#60159

Evaluation of trastuzumab without chemotherapy as a postoperative adjuvant therapy in HER2 positive elderly breast cancer patients: Randomized controlled trial (RESPECT [N-SAS BC07])

M. Sawaki[1], H. Iwata[2], M. Kashiwaba[3], N. Taira[4], N. Tokudome[5], T. Nakayama[6], H. Bando[7], T. Mizuno[8], S. Murakami[9], Y. Yamamoto[10], Yukari Uemura[11] and Yasuo Ohashi[11]

[1]Clinical Oncology and Chemotherapy, Nagoya University Graduate School of Medicine, Nagoya; [2]Breast Oncology, Aichi Cancer Center Hospital, Nagoya; [3]Surgery, Iwate Medical University, Morioka; [4]Okayama University Hospital, Okayama; [5]Medical Oncology, Cancer Institute Hospital of Japanese Foundation for Cancer Research, Tokyo; [6]Breast and Endocrine Surgery, Osaka University Hospital, Osaka; [7]Breast and Endocrine Surgery, Tsukuba University Hospital, Tsukuba; [8]Medical Oncology, Mie University Hospital, Tsu; [9]Surgery, Hiroshima City Asa Hospital, Hiroshima; [10]Depatment of Breast and Endocrine Surgery, Graduate School of Medical Sciences, Kumamoto University, Kumamoto, Japan; [11]Biostatistics, School of Public Health, University of Tokyo, Tokyo, Japan

Abstract

Background: Trastuzumab with chemotherapy is a standard treatment as an adjuvant systemic therapy for human epidermal growth factor receptor type-2 (HER2) positive primary breast cancer. It has clinical significance to demonstrate benefit of trastuzumab monotherapy without toxicity induced by chemotherapy especially in elderly patients. This trial is conducted to investigate clinical positioning between trastuzumab monotherapy (H group) and 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. Our hypothesis is that the H group is non-inferior to the H+CT group in disease free survival, and superior in safety and health-related quality of life (HRQOL).

Methods: Inclusion criteria are the following: histologically diagnosed as invasive breast cancer and received curative operation for primary breast cancer; Stage I (tumor size [pT] ≥1 cm), IIA, IIB or IIIA/ M0; female between 70 and 80 years old; primary cancer is HER2 positive (either 3+ overexpression or positive by fluorescence in situ hybridization); baseline left ventricular ejection fraction is ≥55%; performance status 0-1; sufficient organ function; and signed written informed consent. Patients are randomized to receive either trastuzumab (8 mg/kg loading dose, 6 mg/kg every 3 weeks for 1 year) plus chemotherapy (chemotherapy is selected from regimens specified on the protocol [paclitaxel, docetaxel, doxorubicin + cyclophosphamide (C), epirubicin + C, and C + methotrexate + flurouracil]) or trastuzumab monotherapy. The primary endpoint is disease free survival. Secondary endpoints are overall survival, relapse-free survival, safety, HRQOL, and cost effectiveness analysis.

Results: Patients recruitment has been commenced in October 2009 at IRB approved medical institutions. Enrolment of 300 patients is planned during the four-year recruitment period.

Conclusions: We hereby report the study concept.

Background

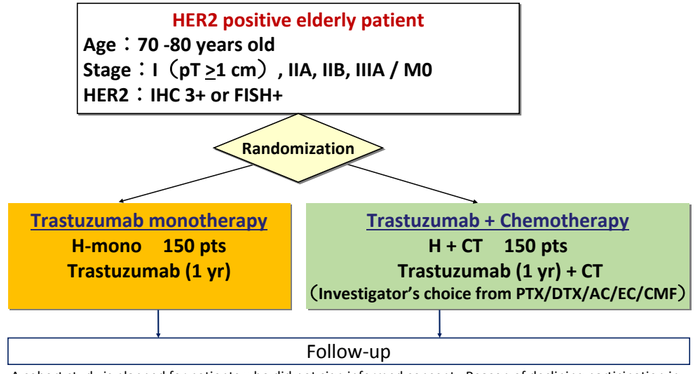
- Trastuzumab with chemotherapy is a standard treatment as an adjuvant systemic therapy for human epidermal growth factor receptor type-2 (HER2) positive primary breast cancer (1-4).
- Overexpression of HER-2 is considered to have association with potentially more aggressive tumors and poor prognosis. Trastuzumab is a key drug in treatment of HER2 positive primary cancer with its efficacy to improve prognosis.
- 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. Furthermore, benefit of trastuzumab in elderly patients has not been investigated for both monotherapy and combination therapy (5).
- Chemotherapy is not always a standard therapy in elderly patients based on analysis of Early Breast Cancer Trialists' Collaborative Group (EBCTCG) because of limited data (6). It has clinical significance to demonstrate benefit of trastuzumab monotherapy without toxicity induced by chemotherapy especially in elderly patients.
- Careful monitoring is necessary for elderly patients because of toxicity; cardiac toxicity associated with anthracycline-containing chemotherapy (7, 8), increase in acute myeloid leukemia (AML) after adjuvant chemotherapy (9).
- This trial is conducted to investigate clinical positioning between trastuzumab monotherapy (H group) and 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.

Objectives

- This study is conducted to investigate clinical positioning between trastuzumab (Herceptin) monotherapy (H group) and combination therapy of trastuzumab and chemotherapy (H+CT group) based on a randomized controlled trial in women over 70 years with human epidermal growth factor receptor type-2 (HER2) positive primary breast cancer. Our hypothesis include following two points.

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

Study Design (Registration Trial Number: NCT01104935 (ClinicalTrials.gov), UMIN000002349 (UMIN))



A cohort study is planned for patients who did not sign informed consent. Reason of declining participation in the study, treatment and outcome of the patients will be investigated in the cohort study.

＜Stratification Factors＞
1. Age at registration：70-75 / 76-80
2. PS：0 / 1
3. Hormone receptor status: positive / negative
4. Pathological nodal status: positive / negative
5. Institution

Endpoints

- **Primary Endpoint**
  - ✓ Disease free survival
- **Secondary Endpoints**
  - ✓ Overall survival
  - ✓ Relapse-free survival
  - ✓ Percentage of participants with adverse events as a measure of safety
  - ✓ Health-related QOL (HRQOL)
  - ✓ Cost effectiveness analysis

Treatment Schedule

- Trastuzumab: 1-year
  - The loading dose is 8 mg/kg of body weight, and the maintenance dose is 6 mg/kg every three weeks for 1 year.
- Chemotherapy: 12 to 24 weeks

Chemotherapy is selected from regimens specified on the protocol based on decision of a physician or a patient.
(i) Paclitaxel (PTX): 80 mg/m^2 weekly administered every week for eleven cycles.
(ii) Docetaxel (DTX): 75 mg/m^2 every 3 weeks for four cycles.
(iii) AC: doxorubicin (A) 60 mg/m^2 and cyclophosphamide (C) 600 mg/m^2 every 3 weeks for four cycles.
(iv) EC: epirubicin (E) 90 mg/m^2 and cyclophosphamide (C) 600 mg/m^2 every 3 weeks for four cycles.
(v) CMF: cyclophosphamide (C) 75-100 mg orally from days 1 to day 14, methotrexate (M) 40 mg/m^2 on days 1 and day 8 intravenously, and 5-fluorouracil (F) 500-600 mg/m^2 intravenously on day 1 and day 8, every 4 weeks for six cycles.
Initiate administration of trastuzumab after completion of chemotherapy as a sequential combination. However, concomitant administration is allowed when combining trastuzumab with PTX, DTX and CMF.

Eligibility Criteria

Inclusion Criteria

- Histologically diagnosed as invasive breast cancer and received curative operation for primary breast cancer.
- Stage: 1 (tumor size [pT] >=1 cm), 2A, 2B or 3A/ M0
- Female between 70 and 80 years old
- Primary region is HER 2 positive: either 3+ overexpression by IHC or positive by FISH
- Baseline left ventricular ejection fraction (LVEF) is ≥55% measured by echocardiography or MUGA scan within 4 weeks before registration.
- PS: 0-1 (ECOG)
- Sufficient organ function meeting following criteria within 4 weeks before registration:
  - Leukocyte ≥2500 mm^3
  - Neutrophil ≥1500 mm^3
  - Platelet ≥100 000 mm^3
  - Serum total bilirubin ≤2.0 x upper limit of normal (ULN)
  - ALT (GPT) or AST (GOT) ≤2.5 x ULN
  - Serum creatinine ≤2.0 x ULN
  - ALP ≤2.5 x ULN
- No previous endocrine therapy or chemotherapy for breast cancer
- Signed written informed consent

Exclusion Criteria

- Active multiple primary cancer (synchronous multiple primary cancer and invasive cancer of other organs)
- Postoperative histological axillary lymph node metastasis ≥4
- Axillary lymph node is not histologically evaluated
- Histologically confirmed positive margin in breast conservation surgery (evaluation of margin status is based on policy of each site)
- History of drug-related allergy which could hinder planned treatment
- Any history or complication of following cardiac disorders
  - History of congestive heart failure, cardiac infarction
  - Complication requires treatment such as: ischemic cardiac disorder, arrhythmia, valvular heart disease
- Poorly controlled hypertension (ex. Systolic arterial pressure ≥180 mmHg or diastolic blood pressure ≥100 mmHg)
- Poorly controlled diabetes
- Continuous visit to a medial institution is considered difficult due to deterioration of activity of daily living (ADL)
- Difficult to participate in the trial because of psychiatric disorder or psychiatric symptoms
- Ineligible to the trial based on decision of an investigator

Main Analysis And Asseessment Criteria

- To evaluate the clinical position of each treatment, the estimated hazard ratio is compared with a threshold hazard ratio of 1.69.
- Specifically, the threshold will be used to determine whether H+CT group is equivalent (not inferior) to the H group with regard to overall survival.
- 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 Estimation

Total number: 300 pts

- The primary endpoint will require 120 events in total, given a power of 80% and a threshold hazard ratio of 1.69. A total of 260 patients will be necessary during 7-year trial period to assess 120 events. 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 assumed to be October 2016 with a registration period for 4 years and a follow-up period for 3 years.

Study Duration: Enrolment 4 years, Follow-up 3 years.

References

1. Romond EH, Perez EA, Bryant J, Suman VJ, Geyer CE, Jr., Davidson NE et al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. N Engl J Med. 2005;353(16):1673-84.
2. Piccart-Gebhart MJ, Procter M, Leyland-Jones B, Goldhirsch A, Untch M, Smith I et al. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. N Engl J Med. 2005;353(16):1659-72.
3. Slamon D, Eiermann W, Robert N, Pienkowski T, Martin M, Pawlicki M et al. Phase III randomized trial comparing doxorubicin and cyclophosphamide followed by docetaxel (AC (R) T) with doxorubicin and cyclophosphamide followed by docetaxel and trastuzumab (AC (R) TH) with docetaxel, carboplatin and trastuzumab (TCH) in HER2 positive early breast cancer patients: BCIRG 006 study. Breast Cancer Research and Treatment. 2005;94:S5-S.
4. Smith I, Procter M, Gelber RD, Guillaume S, Feyereislova A, Dowsett M et al. 2-year follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer: a randomised controlled trial. The Lancet. 2007;369(9555):29-36.
5. Jahanzeb M. Adjuvant Trastuzumab Therapy for HER2-Positive Breast Cancer. Clinical Breast Cancer. 2008;8(4):324-33.
6. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. The Lancet. 2005;365(9472):1687-717.
7. Pinder MC, Duan Z, Goodwin JS, Hortobagyi GN, Giordano SH. Congestive heart failure in older women treated with adjuvant anthracycline chemotherapy for breast cancer. J Clin Oncol. 2007;25(25):3808-15.
8. Du XL, Xia R, Liu CC, Cormier JN, Xing Y, Hardy D et al. Cardiac toxicity associated with anthracycline-containing chemotherapy in older women with breast cancer. Cancer. 2009;115(22):5296-308.
9. Patt DA, Duan Z, Fang S, Hortobagyi GN, Giordano SH. Acute Myeloid Leukemia After Adjuvant Breast Cancer Therapy in Older Women: Understanding Risk. Journal of Clinical Oncology. 2007;25(25):3871-6.

- Study Group: National Surgical Adjuvant Study of Breast Cancer
- Sponsor: Comprehensive Support Project for Oncology Research, Public Health Research Foundation