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Effectiveness of nanoparticle albumin-bound paclitaxel plus carboplatin in non-small lung cancer patients with malignant pleural effusion

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Malignant pleural effusion (MPE) is a common complication occurring in cancer patients, and its management affects the prognosis of these patients. Preclinical and clinical studies have reported that treatment with nanoparticle albumin-bound paclitaxel (nab-paclitaxel) plus carboplatin (CBDCA) is effective against intraperitoneal malignant tumors. To investigate the effectiveness of nab-paclitaxel plus CBDCA therapy for MPEs arising in patients with non-small cell lung cancer (NSCLC), we retrospectively analyzed the clinicopathological characteristics of 40 patients with stage IIIb or IV NSCLC who were treated with nab-paclitaxel plus CBDCA from 2013 to 2016. Out of 26 patients with MPEs who were treated with nab-paclitaxel plus CBDCA in this study, 21 patients (80.8%) had effective responses in MPEs; 6 of 21 patients exhibited complete responses (23.1%) and 15 of 21 had partial responses (57.7%). Kaplan-Meier survival curves and log-rank tests to evaluate the effectiveness of nab-paclitaxel plus CBDCA therapy against MPEs showed longer median progression-free survival (323 days vs. 26 days; p=0.009) and overall survival (not reached vs. 199 days; p=0.047) in patients with complete responses compared with those who achieved no response. There were no statistical differences between therapeutic effects on MPEs and those on systemic lesions. Nab-paclitaxel plus CBDCA therapy may be a preferred therapeutic option for patients with NSCLC who experience MPEs, and its effectiveness in treatment of MPEs may need to be evaluated separately from its therapeutic responses in systemic lesions.

Key words: non-small cell lung cancer, nanoparticle albumin-bound paclitaxel, malignant pleural effusion, albumin transport, survival benefit

Non-small cell lung cancer (NSCLC) accounts for approximately 80–90% of lung cancers. Despite the development of multidisciplinary therapy, more than three-quarters of patients with NSCLC are diagnosed at advanced stages, and consequently experience poor outcomes and high mortality. According to the American Society of Clinical Oncology (ASCO) guideline and the National Comprehensive Cancer Network (NCCN) guideline, platinum-doublet chemotherapy is the standard first-line treatment for advanced NSCLC which do not harbor driver oncogenes [1]. Among the treatment regimens, solvent-bound paclitaxel (sb-paclitaxel) plus carboplatin (CBDCA) therapy is commonly used in clinical practice. Furthermore, the phase III ECOG4599 study showed that the addition of bevacizumab to the sb-paclitaxel plus CBDCA regimen provides significant benefits in overall survival (OS) of patients with non-squamous NSCLC [2].

It is known that sb-paclitaxel needs castor oil (CremophorEL®) as a solvent, which may reduce the therapeutic effects of paclitaxel and augment the occurrence and severity of adverse events, including anaphylaxis, peripheral sensory neuropathy, and myelosuppression [3]. Nanoparticle albumin-bound paclitaxel (nab-paclitaxel) that binds to nanoparticle albumin instead of castor oil is considered to reduce the frequency and severity of these adverse events caused by sb-paclitaxel therapy. In the phase III CA031 trial, patients who were treated with nab-paclitaxel plus CBDCA showed significantly better therapeutic responses and lesser toxicity due to neuropathy than those treated with sb-paclitaxel plus CBDCA [4]. In this context, nab-paclitaxel plus CBDCA is currently deemed a standard therapeutic regimen for patients with advanced NSCLC.

The possible mechanism underlying these favorable outcomes of therapy with nab-paclitaxel can be deduced from

its biological characteristics i.e. its association with albumin. Specifically, albumin transport pathways may induce greater intratumoral delivery and more rapid decrease in the concentrations of paclitaxel [5, 6]. Intriguingly, nab-paclitaxel showed notable effectiveness in the treatment of peritoneal cancers and peritoneal metastases of cancers [7, 8]. In mice models of intraperitoneal gastric cancers, intravenous administrations of nab-paclitaxel were sufficient to significantly decrease the severity of tumor ascites and metastases, even when compared with intraperitoneal administrations of sb-paclitaxel [9]. These findings suggest that therapy with nab-paclitaxel may provide clinical benefits for tumor lesions in the body cavity.

Malignant pleural effusion (MPE) as an intrathoracic tumor lesion is a common complication observed in 19–52% of lung cancers [10]. The onset of MPEs in patients is considered a poor prognostic factor because the median OS of patients with MPEs is approximately 3–5 months [11, 12]. Therefore, the management of MPEs in patients often determines their prognoses. Given the pharmacological characteristics of nab-paclitaxel and its effectiveness in treating intraperitoneal lesions, we hypothesized that treatments with nab-paclitaxel could also provide clinical benefits in intrapleural metastases and MPEs. In the present study, we have retrospectively investigated whether chemotherapy with nab-paclitaxel plus CBDCA is effective in MPEs that occurs in patients with NSCLC, and have attempted to advocate a novel therapeutic strategy of using chemotherapy with nab-paclitaxel plus CBDCA for treatment of such patients.

Patients and methods

Patients. The present study enrolled 40 patients with stage IIIB or IV NSCLC who were treated with nab-paclitaxel plus CBDCA at the Jichi Medical University Saitama Medical Center in Japan, from August, 2013 to July, 2016. All patients received combination chemotherapy with nab-paclitaxel (100 mg/m^2) every week and with CBDCA (area under the curve = 6) every 3 weeks, and the reductions in their doses or cessation of their treatments were determined on the basis of the onset of adverse events and disease progression in these patients. This study included patients who experienced moderately accumulated pleural effusions that did not require immediate drainages, as well as those who did not experience pleural effusions. According to previous reports, pleural effusions were comprised of either pathologically or probably diagnosed MPEs. Probably diagnosed MPEs were defined as unilateral exudative effusions for which the possibility of being caused by benign pleural processes or paramalignant effusions could be ruled out, despite obtaining negative cytological diagnoses of MPE on the basis of cultures and biochemical examinations of pleural fluid, computed tomography (CT) images, and clinical backgrounds, including symptoms, physical findings, and medical histories [12].

Study assessment. The medical records of the patients were retrospectively analyzed after approval of the institutional review board (No. 15-82). The maximal effect of chemotherapy with nab-paclitaxel plus CBDCA on a systemic lesion was classified as a complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD), according to the criteria set by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee [13]. A combination of CR and PR was defined as the objective response (OR) and a combination of OR and SD was defined as the disease control (DC). The therapeutic effect was evaluated based on the objective response rate (ORR; the rate of OR), the disease control rate (DCR; the rate of DC), the time from the initiation of chemotherapy with nab-paclitaxel plus CBDCA to the time of confirmation of disease progression (PFS; progression-free survival) or the time of death of the patient (OS). The effectiveness of nab-paclitaxel plus CBDCA therapy against MPEs was classified as CR, PR, or no response (NR), according to the evaluation criteria employed in the previous studies [14–16]. Briefly, CR, PR, and NR were defined as a complete disappearance of fluid, a distinguishable decrease and failure to meet the above criteria for more than 4 weeks, respectively. Patients included in these three categories were further classified into two groups: the effective group comprising patients who experienced CR and PR, and the ineffective group comprising patients who experienced NR. The occurrence of adverse events associated with nab-paclitaxel plus CBDCA therapy was confirmed by review of medical records of patients and evaluated based on the Common Terminology Criteria for Adverse Events (CTCAE) v4.0.

Statistical analysis. Chi-square tests were used to evaluate differences in the clinicopathological characteristics between the patient groups analyzed in this study. Therapeutic responses to the nab-paclitaxel plus CBDCA regimen were compared between patient groups by using the Mann-Whitney U tests and the Kruskal-Wallis tests. PFS and OS were calculated using the Kaplan Meier method and survival curves were evaluated using the log-rank test. Potentially confounding factors were assessed using the multivariate logistic regression analysis. A p-value <0.05 was considered significant.

Results

Evaluation of clinicopathological characteristics. Out of the 40 patients analyzed, 26 patients (65%) were diagnosed with MPEs. Although patients with MPEs exhibited marginally higher rates of never- and light smoking, there were no significant differences in clinicopathological characteristics between patients with and those without MPEs (Table 1).

Effectiveness of nab-paclitaxel plus carboplatin therapy against malignant pleural effusion. The effectiveness of nab-paclitaxel plus CBDCA therapy against systemic lesions of patients are listed in Table 2. Both ORR (45.0%) and

Table 1. Patients characteristcs.

	All (%)	Malignant effusion (+) (%)	Malignant effusion (–) (%)	p-value
Number of patients	40 (100.0)	26 (65.0)	14 (35.0)	
Age (Median ± SD)	69 ± 10	67 ± 11	70 ± 8	0.560
<70	22 (55.0)	15 (57.7)	7 (50.0)	
≥70	18 (45.0)	11 (42.3)	7 (50.0)	
Sex				0.331
Male	26 (65.0)	15 (57.7)	11 (78.6)	
Female	14 (35.0)	11 (42.3)	3 (21.4)	
Smoking history				0.079
Never smoker	9 (22.5)	8 (30.8)	1 (7.1)	
Light smoker (Pack year ≤20)	6 (15.0)	5 (19.2)	1 (7.1)	
Heavy smoker (Pack year >20)	25 (62.5)	13 (50.0)	12 (85.7)	
EGFR mutations				0.709
Exon 19 deletion	3 (7.5)	2 (7.7)	1 (7.1)	
L858R	1 (2.5)	1 (3.9)	0 (0.0)	
Other mutations	2 (5.0)	2 (7.7)	0 (0.0)	
Negative	26 (65.0)	16 (61.5)	10 (71.4)	
Unknown	8 (20.0)	5 (19.2)	3 (21.4)	
ALK rearrangement				0.625
Positive	1 (2.5)	1 (3.9)	0 (0.0)	
Negative	30 (75.0)	20 (76.9)	10 (71.4)	
Unknown	9 (22.5)	5 (19.2)	4 (28.6)	
Histology				0.309
Adenocarcinoma	19 (47.5)	15 (57.7)	4 (28.6)	
Squamous cell carcinoma	17 (42.5)	8 (30.8)	9 (64.3)	
Adenosquamous cell carcinoma	1 (2.5)	1 (3.9)	0 (0.0)	
Large cell carcinoma	1 (2.5)	0 (0.0)	1 (7.1)	
Pleomorphic carcinoma	1 (2.5)	1 (3.9)	0 (0.0)	
NSCLC (NOS)	1 (2.5)	1 (3.9)	0 (0.0)	
Treatment line				0.813
1st line	20 (50.0)	11 (42.3)	9 (64.3)	
2nd line	10 (25.0)	8 (30.8)	2 (14.3)	
Other line	10 (25.0)	7 (26.9)	3 (21.4)	
Treatment Course (Median)	4	5	3	0.659
< 4	16 (40.0)	9 (34.6)	7 (50.0)	
≥ 4	24 (60.0)	17 (65.4)	7 (50.0)	
Performance status (0–1)				0.912
0–1	36 (90.0)	23 (88.5)	13	
2–3	4 (10.0)	3 (11.5)	1 (7.1)	
Clinical stage				0.068
IIIB	3 (7.5)	0 (0.0)	3 (21.4)	
IV	37 (92.5)	26 (100.0)	11 (78.6)	
Postoperative recurrence	15 (37.5)	12 (46.2)	3 (21.4)	

SD, standard deviation; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase; NSCLC, non-small cell lung cancer; NOS, not otherwise specified.

DCR (82.5%) were higher in patients in this study than in those in the previous phase III trial; however, there were no significant differences between patients with and without MPEs in this study [4]. Out of the 26 patients with MPEs, nab-paclitaxel plus CBDCA therapy demonstrated effectiveness against MPEs in 21 patients (80.8%) (Table 3). Furthermore, out of the 21 patients who had therapeutic responses to MPEs, 6 (23.1%) and 15 (57.7%) patients achieved CR and PR, respectively.

There were no significant differences in clinicopathological characteristics between the effective and the ineffective groups against MPEs when treated with nab-paclitaxel plus CBDCA. In patients with MPEs, no other characteristics, apart from postoperative recurrences, showed statis-

tical differences among the groups of patients with CR, PR, and NR. Furthermore, multivariate logistic regression analysis was used to control potential confounding factors in the effectiveness (defined as patients with CR and PR) of nab-paclitaxel plus CBDCA therapy against MPEs (Table 4). No significant factors were independently associated with the effectiveness of nab-paclitaxel plus CBDCA therapy against MPEs.

Correlation between effectiveness of nab-paclitaxel plus carboplatin therapy against systemic lesions and malignant pleural effusions. The effectiveness of nab-paclitaxel plus CBDCA therapy against systemic lesions and MPEs was compared to investigate the possibility of correlation between them (Table 5). Patients who achieved CR in MPEs did not show PD in systemic lesions. However, there were no statistical differences between the therapeutic responses against systemic lesions and MPEs.

Survival analysis of patients with malignant pleural effusion. Using the Kaplan-Meier survival curves and log-rank tests, PFS and OS were compared among four groups of patients, namely, the three groups of patients achieved CR, PR, and NR in MPEs, respectively (termed the CR, PR, and NR groups, respectively), and the fourth group of patients who did not have MPEs. Compared to the NR group, the CR group had significantly longer median PFS (26 vs. 323 days; p=0.009) (Figure 1A) and median OS (199 days vs. not reached; p=0.047) (Figure 1B). No other therapeutic responses showed significant differences in PFS and OS (data not shown). Intriguingly, the Kaplan-Meier survival curves for PFS and OS showed that the survival curves of the PR group and the group without MPEs were closely distributed between the CR and NR groups.

Adverse events. Non-hematological and hematological adverse events associated with nab-paclitaxel plus CBDCA therapy are listed in supplemental Table 1. In the observed non-hematological adverse events, fatigue was the most frequently occurring adverse event (in 43% patients), and no grade 4 events were reported. Six (15%) patients developed interstitial lung disease; five of these patients developed grade 1 disease, and one grade 2. In the observed hematological adverse events, neutropenia and anemia frequently occurred in 29 (73%) and 30 (30%) patients, respectively, and grade 4 neutropenia occurred in 6 (15%) patients. There were no fatal adverse events in this study.

Table 2. Therapeutic response according to RECIST evaluation.

	All (%)	Malignant effusion (+) (%)	Malignant effusion (–) (%)
Number of patients	40 (100.0)	26 (65.0)	14 (35.0)
Therapeutic response			
CR	2 (5.0)	2 (7.7)	0 (0.0)
PR	16 (40.0)	8 (30.8)	8 (57.1)
SD	15 (37.5)	11 (42.3)	4 (28.6)
PD	7 (17.5)	5 (19.2)	2 (14.3)
Objective response rate (ORR)	45.0%	38.5%	57.1%
Disease control rate (DCR)	82.5%	80.8%	85.7%

RECIST: response evaluation criteria in solid tumors; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

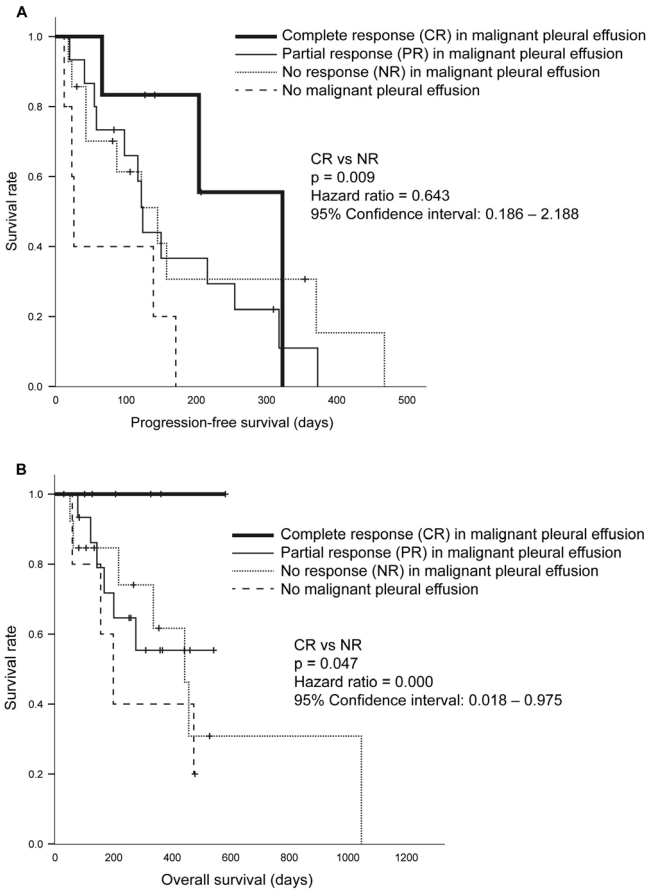

Figure 1. Kaplan-Meier survival curves and log-rank tests for patients with non-small cell lung cancer (NSCLC) who were treated with nanoparticle albumin-bound paclitaxel (nab-paclitaxel) plus carboplatin (CBDCA). Chemotherapy with nab-paclitaxel plus CBDCA significantly prolonged progression-free survival (A) and overall survival (B) in patients who achieved complete response in malignant pleural effusions that arise because of NSCLC, compared with those who achieved no response.

Discussion

Clinicians need to address the critical issue of managing MPEs as their occurrence is linked to the prognosis of patients. Pleural fluid drainage followed by pleurodesis is commonly employed for treatment of MPEs. However, this procedure is sometimes accompanied by adverse events including pain, fever, infection, and emboli, and often fails in patients with incomplete pulmonary expansion. On the other hand, the pharmaceutical management of MPE has

Table 3. Correlation between therapeutic response to malignant effusion and clinicopathological characteristics

	Patients with malignant effusion				p-value (2 groups)	p-value (3 groups)
	Effective group (%)			Ineffective group (%)		
	Total	Complete response (%)	Partial response (%)	No response (%)		
Number of patients	21(80.8)	6 (23.1)	15 (57.7)	5 (19.2)		
Age (Median ± SD)	68 ± 12	67 ± 8	69 ± 13	67 ± 6	0.896	0.951
<70	12 (57.1)	4 (66.7)	8 (53.3)	3 (60.0)		
≥70	9 (42.9)	2 (33.3)	7 (46.7)	2 (40.0)		
Sex					0.270	0.35
Male	11 (52.4)	3 (50.0)	8 (53.3)	4 (80.0)		
Female	10 (47.6)	3 (50.0)	7 (46.7)	1 (20.0)		
Smoking history					0.841	0.655
Never smoker	7 (33.3)	2 (33.3)	5 (33.3)	1 (20.0)		
Light smoker (Pack year ≤ 20)	4 (19.1)	2 (33.3)	2 (13.3)	1 (20.0)		
Heavy smoker (Pack year > 20)	10 (47.6)	2 (33.3)	8 (53.3)	3 (60.0)		
EGFR mutations					0.450	0.237
Exon 19 deletion	1 (4.8)	0 (0.0)	1 (6.7)	1 (20.0)		
L858R	1 (4.8)	1 (16.7)	0 (0.0)	0 (0.0)		
Other mutations	2 (9.5)	0 (0.0)	2 (13.3)	0 (0.0)		
Negative	15 (71.4)	4 (66.7)	11 (73.3)	2 (40.0)		
Unknown	2 (9.5)	1 (16.7)	1 (6.7)	2 (40.0)		
ALK rearrangement					0.373	0.766
Positive	1 (4.8)	0 (0.0)	1 (6.7)	0 (0.0)		
Negative	18 (85.7)	5 (83.3)	13 (86.7)	2 (40.0)		
Unknown	2 (9.5)	1 (16.7)	1 (6.7)	3 (60.0)		
Histology (Ad/Sq)					0.289	0.605
Ad	13 (61.9)	4 (66.7)	9 (60.0)	2 (40.0)		
Sq	6 (28.6)	2 (23.3)	4 (26.7)	2 (40.0)		
Adenosquamous cell carcinoma	0 (0.0)	0 (0.0)	0 (0.0)	1 (20.0)		
Pleomorphic carcinoma	1 (4.8)	0 (0.0)	1 (6.7)	0 (0.0)		
NSCLC (NOS)	1 (4.8)	0 (0.0)	1 (6.7)	0 (0.0)		
Treatment line					0.188	0.949
First line	10 (47.6)	2 (33.3)	8 (53.3)	1 (20.0)		
Seond line	7 (33.3)	1 (16.7)	6 (40.0)	1 (20.0)		
Other line	4 (19.1)	3 (50.0)	1 (6.7)	3 (40.0)		
Treatment Course (Median)	5	6	5	2	0.193	0.146
< 4	6 (28.6)	1 (16.7)	5 (33.3)	3 (60.0)		
≥ 4	15 (71.4)	3 (50.0)	10 (66.7)	2 (40.0)		
Performance status					0.518	0.299
0–1	19 (90.5)	6 (100.0)	13 (86.7)	4 (80.0)		
2–3	2 (9.5)	0 (0.0)	2 (13.3)	1 (20.0)		
Clinical stage						
IIIB	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	Not evaluated	Not evaluated
IV	21 (100.0)	6 (100.0)	15 (100.0)	5 (100.0)		
Postoperative recurrence	8 (38.1)	0 (0.0)	8 (53.3)	4 (80.0)	0.098	0.008

2 groups, effective cases vs ineffective cases; 3 groups, complete response vs partial response vs no response; SD, standard deviation; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase; NSCLC, non-small cell lung cance;, NOS, not otherwise specified.

few valid options. Preclinical studies have mainly reported the effectiveness of bevacizumab against MPEs [17]. In fact, previous clinical studies have demonstrated the effectiveness of combination chemotherapy that included bevacizumab against MPEs that arise because of NSCLC, and the control rates in these cases were 46.4–71.4% [15, 18–21]. Although these bevacizumab-based chemotherapies frequently included the sb-paclitaxel regimen, the effectiveness of treat-

ments for MPEs is mainly attributed to bevacizumab [22]. Furthermore, there have been no reports of the effectiveness of the sb-paclitaxel regimen for MPEs other than its administration by intrapleural injection [23]. The present study demonstrated that combination chemotherapy with nab-paclitaxel plus CBDCA was highly effective against MPEs that arise because of NSCLC: the ORR of 80.8% and 6 (23%) patients achieved CR in MPEs. Besides the significant survival benefits in patients with CR in MPEs compared with those with NR in MPEs, even patients with PR in MPEs had survival benefits comparable to those in patients who did not experience MPEs. These findings may not only corroborate the importance of the control of MPE but also suggest the significance of chemotherapy with nab-paclitaxel plus CBDCA as a less invasive approach for the management of MPE. To our knowledge, this is the first report to evaluate the effectiveness of nab-paclitaxel plus CBDCA against MPEs, although some case reports have described the effectiveness of sb-paclitaxel for MPEs.

While the favorable effectiveness of nab-paclitaxel plus CBDCA therapy against MPEs is presented in the study, its underlying mechanism remains obscure. Given the results from the previous experimental study and case reports, nab-paclitaxel is considered to potentiate the effect on MPEs [9, 24, 25]. In a study using animal models, the comparison between treatments with equal doses of sb-paclitaxel and nab-paclitaxel failed to indicate a statistically significant difference in outcomes of the treated groups [9]. Previous studies suggested that the albumin receptor (gp60) in vascular endothelial cells facilitates the transcytosis of nab-paclitaxel, which in turn binds to the secreted protein acidic and rich in cysteine (SPARC) in tumors and in the stroma [26, 27]. Furthermore, caveolin-1 (CAV-1) has also been reported to activate gp60, leading to enhanced transcytosis of nab-paclitaxel [28]. Another report demonstrated that CAV-1 expression increased in tumor cells in the pleural and peritoneal effusions of ovarian carcinomas, although the status of SPARC expression in effusions remains unknown [29]. The recent phase II trial also demonstrated that higher CAV-1 protein expressions in the stroma of NSCLC were associated with improved therapeutic responses and OS in patients treated with nab-paclitaxel plus CBDCA [30]. These potential mechanisms may concentrate nab-paclitaxel in tumors and in the stroma, which means that the higher dose intensity and lesser toxicity of nab-paclitaxel in comparison with sb-paclitaxel may in clinical settings contribute to its therapeutic effect against MPEs, and systemic lesions in patients.

Although the findings in the present study provide new insights into treatment of MPEs in patients with NSCLC, there are some limitations of this study. Firstly, this small retrospective study may have an undefined bias, although multivariate analysis of the effects on MPEs has been performed to correct an inherent bias. Further large-scale prospective studies will be warranted to confirm our data.

Table 4. Logistic regression analysis for efficacy of carboplatin/nab-paclitaxel for maginant effusion.

	p-value	Hazard ratio	95% Confidence interval
Age (<70 vs ≥70)	0.224	7.045	0.302–3.417
Treatment before nab-paclitaxel	0.077	25.661	0.970–1.098
ECOG performance status (0–1/2)	0.116	0.029	<0.001–2.380
Treatment suspension	0.179	15.642	0.282–866.211
Treatment dose reduction	0.0447	4.042	0.111–147.537
Disease control (CR+PR+SD/PD)	0.111	0.025	<0.001–2.339

nab-paclitaxel, nanoparticle albumin-bound paclitaxel; ECOG, eastern cooperative oncology group; CR, complete response; PR, partial response; SD, stable disease; PD, progressiive disease.

Table 5. Correlation between RECIST evaluation and therapeutic response to malignant effusion.

		Therapeutic response to malignant effusion				p-value
		Complete response	Partial response	No change	Progression	
RECIST evaluation	CR	1	1	0	0	0.256
	PR	2	6	0	0	
	SD	3	5	2	1	
	PD	0	3	1	1	

RECIST: response evaluation criteria in solid tumors, CR: complete response, PR: partial response, SD: stable disease, PD: progressive disease.

Secondly, in some patients, the pathological diagnosis of MPE was negative. Although multiple diagnostic examinations eliminated other potential etiological factors, exclusion diagnosis inherently contains the potential for an unanticipated mechanism. Finally, till date, no standard criteria for assessment of therapeutic responses to MPEs have been established. Thus, the criteria used in multiple studies have been employed in the present study.

Given the effectiveness of nab-paclitaxel plus CBDCA therapy against MPE, this regimen may be a preferred therapeutic option for patients with NSCLC who experience MPEs. Currently, squamous cell carcinomas are not treatable with bevacizumab; however, in the previous phase III trial, chemotherapy with nab-paclitaxel plus CBDCA provided favorable outcomes in patients with squamous cell carcinomas [4]. Thus, nab-paclitaxel plus CBDCA therapy may be particularly appropriate in patients with squamous cell carcinomas, although in the present study, histological types did not exhibit statistically significant differences in their therapeutic responses against MPEs.

In the present study, the effectiveness of nab-paclitaxel plus CBDCA therapy against systemic lesions was inconsistent with the effectiveness against MPEs. This finding suggests that patients who show therapeutic responses to MPEs, but do not exhibit either CR or PR in systemic lesions as classified on the basis of the RECIST evaluation, are classified as SD and are anticipated to have good prognosis. The discord in the effectiveness of nab-paclitaxel

plus CBDCA therapy between MPEs and systemic lesions in patients with NSCLC may suggest that the effectiveness of this therapy against MPEs should be evaluated separately from the effectiveness against systemic lesions, based on the RECIST criteria.

Supplementary information is available in the online version of the paper.

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Supplementary Table 1. Adverse event due to nanoparticle albumin-bound paclitaxel/carboplatin.

	Patients with malignant pleural effusion (%)								Patients without malignant pleural effusion (%) n=14		Total (%) n=40	
	Total (n=26)		Effective group (n=21)		Ineffective group (n=5)							
			Complete response (n=6)		Partial response (n=15)		No response (n=5)					
	Gr 1–2	Gr 3–4	Gr 1–2	Gr 3–4	Gr 1–2	Gr 3–4	Gr 1–2	Gr 3–4	Gr 1–2	Gr 3–4	Gr 1–2	Gr 3–4
Non-hematological												
Fatigue	13 (50)	1 (4)	3 (50)	0	9 (60)	0	1 (20)	1 (20)	3 (21)	0	16 (40)	1 (3)
Constipation	9 (35)	0	1 (17)	0	7 (47)	0	1 (20)	0	3 (21)	1 (7)	12 (30)	1 (3)
Peripheral sensory neuropathy	10 (38)	0	3 (50)	0	6 (40)	0	1 (20)	0	1 (7)	0	11 (28)	0
Anorexia	7 (27)	0	1 (17)	0	4 (27)	0	2 (40)	0	3 (21)	0	10 (25)	0
Nephrotoxicity	5 (19)	0	0	0	5 (33)	0	0	0	4 (29)	0	9 (23)	0
Nausea	6 (23)	0	1 (17)	0	5 (33)	0	0	0	1 (7)	0	7 (18)	0
ILD	2 (8)	0	0	0	2 (13)	0	0	0	4 (29)	0	6 (15)	0
Dysgeusia	3 (12)	0	0	0	2 (13)	0	1 (20)	0	2 (14)	0	5 (13)	0
Diarrhea	4 (15)	0	0	0	1 (7)	0	3 (60)	0	1 (7)	0	5 (13)	0
Fever	2 (8)	0	1 (17)	0	1 (7)	0	0	0	2 (14)	0	4 (10)	0
Hepatotoxicity	3 (12)	0	1 (17)	0	2 (13)	0	0	0	1 (7)	0	4 (10)	0
Skin rash	3 (12)	0	1 (17)	0	2 (13)	0	0	0	0	0	3 (21)	0
Arthlargia	2 (8)	0	1 (17)	0	1 (7)	0	0	0	0	0	2 (14)	0
Hiccups	0	0	0	0	0	0	0	0	2 (14)	0	2 (14)	0
Watering eyes	0	0	0	0	0	0	0	0	0	1 (7)	0	1 (3)
Abdominal pain	0	0	0	0	0	0	0	0	0	1 (7)	0	1 (3)
Anaphyraxis	1 (4)	0	0	0	1 (7)	0	0	0	0	0	1 (3)	0
Hematological												
Neutropenia	7 (27)	12 (46)	2 (33)	4 (67)	5 (33)	6 (40)	0	2 (40)	7 (50)	3 (21)	14 (35)	15 (38)
Anemia	15 (58)	7 (27)	3 (50)	2 (33)	10 (67)	3 (20)	2 (40)	2 (40)	7 (50)	1 (7)	22 (55)	8 (20)
Thrombocytopenia	8 (31)	0	3 (50)	0	3 (20)	0	2 (40)	0	5 (36)	0	13 (33)	0

Gr: grade