role of nab-PTX.

Acknowledgments

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