Evaluation of Trastuzumab Without Chemotherapy as a Post-operative Adjuvant Therapy in HER2-positive Elderly Breast Cancer Patients: Randomized Controlled Trial [RESPECT (N-SAS BC07)]

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Objective: This trial is conducted to investigate the benefit of trastuzumab monotherapy compared with a combination therapy of trastuzumab and chemotherapy in women over 70 years with human epidermal growth factor receptor type-2-positive primary breast cancer.

Methods: Inclusion criteria are the following: histologically diagnosed as invasive breast cancer and received curative operation for primary breast cancer; Stage I, IIA, IIB or IIIA/M0; and baseline left ventricular ejection fraction is ≥55%. Patients are randomized to receive either trastuzumab (8 mg/kg loading dose, 6 mg/kg every 3 weeks for 1 year) plus chemotherapy selected from regimens specified on the protocol or trastuzumab monotherapy. The primary endpoint is disease-free survival. Secondary endpoints are overall survival, relapse-free survival, safety, health-related quality of life, comprehensive geriatric assessment and cost effectiveness.

Results: Patients recruitment has been commenced in October 2009. Enrollment of 300 patients is planned during the 4-year recruitment period.

Conclusions: We hereby report the study concept.

Key words: breast cancer – Phase III – elderly – HER2/neu – trastuzumab – monotherapy

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INTRODUCTION
Trastuzumab with chemotherapy is the standard treatment as an adjuvant systemic therapy for human epidermal growth factor receptor type-2 (HER2)-positive primary breast cancer (1–4). Overexpression of HER2 has also been associated with potentially more aggressive tumors; therefore, trastuzumab is a key drug in the treatment of HER2-positive primary cancer. However, monotherapy of trastuzumab as an adjuvant treatment without concurrent or preceding chemotherapy is not conducted in clinical practice since its benefit has not been investigated as well as elderly patients (5). It has clinical significance to demonstrate the benefit of trastuzumab monotherapy without toxicity induced by chemotherapy, especially in elderly patients. Chemotherapy is not always a standard therapy in elderly patients based on the analysis of Early Breast Cancer Trialists’ Collaborative Group (EBCTCG) because of limited data (6). Careful monitoring is necessary for elderly patients due to toxicity, cardiac toxicity associated with anthracycline-containing chemotherapy (7,8), increasing in acute myeloid leukemia (AML) after adjuvant chemotherapy (9).

This trial is conducted to investigate the clinical positioning between trastuzumab monotherapy (H group) and a combination therapy of trastuzumab and chemotherapy (H + CT group) based on a randomized controlled trial in women over 70 years with HER2-positive primary breast cancer.

DIGEST OF THE STUDY PROTOCOL
PURPOSE
This study is conducted to investigate the clinical positioning between trastuzumab (Herceptin) monotherapy (H group) and a combination therapy of trastuzumab and chemotherapy (H + CT group) based on a randomized controlled trial in women over 70 years with HER2-positive primary breast cancer (Fig. 1). Our hypothesis includes the following two points:

(i) H group is non-inferior to the H + CT group in disease-free survival (DFS).
(ii) H group is superior in safety and health-related quality of life (HRQOL).

STUDY SETTING
This study is a multi-institutional prospective randomized controlled trial with 56 participating centers as of 31 August 2010.

STUDY SUPPORT
This study was funded by Comprehensive Support Project for Oncology Research (CSPOR) of Public Health Research Foundation. 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 DFS. Secondary endpoints are overall survival, relapse-free survival, adverse events, HRQOL, comprehensive geriatric assessment and cost-effectiveness analysis.

ELIGIBILITY CRITERIA
INCLUSION CRITERIA
(i) Histologically diagnosed as invasive breast cancer and received curative operation for primary breast cancer.
(ii) Stage I [tumor size (pT) ≥1 cm], IIA, IIB or IIIA/M0; female between 70 and 80 years old.
(iii) Primary cancer is HER2-positive (either 3+ overexpression or positive by fluorescence in situ hybridization).
(iv) Baseline left ventricular ejection fraction is ≥55% measured by echocardiography or multigated acquisition scan within 4 weeks before registration.
(v) Performance status (PS) 0–1.
(vi) Sufficient organ function meeting the following criteria within 4 weeks before registration:
   (a) Leukocyte ≥2500 mm$^3$
   (b) Neutrophil ≥1500 mm$^3$
   (c) Platelet ≥100 000 mm$^3$
   (d) Serum total bilirubin ≤2.0 × the upper limit of normal (ULN)
   (e) Alanine aminotransferase (glutamic pyruvic transaminase) or aspartate aminotransferase (glutamic oxaloacetic transaminase) ≤2.5 × ULN
   (f) Serum creatinine ≤2.0 × ULN
   (g) Alkaline phosphatase ≤2.5 × ULN
(vii) No previous endocrine therapy or chemotherapy for breast cancer.
(viii) Signed written informed consent.

Figure 1. Study schema. Evaluation of trastuzumab without chemotherapy as a post-operative adjuvant therapy in HER2-positive elderly breast cancer patients: randomized controlled trial [RESPECT (N-SAS BC07)].
HER2, human epidermal growth factor receptor type-2; IHC, immunohistochemistry; FISH, fluorescence in situ hybridization; PTX, paclitaxel; DTX, docetaxel; AC, doxorubicin and cyclophosphamide; EC, epirubicin and cyclophosphamide; CMF, cyclophosphamide, methotrexate and 5-fluorouracil.
EXCLUSION CRITERIA

(i) Active multiple primary cancer (synchronous multiple primary cancer and invasive cancer of other organs).
(ii) Post-operative histological axillary lymph node metastasis \( \geq 4 \).
(iii) Axillary lymph node is not histologically evaluated.
(iv) Histologically confirmed positive margin in breast conservation surgery (evaluation of margin status is based on the policy of site).
(v) History of drug-related allergy which could hinder planned treatment.
(vi) Any history or complication of the following cardiac disorders.
(vii) History of congestive heart failure, cardiac infarction.
(viii) Complication requires treatment such as ischemic cardiac disorder, arrhythmia and valvular heart disease.
(ix) Poorly controlled hypertension (e.g. systolic arterial pressure \( \geq 180 \text{ mmHg} \) or diastolic blood pressure \( \geq 100 \text{ mmHg} \)).
(x) Poorly controlled diabetes.
(xi) Continuous visit to a medial institution is considered difficult due to deterioration of activity of daily living.
(xii) Difficult to participate in the trial because of psychiatric disorder or psychiatric symptoms.
(xiii) Ineligible to the trial based on the decision of an investigator.

PATIENT ASSIGNMENT

The CSPOR Data Center will confirm patient eligibility, and treatment will be automatically assigned according to the assignment adjustment factors for eligible patients. The following five variables will be used as assignment adjustment factors: age (70–75/76–80), PS (0/1), hormone sensitivity, lymph node metastasis and hospital.

TREATMENT

COMBINATION THERAPY OF TRASTUZUMAB AND CHEMOTHERAPY ARM

The loading administration dose of trastuzumab is 8 mg/kg of body weight, and the maintenance dose is 6 mg/kg every 3 weeks for 1 year. Chemotherapy is selected from regimens specified on the protocol based on the decision of a physician or a patient.

(i) Paclitaxel (PTX) 80 mg/m² weekly administered every week for 11 cycles.
(ii) Docetaxel (DTX) 75 mg/m² every 3 weeks for four cycles.
(iii) Doxorubicin (A) 60 mg/m² and cyclophosphamide (C) 600 mg/m² every 3 weeks for four cycles.
(iv) Epirubicin (E) 90 mg/m² and cyclophosphamide (C) 600 mg/m² every 3 weeks for four cycles.
(v) Cyclophosphamide (C) 75–100 mg orally from days 1 to 14, methotrexate (M) 40 mg/m² on days 1 and 8 intravenously, and 5-fluorouracil (F) 500–600 mg/m² intravenously on days 1 and 8, every 4 weeks for six cycles.

Administration of trastuzumab initiates after completion of chemotherapy as a sequential combination. However, concomitant administration is allowed when combining trastuzumab with PTX, DTX and CMF.

If the hormone receptor is positive, hormone therapy is indicated. In the case of after breast conservative operation, irradiation for breast is indicated after chemotherapy.

TRASTUZUMAB MONOTHERAPY ARM

The loading dose of trastuzumab is 8 mg/kg of body weight, and the maintenance dose is 6 mg/kg every 3 weeks for 1 year.

If hormone receptor is positive, hormone therapy is indicated. In case of after breast conservative operation, irradiation for breast is indicated after surgery or concurrent with trastuzumab.

STATIFICATION FACTORS

(i) Age at registration: 70–75/76–80
(ii) PS: 0/1
(iii) Hormone receptor status: positive/negative
(iv) Pathological nodal status: positive/negative
(v) Institution

STATISTICAL ANALYSIS

MAIN ANALYSIS AND ASSESSMENT CRITERIA

To evaluate the clinical position of each treatment, the estimated hazard ratio is compared with a threshold hazard ratio of 1.69. Concretely, the threshold will be used to determine whether the H + CT group is equivalent (not inferior) to the H group with regard to DFS. As an aid to interpret the trial result, we will estimate the three posterior probabilities between and outside the following two thresholds: ‘the upper threshold of hazard ratio (1.69) to select the combination therapy of trastuzumab and chemotherapy’ and ‘the lower threshold (1.22) to select the monotherapy of trastuzumab’, using the posterior distribution of log hazard ratio based on a non-informative prior.

SAMPLE SIZE AND FOLLOW-UP PERIOD

The primary endpoint will require 120 events in total, given a power of 80% and a threshold hazard ratio of 1.69. Giving that the 3-year DFS probability in the study population is 68% and assuming that the survival time follows the exponential distribution, a total of 260 patients will be necessary for 3 years of follow-up after 4 years of registration to assess the 120 events. Therefore, the target number of registration was determined to be 300 since exponential distribution of survival might not be shown because of the elderly population and dropout patients were expected.

This study has been started from October 2009 and completion is scheduled in October 2016 with a registration period for 4 years and a follow-up period for 3 years.
REGISTRATION OF THE PROTOCOL

The protocol was registered at the website of the University Hospital Medical Information Network (UMIN), Japan (protocol ID UMIN000002349), on 1 September 2009. Details are available at the following address: https://upload.umin.ac.jp/cgi-open-bin/ctr/ctr.cgi?function=brows&action=brows&type=summary&recptno=R000002854&language=E.

And also registered at ClinicalTrials.gov (protocol ID NCT01104935), on 6 November 2009. Details are available at the following address: http://clinicaltrials.gov/show/NCT01104935.

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Conflict of interest statement

Hiroji Iwata and Yasuo Ohashi receive honoraria for speaking events from Chugai Pharmaceutical Co., Ltd.

References