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

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Key words

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

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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.

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

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.

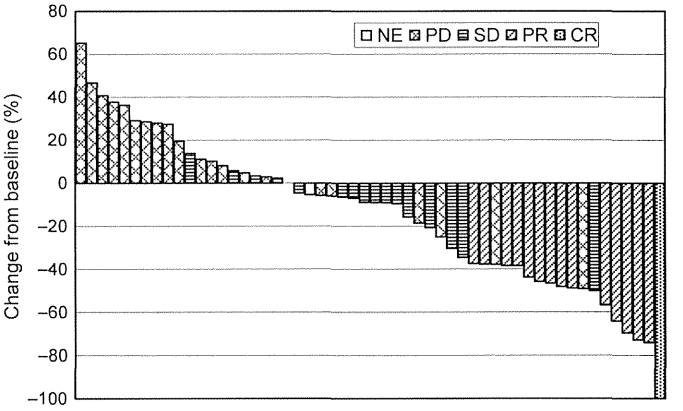

Fig. 1. Waterfall plot of the best overall response to nanoparticle albumin-bound paclitaxel as second-line therapy in the full analysis set of patients with unresectable or recurrent gastric cancer. CR, complete response; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease.

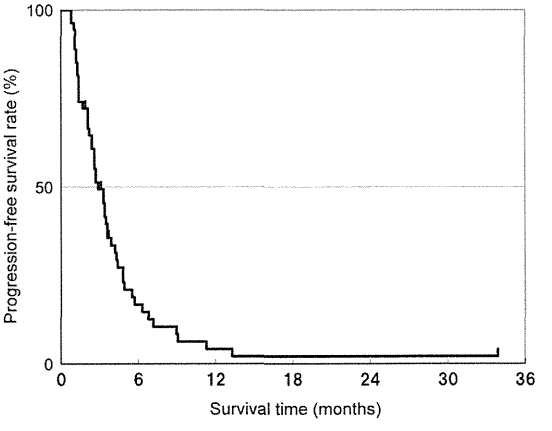

Fig. 2. Kaplan–Meier plots of progression-free survival in the full analysis set of patients with unresectable or recurrent gastric cancer receiving nanoparticle albumin-bound paclitaxel as second-line therapy.

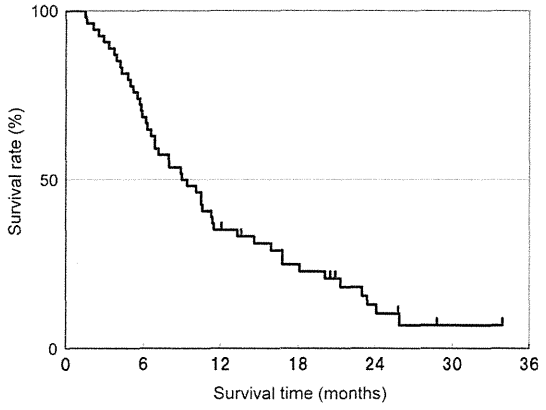

Fig. 3. Kaplan–Meier plots of overall survival in the full analysis set of patients with unresectable or recurrent gastric cancer receiving nanoparticle albumin-bound paclitaxel as second-line therapy.

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

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.

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-

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.

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SHORT COMMUNICATION

Survival analysis of adjuvant chemotherapy with S-1 plus cisplatin for stage III gastric cancer

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Abstract
Background We previously reported that S-1 plus cisplatin was feasible as adjuvant chemotherapy for stage III gastric cancer after D2 gastrectomy. Herein we evaluate the recurrence-free survival and overall survival rates as secondary endpoints based on updated follow-up data.
Methods Patients with stage III gastric cancer who underwent D2 gastrectomy were enrolled. Treatment consisted of 3 cycles of S-1 (40 mg/m^2 PO) twice daily on days 1–21 and cisplatin (60 mg/m^2 IV) on day 8, and S-1 was given on days 1–28 every 6 weeks until 1 year after surgery.
Results From August 2007 to September 2009, 63 patients were accrued. Overall, 34 and 25 patients had stage IIIA and IIIB disease, respectively. After a median follow-up of 3.9 years, 16 patients experienced recurrence and 11 patients died. The 3-year recurrence-free survival rate was 74.1 % (95 % CI: 60.8–83.5 %, IIIA 81.8 %, IIIB 64.0 %). The 3-year overall survival rate was 84.5 % (95 % CI: 72.3–91.6 %, IIIA 87.9 %, IIIB 80.0 %).

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Recurrence sites included the peritoneum ($n = 8$), hematogenous sites ($n = 6$), and lymph nodes ($n = 4$).
Conclusion The present results indicate that adjuvant therapy with S-1 plus 3 cycles of cisplatin may provide a survival benefit to patients with stage III gastric cancer.

Keywords Adjuvant chemotherapy · Gastric cancer · S-1 · Cisplatin

Introduction

In 2007, the Adjuvant Chemotherapy Trial of S-1 for Gastric Cancer (ACTS-GC) demonstrated the efficacy of S-1 for stage II–III Gastric Cancer (GC) patients who underwent curative resection with D2 gastrectomy [1, 2]. The addition of S-1 improved the overall survival (OS) rate, with a low incidence of adverse events and good compliance. According to this result, in Japan, the currently recommended adjuvant treatment after D2 gastrectomy is S-1 for 1 year. However, the 5-year OS rates in stage III patients receiving S-1 have been less satisfactory: 67.1 and 50.2 % for stage IIIA and IIIB, respectively. Therefore, identification of more effective treatments for stage III GC is urgently needed. So firstly we evaluated the feasibility of S-1 plus cisplatin, that is now considered to be one of the standard regimens for metastatic or recurrent GC [3] as adjuvant chemotherapy for Stage III GC after D2 gastrectomy.

As results, treatment completion rates after 3 cycles of S-1 plus cisplatin were 72 % (42/58; 95 % CI: 60–84 %; 57 % [12/21] before and 81 % [30/37] after the protocol amendment). Grade 3/4 toxicities included neutropenia (40 %), anorexia (28 %), and febrile neutropenia (4 %) before the protocol amendment, and neutropenia (37 %), anorexia (8 %), and febrile neutropenia (3 %) after the amendment implementation. Therefore, we concluded that the amended S-1 plus cisplatin regimen is feasible as adjuvant chemotherapy [4].

In this report, we evaluate the recurrence-free survival (RFS) and OS as secondary endpoints based on updated follow-up data.

Methods

Patients eligible for this trial had either stage IIIA (T2,N2; T3,N1; T4,N0) or stage IIIB (T3,N2; T4,N1) [5] gastric adenocarcinoma and had undergone D2 gastrectomy with R0 surgical resection. Additional details were described as previously [4]. The protocol was approved by the institutional review board at each participating center. Treatment according to the original protocol was initiated 4–8 weeks after surgery with 3 cycles of S-1 plus cisplatin (SP) followed by S-1 for up to 1 year. In the SP step, each cycle consisted of 40 mg/m^2 S-1 taken orally twice-daily for 21 days plus a 2-hour infusion of 60 mg/m^2 cisplatin on day 8. Each cycle was administered at 5-week intervals. In the S-1 step, 40 mg/m^2 S-1 was taken for 28 days at 6-week intervals. During enrollment, some toxicity was reported during the first cycle of SP, particularly neutropenia and anorexia. To minimize patient's risk, we elected to amend the protocol. Treatment according to the amended protocol was initiated 4–6 weeks after surgery and consisted of the following: the first cycle of chemotherapy consisted of S-1 monotherapy, and cisplatin was added to cycles 2, 3, and 4. After that, S-1 was administered for up to 1 year. Tumor assessments with ultrasonography, computed tomography, and GI endoscopy and radiography were performed every 6 months for first 2 years after surgery, and annually thereafter (maximum follow-up 5 years). RFS was defined as the time from enrollment to the recurrence or death, whichever occurred first. OS was defined as the time from enrollment to death from any cause.

Results

From August 2007 to July 2009, 63 patients (25 patients in the original protocol, 38 patients in the amended protocol) were accrued from five Japanese institutions. Overall, 34 patients (54 %) had stage IIIA disease and 25 (40 %) had stage IIIB disease. The patient clinical characteristics have been reported previously [4]. After enrollment, 5 patients were deemed ineligible due to confirmed stage II disease ($n = 2$), stage Ib disease ($n = 1$), stage IV disease ($n = 1$), and cancer other than GC ($n = 1$).

OS and RFS were analyzed in 58 eligible patients. At the time of data cut-off on July 31, 2012, 11 patients had died, 5 patients were alive with recurrence, and the remaining 42 patients were alive without recurrence. The median follow-up period was 46 months. All patients could be followed-up for at least 3 years from the date of surgery. Kaplan–Meier estimates are shown that the 3-year OS rate was 84.5 % (95 % CI: 72.3–91.6 %) (Fig. 1a), and the 3-year RFS rate was 74.1 % (95 % CI: 60.8–83.5 %) (Fig. 1b). According to disease stage, the 3-year OS rate of patients with stage IIIA disease was 87.9 % (95 % CI: 70.9–95.3 %) (Fig. 2a), and the 3-year RFS rate was 81.8 % (95 % CI: 63.9–91.4 %) (Fig. 2b). The 3-year OS rate of patients with stage IIIB disease was 80.0 % (95 % CI: 58.4–91.1 %) (Fig. 2a). The 3-year RFS rate was 64.0 % (95 % CI: 42.2–79.4 %) (Fig. 2b).

In addition, there was no significant difference in survival between the original protocol and the amended

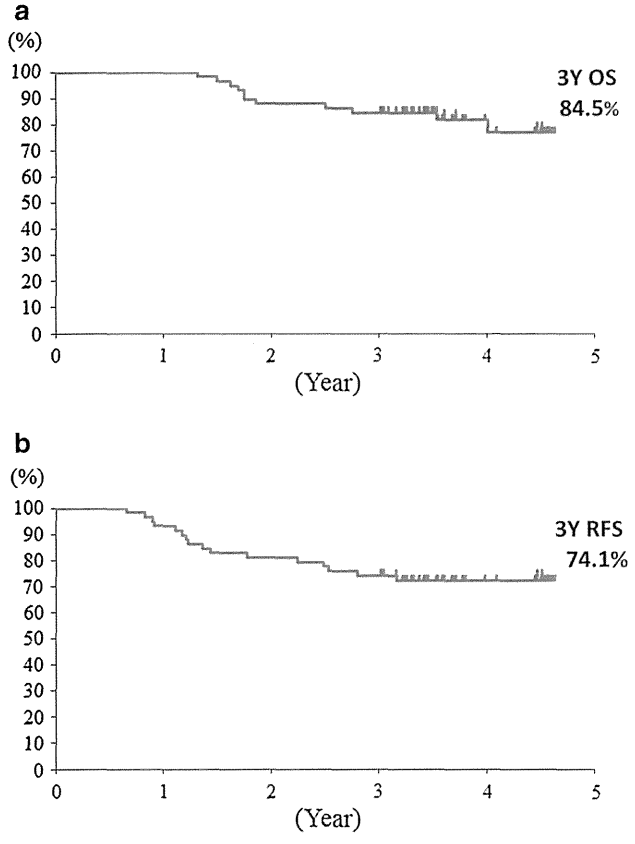

Fig. 1 Kaplan–Meier estimates of **a** overall survival and **b** relapse-free survival for all eligible patients

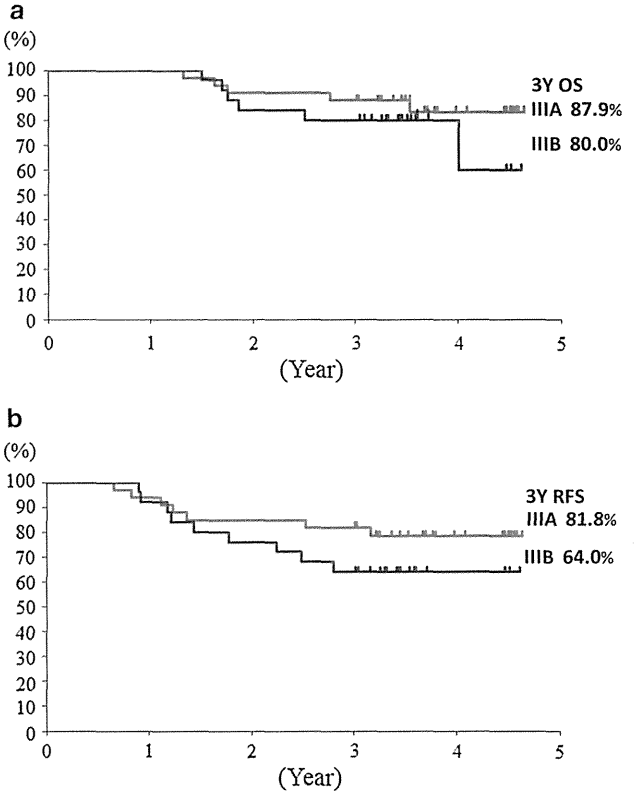

Fig. 2 Kaplan–Meier estimates of **a** overall survival and **b** relapse-free survival for patients with stage IIIA and IIIB gastric cancer

protocol. The 3-year OS rate of patients with stage IIIA disease in the original protocol ($n = 16$) and the amended ($n = 17$) was 87.5 and 88.2 %, respectively, and the 3-year RFS rate was 75.0 and 82.4 %, respectively. The 3-year OS rate of patients with stage IIIB disease was 80.0 % in the original protocol ($n = 5$) and the amended protocol ($n = 20$), and the 3-year RFS rate was 60.0 and 65.0 %, respectively.

The most common sites of relapse were the peritoneum ($n = 8$), hematogenous sites ($n = 6$), and lymph nodes ($n = 4$). Two patients experienced relapses simultaneously in the liver and the lymph nodes. No local relapse was observed. After relapse, the median survival time was estimated to be 351 days. Subsequent therapies were taxanes ($n = 7$), SP ($n = 4$), S-1 ($n = 3$), and CPT-11 ($n = 1$), and 1 case underwent surgery (oophorectomy) followed by paclitaxcel.

Discussion

In this study, postoperative S-1 plus 3 cycles of cisplatin demonstrated promising efficacy with respect to 3-year RFS and OS for stage III GC.

Recently, the results of the CLASSIC trial indicated that adjuvant capecitabine and oxaliplatin improved 3-year disease-free survival (DFS) compared with surgery alone in GC patients [6]. The subgroup analysis suggested that combined capecitabine and oxaliplatin were beneficial not only for stage II patients but also for stage IIIA and stage IIIB patients (the hazard rates compared to surgery alone were 0.57 and 0.57, respectively). This result suggests that combination therapy with fluoropyrimidine and a platinum agent may be more beneficial than fluoropyrimidine alone in patients with stage III disease after D2 gastrectomy.

Although small-sample comparisons should be made with caution, there was no significant difference in survival between the original protocol and the amended protocol. It is suggested that delay of cisplatin administration in our amended protocol didn't sacrifice the efficacy in terms of survival. Consequently, we believe that completion of 3 cycles of cisplatin is important, even though we changed the first cycle to S-1 monotherapy and delayed additional cisplatin until cycles 2, 3, and 4. Moreover, our amended protocol was beneficial in the reduction of grade 3/4 anorexia and nausea, even though we did not use NK-1 receptor antagonists, because they were not approved in Japan at that time. Now we could manage the

cisplatin-induced emesis easier by using NK-1 receptor antagonists with this regimen.

In conclusion, adjuvant therapy with S-1 plus 3 cycles of cisplatin may reduce recurrence and improve survival in patients with stage III GC who underwent D2 gastrectomy. This treatment should be considered for use as an experimental arm for comparison to S-1 in future postoperative adjuvant phase III trials.

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Conflict of interest The authors have declared no conflicts of interest.

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