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Original article

Efficacy and safety of eribulin as first- to third-line treatment in patients with advanced or metastatic breast cancer previously treated with anthracyclines and taxanes

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ABSTRACT

Objectives: Despite the survival benefit and acceptable tolerability of eribulin for advanced/metastatic breast cancer (MBC) patients pretreated with anthracyclines and taxanes, there is limited evidence of the clinical benefit of early eribulin use. We investigated the efficacy and safety of first- to third-line eribulin use in patients with MBC.

Materials and methods: In this phase II, open-label, single-arm study conducted at 14 sites in Kyushu, Japan, women with histologically confirmed human epidermal growth factor receptor 2−negative MBC were enrolled between December 1, 2011 and November 30, 2013 (Data cut-off: November 30, 2014). Objective response rate (ORR; primary endpoint), disease control rate (DCR), progression-free survival (PFS), duration of response (DOR), overall survival (OS), and safety were evaluated.

Results: Of 53 recruited patients, 47 were enrolled. The ORR was 17.0% (95% confidence interval, 7.6−30.8), DCR was 66.0% (51.2−77.8), median PFS was 4.9 months (3.5−7.0), DOR was 6.6 months (1.9−14.3), and median OS was 17.4 months (10.1−not evaluable). The common grade 3/4 adverse events were neutropenia (25 patients; 53.2%), leucopenia (16 patients; 42.1%) and febrile neutropenia (4 patients; 8.5%). Toxicity did not increase during the long-term treatment. Subgroup analysis indicated that first-line treatment led to higher ORR and prolonged PFS and OS than second-/third-line treatment and that incidence of adverse events in patients of second-/third-line treatment was not higher than that in patients of first-line treatment.

Conclusion: Eribulin exhibited efficacy and manageable tolerability in Japanese women with pretreated MBC in first- to third-line use. (ID: UMIN000007121).

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; CR, complete response; DCR, disease control rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; EMT, epithelial mesenchymal transition; ER, estrogen receptor; G-CSF, granulocyte colony-stimulating factor; HER2, human epidermal growth factor receptor 2; MBC, advanced/metastatic breast cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors.

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1. Introduction

Breast cancer is the most common cancer in women with an estimated 1.67 million new cancer cases (25% of all cancers) diagnosed in 2012 [1]. Despite advances in the treatment, advanced/metastatic breast cancer (MBC) is incurable and current therapies for MBC generally focus on palliation, maintaining or improving quality of life, and prolonging survival [2]. Currently, anthracycline- and taxane-based regimens are used as standard chemotherapy options for adjuvant and/or first-line treatment for MBC and few therapeutic options are available for patients with anthracycline- and taxane-resistant or refractory MBC [2]. The long-term survival for women with MBC remains poor. The 5-year survival of stage IV breast cancer can be as low as 21%, compared with 100% in stage I, according to the Surveillance, Epidemiology, and End Results (SEER) Program results (1996–2002 statistics) [3]. Recent 5- and 10-year relative survival rates for women with stage IV breast cancer in Japan were reported as low as 32.6% and 15.6%, respectively [4]. Thus, alternative treatment options for MBC patients with a potential for survival benefits are warranted.

Microtubule polymerization is a key process in cancer cell proliferation and a number of microtubule-targeting agents have been evaluated in preclinical and clinical studies [5]. Eribulin is a nontaxane microtubule dynamics inhibitor belonging to the halichondrin class of antineoplastic agents and has shown anticancer activity in women with MBC [6]. Because eribulin binds to different sites of microtubules and has a different mode of action from taxanes [6], eribulin shows antitumor activity in MBC patients who had well-defined taxane resistance [7]. A randomized phase III study (EMBRACE) demonstrated significant and clinically meaningful improvement in survival with eribulin compared to the treatment of physician's choice in patients with heavily pretreated MBC; overall survival (OS) was improved in the eribulin group (median OS 13.1 months; 95% confidence interval [CI], 11.8–14.3) compared with the treatment of physician's choice (10.6 months; 95% CI, 9.3–12.5; hazard ratio [HR] 0.81; 95% CI, 0.66–0.99; $p = 0.041$) [8]. In another randomized phase III study (301) including pretreated women with locally advanced or MBC, median OS in the eribulin group was 15.9 months versus 14.5 months in the capecitabine group (HR, 0.88; 95% CI, 0.77–1.00; $p = 0.056$) [9]. Although this study did not show any significant improvement in OS, a pooled analysis of the EMBRACE and the 301 phase III trials demonstrated that eribulin significantly prolonged OS compared with control (median OS 15.2 months vs 12.8 months; HR, 0.85; 95% CI, 0.77–0.95; $p = 0.003$), and OS data favored eribulin in the various subgroups assessed [10]. As toxicity does not increase during the long-term treatment, eribulin can maintain stable disease and high quality of life (QOL) [11]. Based on the results of clinical studies, eribulin has been approved for the treatment of patients with inoperable or recurrent breast cancer [12–15], previously treated with anthracycline- and taxane-based regimens. Although eribulin is approved for third- or later-line treatment of MBC patients in other countries including United States and Europe, eribulin can be used in first-line treatment in Japan.

A phase II study of eribulin conducted in Japan with patients with MBC who were pretreated with an anthracycline and a taxane demonstrated both the efficacy and tolerability at first- to fourth-line treatment [16]. Although previous clinical studies have shown a survival benefit and acceptable tolerability for eribulin, there is still limited evidence for its early-line use in patients with MBC. Therefore, we investigated the efficacy and safety of first- to third-line use of eribulin for MBC.

2. Materials and methods

2.1. Patients

Japanese women with histologically confirmed MBC were enrolled between December 1, 2011 and November 30, 2013. The detailed inclusion and exclusion criteria are available elsewhere [17]. Briefly, the main inclusion criteria were: no history of eribulin administration; an Eastern Cooperative Oncology Group performance status (ECOG PS) [18] of 0–2; human epidermal growth factor receptor 2 (HER2)-negative; 20–75 year old; ≥4 weeks from the last dosing of chemotherapy or ≥2 weeks from the last dosing of endocrine or radiation therapy; measurable lesion based on Response Evaluation Criteria in Solid Tumors (RECIST) ver. 1.1 [19]; sufficient organ function; life expectancy of ≥3 months; and no significant abnormalities on electrocardiogram. Estrogen receptor (ER) and progesterone receptor status were tested by immunohistochemistry and >1% was defined as positive. The main exclusion criteria were: history of severe drug allergy; severe renal and/or hepatic dysfunction; radiographically significant interstitial pneumonia or pulmonary fibrosis; pleural fluid or peritoneal effusion requiring drainage; uncontrollable hypertension and/or diabetes mellitus; pregnancy; received blood transfusion or granulocyte colony-stimulating factor (G-CSF) within 7 days prior to study entry; and brain metastases. This study has been registered with the University Hospital Medical Information Network Center (ID: UMIN000007121).

2.2. Study design and assessments

This is a phase II, open-label, single-arm, multicenter study, conducted at 14 sites in the Kyushu area of Japan. Eligible patients received eribulin based on the approved labeling in Japan, via intravenous infusion at a maximum dose of 1.4 mg/m^2 on days 1 and 8 every 3 weeks. The administration of eribulin was discontinued in case of disease progression, unacceptable toxicity, delayed schedule (>2 weeks), withdrawal of consent, or as per the investigator's discretion based on the prescribing information [15]. Dose modification was allowed at the investigator's discretion as per the dose reduction criteria described in the prescribing information [15] which were as follows: the dosage of eribulin was reduced first to 1.1 mg/m^2 and subsequently to 0.7 mg/m^2 if there was grade 3 neutropenia with fever or infection, grade 4 neutropenia for >7 consecutive days, grade ≥3 thrombocytopenia, grade ≥3 nonhematologic toxicity, or cessation of administration at week 2 and restarting the administration thereafter. The dosage of eribulin on day 8 could be omitted due to toxicity. Concomitant therapies other than anticancer therapies (i.e., chemotherapy, radiotherapy, surgery, and immunotherapy) were allowed. Administration of G-CSF was permitted for treatment of neutropenia grade 3/4 or febrile neutropenia.

Tumor assessments including bone metastasis by computed tomography or magnetic resonance imaging scans and tumor marker evaluations (e.g., CEA and CA 15-3 levels) were performed every three cycles. These assessments were centrally reviewed by an independent review committee. Physical examinations and other assessments (i.e., ECOG PS, hematology, and blood chemistry) were performed before administration of eribulin on days 1 and 8 of each cycle. A resting 12-lead electrocardiogram was monitored at study entry, the final visit, and any time deemed necessary.

The primary objective was to determine objective response rate (ORR) defined as the proportion of patients who achieved a complete response (CR) or a partial response (PR), per RECIST criteria (version 1.1) [19]. Secondary objectives included progression-free survival (PFS; the time from the initiation of eribulin therapy