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

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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/m² 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, and is especially frequent in East Asia, including Japan. Although surgical resection is the only curative treatment for gastric cancer, approximately 60% of patients eventually experience relapses after curative surgeries. 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. 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. 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. 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. 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.

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. In phase III trials, nab-paclitaxel significantly increased the ORR and time to progression, compared to conventional PTX, in patients with metastatic breast cancer, and significantly improved the ORR in advanced NSCLC patients, thus achieving the primary endpoint.

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. The definition 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/mm³ or neutrophil count ≥1500/mm³, and platelet count ≥100 000/mm³), 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/m² 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/m²) 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. 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.

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

| Characteristic                              | 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

| Response Category                        | 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, %                 |                          |      |
| 95% CI                                   |                          |      |
| Disease control rate, %                  | 59.3                     |      |
| Overall survival, months                 | 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.
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 H2 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 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. A comparative pharmacokinetic study of nab-paclitaxel and conventional PTX injections was carried out. Patients with advanced solid tumors were randomly assigned to receive nab-paclitaxel (260 mg/m² i.v. over a 30-min period) or the conventional PTX injection (175 mg/m² 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-

| Type                  | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|-----------------------|---------|---------|---------|---------|
| Anemia                | 3       | 12      | 3       | 1       |
| Leukopenia            | 13      | 23      | 11      | 0       |
| Neutropenia           | 0       | 16      | 18      | 9       |
| Lymphopenia           | 2       | 13      | 5       | 1       |
| Thrombocytopenia      | 9       | 0       | 0       | 0       |

Table 3. Subsequent treatment after the study chemotherapy (30-min i.v. infusion of 260 mg/m² nanoparticle albumin-bound paclitaxel every 3 weeks) in patients with unresectable or recurrent gastric cancer

| Treatment                  | 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).
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.\(^{32}\) 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).

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## 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        |
| Trivweekly paclitaxel (210 mg/m\(^2\)) | 26            | 27     | 319        | NA         | 16        |
| Trivweekly paclitaxel (210 mg/m\(^2\)) | 15            | 20.0   | NA         | NA         | 18        |
| Trivweekly 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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