Clinical Trial Note

Application of a Continual Reassessment Method to a Phase I Clinical Trial of Capecitabine in Combination with Cyclophosphamide and Epirubicin (CEX) for Inoperable or Recurrent Breast Cancer

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A phase I clinical trial was started in order to determine the recommended doses of capecitabine and epirubicin, when administered in combination with a fixed dose of cyclophosphamide (600 mg/m² day 1 q3 weeks) in patients with inoperable or recurrent breast cancer. This study consists of five dose levels with combinations of three levels of epirubicin (75, 90 and 100 mg/m² day 1 q3 weeks) and three levels of capecitabine (1255, 1657 and 1800 mg/m²/day consecutive administration for 2 weeks followed by 1 week of rest). Dose escalation and de-escalation decisions are based on a continual reassessment method (CRM). We conducted a survey of the clinical oncologists participating in this trial to determine the dose escalation/de-escalation rule, including a prior distribution for model parameters used in the CRM.

Key words: capecitabine – continual reassessment method – breast cancer – phase I trial

INTRODUCTION

Infusional 5-fluorouracil (5-FU) produces remarkable antitumor effects in breast cancer and has been widely used in combination chemotherapy with cyclophosphamide and Adriamycin (CAF, C: cyclophosphamide, A: Adriamycin, F: 5-FU) as a gold standard (1). However, the accumulation of Adriamycin causes serious cardiotoxic effects. Thus, a phase I clinical trial of CEF chemotherapy in which Adriamycin was replaced with epirubicin, was conducted to determine the recommended doses (RD) (2). Furthermore, infusional 5-FU has not been favored due to its cumbersome mode of administration by drip infusion via a peripheral venous infusion line. Thus, a research team from the European Organization for Research and Treatment of Cancer (EORTC) conducted a phase I clinical trial of the CEX regimen, a combination chemotherapy in which 5-FU was replaced by capecitabine (3).

Capecitabine is a novel oral fluoropyrimidine derivative known to be tolerated at high doses. It is specifically designed to be selectively converted to 5-FU at the tumor lesion through a three-step enzymatic metabolic process, following oral administration (4). Capecitabine monotherapy demonstrated high antitumor activities against metastatic breast cancer (5,6).

Although a phase I study of CEX chemotherapy was conducted by the EORTC research team, a concern was raised regarding the possible differences in the RD of CEX between Caucasians and Japanese. In order to resolve this concern, we decided to conduct a clinical trial to determine the RD for CEX treatment, i.e., combination chemotherapy of epirubicin and capecitabine with a fixed dose of cyclophosphamide, in Japanese breast cancer patients. Assessment of dose escalation and de-escalation of dosage is based on a continual reassessment method (CRM) (7,8). In order to obtain prior information for CRM, more specifically, the reference information used to determine the escalation/de-escalation rule regarding the initial dose and dosage, we conducted a survey of the participating clinical oncologists while setting up the study protocol.
PROTOCOL DIGEST OF THE STUDY

PURPOSE
To determine the maximum tolerated dose (MTD) and recommended dose (RD) for a future phase II trial of combination therapy of capecitabine and epirubicin with a fixed dose of cyclophosphamide in patients with inoperable or recurrent breast cancer.

STUDY SETTING AND PROTOCOL REVIEW
Open-label, phase I clinical trial. The protocol was approved by the Protocol Review Committee of the Japan South West Oncology Group.

ENDPOINTS
Primarily, adverse events. Secondarily, objective tumor response and pharmacokinetics of capecitabine and epirubicin.

ELIGIBILITY CRITERIA
Patients with a histologically-confirmed diagnosis of inoperable or recurrent breast cancer were eligible.

INCLUSION CRITERIA
1. Inoperable (stage IIIB, excluding patients for whom radiation or surgery is not indicated or stage IV) or recurrent (with metastases or local recurrence observed after surgery) breast cancer
2. Histologically-confirmed breast cancer
3. Age ranging from 20–74 years
4. No effects of previous antitumor therapy
5. No radiation therapy at the targeted lesion prior to enrollment
6. ECOG performance status 0–1
7. Sufficient organ function
8. In patients with a history of anthracycline treatment, a left ventricular ejection fraction (LVEF) level confirmed to be within the normal range (not less than 50%) by echocardiography or radionuclide angiocardiography
9. Life expectancy longer than 12 weeks
10. Capable of ingestion
11. Measurable disease according to RECIST
12. Written informed consent

EXCLUSION CRITERIA
1. Women with ongoing pregnancy, breast feeding or contemplating pregnancy
2. History of solid organ or bone marrow transplantation
3. Allergy to fluoropyrimidine-based drugs and a history of severe adverse effects
4. CNS diseases which require clinical treatment
5. Mental disorders that may affect ability or willingness to provide informed consent or abide by the study protocol
6. HBs antigen positive or HCV antibody positive
7. Cardiovascular diseases with any clinical concerns (congestive heart failure, symptomatic coronary artery disease, arrhythmia uncontrolled by medication, etc.)
8. Patients with active multicancer
9. Evidence of pleural fluid/pericardial effusion, which needs medical attention
10. Evidence of active intestinal ulcer or hemorrhage
11. Complications with varicella
12. Any other cases for which the investigator disapproves of participation in this clinical trial

REGISTRATION
Participating investigators should send an eligibility criteria checking report via Fax to the ECRIN Data Center after confirmation of the above criteria. Patients are then registered. Information regarding the necessary follow-up examinations and recommended chemotherapy schedule is then sent from the Data Center.

TREATMENT METHODS
The five dose levels scheduled for epirubicin and capecitabine in combination with 600 mg/m² of cyclophosphamide are as follows: Level 0: 75 mg/m² and 1255 mg/m²; Level 1 (starting dose): 75 mg/m² and 1657 mg/m²; Level 2: 90 mg/m² and 1657 mg/m²; Level 3: 90 mg/m² and 1800 mg/m²; Level 4: 100 mg/m² and 1800 mg/m². These doses were established in light of data from previously conducted phase I trials (3,9,10). Capecitabine is administered orally twice daily for two weeks. In Japan, the approved dosage of capecitabine is 1657 mg/m²/day, and the approved schedule is a three-week administration of this dose followed by one week of rest. In this study, the dose intensity of capecitabine at Levels 3 and 4 is milder than that of the approved regimen. Moreover, although the doses of epirubicin at Levels 2 to 4 (90 and 100 mg/m²) are not approved in Japan, 100 mg/m² of epirubicin has been tested in a phase I trial (3). In this study, cyclophosphamide and epirubicin are administered intravenously on day 1 of each treatment cycle. In addition, based on the body surface area (BSA), the subjects are divided into three subgroups (BSA <1.31 m², 1.31 m² ≤ BSA <1.64 m² and BSA ≥1.64 m²) in order to adjust respective doses. One cycle consists of 3 weeks of consecutive administration and is repeated for two cycles. Toxicological effects are assessed after completion of two cycles. Thereafter, administration is continued for four cycles, if possible. For patients previously treated with adriamycin, extreme caution must be taken so as to not exceed a total dose of 900 mg/m² of epirubicin in each case. Patients should receive capecitabine for as long as possible even after completing the set dosage cycle. Discontinuation of therapy should be based on blood cell counts and hepatic and renal function prior to initiation of each treatment course. Drug doses should not be modified during the first and second cycles.
DEFINITION OF DOSE LIMITING TOXICITY

Dose limiting toxicity (DLT) is defined as the occurrence of any one of the following observed during the first and second cycles of treatment: (a) grade 4 leukopenia and neutropenia for 7 days or more, (b) grade 3 neutropenia along with fever for 3 days or more, (c) grade 4 thrombocytopenia, (d) grade 3 plantar-palmar erythrodysesthesia, (e) grade 3 or greater non-hematologic toxicity excluding alopecia and nausea/vomiting and (f) total treatment interruption lasting for more than 2 weeks.

FOLLOW-UP

Patients are examined by their physicians every week. Thoracic computed tomography or radiography, abdominal computed tomography and measurements of the tumor markers CAE and CA15-3 are performed after every two treatment cycles as well as at baseline. Blood tests and symptom checks are carried out before treatment and every week during treatment. When grade 3 neutropenia is observed, oral antibiotic drugs are prescribed, and the patient is also instructed to contact her or his physician as soon as she or he develops fever. Urinalysis, measurements of body weight and vital signs and assessment of ECOG performance status are done before treatment and at the end of each treatment cycle.

STUDY DESIGN AND STATISTICAL METHODS

In this study, a dose escalation/de-escalation decision is made using the CRM calculations (7,8). The target toxicity level is set at 33%. The RD of this study is determined to be the dose that is closest to the level at which 33% of patients would experience the DLT. The MTD of this trial is defined as the dose level that is one level higher than the final RD. The first included patient is treated at Level 1. After enrollment of the first patient, the CRM runs sequentially in three patients per cohort. Each cohort is treated at the dose level with an estimated probability of DLT closest to the target toxicity level (33%). Bypassing more than one dose level is not permissible in the CRM calculations.

We carried out a survey to determine a prior distribution for a model parameter employed in the CRM. This was done by asking eight breast cancer oncologists participating in this trial, to predict the RD based on their knowledge and experiences with respect to three chemotherapeutic drugs. We employed a gamma distribution as a prior distribution reflecting results of the survey. In addition, this study applies a stopping rule proposed by O’Quigley (2002) to bring the trial to an early halt before including the entire sample size of patients (n = 22) (11). After completing the toxicity assessment for each cohort, we calculate the probability that a certain dose level administered to a cohort is the dose level recommended to all remaining patients in the study and is the final RD.

INTERIM ANALYSIS AND MONITORING

The Data and Safety Monitoring Committee (DSMC) independently reviews the interim analysis and can consider stopping the trial early. Protocol compliance, safety and on schedule study progress are also monitored by the DSMC.

PARTICIPATING INSTITUTIONS

Tokyo Metropolitan Komagome Hospital (Department of Surgery), Jichi Medical School (Department of Surgery), Cancer Institute Hospital (Clinical Chemotherapy), Jikei University School of Medicine (Department of Hematology and Oncology), Aichi Cancer Center Hospital (Department of Breast Surgery) and National Kyushu Cancer Center (Department of Breast Surgery).

References