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A randomized phase II trial of trastuzumab plus capecitabine versus lapatinib plus capecitabine in patients with HER2-positive metastatic breast cancer previously treated with trastuzumab and taxanes: WJOG6110B/ELTOP

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ABSTRACT

Background: For human epidermal growth factor receptor 2 (HER2)-positive metastatic breast cancer (MBC) with progression on trastuzumab-based therapy, continuing trastuzumab beyond progression and switching to lapatinib combined with chemotherapy are both valid options. We conducted an open-label, randomized phase II trial to compare the efficacy of these strategies.

Patients and methods: Women with HER2-positive MBC previously treated with trastuzumab and taxanes were randomly assigned to receive trastuzumab plus capecitabine (HX) or lapatinib plus capecitabine (LX). The primary endpoint was progression-free survival (PFS) and the secondary endpoints included overall survival (OS) and the objective response rate (ORR). To explore the predictive value of the differential benefit of anti-HER2 drugs, *PIK3CA* mutations were assessed using circulating tumor DNA.

Results: Eighty-six patients (43 in each arm) were enrolled. The median PFS was 6.1 months in the HX arm and 7.1 months in the LX arm (hazard ratio, 0.81; 90% CI, 0.55–1.21; $p = 0.39$); the median OS was 31.0 months in the HX arm and was not reached in the LX arm (hazard ratio, 0.58; 95% CI, 0.26–1.31; $p = 0.18$). The ORR was 40% in the HX arm and 41% in the LX arm. *PIK3CA* mutations were detected in 23% of the 35 analyzed patients, and in patients without *PIK3CA* mutations, LX yielded relatively longer PFS and OS than HX.

Conclusion: In women with HER2-positive MBC previously treated with trastuzumab and taxanes, no significant differences in PFS and OS were observed between patients treated with LX and HX.

Trial registration number: UMIN000005219.

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1Introduction

Since the benefit of adding trastuzumab, an anti-human epidermal growth factor receptor 2 (HER2) monoclonal antibody, to first-line chemotherapy was shown [1], HER2-targeted therapy has been widely used in HER2-positive metastatic breast cancer (MBC). At present, trastuzumab, pertuzumab, and taxane for first-line treatment [2] and trastuzumab emtansine (T-DM1) for second-line treatment [3] are strongly recommended in American Society of Clinical Oncology (ASCO) Clinical Practice Guideline [4] and European School of Oncology (ESO) and European Society of Medical Oncology (ESMO) International Consensus Guidelines for Advanced Breast Cancer [5,6]. The ASCO Guideline also states that there are limited data on the first-line treatment with trastuzumab, pertuzumab, and taxane in patients who have received adjuvant or neoadjuvant trastuzumab [4].

In patients whose disease has progressed on trastuzumab-based therapy, continuing trastuzumab beyond progression and switching to lapatinib, a HER2 tyrosine kinase inhibitor, in combination with chemotherapy are both valid options. The GBG 26/BIG 03-05 trial compared trastuzumab plus capecitabine (HX) and capecitabine alone (X) after first-line trastuzumab-based chemotherapy and showed that HX was superior to X in terms of time to progression (TTP) [7]. The EGF100151 trial compared lapatinib plus capecitabine (LX) and X in patients previously treated with anthracyclines, taxanes, and trastuzumab and showed that LX was superior to X in terms of TTP [8]. We have 2 strategies, which are trastuzumab beyond progression or switching to lapatinib; however, it is unclear which strategy is more effective and how we can select the correct strategy for each patient.

Another concern is which systemic treatment is useful for the treatment and prevention of brain metastases. In HER2-positive MBC, brain metastases often develop even when systemic diseases other than brain metastases are controlled by trastuzumab-based treatment. Some studies suggested that lapatinib monotherapy or LX were effective for brain metastases in patients with HER2-positive MBC [9,10].

PIK3CA mutations, which activate the PI3K/AKT/mTOR pathway downstream of HER2, are major mechanisms of resistance to anti-HER2 drugs [11] and are candidate predictors of the differential benefit from anti-HER2 drugs especially after progression on trastuzumab. To determine the gene profiles, analyses of circulating tumor DNA (ctDNA) in the peripheral blood, so-called liquid biopsy, are useful.

We conducted a randomized phase II trial of HX versus LX in women with HER2-positive MBC whose disease progressed on trastuzumab, including those with brain metastases. We also evaluated the mutational status of *PIK3CA* using archival tumor tissues and ctDNA.

2. Patients and methods

2.1. Study design and treatment

The West Japan Oncology Group (WJOG) 6110B/Early switch to Lapatinib versus Trastuzumab beyond Progression (ELTOP) study is an open-label, multicenter, randomized phase II trial to comparatively evaluate the efficacy and safety of HX or LX in women with HER2-positive MBC who were previously treated with taxanes and progressed on trastuzumab-containing regimens. Randomization was stratified by institution, hormone receptor status, number of previous chemotherapy regimens used for metastatic disease (0 or 1 versus 2), and the presence of brain metastasis.

Patients received trastuzumab (4 mg/kg loading then 2 mg/kg weekly or 8 mg/kg loading then 6 mg/kg every 3 weeks) and capecitabine (2500 mg/m^2/day on days 1–14 every 3 weeks) in the HX arm and lapatinib (1250 mg/day) and capecitabine (2000 mg/m^2/day on days 1–14 every 3 weeks) in the LX arm until progression or intolerable toxicity.

The study protocol was approved by the Institutional Review Board of each institution. Written informed consent was provided by all participants prior to inclusion in the trial.

2.2. Patients

Eligible patients were women aged 20 years or older with HER2-positive MBC or unresectable locally advanced breast cancer who were previously treated with taxanes, with progression on trastuzumab-containing regimens. HER2 positivity was defined as 3 + staining by immunohistochemistry or *HER2* gene amplification (HER2:CEP17 signal ratio of 2.0 or more) by in situ hybridization. Patients treated with more than 2 chemotherapy regimens for MBC were excluded. Eligible patients had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–2 and adequate bone marrow, cardiac, hepatic, and renal function. Patients with brain metastases were included if they were asymptomatic.

2.3. Endpoints

The primary endpoint was progression-free survival (PFS) and the secondary endpoints included overall survival (OS), the objective response rate (ORR), the disease control rate (DCR), the proportion of patients with brain metastases as the site of first progression, and safety. Tumor response and progression were assessed using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Chest/abdomen CT was performed at baseline and every 6 weeks. Brain MRI or CT was performed at baseline and every 6 weeks in patients with brain metastases and every 12 weeks in patients without brain metastases.

2.4. Analyses of PIK3CA mutations

Archival tumor tissues of primary lesions or metastases and plasma samples at enrollment were collected from all patients who gave their consent. DNA/RNA extraction from the formalin-fixed paraffin-embedded (FFPE) tumor tissues was performed using an Allprep DNA/RNA FFPE kit (Qiagen, Valencia, CA), according to the manufacturer's instructions. ctDNA was purified using a QIAamp Circulating Nucleic Acid Kit (Qiagen) in accordance with the manufacturer's instructions. *PIK3CA* mutations were measured using the QX100 Droplet Digital PCR System in accordance with the manufacturer's instructions (Bio-Rad, Hercules, CA). The primers and probes for detecting the *PIK3CA* mutations E542K, E545K, and H1047R were purchased from Bio-Rad. Polymerase chain reaction (PCR) was performed using the following cycling conditions: 95 °C for 10 min, 40 cycles of 94 °C for 30 s and 55 °C for 60 s, and enzyme deactivation at 98 °C for 10 min. The digital PCR data were analyzed using the QuantaSoft analytical software package (Bio-Rad).

2.5. Statistical analyses

This randomized phase II study was designed to compare the efficacy of LX as the experimental arm with that of HX as the control arm using PFS as the primary endpoint. The planned sample size was initially 170 randomized patients, to achieve 151 events based on the expected hazard ratio (HR) of 0.667, a one-sided significance level (α) of 0.05, and power of 0.80. However, because of slow accrual, the protocol was amended in February 2014 to decrease the planned sample size to 110, to achieve 93 events based on one-