Cancer Science
Japanese Cancer Association JCA
Open Access

Phase II trial of nanoparticle albumin-bound paclitaxel as second-line chemotherapy for unresectable or recurrent gastric cancer

Yasutsuna Sasaki,[1,2] Tomohiro Nishina,[3] Hirofumi Yasui,[4] Masahiro Goto,[5] Kei Muro,[6] Akihito Tsuji,[7] Wasaburo Koizumi,[8] Yasushi Toh,[9] Takuo Hara[10] and Yoshinori Miyata[11]

[1]Department of Medical Oncology, Saitama Medical University International Medical Center, Hidaka-shi; [2]Division of Medical Oncology, Department of Medicine, Showa University Hospital, Tokyo; [3]Department of Gastrointestinal Medical Oncology, National Hospital Organization Shikoku Cancer Center, Matsuyama-shi; [4]Department of Gastrointestinal Oncology, Shizuoka Cancer Center, Nagaizumi-cho; [5]Cancer Chemotherapy Center, Osaka Medical College, Osaka; [6]Department of Clinical Oncology, Aichi Cancer Center Hospital, Nagoya; [7]Department of Clinical Oncology, Kochi Health Sciences Center, Kochi; [8]Department of Gastroenterology, Kitasato University, Sagamihara-shi; [9]Department of Gastroenterological Surgery, National Kyushu Cancer Center, Fukuoka; [10]Department of Surgery, Kouseiren Takaoka Hospital, Takaoka-shi; [11]Deparment of Gastroenterology, Saku Central Hospital, Nagano, Japan

Key words

Gastric cancer, *nab*-paclitaxel, phase II, second-line chemotherapy, triweekly

Yasutsuna Sasaki, Division of Medical Oncology, Department of Internal Medicine, Showa University School of Medicine, 1-5-8 Hatanodai, Shinagawa-ku, Tokyo 142-8666, Japan.

Tel/Fax: +81-3-3783-8661
E-mail: yasutsuna@med.showa-u.ac.jp

Funding information

Taiho Pharmaceutical Co., Ltd.

Received January 5, 2014; Accepted April 8, 2014

Cancer Sci **105** (2014) 812–817

doi: 10.1111/cas.12419

This multicenter phase II study first investigated the efficacy and safety of nanoparticle albumin-bound paclitaxel (*nab*-paclitaxel) when given every 3 weeks to patients with unresectable or recurrent gastric cancer who had received a prior round of fluoropyrimidine-containing chemotherapy. Patients with unresectable or recurrent gastric cancer who experienced progression despite fluoropyrimidine-containing treatment were studied. *Nab*-paclitaxel was given i.v. at 260 mg/m^2 on day 1 of each 21-day cycle without anti-allergic premedication until disease progression or study discontinuation. The primary endpoint was the overall response rate. The secondary endpoints were the disease control rate, progression-free survival, overall survival, and safety. From April 2008 to July 2010, 56 patients were enrolled, 55 patients received the study treatment, and 54 patients were evaluable for responses. According to an independent review committee, the overall response rate was 27.8% (15/54; 95% confidence interval [CI], 16.5–41.6) and the disease control rate was 59.3% (32/54; 95% CI, 45.0–72.4). One patient had a complete response. The median progression-free survival and overall survival were 2.9 months (95% CI, 2.4–3.6) and 9.2 months (95% CI, 6.9–11.4), respectively. The most common grade 3/4 toxicities were neutropenia (49.1%), leucopenia (20.0%), lymphopenia (10.9%), and peripheral sensory neuropathy (23.6%). There were no treatment-related deaths. *Nab*-paclitaxel, given every 3 weeks, showed promising activity against previously treated unresectable or recurrent gastric cancers, with well-tolerated toxicities. (Trial registration, ClinicalTrials.gov: NCT00661167).

Gastric cancer remains the second leading cause of cancer-related deaths worldwide[1] and is especially frequent in East Asia, including Japan.[2] Although surgical resection is the only curative treatment for gastric cancer, approximately 60% of patients eventually experience relapses after curative surgeries.[3] Globally, fluoropyrimidine-based combination chemotherapy regimens, including fluorouracil or its oral derivatives, taxanes, irinotecan, and platinum compounds, have yielded median progression-free survival (PFS) times of 2–7 months and median overall survival (OS) times of less than 1 year in first-line settings.[4–9] In Japan, the combination of S-1 (tegafur plus gimeracil plus oteracil potassium) and cisplatin is the most frequently prescribed first-line therapeutic regimen for patients with advanced/metastatic and recurrent gastric cancer. Recently, several phase III trials reported improved median OS times of more than 1 year.[10–12] Additionally, in a randomized European trial, irinotecan showed survival benefits, compared to best supportive care (BSC), as second-line treatment in gastric cancer patients after the failure of first-line chemotherapy.[13] A Korean study showed that docetaxel or irinotecan could also significantly prolong OS, compared with BSC, after one or two chemotherapeutic regimens that consisted of fluoropyrimidine and platinum.[14]

In Japan, paclitaxel (PTX) is commonly used as second-line chemotherapy for gastric cancer patients in practice, based on experiences with breast cancer and non-small-cell lung cancer (NSCLC). Paclitaxel yielded overall response rates (ORR) that ranged from 16 to 27%, overall OS times of 5–11 months, and modest toxicity in several phase II trials.[15–18]

The 130-nm nanoparticle albumin-bound paclitaxel (*nab*-paclitaxel) is a novel, solvent polyoxyethylated castor oil (Cremophor)-free, biologically interactive form of PTX. *Nab*-paclitaxel is among the first of a new class of anticancer agents to incorporate albumin particle technology and exploit the unique properties of albumin, a natural carrier of lipophilic molecules in humans. *Nab*-paclitaxel 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,

respectively) and no requirement of premedication for solvent-based hypersensitivity reactions. Additionally, in a preclinical study, *nab*-paclitaxel showed increased PTX transport across endothelial cells and greater antitumor activity, compared to standard PTX.[19] In phase III trials, *nab*-paclitaxel significantly increased the ORR and time to progression, compared to conventional PTX, in patients with metastatic breast cancer,[20] and significantly improved the ORR in advanced NSCLC patients, thus achieving the primary endpoint.[21]

We carried out the first phase II clinical trial to evaluate the efficacy and safety of *nab*-paclitaxel when given every 3 weeks to patients with unresectable or recurrent gastric cancer in whom treatment with one prior fluoropyrimidine-containing chemotherapeutic regimen failed.

Materials and Methods

Study objectives and design. This was a non-randomized, open-label, multicenter phase II registration trial of patients with unresectable or recurrent gastric cancer who had failed treatment with first-line chemotherapy (ClinicalTrials.gov, no. NCT00661167). The primary objective was the ORR, which was assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines, version 1.0.[22] The definition to confirmation of complete response (CR) and partial response (PR) required 4 weeks irrespective of study endpoints. The secondary objectives were PFS, OS, the disease control rate, and safety. This trial was carried out in accordance with Japanese guidelines on Good Clinical Practice and the Declaration of Helsinki. The protocol was approved by the institutional review boards of all participating institutions.

Patients. Eligibility criteria for the study were: histologically confirmed adenocarcinoma of the stomach (regardless of human epidermal growth factor receptor 2 overexpression status); an age of 20–74 years; an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–2; a history of progression or recurrence after one prior fluoropyrimidine-containing regimen (except for taxanes such as PTX and docetaxel); a life expectancy of ≥12 weeks; and adequate bone marrow (hemoglobin level ≥8.0 g/dL, white blood cell count ≤12 000/mm^3 or neutrophil count ≥1500/mm^3, and platelet count ≥100 000/mm^3), liver, and renal function (serum bilirubin level ≤1.5 times the upper limit of normal; aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase levels ≤2.5 times the upper limit of normal; and serum creatinine level ≤1.5 mg/dL). Presence of one or more measurable lesions, according to the RECIST criteria, was also a criterion. Patients were excluded if they had brain or wide-ranging bone metastases, malignant ascites, pleural or pericardial effusion that required drainage, peripheral neuropathy of grade 2 severity or worse according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0 (National Cancer Institute at the National Institutes of Health, Bethesda, MD, USA), a history of drug hypersensitivity, or severe complications such as uncontrolled infection, intestinal obstruction, or pulmonary fibrosis. Patients who required continuous steroid treatment and pregnant or nursing women were also excluded. Patients were not allowed to receive concomitant radiotherapy, other chemotherapy, immunotherapy, or targeted therapy during the trial. Written informed consent was obtained from all patients before enrolment.

Treatment. The baseline evaluations included imaging studies (computed tomography or MRI), a complete physical examination, pregnancy testing for female patients, an assessment of the ECOG PS, a complete blood count, serum chemical and electrolyte analyses, and urinalysis.

Nanoparticle albumin-bound paclitaxel was administered on an outpatient basis by a 30-min i.v. infusion at a PTX dose of 260 mg/m^2 on day 1 of each 21-day cycle; no steroid or antihistamine premedication or colony-stimulating factor support was given. Treatment was continued until disease progression, unacceptable toxicity, or consent withdrawal. Three dose reduction levels (220, 180, and 150 mg/m^2) were implemented under the dose reduction criteria. Complete blood counts, serum chemical analyses, and urinalyses were carried out weekly during the study.

Study assessment. The objective disease status was assessed according to the RECIST guidelines, version 1.0.[22] Imaging studies were repeated at least every 6 weeks after treatment initiation. Safety assessments, including serial history taking and physical examinations, and laboratory assessments were carried out throughout the study. The severity of adverse drug reactions (ADR) was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0. An independent review committee that comprised radiologists and medical oncologists objectively confirmed treatment responses and drug-related adverse events.

Statistics. The primary measure of efficacy was the ORR. The ORR in previous phase II studies of PTX as second-line treatment for metastatic gastric cancer were 24%[15] and 27%.[16] The significant ORR threshold under the null hypothesis was defined as 10%, and the expected ORR under the alternative hypothesis was defined as 25%, based on a previous PTX report. If the ORR for *nab*-paclitaxel was 25%, a sample size of 53 patients would ensure a power of at least 80% for a one-sided significance level of 2.5% in order to reject the null hypothesis that the ORR was <10%. If the lower limit of the exact two-sided 95% confidence interval (CI), based on the ORR distribution, exceeded the 10% threshold, a response rate of 11 out of 53 patients would be met.

The disease control rate was defined as the sum of the percentages of CR, PR, and stable disease (SD) for ≥6 weeks. Overall survival was defined as the time between registration and death from any cause; PFS was defined as the time between registration and disease progression or death from any cause. Both OS and PFS were estimated using Kaplan–Meier curves.

All data obtained until the completion of the study period were included in the safety analyses. The primary efficacy analysis was based on the full analysis set of the patients. The safety analysis included all treated patients who received at least one dose of the experimental drug. The clinical cut-off date for this study was May 25, 2011.

Results

Fifty-six patients were enrolled at 10 centers in Japan between April 2008 and July 2010. One patient was ineligible because of inadequate prior treatment. Another patient was excluded from response evaluation because the initial treatment had been skipped due to rapid disease progression after registration. Fifty-five patients received the study treatment, and 55 and 54 patients were evaluable for safety and clinical response, respectively. Most of the patients were male (76.8%), and the median age was 63.5 years (Table 1). All treated patients had an ECOG PS of 0 or 1 (PS 0 = 58.9%; PS 1 = 41.1%). Thirty-five patients underwent gastrectomy. Twenty-one patients (37.5%)

Table 1. Baseline demographic and clinical characteristics of patients with unresectable or recurrent gastric cancer receiving nanoparticle albumin-bound paclitaxel as second-line therapy

	No. of patients (n = 56)	%
Gender		
Male	43	76.8
Female	13	23.2
Age, years		
Median	63.5	
Range	34–74	
ECOG PS		
0	33	58.9
1	23	41.1
Primary lesion		
Absent	35	62.5
Present	21	37.5
Type of treatment failure		
First line	40	71.4
Adjuvant	16	28.6
Number of metastatic organs		
1	19	33.9
2	22	39.3
≥3	15	26.8
Peritoneal metastasis		
Absent	35	62.5
Present	21	37.5
Metastatic organs (overlapping)		
Liver	30	53.6
Lung	8	14.3
Lymph node	37	66.1
Other	23	41.1
Adjuvant chemotherapy		
S-1	14	25.0
Others	3	5.4
First-line chemotherapy		
S-1-based	34	60.7
Capecitabine-based	5	8.9
Others	2	3.6

ECOG PS, Eastern Cooperative Oncology Group performance status; S-1, tegafur plus gimeracil plus oteracil potassium.

Table 2. Clinical responses of patients with unresectable or recurrent gastric cancer receiving nanoparticle albumin-bound paclitaxel as second-line therapy

	No. of patients (n = 54)	%
Complete response	1	1.9
Partial response	14	25.9
Stable disease	17	31.5
Progressive disease	21	38.9
Not evaluable	1	1.9
Overall response rate,%	27.8	
95% CI	16.5–41.6	
Disease control rate,%	59.3	
95% CI	45.0–72.4	
Progression-free survival, months		
Median	2.9	
95% CI	2.4–3.6	
Overall survival, months		
Median	9.2	
95% CI	6.9–11.4	

CI, confidence interval.

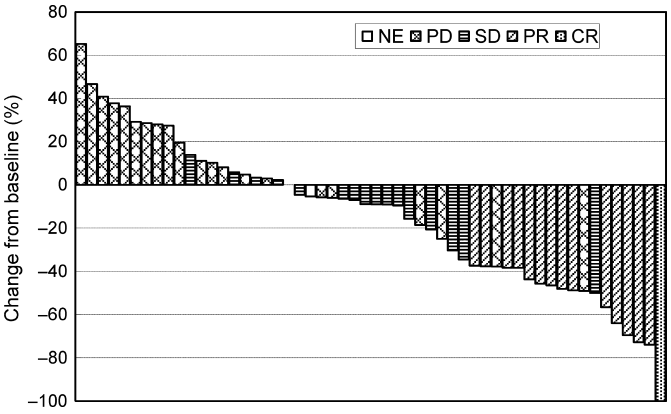

Fig. 1. Waterfall plot of the best overall response to nanoparticle albumin-bound paclitaxel as second-line therapy in the full analysis set of patients with unresectable or recurrent gastric cancer. CR, complete response; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease.

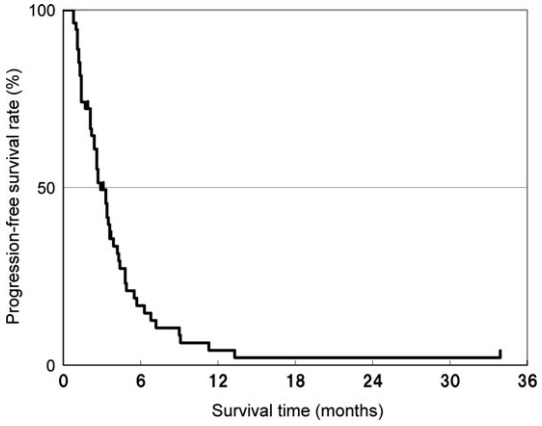

Fig. 2. Kaplan–Meier plots of progression-free survival in the full analysis set of patients with unresectable or recurrent gastric cancer receiving nanoparticle albumin-bound paclitaxel as second-line therapy.

had peritoneal metastases. The most commonly prescribed prior chemotherapeutic agents were S-1 monotherapy as adjuvant treatment (25.0%) or S-1 in combination with cisplatin as first-line chemotherapy (35.7%). The total number of treatment cycles in the full analysis set population was 254. The median number of treatment cycles and relative dose intensity received per patient were 4 (range, 1–18), and 93.4% (range, 63.6–100.0%), respectively.

Overall responses in the 54 patients were reviewed and confirmed by the independent review committee (Table 2). One patient had a CR, 14 had PR, 17 had SD, and 21 had progressive disease. The ORR was 27.8% (95% CI, 16.5–41.6%), which exceeded the threshold response of 10% (Fig. 1). The median time to response was 36 days (range, 29–57 days).

The median PFS was 2.9 months (95% CI, 2.4–3.6 months), with a median follow-up time of 280 days (range, 46–1030 days; Fig. 2). The median survival time was 9.2 months (95% CI, 6.9–11.4 months) (Fig. 3). The median duration of treatment was 79.5 days (range, 22–477 days), with a median cumulative dose of 1574.5 mg (range, 387–6319 mg). Although 19 (34.5%) and 20 (36.4%) patients required dose

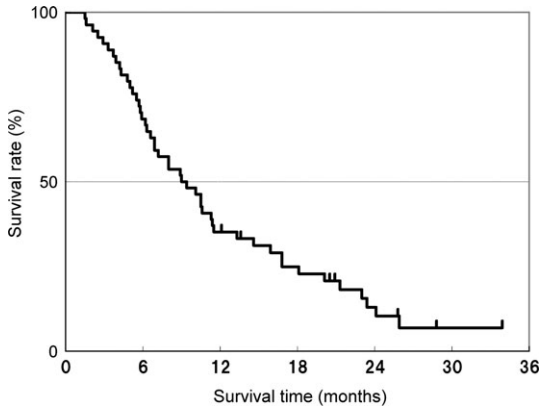

Fig. 3. Kaplan–Meier plots of overall survival in the full analysis set of patients with unresectable or recurrent gastric cancer receiving nanoparticle albumin-bound paclitaxel as second-line therapy.

reductions and delays, respectively, the mean relative dose intensity was 93.4% (range, 63.6–100.0%). Additional chemotherapy was given to the 44 (81.5%) patients in whom treatment with *nab*-paclitaxel failed, of whom, 37 (68.5%) received irinotecan-based chemotherapy (Table 3).

All patients were treated on an outpatient basis, and *nab*-paclitaxel was generally well tolerated. Safety was evaluated in the 55 patients who had received at least one dose of *nab*-paclitaxel. All patients reported at least one drug-related adverse event, but most adverse events were mild to moderate and well managed (Table 4). Although *nab*-paclitaxel was given without any premedication, no patients experienced hypersensitivity or acute infusion reactions. Grade 3 or 4 ADRs with incidence rates of >10% included neutropenia (49.1%), leucopenia (20.0%), lymphopenia (10.9%), and peripheral neuropathy (23.6%). No patients experienced febrile neutropenia in this study. The reasons for treatment withdrawal were mainly disease progression (87.0%) and toxicities (9.3%). There were no treatment-related deaths.

Discussion

Paclitaxel, a microtubule-stabilizing agent, is widely used to treat breast, lung, gastric, and ovarian cancers. However, the Cremophor-containing PTX formulation has been approved and prescribed worldwide because PTX is only slightly soluble in water. Premedication with steroids, antihistamines, and H_2 receptor blockers before the administration of Cremophor-based PTX is essential to reduce allergic, hypersensitivity, and anaphylactic reactions in the clinical setting. *Nab*-paclitaxel is a 130-nm nanoparticle albumin-bound paclitaxel formulation that is devoid of any solvents or ethanol. *Nab*-paclitaxel thus reduces the risk of hypersensitivity reactions and does not require steroid and antihistamine premedication; in fact, hypersensitivity reactions did not occur in this study. Additionally, because the *nab*-paclitaxel formulation does not contain alcohol, it can be administered to poor metabolizers of alcohol[23] and can prevent alcohol-induced hypersensitivity reactions. Furthermore, *nab*-paclitaxel can be given over a shorter time period (30 min) and without special i.v. tubing; therefore, polyethylene-lined i.v. bags composed of polyvinyl chloride can be used for its administration.[24,25] A comparative pharmacokinetic study of *nab*-paclitaxel and conventional PTX injections was carried out.[26] Patients with advanced solid tumors were randomly assigned to receive *nab*-paclitaxel (260 mg/m^2 i.v. over a 30-min period) or the conventional PTX injection (175 mg/m^2 i.v. over a 3-h period) every 3 weeks. The PTX clearance and distribution volumes were significantly higher in patients who received *nab*-paclitaxel than in those who received conventional PTX. Furthermore, Gardner *et al.* reported that the mean fraction of unbound PTX was consider-

Table 3. Subsequent treatment after the study chemotherapy (30-min i.v. infusion of 260 mg/m^2 nanoparticle albumin-bound paclitaxel every 3 weeks) in patients with unresectable or recurrent gastric cancer

	n = 54	%
Any	44	81.5
Irinotecan	29	53.7
Irinotecan + Cisplatin	8	14.8
Paclitaxel	3	5.6
Others†	4	7.4
None	10	18.5

†Other subsequent treatments include 5-fluorouracil/methotrexate (*n* = 2), everolimus or placebo (*n* = 1), and radiation (*n* = 1).

Table 4. Adverse events related to nanoparticle albumin-bound paclitaxel occurring in ≥10% of patients treated for unresectable or recurrent gastric cancer

Type	Grade				Grade 1–4	Grade 3–4
	1	2	3	4	*n* (%)	*n* (%)
Hematologic						
Anemia	3	12	3	1	19 (34.5)	4 (7.3)
Leukopenia	13	23	11	0	47 (85.5)	11 (20.0)
Neutropenia	0	16	18	9	43 (78.2)	27 (49.1)
Lymphopenia	2	13	5	1	21 (38.2)	6 (10.9)
Thrombocytopenia	9	0	0	0	9 (16.4)	0 (0.0)
Laboratory test abnormalities						
AST elevation	16	2	1	0	19 (34.5)	1 (1.8)
ALT elevation	17	3	0	0	20 (36.4)	0 (0.0)
ALP elevation	9	2	0	0	11 (20.0)	0 (0.0)
Hypoalbuminemia	10	3	0	0	13 (23.6)	0 (0.0)
Protein urine	4	4	0	0	8 (14.5)	0 (0.0)
Non-hematologic						
Constipation	5	1	1	0	7 (12.7)	1 (1.8)
Diarrhea	13	1	0	0	14 (25.5)	0 (0.0)
Nausea	19	1	1	0	21 (38.2)	1 (1.8)
Stomatitis	15	3	0	0	18 (32.7)	0 (0.0)
Vomiting	4	1	1	0	6 (10.9)	1 (1.8)
Asthenia	10	6	0	0	16 (29.1)	0 (0.0)
Fatigue	1	8	1	0	10 (18.2)	1 (1.8)
Malaise	7	3	0	0	10 (18.2)	0 (0.0)
Pyrexia	7	3	0	0	10 (18.2)	0 (0.0)
Weight decreased	4	1	1	0	6 (10.9)	1 (1.8)
Anorexia	19	9	1	0	29 (52.7)	1 (1.8)
Arthralgia	16	1	3	0	36 (65.5)	3 (5.5)
Myalgia	16	16	3	0	35 (63.6)	3 (5.5)
Peripheral motor neuropathy	6	3	1	0	10 (18.2)	1 (1.8)
Peripheral sensory neuropathy	20	18	13	0	51 (92.7)	13 (23.6)
Alopecia	37	15	NA	NA	52 (94.5)	NA
Pruritus	11	1	0	NA	12 (21.8)	0 (0.0)
Rash	10	1	0	0	11 (24.4)	0 (0.0)

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; NA, not applicable.

ably higher with *nab*-paclitaxel than with conventional PTX.[27] This pharmacokinetic property of *nab*-paclitaxel might be associated with higher PTX distribution to the tumor. Additionally, in preclinical studies, PTX transport across the endothelium was enhanced by albumin receptor-mediated transcytosis, and PTX delivery to tumors might be enhanced by the binding of albumin-bound PTX to interstitial albumin-binding proteins such as secreted protein acidic and rich in cysteine.[28] In a preclinical model and at equitoxic doses, the *nab*-paclitaxel-treated groups showed more complete regression, a longer time to recurrence, a longer doubling time, and prolonged survival, compared to the Cremophor-containing PTX-treated group.[19] *Nab*-paclitaxel without premedication showed significantly higher response rates and a longer time to tumor progression than PTX or docetaxel in advanced or recurrent breast cancer patients.[20,29] Additionally, weekly *nab*-paclitaxel plus carboplatin-based therapy resulted in a significantly improved ORR in advanced NSCLC patients, compared to that associated with PTX plus carboplatin, with a trend toward improved OS and PFS.[21] And in patients with metastatic pancreatic adenocarcinoma, *nab*-paclitaxel plus gemcitabine significantly improved OS, PFS, and ORR without life-threatening toxicities, which could make this treatment the standard treatment.[30]

Gastric cancer remains one of the most important malignancies, especially in Asian countries. Several phase III studies demonstrated a significantly prolonged OS in patients with advanced or recurrent gastric cancer in response to first-line fluoropyrimidine-based chemotherapies.[7,10,31] Paclitaxel at a dose of 210 mg/m^2, repeated every 3 weeks, was initially evaluated in Japan and yielded an objective PR rate of 28% in a registration trial of untreated or minimally treated gastric cancer patients. Several small-scale phase II studies of weekly-administered PTX reported response rates ranging from 16% to 24%[15,17] for gastric cancer patients in a second-line setting (Table 5). Furthermore, as it resulted in a better survival benefit than irinotecan in the West Japan Oncology Group WJOG4007 trial, weekly PTX could be adopted as a control arm in future phase III trials of second-line chemotherapy for gastric cancer.[32] Based on these clinical trials, weekly PTX has become the most frequently prescribed second-line drug in Japan.

This phase II study of *nab*-paclitaxel is the first phase II trial for the treatment of advanced or recurrent gastric cancer. No significant hypersensitivity or anaphylactic reactions were induced by *nab*-paclitaxel without premedication. The main reason for treatment discontinuation was disease progression, and two patients discontinued the study treatment because of adverse events, which included thrombosis and peripheral sensory neuropathy. No new safety concerns related to *nab*-paclitaxel or conventional PTX were identified, and there were no treatment-related deaths in this study. Although grade 3/4 toxicities such as neutropenia, leucopenia, and lymphopenia were observed, these ADRs were clinically well managed. Grade 3 peripheral sensory neuropathy remains an important problem that might be controlled by dose reductions and delays before the symptoms worsen. The clinical responses and PFS with *nab*-paclitaxel as second-line treatment seem comparable to those obtained in prior PTX trials, although no direct comparison data with PTX are available (Table 5). Recently, survival advantages were reported for irinotecan versus BSC and for irinotecan or docetaxel versus BSC as second-line treatment for gastric cancer patients.[13,14] Weekly PTX failed to show a survival advantage over irinotecan in a phase III trial.[32]

In conclusion, *nab*-paclitaxel, when given every 3 weeks, shows promising activity and well-tolerated toxicities in patients with previously treated unresectable or recurrent gastric cancer. A phase III trial is ongoing to evaluate the clinical benefit of *nab*-paclitaxel as second-line chemotherapy for advanced or recurrent gastric cancer (JapicCTI-132059).

Table 5. Second-line treatments for gastric cancer

Regimen	No. of patients	RR (%)	MST (days)	PFS (days)	Reference
Weekly paclitaxel (80 mg/m^2)	25	24	151	64	15
Weekly paclitaxel (80 mg/m^2)	44	16	237	79	17
Biweekly paclitaxel (140 mg/m^2)	40	17.5	254	111	34
Triweekly paclitaxel (210 mg/m^2)	26	27	319	NA	16
Triweekly paclitaxel (210 mg/m^2)	15	20.0	NA	NA	18
Triweekly docetaxel (75 mg/m^2)	49	16.3	252	76	33
This trial	54	27.8	279	88	NA

MST, median survival time; NA, not applicable; PFS, progression-free survival; RR, response rate.

Acknowledgments

We are grateful to Drs. Hiroya Takiuchi, Toru Sasaki, Satoshi Tanabe, Mizutomo Azuma, Akihisa Tomori, Yusuke Onozawa, Akira Fukutomi, Kentaro Yamazaki, Takeshi Sakamoto, Kohei Shitara, Tomoya Yokota, Motoki Yoshida, Shinichiro Hori, Takeshi Kajiwara, Junichiro Nasu, Eiji Oki, Keishi Yamashita, Hiroo Ishida, Yu Sunakawa, Keiko Mizuno, Ken Shiozawa, Atsushi Sato, Junji Tanaka, Hiroki Yoshikawa, Hiroshi Ariyoshi, Yusuke Tanigawara, Keisuke Aiba, and Nagahiro Saijo for their important contributions to this trial. This trial was supported by Taiho Pharmaceutical Co., Ltd. (Tokyo, Japan).

Disclosure Statement

Y.S. received lecture fees from Taiho Pharmaceutical Co., Ltd. The authors report no other potential conflicts of interest relevant to this article. Taiho Pharmaceutical Co., Ltd., a designer of the study, had funded the study and also collected and analyzed the data contributed to interpretation of the study. All authors had full access to all of the data in the study and had final responsibility for the decision to submit for publication.

References

1 International Agency for Research on Cancer. GLOBOCAN 2008: Estimated cancer Incidence, Mortality, Prevalence and Disability-adjusted life years (DALYs) Worldwide in 2008. [Cited 9 Nov 2013.] Available from URL: http://globocan.iarc.fr/.
2 Center for Cancer Control and Information Services, National Cancer Center. Cancer Statistics in Japan-2012. [Cited 15 Jan 2013.] Available from URL: http://ganjoho.jp/pro/statistics/en/backnumber/2012_en.html.
3 Menges M, Hoehler T. Current strategies in systemic treatment of gastric cancer and cancer of the gastroesophageal junction. *J Cancer Res Clin Oncol* 2009; **135**: 29–38.
4 Ohtsu A, Shimada Y, Shirao K *et al.* Randomized phase III trial of fluorouracil alone versus fluorouracil plus cisplatin versus uracil and tegafur plus mitomycin in patients with unresectable, advanced gastric cancer: the Japan Clinical Oncology Group Study (JCOG9205). *J Clin Oncol* 2003; **21**: 54–9.
5 Dank M, Zaluski J, Barone C *et al.* Randomized phase III study comparing irinotecan combined with 5-fluorouracil and folinic acid to cisplatin combined with 5-fluorouracil in chemotherapy naive patients with advanced ade-

nocarcinoma of the stomach or esophagogastric junction. *Ann Oncol* 2008; **19**: 1450–7.
6 Kang YK, Kang WK, Shin DB *et al.* Capecitabine/cisplatin versus 5-fluorouracil/cisplatin as first-line therapy in patients with advanced gastric cancer: a randomised phase III noninferiority trial. *Ann Oncol* 2009; **20**: 666–73.
7 Van Cutsem E, Moiseyenko VM, Tjulandin S *et al.* Phase III study of docetaxel and cisplatin plus fluorouracil compared with cisplatin and fluorouracil as first-line therapy for advanced gastric cancer: a report of the V325 Study Group. *J Clin Oncol* 2006; **24**: 4991–7.
8 Bolke E, Peiper M, Budach W. Capecitabine and oxaliplatin for advanced esophagogastric cancer. *N Engl J Med* 2008; **358**: 1965; author reply 1965.
9 Al-Batran SE, Hartmann JT, Probst S *et al.* Phase III trial in metastatic gastroesophageal adenocarcinoma with fluorouracil, leucovorin plus either oxaliplatin or cisplatin: a study of the Arbeitsgemeinschaft Internistische Onkologie. *J Clin Oncol* 2008; **26**: 1435–42.
10 Koizumi W, Narahara H, Hara T *et al.* S-1 plus cisplatin versus S-1 alone for first-line treatment of advanced gastric cancer (SPIRITS trial): a phase III trial. *Lancet Oncol* 2008; **9**: 215–21.
11 Boku N, Yamamoto S, Fukuda H *et al.* Fluorouracil versus combination of irinotecan plus cisplatin versus S-1 in metastatic gastric cancer: a randomised phase 3 study. *Lancet Oncol* 2009; **10**: 1063–9.
12 Narahara H, Iishi H, Imamura H *et al.* Randomized phase III study comparing the efficacy and safety of irinotecan plus S-1 with S-1 alone as first-line treatment for advanced gastric cancer (study GC0301/TOP-002). *Gastric Cancer* 2011; **14**: 72–80.
13 Thuss-Patience PC, Kretzschmar A, Bichev D *et al.* Survival advantage for irinotecan versus best supportive care as second-line chemotherapy in gastric cancer: a randomised phase III study of the Arbeitsgemeinschaft Internistische Onkologie (AIO). *Eur J Cancer* 2011; **47**: 2306–14.
14 Kang JH, Lee SI, Lim DH *et al.* Salvage chemotherapy for pretreated gastric cancer: a randomized phase III trial comparing chemotherapy plus best supportive care with best supportive care alone. *J Clin Oncol* 2012; **30**: 1513–8.
15 Hironaka S, Zenda S, Boku N, Fukutomi A, Yoshino T, Onozawa Y. Weekly paclitaxel as second-line chemotherapy for advanced or recurrent gastric cancer. *Gastric Cancer* 2006; **9**: 14–8.
16 Yamada Y, Shirao K, Ohtsu A *et al.* Phase II trial of paclitaxel by three-hour infusion for advanced gastric cancer with short premedication for prophylaxis against paclitaxel-associated hypersensitivity reactions. *Ann Oncol* 2001; **12**: 1133–7.
17 Kodera Y, Ito S, Mochizuki Y *et al.* A phase II study of weekly paclitaxel as second-line chemotherapy for advanced gastric Cancer (CCOG0302 study). *Anticancer Res* 2007; **27**: 2667–71.
18 Yamaguchi K, Tada M, Horikoshi N *et al.* Phase II study of paclitaxel with 3-h infusion in patients with advanced gastric cancer. *Gastric Cancer* 2002; **5**: 90–5.
19 Desai N, Trieu V, Yao Z *et al.* Increased antitumor activity, intratumor paclitaxel concentrations, and endothelial cell transport of cremophor-free, albumin-bound paclitaxel, ABI-007, compared with cremophor-based paclitaxel. *Clin Cancer Res* 2006; **12**: 1317–24.
20 Gradishar WJ, Tjulandin S, Davidson N *et al.* Phase III trial of nanoparticle albumin-bound paclitaxel compared with polyethylated castor oil-based paclitaxel in women with breast cancer. *J Clin Oncol* 2005; **23**: 7794–803.
21 Socinski MA, Bondarenko I, Karaseva NA *et al.* Weekly nab-paclitaxel in combination with carboplatin versus solvent-based paclitaxel plus carboplatin as first-line therapy in patients with advanced non-small-cell lung cancer: final results of a phase III trial. *J Clin Oncol* 2012; **30**: 2055–62.
22 Therasse P, Arbuck SG, Eisenhauer EA *et al.* New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* 2000; **92**: 205–16.
23 Goedde HW, Agarwal DP, Fritze G *et al.* Distribution of ADH2 and ALDH2 genotypes in different populations. *Hum Genet* 1992; **88**: 344–6.
24 Ibrahim NK, Desai N, Legha S *et al.* Phase I and pharmacokinetic study of ABI-007, a Cremophor-free, protein-stabilized, nanoparticle formulation of paclitaxel. *Clin Cancer Res* 2002; **8**: 1038–44.
25 Nyman DW, Campbell KJ, Hersh E *et al.* Phase I and pharmacokinetics trial of ABI-007, a novel nanoparticle formulation of paclitaxel in patients with advanced nonhematologic malignancies. *J Clin Oncol* 2005; **23**: 7785–93.
26 Sparreboom A, Scripture CD, Trieu V *et al.* Comparative preclinical and clinical pharmacokinetics of a cremophor-free, nanoparticle albumin-bound paclitaxel (ABI-007) and paclitaxel formulated in Cremophor (Taxol). *Clin Cancer Res* 2005; **11**: 4136–43.
27 Gardner ER, Dahut WL, Scripture CD *et al.* Randomized crossover pharmacokinetic study of solvent-based paclitaxel and nab-paclitaxel. *Clin Cancer Res* 2008; **14**: 4200–5.
28 Desai NTV, Yao R, Frankel T, Soon-Shiong P. SPARC expression in breast tumors may correlate to increased tumor distribution of nanoparticle albumin-bound paclitaxel (ABI-007) vs Taxol. *Breast Cancer Res Treat* 2004; **88**: S26–7.
29 Gradishar WJ, Krasnojon D, Cheporov S *et al.* Significantly longer progression-free survival with nab-paclitaxel compared with docetaxel as first-line therapy for metastatic breast cancer. *J Clin Oncol* 2009; **27**: 3611–9.
30 Von Hoff DD, Ervin T, Arena FP *et al.* Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. *N Engl J Med* 2013; **369**: 1691–703.
31 Bang YJ, Van Cutsem E, Feyereislova A *et al.* Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. *Lancet* 2010; **376**: 687–97.
32 Hironaka S, Ueda S, Yasui H *et al.* Randomized, open-label, phase III study comparing irinotecan with paclitaxel in patients with advanced gastric cancer without severe peritoneal metastasis after failure of prior combination chemotherapy using fluoropyrimidine plus platinum: WJOG 4007 trial. *J Clin Oncol* 2013; **31**: 4438–44.
33 Lee J-L, Ryu M-H, Chang HM, *et al*. A phase II study of docetaxel as salvage chemotherapy in advanced gastric cancer after failure of fuoropyrimidine and platinum combination chemotherapy. *Cancer Chemother Pharmacol* 2008; **61**: 631–637.
34 Koizumi W, Akiya T, Sato A, *et al*. Second-line chemotherapy with biweekly paclitaxel after failure of fluoropyrimidine-based treatment in patients with advanced or recurrent gastric vancer: a report from the Gastrointestinal Oncology Group of the Tokyo Cooperative Oncology Group, TCOG GC-0501 Trial. *Jpn J Clin Oncol* 2009; **39**: 713–719.