Efficacy and tolerability of nanoparticle albumin-bound paclitaxel in combination with carboplatin as a late-phase chemotherapy for recurrent and advanced non-small-cell lung cancer: A multi-center study of the Fukushima lung cancer association group of surgeons

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Abstract. The present retrospective multi-center study aimed to evaluate the efficacy and feasibility of nanoparticle albumin-bound (nab)-paclitaxel plus carboplatin as a second or late-phase chemotherapy in patients with non-small cell lung cancer (NSCLC). A total of 25 patients with recurrent or advanced NSCLC who had received previous chemotherapy were treated with nab-paclitaxel (70-100 mg/m², intravenously) on days 1, 8 and 15 every 28 days with a carboplatin area under the concentration-time curve of 4-6 on day 1. The overall response rate, disease control rate, progression-free survival (PFS), overall survival (OS) and toxicities were statistically evaluated. Of the 25 patients, there were 9 cases of recurrent disease following surgery, 16 cases of advanced disease, 13 cases of adenocarcinoma, 11 cases of squamous cell carcinoma and 1 case of large cell carcinoma. A total of 13 patients received second-line chemotherapy and 12 received fourth-line or later chemotherapy. One patient exhibited a complete response, 7 had a partial response, 10 exhibited stable disease and 7 had progressive disease. The overall response rate was 32.0% and the disease control rate was 72.0%. The median PFS and median OS following nab-paclitaxel treatment were 4.0 and 14.0 months, respectively. Frequent treatment-associated adverse events were myelosuppression, peripheral neuropathy, gastrointestinal symptoms and baldness, the majority of which were grade 1-2. Grade 3-4 neutropenia, thrombocytopenia and anemia occurred in 7 (28.0%), 3 (12.0%) and 2 (8.0%) patients, respectively. No patients experienced grade 3-4 sensory neuropathy and no grade 5 adverse effects were observed. Nab-paclitaxel plus carboplatin as second-phase or later chemotherapy provided a small but significant survival benefit for patients with recurrent or advanced NSCLC, with tolerable adverse effects. To the best of our knowledge, the results of the present study demonstrated for the first time that nab-paclitaxel plus carboplatin is a promising and feasible late-phase chemotherapeutic agent for NSCLC.

Introduction

Lung cancer is the leading cause of cancer-associated mortality worldwide (1). Advances in the treatment of non-small cell lung cancer (NSCLC) in the past decade include third-generation platinum doublets, epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) in EGFR
The present study included 19 male and 6 female patients. Classification and Staging System (to the 7th Edition Lung Cancer Tumor Node Metastasis stage IIIB/IV NSCLC. The staging was performed according to the Declaration of Helsinki and Good Clinical Practice guidelines. Written consent was obtained from each patient or their family members at the time of enrollment in the study.

### Materials and methods

#### Study population.

The present retrospective study included 25 eligible patients treated at the Division of Chest Surgery of Fukushima Medical University (Fukushima, Japan) and Fukushima Lung Cancer Association Group of Surgeons participating institutions, including the Department of Thoracic Surgery, Shirakawa Kosei General Hospital (Shirakawa, Japan), the Department of Thoracic Surgery, Takeda General Hospital (Aizuwakamatsu, Japan), the Department of Surgery, Fukushima Rosai Hospital (Iwaki, Japan), the Department of Thoracic Surgery, Southern Tohoku General Hospital (Koriyama, Japan) and the Department of Thoracic Surgery, Fukushima Red Cross Hospital (Fukushima, Japan), between July 2013 and January 2015. These patients were histologically or cytologically confirmed as having NSCLC prior to receiving chemotherapy. The inclusion criteria were as follows: Patients with recurrent NSCLC following radical surgery and patients with unresectable stage IIIB/IV NSCLC. The staging was performed according to the 7th Edition Lung Cancer Tumor Node Metastasis Classification and Staging System (21). Histological evaluation was performed according to World Health Organization classification of tumors of the lung, pleura, thymus and heart (22). The present study included 19 male and 6 female patients aged 54-78 years, with a mean age of 66.0±6.5 years. In all patients, the presence of measurable lesions was confirmed using computed tomography (CT) scans, and the Eastern Cooperative Oncology Group scores (23) were 0-1. Patient clinicopathological features are summarized in Table I. The protocol was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. Written consent was obtained from each patient or their family members at the time of enrollment in the study.

### Nab-paclitaxel treatment plan.

A total of 25 patients, who had received previous chemotherapy, were treated with nab-paclitaxel (Abraxane®; Taiho Pharmaceutical Co., Ltd., Tokyo, Japan) at a dose of 70-100 mg/m² administered intravenously on days 1, 8 and 15, with a carboplatin area under the concentration-time curve (AUC) of 4-6 on day 1, every 28 days. Treatment was repeated every 4-6 weeks until disease progression or unacceptable toxicity occurred. If patients experienced hematological toxicities such as grade 3 or 4 neutropenia or thrombocytopenia during treatment, subcutaneous injection of granulocyte colony-stimulating factor was recommended.

### Assessment of response rate and adverse events.

The response to nab-paclitaxel plus carboplatin was evaluated using the Response Evaluation Criteria in Solid Tumors 1.1 (25). Target lesions were assessed using CT scans, and the observation indicators included complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD). Furthermore, the overall response rate (ORR) and disease control rate (DCR) were assessed. Patients who completed >2 cycles of nab-paclitaxel treatment were evaluated for toxicity. Treatment-associated toxicities were scored according to the National Cancer Institute’s Common Terminology Criteria for Adverse Events version 4.0 (26).
Statistical analysis. The Fisher’s exact test was used for the analysis of categorical variables and an unpaired Student’s t-test was used for the analysis of continuous variables. Survival probabilities were estimated using the Kaplan-Meier method. Statistical analysis was conducted using SPSS version 21.0 (IBM SPSS, Armonk, NY, USA). All tests were two-sided and P<0.05 was considered to indicate a statistically significant difference.

Results

Patients characteristics. Of the 25 patients, there were 9 cases of recurrent disease following surgery and 16 advanced cases. Of these patients, there were 11 cases of squamous cell carcinoma, 13 cases of adenocarcinoma, and 1 case of large cell carcinoma. EGFR mutation status was positive in 5 (20.0%) patients, and all patients received EGFR-TKIs, including gefitinib or erlotinib, as a component of serial chemotherapy. There were no positive cases of ALK translocation in the present study. All patients had undergone previous chemotherapy, and the regimen of nab-paclitaxel plus carboplatin was administered as a second-line chemotherapy in 13 (52.0%) patients, third-line chemotherapy in 6 (24.0%) patients, fourth-line chemotherapy in 3 (12.0%) patients and fifth-line or later chemotherapy in 3 (12.0%) patients. Individual patients underwent 2-6 cycles (mean, 3.1 cycles) of this regimen. The chemotherapy regimens administered prior to nab-paclitaxel plus carboplatin were primarily S-1 (tegafur/gimeracil/oteracil) plus platinum, pemetrexed plus platinum, gemcitabine plus platinum, EGFR-TKI and docetaxel monotherapy (Table II). Furthermore, later chemotherapy regimens, administered following nab-paclitaxel plus carboplatin, included docetaxel monotherapy, EGFR-TKI, S-1 monotherapy, radiation therapy and best supportive care. The later phase chemotherapy regimens, received following nab-paclitaxel plus carboplatin, are detailed in Table III.

Response to treatment and survival analysis. CR was observed in 1 patient, PR in 7 patients, SD in 10 patients and PD in 7 patients. The mean overall survival (OS) time following first-line chemotherapy was 30.0 months. The ORR and DCR obtained following treatment with nab-paclitaxel with carboplatin were 32.0 and 72.0%, respectively (Table IV). The median progression-free survival (PFS) time and median survival time (MST) following nab-paclitaxel plus carboplatin treatment were 4.0 and 14.0 months, respectively (Fig. 1). Subgroup analysis involved the evaluation of the ORR and DCR according to gender (male vs. female), age (<70 vs. ≥70 years), histology (squamous vs. non-squamous) and chemotherapy phase (second vs. third or later phase; Table IV). In these subgroup analyses, the only parameter that differed significantly was the ORR, which was 16.7 vs. 71.4% in patients aged <70 and ≥70 years, respectively (P=0.008). However, no significant differences in DCR were identified between these age groups (P=0.968). In the groups subdivided according to histology (squamous vs. non-squamous), no significant differences were observed in the PFS and OS between the two groups (P=0.110 and P=0.245, respectively; Fig. 2). In the subgroups divided according to age (<70 vs. ≥70 years), no significant differences were identified in the PFS and OS between the two groups (P=0.727 and P=0.270, respectively; Fig. 3).

Adverse events. The treatment-associated adverse events that occurred most frequently were myelosuppression, sensory neuropathy, gastrointestinal symptoms and baldness, the majority of which were grade 1-2 (Table V), whereas grade 3-4 neutropenia was present in 7 (28.0%) patients.
thrombocytopenia in 3 (12.0%) patients and anemia in 2 (8.0%) patients. No grade 3–4 sensory neuropathies were observed. Dose reduction was required in 28.0% of patients due to toxicity, but no grade 5 adverse effects were observed. In addition, 5 (20.0%) patients did not experience any adverse events.

**Discussion**

In patients with recurrent or advanced NSCLC who relapsed following previous platinum-based chemotherapy or EGFR-TKI treatment, docetaxel monotherapy is considered to be the current standard treatment (5,7). During a previous phase III study, in which docetaxel was administered to NSCLC patients who had previously been treated with platinum-based chemotherapy, the time to progression and MST following docetaxel monotherapy was 2.4 and 7.0 months, respectively (6). In the current retrospective study, the median PFS and MST following nab-paclitaxel plus carboplatin treatment were 4.0 and 14.0 months, respectively. These results reveal that nab-paclitaxel plus carboplatin treatment, administered as a second or later-line chemotherapy, may be a promising therapeutic approach; however, careful consideration is required, as the present study was retrospective with a small sample size. In addition, the dose setting for each agent varied as the condition of the patients depended on their previous treatments and disease status.

The use of nab-paclitaxel in combination with carboplatin in chemotherapy-naive patients with stage III/IV NSCLC has exhibited a promising efficacy (16). A previous phase III trial revealed that the ORR of nab-paclitaxel with carboplatin was significantly higher, compared with that obtained following traditional solvent-based paclitaxel treatment, and that the PFS and OS were similar in the two groups (PFS, 6.3 vs. 5.8 months; and OS, 12.1 vs. 11.2 months; P=0.214 and P=0.271, respectively) (16).

In the present study, 11/25 (44%) patients had squamous cell carcinoma. The prognosis of squamous cell carcinoma is poor, as compared with that of other non-squamous subtypes (27). The treatment options for patients with squamous cell carcinoma are also currently limited (National Comprehensive Cancer Network guidelines) (28), and EGFR mutations and ALK rearrangements, which are targetable by TKIs, are rare (29). In addition, bevacizumab and pemetrexed are not indicated for use in these patients (2,30). A subset analysis of previous phase III trials (14), based on predefined stratification factors, revealed that patients with squamous histology treated with nab-paclitaxel in combination with carboplatin had a significantly higher ORR, compared with those patients who received solvent-based paclitaxel plus carboplatin (41 vs. 24%; P<0.001). In the current study, the ORR and DCR of the patients with squamous cell carcinoma treated with nab-paclitaxel plus carboplatin were observed to be 36.4 and 81.8%, respectively. These results demonstrate a higher efficacy, compared with that of traditional solvent-based paclitaxel, and may be useful as a second-phase or later chemotherapy for the treatment of squamous cell carcinoma.

In the present study, the most common adverse effects observed during nab-paclitaxel treatment were myelosuppression, sensory neuropathy, gastrointestinal reactions and

| Table II. Treatment prior to the administration of nanoparticle albumin-bound-PTX plus carboplatin therapy. |
|---------------------------------------------------------------|
| Regimen                      | 1st line | 2nd line | 3rd line | 4th line | 5th line or later |
|-------------------------------|----------|----------|----------|----------|-------------------|
| S-1+platinum                  | 8        | 0        | 0        | 0        | 0                 |
| BEV+PEM+platinum             | 7        | 3        | 0        | 0        | 0                 |
| PEM+platinum                  | 4        | 1        | 0        | 0        | 0                 |
| PTX+platinum                  | 2        | 0        | 0        | 0        | 0                 |
| GEM+platinum                  | 1        | 1        | 0        | 0        | 0                 |
| EGFR-TKI                      | 2        | 4        | 1        | 0        | 4                 |
| Single DOC                    | 0        | 4        | 1        | 0        | 0                 |
| Others                        | 1        | 0        | 0        | 2        | 4                 |

S-1, tegafur/gimeracil/oteracil; BEV, bevacizumab; PEM, pemetrexed; PTX, paclitaxel; GEM, gemcitabine; EGFR-TKI, epidermal growth factor receptor-tyrosine kinase inhibitor; DOC, docetaxel.

| Table III. Later phase treatments following nab-PTX plus carboplatin therapy. |
|-----------------------------------------------|
| Regimen | Following nab-PTX, n | Later phase, n | Total, n |
|---------|----------------------|----------------|----------|
| Continuation | 7         | 0         | 7        |
| BSC     | 5        | 3        | 8        |
| Single DOC | 4        | 2        | 6        |
| Single S-1 | 3        | 3        | 5        |
| EGFR-TKI | 2        | 1        | 3        |
| RTx     | 0        | 2        | 2        |
| Others  | 4        | 2        | 6        |

BSC, best supportive care; DOC, docetaxel; S-1, tegafur/gimeracil/oteracil; EGFR-TKI, epidermal growth factor receptor-tyrosine kinase inhibitor; RTx, radiation therapy; nab-PTX, nanoparticle albumin-bound paclitaxel.
The majority of patients experienced grade 1 or 2 adverse events and there were no treatment-associated mortalities during or following treatment with nab-paclitaxel. In a previous phase III trial, grade ≥3 neutropenia, thrombocytopenia, anemia and sensory neuropathy were reported at a rate of 41, 18, 27 and 3%, respectively, in the nab-paclitaxel with carboplatin treatment group. The present study observed rates of 28, 12, 8 and 0%, respectively, which were comparable with the prospective data, despite the inclusion of patients who had undergone previous chemotherapy that may have adversely affected their physical condition. Therefore, nab-paclitaxel in combination with platinum appears to be an optimal late-phase treatment option, due to its efficacy and favorable safety profile.

The number of elderly patients diagnosed with lung cancer has increased worldwide. Comorbid diseases and adverse medical conditions, including chronic lung disease, insufficient cardiac function, renal impairment and other age-associated conditions, have become major concerns in the treatment of elderly NSCLC patients, who occasionally experience difficulties in undergoing cytotoxic chemotherapy. Regimens that may be used to treat elderly patients with comorbidities are restricted. In the current study, the ORR of patients aged ≥70 years were superior to that of patients aged <70 years, and the DCR of patients aged ≥70 years were similar to that of patients aged <70 years. In addition, the adverse events observed in patients aged ≥70 years were similar to those observed in patients aged <70 years. These findings demonstrate that this regimen may also be promising for use in elderly patients with NSCLC.

In the present study, the previous chemotherapy regimens administered prior to nab-paclitaxel primarily consisted of platinum-doublets or EGFR-TKI (Table II). In addition, later chemotherapy regimens, which were administered following nab-paclitaxel plus carboplatin treatment, included docetaxel monotherapy, EGFR-TKI, S-1 monotherapy, radiation therapy and best supportive care. In later chemotherapy phases, platinum-doublet chemotherapy is rarely selected, as the physical condition of patients who require later-phase chemotherapy is typically poor. Two retrospective studies evaluated the efficacy of nab-paclitaxel monotherapy following previous chemotherapy, and reported that the ORR was 30.0 (34) and 28.6% (35), and the median PFS was 5.0 (34) and 4.0 months (35), respectively. In the current study, the median PFS was 4.0 months, which was comparable to the PFS reported in previous studies; the PFS was also high, as compared with the PFS obtained using docetaxel monotherapy as a second-line chemotherapy.

Table IV. Response rates following nanoparticle albumin-bound-paclitaxel plus carboplatin treatment.

| Clinical factor | Number of patients | CR | PR | SD | PD | ORR, % | P-value | DCR, % | P-value |
|----------------|--------------------|----|----|----|----|--------|---------|--------|---------|
| Gender         |                    |    |    |    |    |        |         |        |         |
| Male           | 19                 | 1  | 6  | 7  | 5  | 36.8   | 0.356   | 73.7   | 0.739   |
| Female         | 6                  | 0  | 1  | 3  | 2  | 16.7   |         | 66.7   |         |
| Age, years     |                    |    |    |    |    |        |         |        |         |
| <70            | 18                 | 0  | 3  | 10 | 5  | 16.7   | 0.008†  | 72.2   | 0.968   |
| ≥70            | 7                  | 1  | 4  | 0  | 2  | 71.4   |         | 71.4   |         |
| Histology      |                    |    |    |    |    |        |         |        |         |
| Sq             | 11                 | 0  | 4  | 5  | 2  | 36.4   | 0.678   | 81.8   | 0.332   |
| Non-Sq         | 14                 | 1  | 3  | 5  | 2  | 28.6   |         | 64.3   |         |
| Phase          |                    |    |    |    |    |        |         |        |         |
| 2nd line       | 13                 | 0  | 6  | 4  | 3  | 46.2   | 0.114   | 76.9   | 0.568   |
| 3rd line or later | 12   | 1  | 1  | 6  | 4  | 16.7   |         | 66.7   |         |
| Total          | 25                 | 1  | 7  | 10 | 7  | 32.0   | N.A.    | 72.0   | N.A.    |

*P<0.05 indicates a statistically significant difference. CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, overall response rate; DCR, disease control rate; Sq, squamous cell carcinoma; N.A., not applicable.

Table V. Grade of adverse events following treatment with nanoparticle albumin-bound-paclitaxel plus carboplatin.

| Adverse events              | CTCAE grade |
|-----------------------------|-------------|
|                            | I/II (%) | III (%) | IV (%) |
| Leukopenia                  | 5 (20)    | 6 (24)  | 1 (4)   |
| Thrombocytopenia            | 4 (16)    | 3 (12)  | 0 (0)   |
| Anemia                      | 0 (0)     | 2 (8)   | 0 (0)   |
| Neurotoxicity               | 7 (28)    | 0 (0)   | 0 (0)   |
| Gastrointestinal symptoms   | 5 (20)    | 1 (4)   | 0 (0)   |
| Baldness                    | 3 (12)    | 0 (0)   | 0 (0)   |
| Edema                       | 1 (4)     | 0 (0)   | 0 (0)   |
| Vertigo                     | 1 (4)     | 0 (0)   | 0 (0)   |

CTCAE, common terminology criteria for adverse events.
To the best of our knowledge, the results of the present study are the first to demonstrate that nab-paclitaxel plus carboplatin is a promising and tolerable late-phase chemotherapy for NSCLC. However, the current study had two limitations. Firstly, only a small sample size of 25 patients was evaluated, and, secondly, there was a risk of selection bias due to the retrospective nature of the study. In conclusion, nab-paclitaxel plus carboplatin administered as a second-phase or later-phase chemotherapy offers a small but significant survival benefit for patients with recurrent and advanced-stage IIIB/IV NSCLC, with tolerable adverse effects. However, further prospective studies of this regimen as a late-phase chemotherapeutic agent are required.

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