

Randomized, Optimal Dose Finding, Phase II Study of Tri-Weekly Nab-Paclitaxel in Patients with Metastatic Breast Cancer (ABROAD)

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Abstract

Nab-paclitaxel (nab-PTX) is a paclitaxel albumin-stabilized nanoparticle formulation. Nab-PTX has demonstrated superiority over conventional PTX in terms of objective response rate (ORR) and progression free survival in metastatic breast cancer.

However chemotherapy induced grade 3 or higher peripheral neuropathy (CIPN) was more frequently observed in nab-PTX. More recent phase 3 study CALGB 40502 could not prove superiority of weekly nab-PTX to weekly PTX because of higher incidence of toxicity by standard dose of nab-PTX. Taken together, there is a room for the further study to find the optimal dose of nab-PTX. In a single arm phase 2 study CA002-0LD, low dose tri-weekly nab-PTX 175 mg/m² showed good ORR (39.5%) and no CIPN of grade 3 or higher. Thus we conducted randomized phase 2 study (ABROAD) for optimal dose finding of nab-PTX, comparing three different dose of tri-weekly nab-PTX (180 mg/m² vs. 220 mg/m² vs. 260 mg/m²) in patients with metastatic breast cancer.

Keywords: Metastatic breast cancer; Chemotherapy; Nab-paclitaxel; Optimal dose; Peripheral neuropathy; HRQoL; Single-nucleotide polymorphisms

Introduction

Nab-paclitaxel (nab-PTX) is paclitaxel albumin-stabilized nanoparticle formulation. It can be administered without ethanol or steroid premedication and delivered to tumor tissue efficiently [1]. Currently nab-PTX has been approved for breast, gastric, lung and pancreatic cancer in Japan.

Phase III study, CA012 comparing PTX 175 mg/m²/3weeks with nab-PTX 260 mg/m²/3weeks was carried out in metastatic breast cancer [2]. The response rate and progression free survival (PFS) were significantly superior in nab-PTX arm, compared to in PTX arm. However chemotherapy induced peripheral neuropathy (CIPN) for grade 3 or higher was more frequently observed in nab-PTX (10.5%) arm than those in PTX arm (2.2%). Higher incidence of neurotoxicity was considered as a cause of administration of approximately 1.5 times paclitaxel in nab-PTX arm as that in PTX arm.

Another phase III trial, CALGB 40502 compared among three regimens, weekly PTX at 90 mg/m², weekly nab-PTX at 150 mg/m², and ixabepilone at 16 mg/m² (unapproved drug in Japan) with bevacizumab at 10 mg/kg every 2 weeks as a first line chemotherapy

for metastatic breast cancer [3]. Median PFS was 10.6 months in the PTX arm, 9.2 months in the nab-PTX arm (HR=1.19, p=0.12), and 7.6 months in the ixabepilone arm (HR=1.53, p<0.0001). Nab-PTX could not only prove superiority to PTX, but also it seemed to be less effective than PTX. The reason for these results was considered that the incidences of grade 3 or greater hematologic toxicities (51% vs. 21%) and CIPN (25% vs. 16%) were significantly higher for the nab-PTX, compared to the PTX. Dose reductions by cycle 3 were necessary for 45% of the nab-PTX, compared with 15% of the PTX. There were more patients who had their therapy stopped in each cycle because of toxicity in the nab-PTX arm than in the PTX arm. Again, weekly nab-PTX at 150 mg/m² (1.67 times as PTX) as the standard dosage might be overdose and was considered the problem in continuation of therapy.

According to the post-marketing surveillance of nab-PTX use in Japanese breast cancer patients, one third of the patients required dose reduction from the initial dose [4]. Also 27.3% of the patients starting with standard dose required dose reduction. Myelosuppression and CIPN attributed to the main cause of dose reduction. More than grade 2 (42.5%) and Grade 3 CIPN (10.8%) were frequently observed.

Taken together, there is a room for the further study on the optimal dose of nab-PTX. As the characteristics of a nanoparticle drug, nab-PTX is promptly collapsed in the blood vessels and ends up albumin-bound nab-PTX. And it efficiently reaches to the tumor cells [5]. From

this point, the use of nab-PTX is possibly equal to or more significant than the use of PTX even if the same dose is given. As so far, CA002-0LD is the only trial that the method of tri-weekly nab-PTX with a dose reduction is examined [6]. This was a single arm Phase II trial that tri-weekly nab-PTX was given at 175 mg/m² (which is the same dose as the standard therapy for paclitaxel provided to metastatic breast cancer patients). The overall response rate was 39.5% and no CIPN of grade 3 or higher was observed. Therefore it is considered that lower-dose nab-PTX could be effective and well tolerated. Thus we conducted randomized phase 2 study (ABROAD) for optimal dose finding of nab-PTX, comparing three different dose of tri-weekly nab-PTX (180 mg/m² vs. 220 mg/m² vs. 260 mg/m²) in patients with metastatic breast cancer in Japan.

Design of the Study Protocol

Study purpose

This study was designed to evaluate the following two variables in women with metastatic breast cancer.

To evaluate non-inferiority of low dose nab-PTX compared to current standard dose 260 mg/m² of nab-PTX in 1st or 2nd line chemotherapy for metastatic breast cancer.

To compare adverse events including chemotherapy-induced peripheral neuropathy (CIPN), health-related QOL (HRQOL), and Patient Reported Outcomes (PROs) between the three different doses of nab-PTX.

Study setting

This study is a multi-institutional prospective randomized controlled phase II trial with 41 participating institutions as of 6 July 2015.

Funding

This study was funded by Comprehensive Support Project for Oncology Research of Breast Cancer (CSPOR-BC). All decisions concerning the planning, implementation and publication of this study were made by the executive committee of this study.

Endpoints

The primary endpoint is progression-free survival (PFS). Secondary endpoints include time to treatment failure (TTF), overall survival (OS), response rate (RR), disease control rate (DCR), adverse events, and PROs/HRQoL.

Eligibility Criteria

Inclusion criteria

1. Histologically proven breast cancer.
2. One of the following conditions has to be met for a diagnosis of metastatic breast cancer.

*At presentation, the patients have distant metastasis.

*The patient has breast cancer that has worsened or recurred in association with distant metastasis after treatment (after surgery and

pre- and post-operative treatment); however, local recurrence is excluded.

3. Age of 20-75 years.
4. Performance status (ECOG scale): 0-1
5. Patients who have had no chemotherapy within 14 days, hormonal therapy within 7 days, and radiotherapy within 14 days prior to enrollment.
6. Adequate major organ functions within 14 days before enrollment as defined below:
 - Neutrophil count $\geq 1,500/\text{mm}^3$
 - Platelet count $\geq 100,000/\text{mm}^3$
 - Hemoglobin ≥ 9.0 g/dL
 - Total bilirubin <1.5 mg/dL
 - AST <100 U/L
 - ALT <100 U/L
 - Serum creatinine <1.5 mg/dL
7. Written informed consent.

Exclusion criteria

1. Overexpression of human epidermal growth factor receptor 2 (HER2), or the results of fluorescence in situ hybridization are positive.
2. The presence of other active cancers (synchronous double cancers or metachronous double cancers with a disease-free interval of 5 years or less).
3. Grade 2 or greater peripheral neuropathy
4. Severe allergic history against medicines
5. Severe complications, e.g., lung fibrosis, interstitial pneumonitis, uncontrollable diabetes mellitus, severe cardiac dysfunction, renal failure, liver failure, cerebral vascular disorder, ulcer requiring blood transfusion.
6. Concurrent active infections.
7. The presence of brain metastasis requiring treatment
8. Psychiatric disorder affecting to get informed consent
9. Physician concludes that the patient's participation in this trial is inappropriate

Patient Assignment

The Japan Clinical Research Support Unit CSPOR Data Center will confirm patient eligibility, and treatment will be assigned according to the stratification factors for eligible patients. The stratification factors will be included: institutions, hormone sensitivity, prior taxane treatment and disease free interval from surgery.

Treatment

Interventions

Control arm: Nab-PTX 260 mg/m² (SD260 arm) every 21 days, until disease progression

Experimental arms 1: Nab-PTX 220 mg/m² (MD220 arm) every 21 days, until disease progression

Experimental arms 2: Nab-PTX 180 mg/m² (LD180 arm) every 21 days, until disease progression

Statistical Analysis

Main analysis and assessment criteria

The purpose of the main analysis is to select the one optimal dose among the three which has good PFS and tolerable neurotoxicity. In this study, we define the optimal dose as the dose whose PFS is equivalent to that of SD260 and the grade 3 neurotoxicity rate is no more than 10%. PFS is defined as the time from random assignment to disease progression by RECIST or death from any cause. PFS is analyzed by the Cox regression including the doses as dummy variables, while the grade 3 neurotoxicity rates of the three doses are estimated by the logistic regression including the doses as a continuous variable. The selection consists of two steps [7]. In the first step, drop the inferior dose(s) which is defined as the dose whose hazard ratio of PFS to the most effective dose is greater than 1.333. If two doses are dropped, the most effective dose is the champion irrespective of its neurotoxicity. Otherwise, proceed to the second step. In this step, select as the champion the greatest dose among the doses left and whose estimated grade 3 neurotoxicity rate is less than 10%. If all of the estimated neurotoxicity rates of the doses left exceed 10%, choose the lowest dose instead.

Sample size and follow-up period

The study was planned to ensure to select MD220 with a probability of 70%, when the one-year PFSs of the three doses are all 30% and the grade 3 neurotoxicity rates of SD260, MD220 and LD180 are 15%, 8% and 0.1%, respectively, which requires 40 patients per group with expected registration period of two years and mean follow-up period of two years, and finally 42 patients per group was chosen. With this sample size, alternatively, if their neurotoxicity rates are 8%, 3% and 0.1%, respectively, and their one-year PFS are 30%, 26.6% (HR=1.1) and 23.6% (HR=1.2), respectively, then SD260 will be selected with a

probability of 65%. These calculations were based on simulations assuming the exponential and the binomial distribution for PFS and grade 3 neurotoxicity, respectively, and employing the main analysis procedure.

Registration of the protocol

The protocol was registered at the website of the University Hospital Medical Information Network (UMIN), Japan (protocol ID UMIN000012429), on 1st November 2014. The details are available at the following web address: <http://www.umin.ac.jp/ctr/>

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