Clinical Trial Note

A randomized Phase III trial of weekly or 3-weekly doses of nab-paclitaxel versus weekly doses of Cremophor-based paclitaxel in patients with previously treated advanced gastric cancer (ABSOLUTE Trial)

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Abstract

Paclitaxel is an agent widely used in second-line chemotherapy for advanced gastric cancer. The aim of this trial is to evaluate the efficacy and safety of 3-weekly or weekly doses of nanoparticle albumin-bound-paclitaxel compared with weekly doses of Cremophor-based paclitaxel in patients with unresectable or recurrent gastric cancer refractory to first-line chemotherapy comprising fluoropyrimidines. A total of 730 patients will be enrolled from 72 institutions. The primary endpoint is the overall survival, and the secondary endpoints are progression-free survival, time to treatment failure, overall response rate, disease control rate, quality of life (by using the EQ-5D system) and safety.

Key words: gastric cancer, nab-paclitaxel, Phase III, second-line chemotherapy, weekly

Introduction

Gastric cancer remains the second leading cause of cancer-related deaths worldwide (1), and it is especially frequent in East Asia, including Japan (2). Paclitaxel (PTX) is the most commonly used agent in second-line chemotherapy for advanced gastric cancer (AGC) in Japan (3,4).

In Japan, the standard first-line treatment for unresectable or recurrent gastric cancer is systemic chemotherapy consisting of S-1 (oral fluoropyrimidine) plus cisplatin or S-1 alone. According to the SPIRITS (5) and JCOG9912 (6) trials, the combination of S-1 plus cisplatin is the most frequently prescribed chemotherapy regimen for gastric cancer. However, standard second-line chemotherapy is not well established. Several Phase III studies have shown a survival benefit with second-line chemotherapy when compared with best supportive care (BSC) (7–9).

A previously conducted Phase III trial (WJOG4007) compared weekly doses of PTX and irinotecan in previously treated gastric cancer patients. In this trial, no benefit in the overall survival (OS) was demonstrated with irinotecan (experimental arm) compared with weekly doses of PTX (control arm). Furthermore, PTX resulted in a better survival benefit than irinotecan did. The authors concluded that both chemotherapies were reasonable second-line treatment options (10).

PTX, a microtubule-stabilizing agent, is widely used to treat breast, lung, gastric and ovarian cancers. The Cremophor® (solvent polyethoxylated castor oil)-containing PTX formulation has been approved, and it is prescribed worldwide. However, premedication with steroids and antihistamines- and H2-receptor blockers is essential before the administration of Cremophor-based PTX to reduce allergic reaction, hypersensitivity and anaphylactic reactions in the clinical setting.
Nanoparticle albumin-bound-paclitaxel (nab-PTX) is a 130-nm nanoparticle albumin-bound PTX formulation that does not require Cremophor or anhydrous ethanol. Nab-PTX thus reduces the risk of hypersensitivity reactions and does not require steroidal or antihista-
mine premedication. Furthermore, because the nab-PTX formulation does not contain alcohol, it can be administered to patients with poor alcohol metabolism (11), thereby preventing alcohol-induced hyper-
sensitivity reactions. Therefore, nab-PTX can be administered in shorter period of time (30 min) and without the need for special intrave-
 nous (i.v.) tubing; as such, polyethylene-lined i.v. bags composed of polyvinyl chloride can be used for nab-PTX administration (12,13).

A Phase II trial investigating the efficacy of 3-weekly doses of nab-PTX for AGC, by using the response rate (RR) as the primary endpoint, indicated promising results with a RR of 27.8% (95% con-
fidence interval: 16.5–41.6%). The clinical response observed with second-line nab-PTX treatment appears to be comparable to that obtained in prior PTX trials (14), although no direct comparison of the data has been performed.

In response to the results of this Phase II trial, we designed an investigational-drug arm-based Phase III trial with the purpose of establishing whether there is evidence to support 3-weekly doses of nab-PTX. In addition, weekly nab-PTX was included as another investigational-drug arm; based on the WJOG4007 trial, we judged it was appropriate to use weekly doses of Cremophor-based PTX as a control arm.

Details of the ABSOLUTE Trial protocol

Purpose
This study was designed to evaluate and compare the efficacy and safety of 3-weekly nab-PTX, weekly nab-PTX, and weekly Cremophor-based PTX for the treatment of patients with unresectable or recurrent gastric cancer refractory to prior chemotherapy containing fluoropyrimidines.

Study setting
This trial is a multiinstitutional (72 institutions), prospective, open-
label, randomized Phase III trial commencing in January 2013 in Japan.

Endpoints
The primary endpoint is OS, and the secondary endpoints are progression-free survival, time to treatment failure, overall response rate, disease control rate, quality of life (using the EQ-5D system) and safety.

Eligibility criteria
Prior to enrollment in the study, patients must fulfill all the following inclusion and exclusion criteria.

Inclusion criteria
(i) Provision of signed written informed consent.
(ii) Histologically or cytologically confirmed gastric adenocarcin-
oma, measurable or non-measurable disease as per the Re-
sponse Evaluation Criteria In Solid Tumors (RECIST) criteria, metastatic or recurrent AGC (based on the 14th edition of Japanese Classification of Gastric Carcinoma, the 14th edition, including the gastro-esophageal junction);
(iii) Refractory to a fluoropyrimidine containing regimen.
(iv) Eastern Cooperative Oncology Group (ECOG) performance status of 0–2.
(v) Adequate bone marrow reserve and hepatic and renal function —white blood cell count ≥12 000/mm³, neutrophil count ≥1500/mm³, hemoglobin level ≥8.0 g/dl, platelet count ≥100 000/mm³, serum albumin level ≥3.0 g/dl, total bilirubin level ≤1.5 × upper limit of normal (ULN) in each institution (≤5 times in the case of metastases to the liver), aspartate ami-
notransferase (glutamic oxaloacetic transaminase), alanine transaminase (glutamic pyruvate transaminase) and alkaline phosphatase levels ≤2.5 × ULN in each institution (≤5 times in the case of metastases to the liver), serum creatinine level ≤1.5 mg/dl.
(vi) Age ≥20 years at the time that informed consent is obtained.
(vii) Life expectancy of ≥90 days.

Exclusion criteria
(i) Serious agent hypersensitivity.
(ii) Previous history of chemotherapy including PTX.
(iii) Previous treatment with anti-cancer agents within 2 weeks of registration.
(iv) Pleural effusion and ascites to a degree which require drainage within 2 weeks of registration.
(v) Transfusion, blood products or granulocyte colony stimulat-
ing factor given within 2 weeks of registration.
(vi) Other investigational drug given within 4 weeks of registra-
tion.
(vii) History of other malignancies in the last 5 years.
(viii) History of chemotherapy for a malignant tumor in 5 years, except chemotherapy for the gastric cancer.
(ix) Recipient of prior radiotherapy which included the abdomen in the radiation field
(x) Patients experiencing the following complications or with the following medical histories: severe lung disease, severe heart disease, severe cerebrovascular disorders, severe liver disease and other serious diseases (e.g. renal failure, collagenosis, leu-
kemia, human immunodeficiency virus infection).
(xi) Patients of continuous systemic steroid administration.
(xii) Active infection which requires systemic treatment.
(xiii) Peripheral sensory neuropathy: ≥Grade 2.
(xiv) Patients with extensive bone metastases.
(xv) Patients with metastasis to the central nervous system.
(xvi) Uncontrollable diabetes.
(xvii) Patients with a mental disorder or neurologic manifestation.
(xviii) Patients experiencing clinically significant symptoms relating to surgery that was performed prior to registration.
(xix) Women who are pregnant, breastfeeding or trying to become pregnant.
(xx) Principal investigators’ (subinvestigators’) judgment of ineligi-
bility.

Registration/randomization
After confirmation of the eligibility, registration is made via a fax to the nab-PTX Registration Center. Patients are randomized at the ABI-007 Registration Center by using a minimization method that balances the arms considering the use of docetaxel as prior chemotherapy (present vs. absent), presence of peritoneal metastases (present vs. absent) and ECOG performance status (PS; 0 vs. 1 vs. 2) patients. Entered patients will be assigned randomly in a ratio of 1:1:1 to the 3-weekly nab-PTX arm, weekly nab-PTX arm and weekly Cremophor-based PTX arm.
Treatment methods
The following treatment methods will be repeated until the withdrawal criteria are met. Dose modification will depend upon the toxicities. The investigators will evaluate toxicities in order to appropriately adjust further treatment doses; dose modification will depend on the clinical judgment of the investigators. Neutrophil and platelet counts will be given particularly close attention. Once the study drug dose has been reduced, reescalation will not be allowed.

(A-arm) 3-weekly doses of nab-PTX
On Day 1 of each 21-day cycle, patients will receive a single infusion of 260 mg/m² of body surface area (BSA) during a 30-min period. An additional three reduced dose levels (220 mg/m², 180 mg/m² and 150 mg/m²) are acceptable if a patient experiences toxicity. The precautions on dosage and administration for the A-arm are described below.

Start of a cycle: If the patient’s baseline neutrophil count is <1500/mm³ or the platelet count is <75 000/mm³, drug administration should be suspended until bone marrow function improves. If serious (≥Grade 3) peripheral neuropathy develops, drug administration should be suspended until the neuropathy improves to <Grade 3.

Dose modification: If the patient’s neutrophil count is <500/mm³, the platelet count is <50 000/mm³, the patient develops febrile neutropenia, or serious (≥Grade 3) peripheral neuropathy develops, the dosage must be reduced one dose level. If <Grade 3 peripheral neuropathy develops, the dosage could also be reduced.

(B-arm) weekly doses of nab-PTX
On Days 1, 8 and 15 of each 28-day cycle, patients will receive a single i.v. infusion of 100 mg/m² of BSA during a 30-min period. An additional two reduced dose levels (80 mg/m² and 60 mg/m²) are acceptable if the patient experiences toxicity. The precautions on dosage and administration for the B-arm are described below.

At administration on Days 1, 8 and 15: If the patient’s baseline neutrophil count is <1000/mm³ or the platelet count is <75 000/mm³, drug administration should be suspended until bone marrow function improves. If serious (≥Grade 3) peripheral neuropathy develops, drug administration should be suspended until the neuropathy improves to <Grade 3.

Dose modification: If the patient’s neutrophil count is <500/mm³, the platelet count is <25 000/mm³, or the patient develops febrile neutropenia, or serious (≥Grade 3) peripheral neuropathy, the dosage must be reduced one dose level. If <Grade 3 peripheral neuropathy develops, the dosage could also be reduced one dose level.

(C-arm) weekly doses of Cremophor-based PTX
On Days 1, 8 and 15 of each 28-day cycle, patients will receive a single i.v. infusion of 80 mg/m² of BSA during a 1-h period. An additional two reduced dose levels (220 mg/m², 180 mg/m² and 150 mg/m²) are acceptable if a patient experiences toxicity. The precautions on dosage and administration for the C-arm are the same as the B-arm.

Follow-up
Patients are assessed according to the Common Terminology Criteria for Adverse Events version 4.03 to detect any adverse events that develop during the treatment protocol. Patients are assessed via a verbal interview, physical examination and blood tests until any of the criteria for withdrawal from the study are met. The blood tests include a complete blood cell count, measurement of liver and renal function and tumor marker evaluations (carcinoembryonic antigen and carbohydrate antigen 19-9). Testing and observation assessments are performed every week during the first cycle, and at every administration thereafter.

Data on the OS, progression-free survival and objective response rate and time to progression evaluated according to the RECIST version 1.1 criteria will be collected. Computed tomography and magnetic resonance imaging will be performed every 8 weeks for measurements and evaluation. The patient’s quality of life will be assessed by using the EQ-5D system.

Study design and statistical method
This randomized trial was designed to demonstrate that 3-weekly doses of nab-PTX or weekly doses of nab-PTX are not inferior to weekly doses of Cremophor-based PTX in terms of the OS.

The median OS is assumed to be 10.0 months in both the A-arm and B-arm, and 9.0 months in the C-arm, which corresponds to a hazard ratio (HR) of 0.9 for both the comparison between the nab-PTX treatment arms (A-arm and B-arm) and the comparison with the conventional PTX arm (C-arm). Assuming that the median OS with nab-PTX is not less than that with weekly PTX by >30% of the difference between weekly PTX and BSC (7–9), the upper non-inferiority margin is calculated to be 1.25 for the HR. The overall significance level is set at 0.05, and the primary analysis will be performed by using the Holm method for multiple comparisons. To test the hypotheses with an 80% power, a registration period of 18 months, and a minimum follow-up period of 12 months, 230 patients per arm or 690 patients in total are required for analysis. Considering the possibility that 5% of the enrolled patients will be excluded from the analysis, the number of patients to be enrolled is set at 730. Patients will be randomly assigned in a 1:1:1 ratio to the A-arm, B-arm or C-arm via a minimization method with docetaxel-containing first-line treatment, peritoneal metastasis, and ECOG PS as the allocation factors.

The primary analysis will aim to test the following two comparisons with respect to the OS:

(i) Non-inferiority of 3-weekly nab-PTX to weekly PTX as a control
(ii) Non-inferiority of weekly nab-PTX to weekly PTX as a control

Using data from the full analysis set, the confidence interval for the HR of OS with the study treatment will be calculated for each comparison by using a Cox proportional hazard model with treatment and stratification factors as the covariates. If the upper limit of the 97.5% confidence interval is below the non-inferiority margin of 1.25 for a comparison with a lower P value of the two, it will be judged that the nab-PTX regimen of the first comparison has been demonstrated to be non-inferior to weekly PTX. If the nab-PTX regimen of the first comparison is demonstrated to be non-inferior to weekly PTX, a non-inferiority test of another comparison will be performed by using the Holm method for multiple comparisons.

Interim analysis and monitoring
No interim analysis is planned. The Data and Safety Monitoring Committee are installed as independent reviewers.

Registration of the protocol
The study protocol was registered at the website of the JAPIC Clinical Trials Information, JapicCTI-132059, on 30 January 2013. Details are searchable at the following address: http://www.clinicaltrials.jp/user/cteSearch.jsp.
Participating institutions

The participating institutions are as follows: Hakodate Goryoukaku Hospital, Hokkaido University Hospital, Sapporo City General Hospital, Koyukai Sapporo Hospital, Yamagata Prefectural Central Hospital, Tohoku University Hospital, Hirotsu University School of Medicine & Hospital, Iwate Medical University, Ohia Nishinouchi Hospital, Saitama Cancer Center, Gunma University, Gunma Prefectural Cancer Center, National Defense Medical College Hospital, Jichi Medical University Hospital, Nagoaoka Chuo General Hospital, Showa University Hospital, The Cancer Institute Hospital Japanese Foundation for Cancer Research, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, National Cancer Center Hospital, Toranomon Hospital, Keio University Hospital, Tokyo Metropolitan Tama Medical Center, Toshiba Hospital, National Cancer Center Hospital East, Chiba City Cancer Center, University of Tsukuba Hospital, Chiba University, Ibarkai Prefectural Central Hospital, Kitasato University Hospital, Kanagawa Cancer Center, St. Marianne University School of Medicine, Showa University Northern Yokohama Hospital, Yokohama City University Medical Center, Shizuoka General Hospital, Shizuoka Cancer Center, Hamamatsu University Hospital, Aichi City Central Hospital, Saku Central Hospital Advanced Center, Nagoya University Hospital, Gifu University, Japanese Red Cross Nagoya Daichi Hospital, Aizawa Hospital, Koushiren Takaoka Hospital, Toyama University Hospital, Kyoto University, Kyoto Prefectural University of Medicine Hospital, Osaka Medical College Hospital, Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka University Hospital, Kinki University Faculty of Medicine, Sakai City Hospital, Osaka Prefectural General Medical Center, National Hospital Organization Osaka National Hospital, Nara Hospital Kinki University Faculty of Medicine, Toyonaka Municipal Hospital, Osaka Rosai Hospital, Kobe City Medical Center General Hospital, Kobe University Hospital, Hyogo Cancer Center, Hiroshima University Hospital, Hiroshima City Hospital, Hiroshima Prefectural Hospital, Shikoku Cancer Center, Kyushu University, National Kyushu Cancer Center, National Hospital Organization National Kyushu Medical Center, Oita University Faculty of Medicine, Saseikai Fukuoka General Hospital, Kumamoto University Hospital. In each institution, approval by the institutional review board is obtained before starting patient accrual.

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Conflict of interest statement

Wasaburo Koizumi, Satoshi Morita and Yuh Sakata have received expert testimony fees for their contributions to this study from Taiho Pharmaceutical Co., Ltd.

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