Randomized Study of Taxane Versus TS-1 in Women with Metastatic or Recurrent Breast Cancer (SELECT BC)

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This randomized controlled trial will compare oral 5-fluorouracil derivatives, TS-1, with intravenous standard chemotherapy such as taxanes in women with metastatic or recurrent breast cancer. Patients with hormone-resistant breast cancer are assigned to either TS-1 (40–60 mg twice daily for 28 consecutive days, followed by a 14-day rest period) or standard chemotherapy (docetaxel 60–75 mg/m² at 3- or 4-week intervals, paclitaxel 175 mg/m² at 3- or 4-week intervals or paclitaxel 80–100 mg/m² weekly, followed by a 1-week rest period). Treatment will be repeated until tumor progression or ≥4 courses for TS-1 and ≥6 courses for taxanes. The primary endpoint is overall survival. Secondary endpoints are progression-free survival, time to treatment failure, adverse events, health-related quality of life and cost-effectiveness. A threshold hazard ratio of 1.333 will be used to determine whether overall survival in the TS-1 group is equivalent (not inferior) to that in the taxane group. The target number of registered patients is 600.

Key words: metastatic breast cancer – Phase III – QOL – taxane – TS-1

INTRODUCTION

It is difficult to effectively manage metastatic breast cancer with currently available drug regimens. The objectives of therapy are to prolong survival and improve patients’ quality of life (QOL) (1). In line with these objectives, the general strategy for treatment is as follows: hormone therapy is initially administered to patients who are likely to respond to such therapy, and chemotherapy is initially administered to patients whose disease is resistant to hormone therapy (1). Currently, the general treatment strategy for patients with metastatic breast cancer who receive chemotherapy is to initially use chemotherapeutic agents in the order of their effectiveness for shrinking tumors, rather than their relative intensity of side effects. Historically, the underlying reason for this strategy is that chemotherapy for hematologic malignancies was introduced for the chemotherapy of solid cancers, including breast cancer. Therefore, the basic concept that ‘regimens combining multiple anticancer drugs to achieve total cell kill are most effective’ was followed (2). Many clinical studies have been performed to validate the ‘usefulness’ of using combinations of drugs with high response rates as first-line treatment. However, very few studies have demonstrated an improvement in survival [although response rates and progression-free survival (PFS) have improved] (3,4). On the basis of these results, emphasis has shifted to the QOL of patients rather than response rates in clinical practice, and the use of oral anticancer drugs as first-line treatment is increasing. Recent data obtained in
patients with colorectal cancer have shown that using as many drugs as possible is an important determinant of overall survival, whereas the drug(s) selected for first-line treatment is(are) of little relevance (5).

The primary endpoints of many previous clinical trials in patients with metastatic breast cancer were PFS and time to treatment failure (TTF). This is because PFS and TTF were thought to function as surrogate markers of the real endpoint of overall survival. However, the results of many recently reported clinical trials do not necessarily support this notion (3,4,6). In addition, since the objective of the present study was not solely to ascertain the difference in potency between taxane derivatives and TS-1, overall survival, which reflects the final benefit to patients, was designated as the primary endpoint. Because one treatment objective in patients with metastatic breast cancer is an improved QOL, adverse events and cost-effectiveness are important factors in drug selection. These factors were thus designated as secondary endpoints.

Currently, standard, first-line chemotherapy for metastatic breast cancer is based on anthracycline derivatives or taxane derivatives. With anthracycline derivatives, however, side effects such as severe nausea, vomiting and cardiotoxicity are an important concern. Historical trends suggest that the use of anthracycline derivatives will decrease gradually in the future. This downward trend will probably be associated with a further increase in the use of taxanes. Taxane derivatives were therefore selected for the standard arm. Nonetheless, many physicians continue to have high expectations for anthracycline derivatives. Therefore, the use of anthracycline derivatives for second-line and subsequent therapy was permitted.

Oral drugs are clearly more convenient than parenteral preparations. Given that oral 5-fluorouracil derivatives have good toxicity profiles including low risk of causing hair loss, these drugs were considered best suited for the trial arm of the present study. TS-1 and capecitabine are widely used oral 5-fluorouracil derivatives in Japan. Two Phase II studies of TS-1 in patients with metastatic breast cancer, including subjects who had received prior chemotherapy as well as those who had not, have been performed in Japan. The response rates were 42.0% and 40.7%, respectively, comparable to the response rates with taxane derivatives (7,8). Two Phase II studies of capecitabine in patients who had received up to one regimen of prior chemotherapy have also been conducted in Japan. Response rates were 28.3% and 20.0%, respectively (data for both studies from the clinical trial summary report). An important concern of these studies was that the incidences of hand-foot syndrome of Grade 3 or higher were 18.0% and 13.3%, respectively. Capecitabine is widely used in Europe and the USA, as well as in Japan. Clinical trials comparing capecitabine with taxane derivatives as first-line treatment for metastatic breast cancer are currently underway in Europe. However, the primary endpoint of these trials is PFS, which differs from that of the present study. In contrast, TS-1 is approved only in Japan, Korea and China. The use of this drug is attractive because unique data can be generated. We therefore selected TS-1 as a representative oral anticancer drug for the trial arm of this study. Given the results of the clinical trials described above, we believe that there is no problem in using TS-1 for first-line chemotherapy.

**DIGEST OF THE STUDY PROTOCOL**

**Purpose**

This study was designed to evaluate the following two variables in women with metastatic breast cancer.

(i) To verify that overall survival in the TS-1 group is equivalent to or better than (i.e. not inferior to) that in the taxane group in women with metastatic breast cancer who receive either a taxane preparation or TS-1 as first-line therapy, followed by drug treatments at the discretion of the investigator. Progression-free survival and TTF will also be compared between the two groups.

(ii) To compare adverse events, health-related QOL (HRQOL) and cost-effectiveness between the two groups.

**Study Setting**

This study is a multi-institutional prospective randomized controlled trial, with 254 participating centers as of 31 July 2009.

**Study Support**

This study was funded by Comprehensive Support Project for Oncology Research (CSPOR) of Public Health Research Foundation. The research fund was provided to CSPOR by Taiho Pharmaceutical Co., Ltd. Taiho Pharmaceutical took no part in this study other than providing information relevant to proper use of the study drug. All decisions concerning the planning, implementation and publication of this study were made by the executive committee of this study.

**Endpoints**

The primary endpoint is overall survival. Secondary endpoints are PFS, TTF, adverse events, HRQOL and cost-effectiveness.

**Eligibility Criteria**

(i) Women with a histologically confirmed diagnosis of breast cancer.

(ii) One of the following conditions has to be met for a diagnosis of metastatic breast cancer.

(a) At presentation, the patient has distant metastasis.
(b) The patient has breast cancer that has worsened or recurred in association with distant metastasis after treatment (after surgery and pre- and post-operative treatment); however, local recurrence is excluded.

(iii) The presence of at least one assessable lesion. However, sites treated by radiotherapy are not considered assessable lesions.

(iv) No chemotherapy with anticancer drugs since the diagnosis of metastatic breast cancer.

(v) An age of 20–75 years.

(vi) A performance status of 0–1 according to the ECOG scale.

(vii) Either of the following conditions has to be met concerning previous treatment with taxane derivatives (paclitaxel or docetaxel).
   (a) Not administered previously.
   (b) If such drugs have been administered as pre- or post-operative adjuvant chemotherapy, at least 6 months (168 days, 24 weeks) have elapsed since the final day of treatment.

(viii) Either of the following conditions has to be met concerning a history of treatment with oral 5-fluorouracil derivatives.
   (a) Not administered previously.
   (b) If such drugs have been administered as pre- or post-operative adjuvant chemotherapy, at least 6 months (168 days, 24 weeks) have elapsed since the final day of treatment.

(ix) Both of the following conditions have to be met concerning preceding treatment.
   (a) Hormone therapy: at least 7 days have elapsed since the final day of drug treatment (irrespective of the details of treatment).
   (b) Radiotherapy: at least 14 days have elapsed since the final dose of radiation.

(x) Resistance to hormone therapy is defined as any of the following.
   (a) Estrogen receptors or progesterone receptors are negative on examination of the primary lesion or recurrent lesion(s). However, if both the primary lesion and recurrent lesion(s) are examined and the results differ, the results for the recurrent lesion(s) will apply.
   (b) Hormone therapy is ineffective after recurrence.
   (c) Recurrence occurs during post-operative adjuvant hormone therapy or within 6 months after the final dose.

(xi) All of the following conditions have to be met regarding organ function (within 21 days before registration).
   (a) A neutrocyte count (stab cells + segmented cells) of 1500/mm³ or higher, or a white cell count of 3000/mm³ or higher.
   (b) A platelet count of 100 000/mm³ or higher.

(c) A total bilirubin concentration of not more than 2.5 times the upper limit of normal at the laboratory where the test was performed.

(d) Aspartate aminotransferase (AST, GOT) and alanine aminotransferase concentrations (ALT, GPT) of not more than 2.5 times the upper limit of normal at the laboratory where the test was performed.

(e) A serum creatinine concentration of not more than the upper limit of normal at the laboratory where the test was performed.

(xii) At least one of the following conditions has to be met for cardiac function.
   (a) No cardiac disease: absence of fatigue, palpitations, shortness of breath and anginal pain during daily activities as confirmed by interview.
   (b) Cardiac disease is present, but exercise restriction is not required, and the absence of fatigue, palpitations, shortness of breath and anginal pain during daily activities can be confirmed and is expected to be maintained during treatment.

(xiii) Written informed consent has been obtained directly from the subject.

EXCLUSION CRITERIA

(i) Women who are pregnant, breast feeding or intend to become pregnant.

(ii) Overexpression of human epidermal growth factor receptor 2 (Her2/neu, Erb B2), or the results of fluorescence in situ hybridization are positive.

(iii) A past history of hypersensitivity to the protocol treatment drugs or their solvents.

(iv) The presence of other active cancers (synchronous double cancers or metachronous double cancers with a disease-free interval of 5 years or less).

(v) The presence of brain metastasis requiring treatment because of increased intracranial pressure or emergency brain irradiation.

(vi) The presence of extensive liver metastasis or lymphatic pulmonary metastasis associated with dyspnea.

(vii) The presence of only one assessable lesion located at a previously irradiated site.

(viii) The presence of pleural effusion, ascites or pericardial effusion requiring emergency treatment.

(ix) Concurrent active infections.

(x) The presence of interstitial pneumonia or pulmonary fibrosis.

(xi) Positive test results for hepatitis B surface antigen.

(xii) Patients with diabetes mellitus that is poorly controlled or being treated with insulin.

(xiii) Participation in the study is precluded by mental disease or psychological symptoms.

(xiv) Other reasons that preclude participation in the study as judged by the investigator.
PATIENT ASSIGNMENT

The CSPOR Data Center will confirm patient eligibility, and treatment will be automatically assigned according to the assignment adjustment factors for eligible patients. The following six variables will be used as assignment adjustment factors: hospital, liver metastasis, hormone sensitivity, previous use of taxane derivatives, previous use of oral 5-fluorouracil derivatives and the period from the date of surgery to the date of recurrence.

TREATMENT

**TAXANE ARM**

For the taxane arm, one of the three regimens described below will be selected. Before the start of treatment, the treatment regimen will be selected at the discretion of the investigator. The same regimen will be used for the duration of first-line treatment. The reason for selecting the regimen will be reported in the ‘Follow-up Report.’

(i) Docetaxel 60—75 mg/m^2^ administered at 3- or 4-week intervals. Treatment will be repeated until tumor progression or for at least six courses (18 or 24 weeks).

(ii) Paclitaxel 175 mg/m^2^ administered at 3- or 4-week intervals. Treatment will be repeated until tumor progression or for at least six courses (18 or 24 weeks).

(iii) Paclitaxel 80—100 mg/m^2^ administered every week. Weekly treatment for 3 consecutive weeks, followed by a 1-week rest period will comprise one course. Treatment will be repeated until tumor progression or for at least six courses (24 weeks).

**TS-1 ARM**

TS-1 will be administered orally in doses of 40–60 mg twice daily for 28 consecutive days. The dose will be assigned according to body weight. Treatment will be followed by a 14-day rest period to complete one course. Treatment will be repeated until tumor progression or for at least four courses (24 weeks).

SUBSEQUENT TREATMENT

The possibility that inappropriate therapy during the course of treatment might affect outcomes cannot be ruled out. Therefore, second-line chemotherapy was limited to standard treatments.

STATISTICAL ANALYSIS

**MAIN ANALYSIS AND ASSESSMENT CRITERIA**

A threshold hazard ratio of 1.333, which was calculated by a proportional hazards model, will be used to determine whether the TS-1 group is equivalent (not inferior) to the taxane group with regard to overall survival.

**SAMPLE SIZE AND FOLLOW-UP PERIOD**

Validation of whether the TS-1 group is not inferior to the taxane group with regard to overall survival, the primary endpoint, will require 190 events (deaths) per group, given a two-sided α value of 5%, a power of 80% and a non-inferiority threshold hazard ratio of 1.333. Given that the median survival time in the study population is 24—28 months, 294—323 patients per group will be required for validation during a mean follow-up of 3 years, taking into account a registration period of more than 2 years. If mean follow-up is 3.5 years, 271—294 patients will be required. The target number of registered patients for both groups combined will therefore be 600.

REGISTRATION OF THE PROTOCOL

The study protocol was registered at the website of the University Hospital Medical Information Network (UMIN), Japan (protocol ID C000000416), on 1 June 2006. Details are available at the following address: https://center.umin.ac.jp/cgi-open-bin/ctr/ctr.cgi?function=brows&action=brows&type=summary&reptno=R000000504&language=E.

Conflict of interest statement

Yasuo Ohashi received payments for consultation and lectures from Taiho Pharmaceutical Co., Ltd.

References