Efficacy of Nab-Paclitaxel as Second-line Chemotherapy for Unresectable or Recurrent Gastric Cancer

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Abstract. *Aim: To evaluate the efficacy and safety of nanoparticle albumin-bound-paclitaxel (nab-PTX) as second-line chemotherapy (CT) for patients with unresectable or recurrent gastric cancer (GC). Patients and Methods: The clinicopathological and survival data of 37 patients with unresectable or recurrent GC who underwent nab-PTX monotherapy as second-line CT, were retrospectively analyzed. Results: The median number of cycles and relative dose intensity administered per patient were 5 and 90%, respectively. Their overall response rate was 24.3% and the disease control rate was 59.5%. Median progression-free survival (PFS) and overall survival were 4.8 months and 10.4 months, respectively. Thirteen patients had grade 3 or 4 toxicities and were managed. In multivariate Cox regression analysis, cycles of chemotherapy ≥ 5 (odds ratio, 0.20; 95% confidence interval, 0.08-0.50; $p < 0.01$) was the only significant independent predictor of longer PFS. Conclusion: Nab-PTX may effectively prevent disease progression as second-line CT by increasing treatment cycles and managing adverse effects.*

Gastric cancer (GC) is the third leading cause of cancer-related death worldwide. Although the GC mortality rate has decreased in many countries, it remains the second leading cause of cancer death in Japan (1). Advanced GC is generally treated with both surgery and chemotherapy (CT); unresectable or recurrent GC is treated with CT alone. In Japan, the SPIRITS trial, a phase-III study, established S-1 plus cisplatin as a standard first-line CT regimen for unresectable or recurrent GC (2). Several recent phase-III

studies showed a survival benefit with second-line CT compared with best supportive care (3-5). In Japan, paclitaxel (PTX) is the most commonly used second-line CT agent for unresectable or recurrent GC, and has shown overall response rates (ORR) of 16-27%, overall survival (OS) times of 5-11 months and modest toxicity in several phase-II studies of advanced GC (6-9). With regard to OS, the recent phase-III WJOG trial failed to show CPT-11's superiority to weekly PTX (10).

PTX is insoluble in water and therefore had been dissolved in Cremophor EL (polyoxyethylene castor oil) and anhydrous ethanol; however, these vehicles have led to toxicity associated with PTX use. Nanoparticle albumin-bound paclitaxel (*nab-PTX*) was created to resolve these vehicle-related problems by binding PTX to albumin and thereby making it soluble in physiological saline. *Nab-PTX* allows the safe infusion of significantly higher doses of PTX than those used in standard PTX therapy, with shorter infusion schedules (30 min vs. 3 h) and no requirement of premedication for solvent-based hypersensitivity reactions. In Japan, *nab-PTX* has been established as a treatment for GC; results of a phase-II study were published in 2014 (11). However, the efficacy of *nab-PTX* as second-line CT for unresectable or recurrent GC has not yet been clinically evaluated. In this study, we retrospectively examined the clinicopathological and progression-free survival (PFS) data of patients with unresectable or recurrent GC after failure of first-line CT to evaluate the efficacy and safety of *nab-PTX* as second-line CT.

Patients and Methods

Patients. A database of 37 patients with unresectable or recurrent GC who underwent CT with *nab-PTX* after the failure of first-line CT at the Saitama Medical Center of the Saitama Medical University from September 2013 to October 2015, was retrospectively reviewed. *Nab-PTX* has been mainly selected as second-line CT for patients with unresectable or recurrent GC at this time. We evaluated the efficacy and safety of *nab-PTX* monotherapy and the outcomes in these 37 patients. This retrospective study was approved by the local ethics committee of Saitama Medical Center of Saitama Medical University (No. 613- II).

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Tumor classification and histopathological grading were performed according to the Union for International Cancer Control pTNM staging guidelines, seventh edition (12). Terminology defined by the Japanese Gastric Cancer Association was used to avoid unnecessary confusion (13). All patients had at least one proven lesion with any non-curative factor such as peritoneal (P1), hepatic (H1) and distant metastasis (M1). Additionally, eligible patients were required to have an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1.

Chemotherapy schedule. Patients received a single infusion nab-PTX (260 mg/m²) on an outpatient basis during a 30-minute period on day 1 of a 3-week cycle (11). Treatment was discontinued at onset of disease progression, development of severe toxic effects, or patient's request. Three dose reduction levels (220, 180, and 150 mg/m²) were implemented under the dose reduction criteria. Tumor response was objectively assessed after each treatment course according to the Response Evaluation Criteria in Solid Tumors. Adverse events were evaluated by the Common Terminology Criteria for Adverse Events, version 4.0.

Follow-up schedule. Disease progression and new lesion development were evaluated as needed by radiography and computed tomography. Tumor markers carcinoembryonic antigen and CA 19-9 were measured at baseline and at least every 4–6 weeks during treatment. Responses were evaluated every 6 weeks or earlier in patients with evidence of treatment failure. Physical examinations and laboratory tests were performed before treatment and at least every 3 weeks during treatment.

Statistical analysis. Continuous variables are expressed as medians and ranges. Grouping of categorical and continuous variables was carried out using standard thresholds. Cox proportional hazard regression analysis was used to identify significant independent factors for PFS. Factors for which $p < 0.05$ according to univariate analysis were assessed by multivariate analysis. In the univariate and multivariate analyses, odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. All statistical analyses were performed with JMP 5.0 software (SAS Institute, Cary, NC, USA). $p < 0.05$ was considered to be significant.

Results

Patients' characteristics. Characteristics of the 37 patients who underwent second-line CT with nab-PTX are presented in Table I. These 37 patients included 27 men and 10 women with a median age of 65 years (range: 32–81 years). Of the 37 patients, 26 (70%) underwent gastrectomies. The most commonly prescribed agents prior CT, were S-1 monotherapy as adjuvant CT (20%) or S-1 plus cisplatin as first-line CT (59%). The respective median number of cycles was 5 (range: 2–16) and the relative dose intensity (RDI) administered per patient was 90% (range: 49–100%), with 13 (35%) and 16 (43%) patients requiring dose reductions and delays, respectively.

Response. All 37 patients were assessable for response (Table II). Four patients (10.8%) had complete responses (CR), five (13.5%) had partial responses, thirteen (35.1%)

Table I. *Characteristics of 37 patients with unresectable or recurrent gastric cancer receiving nab-paclitaxel as second-line chemotherapy.*

Characteristic	
Median age (range), years	65 (32–81)
Gender, n	
Male/female	27/10
Performance status, n	
0/1	30/7
Location, n	
U/M/L	16/8/13
Histological type, n	
G1/2/3	6/10/21
Primary lesion, n	
Absent/present	26/11
Type of treatment failure, n	
First line/adjuvant	28/9
Number of non-curative factors, n	
1/2/3	25/10/2
Organs of noncurative factor, n (overlapping)	
Peritoneum	13
Liver	6
Lung	8
Lymph node	16
Others	5
Median number of cycles (range)	5 (2–16)
Relative dose intensity (range), %	90 (49–100)
Adjuvant chemotherapy, n	
S-1	7
UFT	2
First-line chemotherapy, n	
S-1 based	26
Others	2
Third-line chemotherapy, n	
Irinotecan	10
Docetaxel	3
Others	3

UFT, Tegafur-uracil.

Table II. *Clinical responses of patients with unresectable or recurrent gastric cancer receiving nab-paclitaxel as second-line chemotherapy.*

Characteristics	
Complete response, n (%)	4 (10.8)
Partial response, n (%)	5 (13.5)
Stable disease, n (%)	13 (35.1)
Progressive disease, n (%)	15 (40.5)
Overall response rate, %	24.3
Disease control rate, %	59.5
Median progression-free survival, months	4.8
Median overall survival, months	10.4

had stable disease and fifteen (40.5%) had progressive disease. The overall response rate (ORR) was 24.3% and the disease control rate was 59.5%.

Table III. Univariate and multivariate predictors of progression-free survival in patients with unresectable or recurrent gastric cancer receiving nab-paclitaxel as second-line chemotherapy.

Variables	n	Univariate		Multivariate	
		Odds ratio (95% CI)	p-Value	Odds ratio (95% CI)	p-Value
Age; years					
<65	18	0.86 (0.58-1.26)	0.44		
≥65	19	1			
Gender					
Male	27	1			
Female	10	0.96 (0.60-1.45)	0.86		
Performance status					
0	30	0.79 (0.49-1.38)	0.38		
1	7	1			
Location					
U/M	24	1		1	
L	13	0.59 (0.37-0.89)	0.01	0.64 (0.37-1.06)	0.08
Histological type					
G1, G2	16	1			
G3	21	0.73 (0.34-1.59)	0.43		
Primary lesion					
Absent	26	0.63 (0.41-1.00)	0.05	0.70 (0.44-1.13)	0.15
Present	11	1		1	
No. of noncurative factors					
1 factor	25	0.84 (0.57-1.26)	0.40		
2, 3 factors	12	1			
Number of cycles					
<5	18	1		1	
≥5	19	0.21 (0.09-0.48)	<0.01	0.20 (0.08-0.50)	<0.01
Relative dose intensity; %					
<90	16	0.63 (0.42-0.94)	0.02	0.89 (0.55-1.42)	0.64
≥90	21	1		1	
Toxicity					
Grade 1, 2	25	0.82 (0.34-1.79)	0.62		
Grade 3, 4	12	1			

CI, Confidence interval.

Survival. Median PFS was 4.8 months, with a median follow-up time of 8.1 months (range: 2.0-24.9 months). Median OS was 10.4 months (Table III). Median duration of treatment was 89.0 days (range: 22-477 days).

We selected the following 10 variables for univariate analysis with regard to PFS: age (<65 *vs.* ≥65 years), sex (male *vs.* female), PS (0 *vs.* 1), location (U or M *vs.* L), histologic type (G1 or 2 *vs.* G3), primary lesion (absent *vs.* present), number of noncurative factors (1 *vs.* 2, 3), cycles of CT (<5 *vs.* ≥5), RDI (<90 *vs.* ≥90%) and toxicity grade (grade 1 or 2 *vs.* 3 or 4). In univariate analysis, lower location ($p=0.01$), absent primary lesion ($p=0.05$), RDI <90% ($p=0.02$) and cycles of CT ≥5 ($p<0.01$) were significantly associated with longer PFS. In multivariate Cox regression analysis, only cycles of CT ≥5 (OR, 0.20; 95% CI=0.08–0.50; $p<0.01$) was an independent predictor of longer PFS (Table III).

Adverse effects. All patients reported at least one drug-related adverse effect (Table IV). Thirteen patients (35.1%) had grade 3 or 4 toxicities with incidence rates of ≥10% included neutropenia (21.6%), leukopenia (10.8%) and grade 1-3 toxicities included anemia (97.3%) and peripheral sensory neuropathy (91.9%).

Discussion

Patients with unresectable or recurrent GC usually have poor prognoses and generally undergo standard first-line CT. They may undergo second-line CT after the failure of first-line CT. In Japan, PTX is the most commonly used second-line agent for unresectable or recurrent GC; *nab*-PTX has been similarly used. In two phase-II studies, PTX resulted in ORR of 16-27%, and median OS of 5-8 months for advanced GC in second-line setting (6, 8). However, the efficacy of *nab*-

Table IV. Adverse events related to nab-paclitaxel occurring in $\geq 10\%$ of patients with unresectable or recurrent gastric cancer receiving as second-line chemotherapy.

Type	Grade				Grade 1-4	Grade 3 or 4
	1	2	3	4	n (%)	n (%)
Hematologic						
Anemia	24	12	0	0	36 (97.3)	0 (0.0)
Leukopenia	2	4	4	0	10 (27.0)	4 (10.8)
Neutropenia	1	1	5	3	10 (27.0)	8 (21.6)
Thrombocytopenia	2	1	0	1	4 (10.8)	1 (2.7)
Laboratory test abnormalities						
AST elevation	2	1	1	0	4 (10.8)	1 (2.7)
ALT elevation	2	2	0	0	4 (10.8)	0 (0.0)
Non-hematologic						
Constipation	15	0	0	0	15 (40.5)	0 (0.0)
Diarrhea	4	0	0	0	4 (10.8)	0 (0.0)
Stomatitis	3	2	0	0	5 (13.5)	0 (0.0)
Nausea/vomiting	9	1	1	0	11 (29.7)	1 (2.7)
Fatigue	7	2	0	0	9 (24.3)	0 (0.0)
Anorexia	9	0	0	0	9 (24.3)	0 (0.0)
Dysgeusia	6	0	0	0	6 (16.2)	0 (0.0)
Arthralgia	7	0	0	0	7 (18.9)	0 (0.0)
Myalgia	11	1	0	0	12 (32.4)	0 (0.0)
Peripheral motor neuropathy	3	4	0	0	7 (18.9)	0 (0.0)
Peripheral sensory neuropathy	20	12	2	0	34 (91.9)	2 (5.4)
Alopecia	5	1	0	0	6 (16.2)	0 (0.0)
Pruritus	6	4	0	0	10 (27.0)	0 (0.0)

AST, Aspartate aminotransferase; ALT, alanine aminotransferase.

PTX as second-line CT for unresectable or recurrent GC has not yet been clinically evaluated. In a phase-II study, nab-PTX given at 260 mg/m² every 3 weeks as a second-line CT for previously 5-FU-treated unresectable or recurrent GC resulted in a 27.6% ORR, a median PFS of 2.9 months and OS of 9.2 months (11). Our data indicate that nab-PTX as a second-line CT gave a 24.3% ORR, a median PFS of 4.8 months and OS of 10.4 months, comparable to the phase-II study. Moreover, one patient (1.9%) had a CR in the phase-II study (11), whereas four patients (10.8%) unexpectedly had CRs in this study. Based on these findings, nab-PTX seemed to be an effective second-line drug in clinical practice.

Our data also showed that number of treatment cycles of nab-PTX is the only independent factor for longer PFS. Adverse events led to dose reductions in 13 (35%) patients and delays in 16 (43%) patients in this study. However, the number of treatment cycles but not RDI, of which this study had a relatively high rate (median: 90%), was associated with better PFS. Therefore, continuing to treat patients who responded to nab-PTX therapy for a longer time while attending adverse events in a timely manner (even if dose reductions or delays are needed) seems critical to its efficacy. However, thus managed, weekly nab-PTX regimens may be expected to be similar to weekly PTX regimens. Currently,

the non-inferiority of triweekly (260 mg/m²) or weekly (100 mg/m²) nab-PTX to weekly PTX used as a control arm in terms of OS is being evaluated to establish the appropriateness of nab-PTX as second-line CT for unresectable or recurrent GC in the ABSOLUTE trial, a phase-III study (14).

This study found no significant hypersensitivity or anaphylactic reactions were induced by nab-PTX therapy without premedication, similar to the phase-II study. Reasons for treatment withdrawal were mainly disease progression (97%); one patient (3%) discontinued the treatment because of grade 4 thrombocytopenia. Although grade 3 or 4 toxicities such as neutropenia and leukopenia were found, these adverse events were clinically managed. Especially, the most common grade 1-3 toxicities were anemia (97.3%) and peripheral sensory neuropathy (91.9%). Anemia might be affected by not only adverse events but also post-gastrectomy complication or tumor bleeding in patients with unresectable or recurrent GC. All such cases were well-managed in this study, as they were all grade 1 or 2 toxicities. However, grade 2-3 peripheral sensory neuropathy remains an important problem that might be controlled by dose reductions and delays before the symptoms worsen. In this study, grade 2-3 peripheral sensory neuropathy led to

dose reductions in 7 (19%) patients and delays in 10 (27%) patients. Ohno *et al.* have reported that both compression therapy using stockings and sleeves, and medication therapy using selected prophylactic drugs (such as goshajinkigan or mecobalamin) improve the grade of peripheral neuropathy by controlling microcirculation for breast cancer patients treated with *nab*-PTX (15). Referring to this study, we also applied this therapy for unresectable or recurrent GC patients treated with *nab*-PTX and some patients appeared to improve their grade of peripheral neuropathy.

In conclusion, *nab*-PTX may become an effective therapy to prevent disease progression when used as second-line CT, by prolonging the number of treatment cycles and managing adverse events, even if requiring dose reductions or delays. Even though the current retrospective study was performed at a single center in a limited patient population and was therefore subject to selection bias, our findings should stimulate further inquiry into how to manage unresectable or recurrent GC in patients treated with *nab*-PTX as second-line CT.

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