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Original Article

Efficacy and Safety of Ramucirumab/nab-paclitaxel for Previously Treated Advanced Gastric Cancer in Community Hospitals

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As the nanoparticle albumin-bound paclitaxel (nab-PTX) is free of ethanol and premedication, the duration of administration is shorter and patients can drive themselves to and from the hospital. In the 2018 Japanese gastric cancer treatment guidelines, ramucirumab (RAM) plus weekly nab-PTX is conditionally recommended for previously treated patients with advanced gastric cancer. Here, we retrospectively analysed the efficacy and safety of RAM+nab-PTX for such patients in community hospitals. From January 2018 to December 2019, 43 patients with metastatic and recurrent gastric cancer received RAM+nab-PTX treatment. Six patients (13.9%) were older than 80 years and 9 patients (20.9%) showed ECOG-PS 2. Progression-free survival (PFS), overall survival (OS), overall response rate (ORR), disease control rate (DCR), and adverse events (AEs) were reviewed retrospectively. Median PFS was 114 days (95% confidence interval [CI]: 84-190) and median OS was 297 days (95% CI: 180-398). ORR and DCR were 32.4% and 72.2%, respectively. The incidence rates of ≥ grade 3 neutropenia and febrile neutropenia were 53.5% and 2.3%, respectively. No treatment-related deaths occurred. RAM plus nab-PTX combination therapy demonstrated manageable toxicity even patients who were elderly or had an ECOG-PS 2. This treatment is useful in community hospital settings.

Key words: gastric cancer, ramucirumab, nab-paclitaxel

Gastric cancer is one of the leading causes of cancer-related death worldwide [1]. Combination therapy with fluoropyrimidine and a platinum agent is used as the first-line treatment for unresectable or recurrent gastric cancer [2], and the survival benefits conferred by several second-line regimens have been demonstrated in randomized trials [3-5]. Patients treated with weekly solvent-based paclitaxel (sb-PTX) showed overall survival (OS) rates similar to those of patients treated with irinotecan [6], and the RAINBOW trial demonstrated the superiority of ramucirumab (RAM) plus weekly sb-PTX over weekly sb-PTX alone as a second-line regimen [7]. Therefore, RAM plus weekly sb-PTX is now recommended as a second-line treatment in the 2018 Japanese gastric cancer treatment guidelines (5th edition) [8].

Nanoparticle albumin-bound paclitaxel (nab-PTX) is a solvent-free, albumin-bound 130-nm particle form of PTX that carries a reduced risk of polyethoxylated castor oil-associated hypersensitivity reactions and does not require the use of hydrated ethanol as a solvent [9]. The non-inferiority of weekly nab-PTX compared to weekly sb-PTX was demonstrated in the ABSOLUTE trial [10], and the safety and efficacy of RAM plus weekly nab-PTX were shown in a phase II trial [11].

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Therefore, RAM plus weekly nab-PTX (RAM+nab-PTX) is conditionally recommended as a second-line chemotherapy regimen in the 2018 Japanese gastric cancer treatment guidelines (5th edition) [2]. As this regimen is ethanol-free and does not require premedication, it is particularly appropriate for use in rural settings. Accordingly, RAM+nab-PTX has been in use at our hospital since 2018. In this study, we retrospectively analyzed the efficacy and safety of RAM+nab-PTX in previously treated patients with advanced gastric cancer in a community hospital.

Patients and Methods

Patients. Between January 2018 and December 2019, we used RAM+nab-PTX as a second-line chemotherapy to treat patients with metastatic or recurrent gastric cancer with histologically confirmed adenocarcinoma. RAM+nab-PTX treatment was prescribed by the attending doctor, according to the Eastern Cooperative Oncology Group (ECOG) performance status (PS), basal disease, and the patient's consent. Patients were excluded if their ECOG-PS was 3 or 4, or if they had inadequate bone marrow, or hepatic or renal function. Patients with a history of thromboembolism were included if they were anticoagulated. Age and previous treatment regimen were not considered. General consent was obtained before treatment, and individual consent to participate in this study was obtained from each subject after approval of the study design by the ethics review board of our institution.

Treatment. Patients received nab-PTX (100 mg/m^2) on days 1, 8, and 15, and RAM (8 mg/kg) on days 1 and 15 of a 28-day cycle. The criteria for treatment were based on the JapicCTI-153088 trial [11], with modifications made by the attending doctor as required. Treatment was continued until disease progression, deterioration of general condition, unacceptable toxicity, or the patient wished to stop treatment.

Patient evaluation. Physical examination and blood laboratory tests were conducted before every drug administration, and computed tomography (CT) scans were performed every 2-3 cycles. We retrospectively reviewed clinical records regarding patient characteristics, dosage, schedule, relative dose intensity (RDI), adverse events (AEs), tumor response, progression-free survival (PFS), and overall survival (OS). AEs were evaluated according to the Common Terminology Criteria for Adverse Events (ver. 4) [11]. Measurable solid tumors were evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) [12]. In the absence of measurable tumors, the volume of ascites or pleural effusion, tumor markers (carcinoembryonic antigen [CEA] and carbohydrate antigen [CA] 19-9) were evaluated, according to the radiologist and attending doctor's diagnosis.

Statistical methods. PFS and OS were analyzed using the Kaplan-Meier method, and JMP ver. 10.0.2 (SAS Institute, Cary, NC, USA) was used for statistical analysis.

Results

Patient characteristics. Forty-three patients received RAM+nab-PTX treatment at our institution. Patient characteristics are shown in Table 1. The median age was 70 years, with 34 patients (79.1%) older than 65, and 6 (14%) older than 80. Nine patients had ECOG-PS 2 (20.9%). Measurable tumors were present in 29 cases, while 14 cases had none. Previous chemotherapy regimens are shown in Table 1.

Treatment. The median number of cycles was 3 (range: 1-11). The regimen was discontinued during the first cycle in 7 cases. The average RDIs of nab-PTX and RAM were 59.4% (range: 25.9-100.0%) and 80.2% (range: 14.3-100.0%), respectively. The average total doses of nab-PTX and RAM were 1,041.0 mg (range: 100-2,350 mg) and 3,724.4 mg (range: 250-8,600 mg), respectively (Table 2).

Efficacy. The median PFS was 114 days (95% confidence interval [CI]: 84-190) and the median OS was 297 days (95% CI: 180-398) (Fig. 1). Treatment was discontinued before efficacy evaluation in 6 cases, which were therefore disregarded in this assessment. The overall response rate (ORR) and disease control rate (DCR) were 32.4% and 70.2%, respectively (Table 2). Of the 37 assessed patients, 4 showed complete response; 8, partial response; 14, stable disease; and 11, progressive disease.

In patients with measurable tumors, the ORR and DCR were 32.0% and 64.0%, respectively. In patients without measurable tumors, the ORR and DCR were 33.3% and 83.3%, respectively. Additionally, there was reduced massive pleural effusion or reduced ascites in 4 of 9 cases (44.4%).

AEs. Treatment-related AEs are listed in Table 3.

Table 1 Patients Characteristics

	Patients (N = 43)
Sex	
Male	28 (65.1%)
Female	15 (34.9%)
ECOG-PS	
0	8 (18.6%)
1	26 (60.5%)
2	9 (20.9%)
Age (years)	
Median (range)	70 (36–90)
Histological type	
Diffuse	25 (58.1%)
Intestinal	18 (41.9%)
Measurable tumors	
Presence	29 (67.4%)
Absence	14 (32.6%)
Gastrectomy	
performed	21 (48.8%)
not performed	22 (51.2%)
Massive pleural effusion or ascites	
Presence	9 (20.9%)
Absence	34 (79.1%)
Previous chemotherapy regimen	
S-1	4 (9.3%)
S-1 + cisplatin	7 (16.3%)
S-1 + oxaliplatin	17 (39.5%)
S-1 + docetaxel	5 (11.6%)
capecitabine + oxaliplatin	7 (16.3%)
capecitabine + oxaliplatin + trastuzumab	2 (4.7%)
FOLFOX	1 (2.3%)

Table 2 Result in our institution

	Patients (N = 43)
Median PFS	114 days
Median OS	297 days
ORR	32.4%
DCR	70.2%
Median total cycles (range)	3 cycles (1–11 cycles)
Relative dose intensity (range)	
nab-PTX	59.4% (25.9–100.0%)
RAM	80.2% (14.3–100.0%)
Total dose (range, mg/patient)	
nab-PTX	1041.0 (100–2350)
RAM	3724.4 (250–8600)
Transition rate to 1st post-treatment (%)	74.4%
Transition rate to 2nd post-treatment (%)	40.7%
1st post-treatments	
Nivolumab	20 (46.5%)
CPT-11	1 (2.3%)
TAS-102	1 (2.3%)
RAM monotherapy	2 (4.7%)
Conversion surgery	2 (4.7%)
Radiotherapy	3 (7.0%)
None	10 (23.3%)
Ongoing RAM+nab-PTX	4 (9.3%)
2nd post-treatments	
Nivolumab	4 (9.3%)
CPT-11	2 (4.7%)
TAS-102	4 (9.3%)
RAM monotherapy	1 (2.3%)
None	27 (62.8%)
Ongoing RAM+nab-PTX	4 (9.3%)
Ongoing 1st post-treatment	1 (2.3%)
Reason of regimen stop	
Progressive disease	27 (62.8%)
Adverse event	2 (4.7%)
General Condition	6 (14.0%)
Intervention Treatment (surgery, radiotherapy)	2 (4.7%)
Patient's intension	2 (4.7%)
Ongoing RAM+nab-PTX	4 (9.3%)

Given that AEs were evaluated retrospectively using clinical records, several subjective AEs may have been missed.

There were no infusion reactions. Although ≥ grade 3 neutropenia occurred in 23 cases (53.5%) and grade 4 neutropenia occurred in 14 cases (32.6%), febrile neutropenia occurred in only one case (2.3%). The patient who experienced grade 3 febrile neutropenia recovered with antibiotic treatment and was able to continue receiving the chemotherapy regimen. Treatment was discontinued in 2 cases, 1 each due to grade 3 neutropenia and grade 2 peripheral neuropathy. No treatment-related deaths occurred.

Post-treatment follow-up. Treatment was discontinued in 27 cases because of progressive disease, and in 6 cases because of deterioration of the patient's general condition though disease progression was not confirmed. Two patients underwent conversion surgery and radiotherapy, 2 discontinued treatment because of AEs, and 2 were transferred to supportive care at the patient's request. Treatment was ongoing in 4 cases at the time of writing (March 2020).

Of the 39 patients who stopped the regimen, 29 cases (74.4%) received third-line therapy. Twenty patients received nivolumab treatment; 1 received trifluridine-tipiracil (TAS-102); 1 received irinotecan (CPT-11); 3 received radiotherapy; and 2 underwent conversion surgery. In 2 cases, nab-PTX treatment was interrupted because of nab-PTX-related AEs, although RAM treatment was continued.

Ten patients could not receive subsequent treatment.

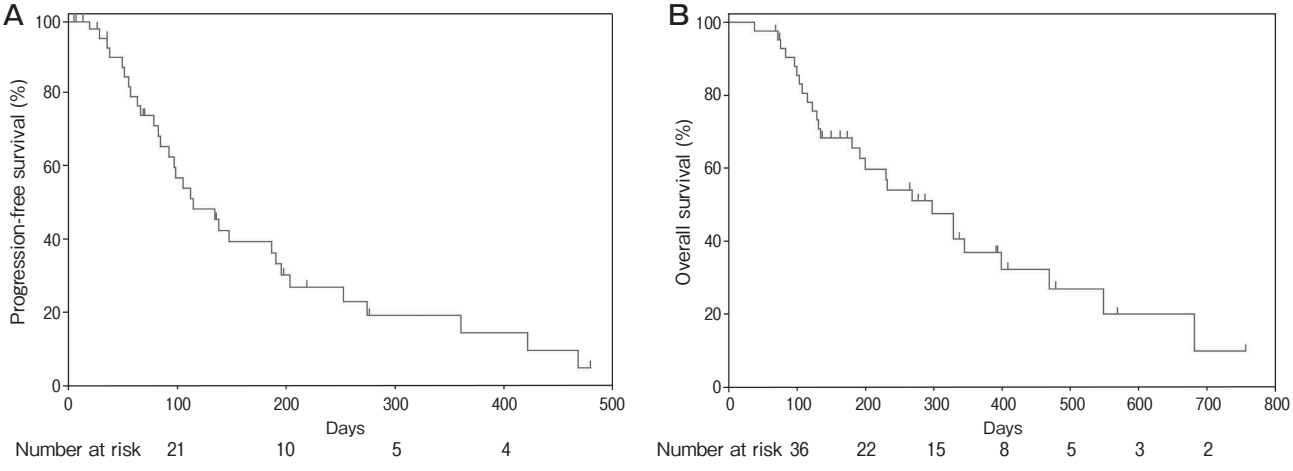

Fig. 1 Kaplan-Meier plot showing progression-free survival (**A**) and overall survival (**B**).

Table 3 Adverse events in our institution

	Patients (N = 43)			
	Grage 1–2	Grade 3	Grade 4	Grade 5
Haemotological events				
Leucopenia	13 (30.2%)	13 (30.2%)	0	0
Neutropenia	7 (16.3%)	9 (20.9%)	14 (32.6%)	0
Anemia	19 (44.2%)	2 (4.7%)	0	0
Thrombopenia	4 (9.3%)	0	0	0
Febrile neutropenia	0	0	1 (2.3%)	0
Non-haemotological events	0	0	0	0
Bleeding	6	0	0	0
Proteinuria	13 (30.2%)	1 (2.3%)	0	0
Hypertension	7 (16.3%)	0	0	0
Infusion reaction	0	0	0	0
Peripheral neuropathy	20 (46.5%)	0	0	0
Vomitting	6 (14.0%)	0	0	0
Appetite loss	15 (34.9%)	4 (9.3%)	0	0
Diarrehea	11 (25.6%)	0	0	0
Alopecia	14 (32.6%)	0	0	0

Of these, one patient died of another disease, and the others could not receive this regimen for more than two cycles.

At the time of writing, third-line treatment was ongoing in one case, and one case showed no recurrence after conversion surgery. Of the 27 patients who failed third-line therapy, 11 (40.7%) received subsequent therapy. These regimens are shown in Table 2.

Discussion

The second-line chemotherapy regimen recommended in the 2018 Japanese gastric cancer treatment guidelines (5th edition) [2] is a RAM plus weekly sb-PTX regimen, while the RAM plus weekly nab-PTX regimen is recommended conditionally.

The sb-PTX regime requires premedication because of the inclusion of polyethoxylated castor oil and hydrated ethanol as solvents. Because patients who receive sb-PTX are not able to drive due to the premed-

ication and alcohol, the nab-PTX regimen is more useful for patients attending the hospital from home, especially in the countryside. Additionally, nab-PTX reduces the risk of polyethoxylated castor oil-associated hypersensitivity reactions, and the administration time of nab-PTX is shorter than that of sb-PTX. Thus, nab-PTX helps to mitigate the congestion of the outpatient chemotherapy facility. Accordingly, RAM+nab-PTX has been in use at our hospital as a standard treatment since 2018.

Although the non-inferiority of weekly nab-PTX compared to weekly sb-PTX has been confirmed [10, 11], there are insufficient practical data regarding the use of RAM plus weekly nab-PTX. Here, we retrospectively analyzed the efficacy and safety of RAM plus weekly nab-PTX at our institution. As this study is both retrospective and a single-center analysis, it may have some bias.

At our institution, the ORR, DCR, and PFS were 32.4%, 72.2%, and 3.8 months, respectively, all of which are lower than those reported in a previously reported phase II trial of RAM+nab-PTX (54.8%, 92.9%, and 7.6 months, respectively) [10]. However, ≥ grade 3 neutropenia occurred in 53.5% of cases in the present study, which was also lower than reported in the phase II trial (76.7%). Although PFS was shorter than that reported in the phase II trial, the RDIs of nab-PTX and RAM at our institution were 59.4% and 80.2%, respectively, which are similar to those reported in the phase II trial (61.8% and 87.6%, respectively) [10].

The discrepancies of these results may be caused by the fact that 20.9% of the patients included in the present study had an ECOG-PS of 2, and some were near to having an ECOG-PS of 3. The RAM+nab-PTX regimen was administered even to patients with a relatively poor ECOG-PS, given the low occurrence of non-hematological AEs. As patients with a poorer ECOG-PS were more likely to have relatively progressive cancer, this may have led to the comparatively worse ORR, DCR, and PFS values in our study.

Although the patient characteristics and PFS were worse in the present study, OS was 9.9 months, which is longer than that reported in a RAM plus sb-PTX phase III trial (RAINBOW trial, 9.6 months) [7]. The OS of the RAM+nab-PTX trial was not reported. OS may be affected by changes made to the regimen according to the attending doctor's diagnosis before CT, and the use of new reagents such as nivolumab or TAS-102 [12, 13]. Post-regimen analysis suggests that regimen changes in the early phase may prolong the prognosis of patients with advanced gastric cancer, and this approach may shorten PFS.

Several reports have suggested the efficacy of nab-PTX for peritoneal metastasis or ascites [14-16], though these were negative prognostic factors in the RAM plus sb-PTX trial [7]. In the present study, reduced massive pleural effusion or reduced ascites were found in 4 of 9 cases (44.4%). The fact that this percentage is higher than that of the ORR in our study (32.4%) suggests that nab-PTX is effective in treating ascites.

Although the frequency of ≥ grade 3 neutropenia was 53.5%, febrile neutropenia occurred in only one case (2.3%). The occurrence of these AEs was lower than that reported in clinical trials (76.7% and 4.7%, respectively, RAM plus nab-PTX, JapicCTI-153088; 40.7% and 3.1%, respectively, RAM plus sb-PTX, RAINBOW), and to the best of our knowledge, no other critical AEs have been reported [7, 10]. Therefore, regardless of differences in the characteristics of patients in trials and in real clinical practice, RAM+nab-PTX appears to be safe.

In conclusion, RAM+nab-PTX combination therapy demonstrated manageable toxicity even in patients who were elderly or had an ECOG-PS of 2, as well as favourable efficacy, especially for disseminated gastric cancer. This treatment is especially useful in community hospital settings, given its relatively shorter duration of administration and the fact that patients are able to drive themselves to and from the hospital.

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