Phase II, Multicenter, Single-Arm, Feasibility Study of Eribulin Combined With Capecitabine for Adjuvant Treatment in Estrogen Receptor-Positive, Early-Stage Breast Cancer

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Abstract

Eribulin plus capecitabine as adjuvant therapy was feasible in postmenopausal women with early-stage, human epidermal growth factor receptor 2-negative, estrogen receptor-positive breast cancer. The mean relative dose intensity was 90.6%, and the feasibility rate was 81.3% with the standard dosing schedule for both drugs. An alternative schedule for capecitabine (7 days on, 7 days off) was better tolerated in a supplemental group of 10 patients.

Background: The present phase II, open-label, multicenter study explored the feasibility, safety, and tolerability of eribulin, a novel non-taxane microtubule inhibitor, plus capecitabine as adjuvant therapy. **Patients and Methods:** Postmenopausal women with early-stage, human epidermal growth factor receptor 2 (HER2)-negative, estrogen-receptor (ER)-positive breast cancer received four 21-day cycles of treatment with eribulin mesylate (1.4 mg/m^2 intravenously on days 1 and 8 of each cycle) combined with capecitabine (900 mg/m^2 orally twice daily on days 1-14 of each cycle [standard schedule] or 1500 mg orally twice daily using a 7-days on/7-days off schedule [weekly schedule]). Feasibility was determined by the relative dose intensity (RDI) of the combination using prespecified criteria for 80% of patients achieving an RDI of $\geq$ 85%, with a lower 95% confidence boundary $>$ 70%. **Results:** The mean RDI was 90.6%, and the feasibility rate was 81.3% among women (n = 67, mean age, 61.3 years) receiving the standard schedule and 95.6% and 100% among women (n = 10, mean age 62.3 years) receiving the weekly schedule. Dose reductions, missed doses, and withdrawals due to adverse events (most commonly hand-foot syndrome) ascribed to capecitabine led to a higher RDI (93.5% vs. 87.8%) and feasibility rate (82.8% vs. 71.9%) for eribulin than for capecitabine using the standard dosing schedule. The most common adverse events were alopecia and fatigue. **Conclusion:** Eribulin plus capecitabine with standard or weekly dosing schedules is feasible in patients with early-stage, HER2-negative, ER-positive breast cancer. Full-dose eribulin (1.4 mg/m^2 on days 1 and 8) with capecitabine (1500 mg orally twice daily, 7 days on/7 days off) is recommended as a regimen for further evaluation.

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Introduction

Standard adjuvant chemotherapy for early-stage human epidermal growth factor receptor-2 (HER2)-negative breast cancer is effective but has been associated with cumulative and overlapping toxicities, such as myelosuppression and gastrointestinal events, among others, that can limit the therapeutic utility of current drug combinations.[1,2] Therefore, new drug combinations that are better tolerated and will improve outcomes are needed. One possibility is

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to optimize combination chemotherapy regimens by the addition of new, promising cytotoxic agents.

Eribulin mesylate is a novel non-taxane microtubule inhibitor that induces mitotic arrest and apoptosis in cancer cells by mechanistically distinct effects on microtubule dynamics that are not shared by other known anticancer tubulin-targeted agents.[2-5] It has been approved by the US Food and Drug Administration for the treatment of patients with metastatic breast cancer who have previously received $\geq$ 2 chemotherapeutic regimens (including an anthracycline and a taxane in either the adjuvant or metastatic setting).[6] Eribulin has shown efficacy in patients with extensively pretreated locally advanced or metastatic breast cancer. The objective response rate in a phase III clinical study was significantly greater for patients treated with eribulin than for those receiving treatment of physician's choice (12% vs. 5%; $P = .002$), accompanied by an increase in overall survival (hazard ratio, 0.81; 95% confidence interval [CI], 0.66-0.99; $P = .04$).[2,7] Eribulin has also shown a predictable side effect profile, with the most common adverse events (AEs) associated with treatment generally neutropenia, fatigue, alopecia, nausea, and anemia.[2,7,8]

The focus of the present study was to explore the feasibility of adding eribulin to capecitabine as adjuvant therapy in patients with early-stage, estrogen receptor (ER)-positive breast cancer. Capecitabine was previously studied in the adjuvant setting versus standard chemotherapy in postmenopausal women > 65 years old and in the ER-positive subset.[9] No difference was seen in the outcomes.[9] Eribulin and capecitabine have key toxicities that do not overlap; thus, theoretically, the eribulin plus capecitabine combination could improve the probability that the regimen will be well tolerated and more efficacious. Preliminary safety data from a phase II study of the combination and efficacy data indicating considerable activity in metastatic breast cancer patients also provided justification for the initiation of this pilot adjuvant study.[10]

Patients and Methods

The present study was conducted at 20 centers in The US Oncology Network after approval of the protocol by the central US Oncology investigational review board. Each patient voluntarily provided written informed consent before study participation, and the patients were free to discontinue at any time. The present study was conducted in accordance with the principles of the World Medical Association Declaration of Helsinki, 2008, the International Conference on Harmonization Guideline for Good Clinical Practice, and applicable national and local laws and regulations.

Patients

Eligible patients included postmenopausal women with histologically confirmed early-stage (stage I-II), HER2-negative, ER-positive breast cancer. Patients also must have had adequate liver, renal, and bone marrow function, had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1, and been eligible for adjuvant therapy to begin within 84 days of the final surgical procedure for breast cancer.

The exclusion criteria included stage III and IV invasive breast cancer; any nonmalignant systemic disease that would preclude the use of any of the study therapy drugs, including current gastrointestinal disease or other conditions resulting in an inability to take or absorb oral medications; and pre-existing neuropathy (grade > 2). Premenopausal women were not eligible because of the absence of cyclophosphamide, which has ovarian function suppressive effects.

Study Design

The present study was a single-arm, open-label, phase II feasibility study conducted from August 2011 to April 2014. The study treatment phase included four 21-day cycles of treatment (eribulin combined with capecitabine). Protocol eligibility was confirmed, and hematology, clinical chemistry, vital signs, and ECOG PS assessments and physical examinations were conducted within 2 weeks before the start of study treatment. Also, a baseline 12-lead electrocardiogram (ECG) was performed within 3 days of the first day of the first treatment cycle.

Eligible patients were treated with eribulin mesylate 1.4 mg/m^2 administered intravenously over 2 to 5 minutes on days 1 and 8 of each 21-day cycle. Eribulin was given in combination with capecitabine, which was administered using 1 of 2 different dosage regimens. In the first regimen, used for most patients (n = 67), 900 mg/m^2 capecitabine was administered orally twice daily (a total of 1800 mg/m^2) on days 1 through 14 of each 21-day cycle. The second dosing regimen for capecitabine was initiated after dose reductions and treatment discontinuations were noted and attributed to capecitabine-related toxicities, including grade 3 or 4 gastrointestinal events and hand-foot syndrome, such that the feasibility of administering $\geq$ 85% of the planned capecitabine dose was 71.9%. Thus, capecitabine was administered to an additional cohort of 10 patients at a fixed dose of 1500 mg given orally twice daily on a 7-days on/7-days off schedule continuously during the 4 cycles. This regimen for capecitabine was based on mathematical modeling[11] and has been shown to have an acceptable toxicity profile, including minimal gastrointestinal toxicity, when given in combination with bevacizumab to patients with metastatic breast cancer.[12] Eribulin was administered at the study site, ensuring compliance with eribulin dosing. The patients recorded in a daily diary the number of tablets of capecitabine taken.

Toxicities were managed in individual patients by treatment interruptions and subsequent dose reductions of eribulin or capecitabine, or both. A maximum of 2 dose reductions of either drug was allowed. Treatment could be delayed in the event of grade 3 or 4 toxicities resulting from either agent. If relationship to a specific study drug could be ascertained, the dosage of only that study drug was modified.

Warfarin was not permitted because of the likelihood of drug−drug interactions between capecitabine and warfarin-derived anticoagulant therapy. Granulocyte colony-stimulating factor (filgrastim only) could be used in cycles 2, 3, and 4 if the patient required a treatment delay of a new cycle owing to an episode of neutropenia; pegfilgrastim was not allowed.

The evaluations included hematology and clinical chemistry assessments, vital signs, and physical examinations, which were performed before study treatment administration on day 1 of each treatment cycle. The hematology assessments and vital signs were also performed before treatment on day 8 of each treatment cycle. An ECG was performed on days 1 and 8 of cycle 1 only (before dosing and immediately after eribulin administration). AEs and concomitant medications were assessed throughout the study. The