Journal of Clinical Trials
ISSN: 2167-0870

Taira et al., J Clin Trials 2016, 6:2
DOI: 10.4172/2167-0870.1000260

Protocol Open Access

Cohort Study of Secondary Endocrine Therapy in Metastatic Breast Cancer with a Poor Response to Initial Endocrine Therapy

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Received date: March 04, 2016; **Accepted date:** April 08, 2016; **Published date:** April 15, 2016

Abstract

Background: Several classification models of sensitivity and resistance to endocrine therapies have been proposed for the clinical course of initial endocrine therapy for metastatic breast cancer. However, the efficacy and safety of secondary endocrine therapy in cases with a poor response to the initial endocrine therapy have not been examined.

Methods: A multicenter prospective observational study is planned with the objectives of demonstrating the efficacy and safety of secondary endocrine therapy in estrogen receptor (ER)-positive, human epidermal growth factor receptor type2 (HER2)-negative postmenopausal metastatic breast cancer for which initial endocrine therapy did not have a favorable clinical effect (i.e., low sensitivity to initial endocrine therapy). The subjects are patients with breast cancer with low sensitivity to initial endocrine therapy, and are defined as cases with recurrence during 5 years of adjuvant therapy or those with metastatic breast cancer that showed progression within 9 months after initial endocrine therapy. The efficacy and safety of current endocrine therapeutic agents selected by physicians and patients will be examined using outcomes including clinical benefit, progression-free survival, overall survival, time to treatment failure, time to chemotherapy, response, health-related quality of life, and adverse events.

Conclusion: Evaluation of the efficacy and safety of secondary endocrine therapy for breast cancer with low sensitivity to initial endocrine therapy will provide information for evidence-based selection of appropriate secondary endocrine therapy. The results will also clarify the remaining clinical issues to be resolved and provide a foundation for planning of future clinical research.

Keywords: Breast cancer; Secondary endocrine therapy; Low sensitivity to initial endocrine therapy; Metastatic; Efficacy; Safety; Multicenter trial

Introduction

Background to the proposed research

It is rare to achieve complete cure for breast cancer with inoperable distant metastasis at the first visit (stage IV) or for recurrent breast cancer caused by distant metastasis. Therefore, the major purposes of treatment in such cases are alleviation of symptoms due to metastasis, life extension, and maintenance and improvement of quality of life (QoL) [1]. Metastatic breast cancer is mainly treated by drug therapy, with addition of radiotherapy or surgery as needed, to alleviate symptoms and maintain activities of daily life.

Selection of therapies based on the biological characteristics of individual tumors has been emphasized in treatment of breast cancer in recent years. Breast cancer is classified into several subtypes, which are determined based on the expression of estrogen receptor (ER) and human epidermal growth factor receptor type2 (HER2). These proteins are important predictors of prognosis and clinical effects of endocrine therapy, chemotherapy, and molecular targeted agents; therefore, selection of therapy is based on the subtype classification. An algorithm proposed by Hortobagyi has been implemented in clinical practice as a treatment strategy [1]. For ER-positive metastatic breast cancer, treatment usually begins with endocrine therapy and moves to different treatments as soon as the first therapy loses its efficacy, if there is no distant metastasis threatening survival. For cases responsive to the initial endocrine therapy, secondary endocrine therapy is performed because an antitumor effect is still likely, even if the initial therapy loses its efficacy [1].

Several classification models for sensitivity and resistance to endocrine therapies have been proposed for the clinical course associated with initial endocrine therapy. The 2nd International Consensus Guidelines for Advanced Breast Cancer (ABC2), which

were developed at an international conference on recurrent breast cancer, propose classification of resistance to endocrine therapies for ER-positive metastatic breast cancer according to the period from the start of initial endocrine therapy to recurrence or progression [2]. In these guidelines, primary endocrine therapy-resistant breast cancer is defined as a case with recurrence within 2 years after initiation of postoperative adjuvant endocrine therapy, or a case with disease progression within 6 months after initial endocrine therapy for metastatic breast cancer. Secondary endocrine therapy-resistant breast cancer is defined as a case with recurrence within 2 years after initiation of postoperative adjuvant endocrine therapy or within 12 months after completion of the endocrine therapy, or a case with disease progression within 6 months after the start of initial endocrine therapy for metastatic breast cancer.

A different classification scheme has been proposed based on drug sensitivity, in which cases with recurrence within 2 years after initiation of postoperative adjunct endocrine therapy and those with progression within 3 months after the start of initial endocrine therapy are classified as having "very low" drug sensitivity, while cases that show recurrence after 2 years from initiation of postoperative adjunct endocrine therapy have "low" drug sensitivity [3].

Review of the literature

Aromatase inhibitors are the first-line drugs for postoperative and primary endocrine therapy for metastatic breast cancer, but optimal post-aromatase inhibitor treatment is uncertain [3]. Drugs for breast cancer that have a mechanism of action differing from that of existing drugs have recently become available, including selective estrogen receptor modulators (e.g., tamoxifen, toremifene), other aromatase inhibitors (with a different mechanism of action), fulvestrant, megestrol acetate, and everolimus+aromatase inhibitors.

There have been several studies of use of other aromatase inhibitors as secondary treatment. In a phase 2 study of a steroidal aromatase inhibitor, exemestane, in non-steroidal aromatase inhibitor-treated cases with aggravation, the clinical benefit rate was 24.3% [4]. In this study, clinical benefit was obtained in 24.7% of cases, even in patients in whom no benefit was obtained by primary treatment with a non-steroidal aromatase inhibitor. This suggests that a second aromatase inhibitor is useful for patients who had a poor response to initial endocrine therapy. In another phase 2 study in 91 patients who became resistant to a non-steroidal aromatase inhibitor and were randomly allocated to toremifene or exemestane treatment, the clinical benefit rates were 44.2% with toremifene and 26.7% with exemestane group [5].

Fulvestrant does not have a partial agonistic effect on ER, in contrast to that for tamoxifen, but instead down regulates ER expression in breast cancer cells; therefore, fulvestrant is classified as a selective estrogen receptor down regulator (SERD) [6-8]. Based on the results of a Phase II comparative study of anastrozole and fulvestrant as primary endocrine therapies in metastatic breast cancer (First-Line Study Comparing Endocrine Treatments [FIRST] trial), fulvestrant has clinical efficacy for metastatic breast cancer that is equivalent to that of anastrozole [9].

Everolimus is an inhibitor of mammalian target of rapamycin (mTOR), which is situated downstream of the PI3K/AKT pathway, a key signaling pathway controlling cell proliferation. Thus, inhibition of mTOR blocks cancer cell proliferation and extends progression-free survival (PFS) with combined administration of endocrine therapies in breast cancer that has become endocrine therapy-resistant [10-12]. A clinically significant treatment effect is likely with use of these drugs in secondary endocrine therapy, even for cases with a poor response to initial endocrine therapy.

Identification of research gaps

Validation of a randomized controlled study in cases with poor responsiveness to initial endocrine therapy is required to establish a standard treatment. However, no clinical trials have evaluated the efficacy and safety of secondary endocrine therapy in such cases. Furthermore, there is a wide range of drugs available for secondary endocrine therapy for breast cancer. Fundamental information, such as the basis for selection of the target population indicated for secondary endocrine therapy and the expected treatment effect for overall secondary endocrine therapy and for each drug are required to plan a comparative clinical trial of these drugs. This observational study was planned based on this background.

Methods

Objectives of the study

There are two objectives of the study. First, to evaluate the efficacy and safety of secondary endocrine therapy in general and those of specific drugs in ER-positive, HER2-negative postmenopausal metastatic breast cancer for which initial endocrine therapy had no favorable clinical effect (low sensitivity to initial endocrine therapy). Second, to determine the effects of response to the previous endocrine therapy (period from the start of adjuvant endocrine therapy to recurrence) and the tumor biological characteristics (expression level of ER and presence or absence of progesterone receptor [PgR] expression) on the results of secondary endocrine therapy, and to obtain information to complement Hortobagyi's therapeutic algorithm.

Hypotheses to be tested

To achieve the above objectives, the following two hypotheses will be tested in the study. First, a clinical benefit rate of at least 30% can be expected for the latest endocrine drugs for breast cancer with low sensitivity to initial endocrine therapy. Second, the effect of secondary endocrine therapy can be predicted from the response to previous treatment and the biological characteristics of the tumor in cases with low sensitivity to initial endocrine therapy.

Study design and selection of subjects

A multicenter prospective observational study will be performed in patients with "ER-positive, HER2-negative postmenopausal metastatic breast cancer with low sensitivity to initial endocrine therapy". We note that there is no current consensus on this definition, and therefore we have established the following criteria for this study: (1) cases with continuing postoperative adjunct endocrine therapy that show recurrence within 5 years after initiation of therapy, and (2) cases with disease progression within 9 months of initial endocrine therapy for metastatic breast cancer. Cases that fit either definition are potentially eligible for the study.

Cases that satisfy all of the following inclusion criteria and do not meet the exclusion criteria will then be included in the study. The inclusion criteria are (1) a patient with ER-positive postmenopausal

breast cancer and a histological diagnosis of breast cancer; (2) a diagnosis (with or without the presence of measurable lesions) of (a) stage IV breast cancer associated with distant metastasis that is inoperable at the first visit, or (b) breast cancer associated with progression or recurrence caused by distant metastasis after initial treatment aimed at cure; (3) planned endocrine therapy for metastatic breast cancer; (4) ECOG performance status (PS) of 0 or 1; (5) previous endocrine therapy (with any endocrine drug) as (a) continuous postoperative adjuvant therapy with recurrence within 5 years after initiation of the endocrine therapy, or (b) initial treatment for metastatic breast cancer with disease progression within 9 months after initiation of the endocrine therapy; (6) no previous chemotherapy for breast cancer or chemotherapy given as pre- or postoperative adjuvant therapy completed at least 6 months before the start of this study; (7) previous radiotherapy for breast cancer that was completed at least 14 days before the start of this study; and (8)agreement from the patient regarding participation in the study using the consent form.

Cases that meet any of the following exclusion criteria will be excluded from the study: (1) HER2-positive breast cancer, (2) a case not indicated for endocrine therapy, and (3) any patient that a physician determines to be unsuitable for participation in the study.

Selection of treatment

The objective of the study is to evaluate the efficacy and safety of secondary endocrine therapy used in regular clinical practice for the target population. However, there are a broad range of endocrine drugs and the optimal therapies for this population are not established. The treatment choices include all drugs covered by insurance for use as endocrine therapy for postmenopausal breast cancer in Japan, except for those used in initial treatment. The drugs, dosages and administration routes approved as endocrine therapy for postmenopausal breast cancer in Japan are shown in Table 1.

Classification	Drug name	Dosage and administration
Selective estrogen receptor modulators (SERMs)	Tamoxifen	Orally administered as 20 mg daily in 1 to 2 divided doses. Dosage may be appropriately increased depending on the symptoms, but the daily maximum dose of tamoxifen is 40 mg.
	Toremifene	Orally administered as 40 mg toremifene once daily in adults, or as 120 mg toremifene once daily in previously treated adults with no response to drugs or radiotherapy. Dosage is appropriately increased depending on the symptoms.
Aromatase inhibitor (AI)	Anastrozole	Orally administered as 1 mg anastrozole once daily in adults.
	Letrozole	Orally administered as 2.5 mg letrozole once daily in adults.
	Exemestane	Orally administered after meals as 25 mg exemestane once daily in adults.
Selective estrogen receptor down regulator (SERD)	Fulvestrant	Gluteal injection of 500 mg fulvestrant administered intramuscularly into each side once at the first administration, 2 and 4 weeks later, and every 4 weeks thereafter in adults.
Progestational hormone agent	Medroxyprogesterone acetate	Orally administered orally as 600-1200 mg medroxyprogesterone acetate daily in 3 divided doses in adults.

Table 1: Drug name and dosage approved as endocrine therapy for postmenopausal breast cancer in Japan.

Treatment will be selected based on discussions between physicians and patients. However, use of agents with an antitumor effect (chemotherapeutic agent, concomitant use of a molecular targeted drug, and other endocrine therapy) is recommended, in combination with other treatment (surgery, radiotherapy) as appropriate and in accordance with published guidelines [1]. Furthermore, when these therapies are implemented in combination with endocrine therapy, the details will be described in the patient's progress report. Planned treatment will be clearly indicated on the case registration card when a patient participates in the study.

Combination use of mTOR inhibitor

Significant extension of PFS was reported in the everolimus +exemestane group compared with the placebo+exemestane group in a Phase III global clinical trial in ER-positive, HER2-negative, locally advanced or metastatic postmenopausal breast cancer that was resistant to nonsteroidal aromatase inhibitors (letrozole or anastrozole) [10,11]. In addition, extensions of the time to significant PFS and overall survival (OS) were observed in the everolimus+tamoxifen group compared with the tamoxifen group in a Phase II randomized trial for locally advanced or metastatic postmenopausal breast cancer resistant to aromatase inhibitors [12]. Administration of everolimus in combination with endocrine therapy for inoperable or recurrent breast cancer is allowed in Japan. Therefore, combination use of endocrine therapy with everolimus is an option in this study. This combination therapy may affect efficacy and adverse events, and thus everolimus will be described as a concomitant drug in the progress report.

Categorization of drug types used in analysis

Currently, aromatase inhibitors (AIs) are the first-line drugs for initial and postoperative endocrine therapy for metastatic breast cancer. Therefore, it is likely that most of the cases registered in this study will have received treatment with aromatase inhibitors. There are also several AIs that are available for use as secondary therapy. Four cohorts will be defined based on the principal mechanisms of action of the drugs used in the study: selective estrogen receptor modulator (SERM): tamoxifen, toremifene; AI: anastrozole, letrozole, exemestane; SERD: fulvestrant; and mTORi: combined use of an endocrine drug and everolimus, an mTOR inhibitor. Cases in which everolimus is used will be categorized in the fourth cohort, regardless of the type of endocrine therapy. Efficacy and safety will be evaluated in each cohort and for general secondary endocrine therapy.

Surveys

The following surveys and examinations will be used to evaluate the efficacy and safety of the protocol treatment, using the schedule shown in Table 2: medical history, physical findings, diagnostic imaging of breast cancer focus, survey of adverse events, treatment survey (selected drug and reasons for selection, compliance, combination treatment) at 3 and 6 months after initiation of treatment; a survey of health-related quality of life (HRQoL) using the Functional Assessment of Cancer Therapy (FACT)-Endocrine Symptoms (ES) and Breast Scale at 1 and 3 months after initiation of treatment, and a post-treatment survey and prognosis survey every year for 4 years after registration.

Survey term	Before registration	1 month after the initiation of protocol treatment	3 months after the initiation of protocol treatment	6 months after the initiation of protocol treatment
Medical history	x			
Physical findings	x		x	x
Height, weight, performance status	x		x	x
Imaging assessment	x		x	x
Adverse event	x		x	x
Treatment survey	x	x	x	
Health related quality of life				
Survey aftertreatment		Survey is implemented every year after registration for 4 years.		
Prognosis survey				

Table 2: Survey schedule.

Outcomes

Outcome measures

The primary outcome is clinical benefit, which is defined as no disease progression for 6 months from initiation of treatment. The clinical benefit rate (CBR) is defined as the proportion of patients who achieve a clinical benefit.

The secondary outcomes are PFS, OS, and time to treatment failure (TTF), time to chemotherapy (TTC), response, HRQoL, and adverse events. In all definitions, the start of the period is the day of registration in the study. PFS is then defined as the period until progression is detected or the day of death from all causes (whichever is earlier), OS is the period until death from all causes, TTF is the period until progression, death from all causes, or discontinuation of secondary endocrine therapy (whichever is earlier), and TTC is the period until the first administration of a chemotherapeutic drug. The best overall response with measurable lesions is defined as complete response or partial response. The response rate (RR) is the proportion of patients with a response in all cases that underwent treatment.

Analysis plan

Whether CBR, the primary outcome, exceeds 30% will be examined using exact tests based on a binomial distribution and the corresponding 90% confidence interval (CI) in each cohort and for all secondary endocrine therapy. The analysis set includes all treated cases, and a significance level of 5% is set for 1-sided tests. Analysis of the interaction effect of CBR will be conducted for response to initial endocrine therapy, ER expression level, and presence or absence of PgR expression for all registered cases to examine the significance of effect predictors of secondary endocrine therapy.

Analyses of secondary outcomes will also be conducted for each cohort. For RR defined by a binary endpoint (response), an accurate 90% CI and point estimate will be calculated based on the binomial distribution. For PFS, OS, TTF, and TTC, which are time-to-event outcomes, survival curves will be estimated using the Kaplan-Meier method and 90% CIs of the survival rate for each event will be calculated using Greenwood's formula. The interaction effect will be analyzed with effect predictors in the same manner as that used for the primary outcome.

Analysis of adverse events will be performed in all treated cases. Incidence by type and grade will be calculated for reported adverse events. For analysis of HRQoL, cases with decreases in scores exceeding the threshold value compared with scores at registration will be identified and the rate of maintenance of HRQoL will be calculated using minimally important differences (MIDs) [13].

Sample size determination

This study is an observational study in which therapy is selected based on the preferences of physicians and patients. The study does not aim to compare different cohorts. To test the major hypothesis, the threshold CBR is set at 30%, and the expected CBR is set at 50% in each cohort. Assuming use of an accurate binomial test, it is estimated that the required number of cases is 43 under a condition of α=0.05 (one-tailed) and β=0.2. Assuming a dropout rate of about 10%, the estimated target sample size required for each cohort is 50. Cases will not necessarily be evenly distributed among cohorts, but the sample size needs to correspond to four groups at a maximum. Therefore, a target population of at least 200 is required. Registration will continue until all four groups achieve the target number of 50 cases per group

within the time frame for registration, even after a total registration number of 200 cases is achieved.

Discussion

About 70% of breast cancer cases are ER-positive, and thus the proportion of ER-positive cases is also high in metastatic breast cancer. Endocrine therapy chosen using Hortobagyi's algorithm is implemented on a daily basis. However, there is no evidence showing the optimum secondary therapy for breast cancer with low sensitivity to initial endocrine therapy. In a previous clinical trial, the treatment effect of secondary endocrine therapy for metastatic breast cancer was investigated using the effect of initial endocrine therapy as a stratifying factor [4], but no study has been performed in patients with low sensitivity to initial endocrine therapy. In this study, evaluation of the efficacy and safety of secondary endocrine therapy in such cases will produce important information for evidence-based selection of secondary endocrine therapy.

There are several proposed definitions for low sensitivity to initial endocrine therapy, but no clear criteria have been established. In this study, the target patients are defined as having low sensitivity to initial endocrine therapy using relatively wide criteria. Thus, the subjects include patients with recurrence and aggravation within a short time and patients in whom a relatively long-term effect could be obtained. The second objective of this study is to determine the effects of response to previous endocrine therapy, for which we are planning to perform stratification using the effect of previous treatment and exploratory analysis to determine how the effect of initial endocrine treatment influences the effect of secondary treatment.

A limitation of this study is that it is not designed as a comparative study of a specific drug for secondary treatment or to determine superiority or inferiority of drugs. The target population is too small to perform a comparative study, and there are many therapeutic drugs that may be chosen. Under these conditions, opinions may vary on selection of treatment for patients with low sensitivity to initial endocrine therapy. Therefore, we designed a cohort study to examine how therapy was actually selected and the extent of the effect obtained.

The results of this study will clarify the remaining clinical issues to be resolved and provide a firm foundation for planning of future clinical research. To date, no clinical studies have been conducted in breast cancer with low sensitivity to initial endocrine therapy. Hence, this study also has great significance in terms of its originality.

Ackowledgement

This study will be conducted with the support of research funds from the Investigator Initiated-Sponsored Research (IISR) (investigator sponsored study) of the Externally Sponsored Research program of AstraZeneca K.K. awarded to the General Incorporated Association of Comprehensive Support Project for Oncological Research in Breast Cancer (CSPOR-BC). All responsibilities for planning and implementation of the study; implementing institutes and facilities; approval of ethical review boards; analysis, interpretation, and publication of the results; and ensuring transparency of the study are assumed by the authors.

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