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Clinical Study Protocol

A Phase I Trial of 100 mg/m^2 Docetaxel in Patients with Advanced or Recurrent Breast Cancer

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Docetaxel is a standard treatment for patients with advanced or recurrent breast cancer. The recommended dose is 60 to 100 mg/m^2. Previous study have shown that the tumor response rates of patients who received docetaxel monotherapy at doses of 60, 75, and 100 mg/m^2 were 22.1%, 23.3%, and 36.0%, respectively, and there was a significant relationship between the dose and response. In Europe and the United States, docetaxel is approved at a dose of 100 mg/m^2, and Japanese guidelines also recommend a dose of 100 mg/m^2. However, the approved dose in Japan is up to 75 mg/m^2. We have launched a phase I trial evaluating 100 mg/m^2 docetaxel in patients with advanced or relapsed breast cancer. The major eligibility criteria are as follows: age ≥ 20 years, pathologically diagnosed breast cancer, recurrent or advanced breast cancer, a good performance status, and HER2 [human epidermal growth factor receptor 2] negative. The primary endpoint is demonstrated safety of 100 mg/m^2 docetaxel. This study will clarify whether 100 mg/m^2 docetaxel can be administrated safely in Japanese patients with advanced or recurrent breast cancer.

Key words: breast cancer, phase I trial, docetaxel

In the treat of patients with advanced or recurrent breast cancer, docetaxel is one of the drugs to use as standard treatment. The recommended dose of docetaxel in patients with advanced or recurrent breast cancer is 60 to 100 mg/m^2 (https://www.nccn.org/professionals/physician_gls/f_guidelines.asp, http://www.cancer.gov/types/breast) [1-3]. Harvey showed that the tumor response rates in patients who received 60, 75, and 100 mg/m^2 docetaxel monotherapy were 22.1%, 23.3%, and 36.0%, respectively, and there was a significant relationship between the dose and response [4]. In Europe and the Unite States, docetaxel is approved for use at 100 mg/m^2, which is also the dose recommended by Japanese guidelines of the therapy of breast cancer.

However, the approved dose in Japan is up to 75 mg/m^2, due to lack of evidence in Japanese patients. Taguchi [5] demonstrated the pharmacokinetics, tolerability, and safety of 70-90 mg/m^2 docetaxel in Japanese patients but did not evaluate 100 mg/m^2 docetaxel. Nakamura [6] used 100 mg/m^2

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docetaxel for neoadjuvant therapy of primary breast cancer. Because no pharmacokinetic or safety data for 100 mg/m^2 docetaxel are available in Japanese patients with advanced or recurrent breast cancer, we aim to evaluate the pharmacokinetics, tolerability, and safety of 100 mg/m^2 docetaxel in Japanese patients with advanced or relapsed breast cancer. (UMIN registration No. 000015820)

Endpoints

This study aims to evaluate the safety of 100 mg/m^2 docetaxel in advanced or recurrent breast cancer patients. Secondary outcome measures include pharmacokinetic/pharmacodynamic data and efficacy.

We have launched a phase I trial. Six patients from Okayama University Hospital and NHO Kure Medical Center will be enrolled. All patients will receive 100 mg/m^2 docetaxel.

Eligibility Criteria

The main inclusion and exclusion criteria are listed in Table 1. Written informed consent must be obtained from patients before performing any screening or inclusion procedure. This study is conducted in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines, and the protocol has been approved by the institutional review board of (Okayama University Hospital, No. 260201).

Treatment Methods

The treatment will be repeated every 3 weeks at the same dose. The treatment will be continued until the patient meets the cancellation criteria. Docetaxel at a dose of 100 mg/m^2, diluted in 250 ml physiological saline or 5% glucose solution, will be administered by intravenous infusion over 1 h once every 3 weeks. In the first cycle, all patients will be given 16 mg

Table 1 Patient eligibility

Inclusion criteria
Aged 20 years or older
Pathologically proven breast cancer
Recurrent breast cancer that is stage IV, unresectable, or unsuitable for radiotherapy
Eastern Cooperative Oncology Group (ECOG) performance status of 0–1
Adequate organ function as defined below: hemoglobin level $\geq$ 8 g/dl, neutrophil count $\geq$ 1,500/μl, platelets $\geq$ 100,000/μl, aspartate aminotransferase/alanine transaminase levels $\leq$ 2.0-fold the institutional upper limit of normal (ULN), total bilirubin level $\leq$ 1.5 mg/dl, alkaline phosphatase level $\leq$ 2.5-fold the institutional ULN, creatinine level $\leq$ 1.0 mg/dl
More than 2 weeks since surgery, more than 2 weeks since chemotherapy or hormone therapy, or more than 2 weeks since radiation therapy
A life expectancy of $\geq$ 3 months
Negative human epidermal growth factor receptor 2 (HER2) status or positive HER2 status but unsuitable for anti-HER2 therapy
Recovery of all clinically important toxicities from previous treatments to lower than grade 1 according to the Common Terminology Criteria for Adverse Events, v4.0 (CTCAE v4)
Written informed consent from the patient herself
Exclusion criteria
History of intolerance or hypersensitivity to docetaxel, alcohol, or drugs containing polysorbate 80
History of mental disease or mental manifestations that limit compliance with the study requirements
Uncontrollable active infection such as fungal, viral, or bacterial infection
Unstable or untreated central nervous system metastasis
Uncontrolled heart disease including cardiomyopathy, a New York Heart Association class III or IV heart disorder, arrhythmia, unstable angina pectoris, or heart infarction
Prior medical record of docetaxel treatment for advanced or recurrent breast cancer
Unsuitable for dexamethasone treatment
History of another malignancy within the last 5 years
HIV antibody positive, HBs antigen positive or HCV antibody positive
Peripheral neuropathy greater than grade 2 according to the CTCAE v4.0
Pregnant or potentially pregnant or breastfeeding
Fertile patients who do not agree to prevent conception during the period 2 weeks prior to treatment to 120 days after treatment
Patients who cannot be hospitalized for at least 15 days from the start of the first course of treatment

dexamethasone orally on days 3 to 5, and in the second and subsequent cycles, all patients will be given dexamethasone starting 24 h before docetaxel infusions for 3 days, because the pharmacokinetics and pharmacodynamics of docetaxel will be measured only during the first cycle. The treatment will be terminated if disease progression or unacceptable toxicity is observed or if the patient refuses further treatment. Initiation of the next cycle of chemotherapy will be delayed until the neutrophil count recovers to $\geq 1500/\mu l$, platelet count to $\geq 10 \times 10^4/\mu l$, creatinine level to ≤ 1.0 mg/dl, aspartate aminotransferase/alanine transaminase levels to ≤ 2-fold the institutional upper limit of normal, total bilirubin level to ≤ 1.5 mg/dl, and non-hematological toxicities to $\leq$ grade 1. If grade 4 febrile neutropenia or grades 3 or 4 severe non-hematological toxicities are observed despite supportive therapies, the next cycle of treatment will be postponed until recovery to grade 1 or baseline, and docetaxel will be reduced in the next cycle. If the discontinuation period is longer than 14 days, the treatment will be cancelled.

Pharmacokinetic Analysis

Blood samples for pharmacokinetic analysis will be obtained days 1 to 3 of the first cycle using an indwelling venous catheter placed in the arm contralateral to that used for drug infusion. Two milliliters of blood will be collected in heparinized tubes before drug administration, at the end of docetaxel infusion, and 0.25, 0.5, 1, 3, 5, 9, 24, and 48 h after dosing. After centrifugation, the plasma specimens will be stored at -80℃ until used for the assays.

The pharmacokinetic/pharmacodynamic data, maximum concentration (C_{max}), maximum drug concentration time, area under the blood concentration-time curve (AUC), elimination rate constant, drug half-life, plasma clearance, and apparent distribution volume will be calculated according to the blood drug concentration of each individual. The dose proportionality of the C_{max} and AUC and the relationship between the C_{max} and adverse events will be evaluated.

Statistical Consideration

We will assess the safety, the primary endpoint, by evaluating adverse events according to the Common Terminology Criteria for Adverse Events criteria, v4.0. The 3 + 3 cohort design is the most popular method in phase I oncology trials. Because the cohort size is up to six in this design, we planned to enroll 6 patients in this trial. We will evaluate patients who are given 100 mg/m^2 docetaxel at least once from a group targeted for safety analysis. We will estimate the incidence of adverse events as two-sided 95% confidence intervals based on the binominal distribution. Efficacy, the secondary endpoint, will be evaluated according to the response rate, progression-free survival, and overall survival. Progression-free survival will be defined as the time between period to early one in recurrence, exacerbation or death days from study registration. Overall survival will be defined as the time from study registration until the date of death or the patient's last visit. Progression-free survival and overall survival curves will be constructed using the Kaplan-Meier product-limit method.

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