Efficacy of S-1 in Patients with Capecitabine-resistant Breast Cancer–Japan Breast Cancer Research Network (JBCRN) 04-1 Trial

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Abstract. Background: S-1 is an orally administered fluorinated pyrimidine with high activity in metastatic breast carcinoma (MBC) and in chemotherapy-pretreated metastatic breast carcinoma. Patients and Methods: Forty patients with MBC who did not respond to capecitabine-based chemo-therapy and then received S-1 were identified from our data base of records between 2006 and 2008. The clinico-pathological data and outcomes of these patients were then reviewed. Results: The overall response rate was 27.8%. The median survival was 19.2 months, and the median time to disease progression was 6.2 months. The most common treatment-related adverse events (all grades) were hand-foot syndrome (15%), nausea (15%), vomiting (7.5%), disorder of taste (7.5%), and diarrhea (5%). However, the majority were mild to moderate in intensity, and only one patient experienced grade 3 (according to the National Cancer Institute of Canada Common Toxicity criteria) adverse events. Myelosuppression and alopecia were rare, and there were no reported treatment-related deaths. Conclusion: The results of the current study demonstrate that S-1 is an effective and well-tolerated treatment in patients with capecitabine-resistant MBC. In addition, it is a convenient, orally administered drug, which makes it an attractive agent for use in outpatient treatment.

Breast carcinoma is the most frequent neoplasia in the U.S., and Europe, and even in Japan, and it is the most common cause of cancer mortality in this population (1). Approximately 40%-45% of all patients with breast cancer will develop metastasis, and the mean survival time from diagnosis of recurrence for these patients is 18 to 30 months. Therefore, the treatment of patients with metastatic breast cancer (MBC) aims to prolong survival while relieving symptoms and maintaining a good quality of life (QOL) (1-3).

Capecitabine is an orally administered fluoropyrimidine that has been reported to be effective in MBC patients. Capecitabine as a single agent produced an overall response rate (RR) of 29% and a median time to disease progression of 4.6 months in large phase II trials involving taxane-pretreated MBC patients (4-6). The convenient oral delivery of capecitabine causes mild gastrointestinal toxicity and myelosuppression without hair loss. The major toxicity of capecitabine is the hand-foot syndrome (HFS). The majority of cases are grade 1 or 2, but grade 3 HFS has also been reported in 10-24% of patients receiving capecitabine at the registered dose in phase II and III trials (7-10). Since capecitabine can sustain the QOL of MBC patients, it has been widely used as a third-line or subsequent chemotherapy regimen for heavily treated patients.

On the other hand, S-1 is another orally administered fluorinated pyrimidine that has been reported to be a well-tolerated and active agent against solid tumors. In a phase II study of S-1, the RR was 41.7% and the median survival time was 872 days among taxane-pretreated patients with MBC. Therefore, S-1 has been approved for MBC patients in Japan (11, 12).
However, there is no clinical data on the activity of S-1 in capecitabine-pretreated patients with MBC. Here, we evaluated the efficacy and side-effects of S-1 in patients with capecitabine-resistant MBC retrospectively.

Patients and Methods

A retrospective, multicenter study was conducted. Forty patients with MBC who were resistant to capecitabine-based chemotherapy, received S-1 between January 2006 and December 2008 at six centers. Resistance to capecitabine was defined as either disease progression during treatment, failure to achieve disease regression after at least four courses, or rapid recurrence after the completion of therapy. The best response to S-1 for each patient was assessed according to the WHO criteria (13). The patient population was identified from a database of the Japan Breast Cancer Research Network (JBCRN). The patients with HER2-positive cancer (HER2 gene was amplified two-fold or greater in fluorescence in situ hybridization) were excluded.

Treatment plan. S-1 was given orally twice daily for 28 days, followed by 14 days rest. Three dosage levels of S-1 were defined according to body surface area (BSA) as follows: BSA of less than 1.25 m²: 40 mg twice daily; BSA of 1.25 to 1.5 m²: 50 mg twice daily; and BSA of more than 1.5 m²: 60 mg twice daily. S-1 was temporarily discontinued, and the same dose was retried when a patient experienced grade 2 nonhematological toxicities, grade 3 thrombocytopenia, or uncomplicated grade 4 neutropenia. If the toxicity recurred or grade 3 nonhematological toxicities, grade 4 thrombocytopenia, or febrile neutropenia occurred, S-1 was interrupted until the toxicity subsided to grade 1 or less. The BSA-adjusted S-1 dose was then reduced from 120 to 100 mg per day, from 100 to 80 mg per day, or from 80 to 50 mg per day. The treatment was continued until the occurrence of disease progression, unacceptable toxicities, or the patient refused to continue. In the case of grade 2 or worse toxicity, S-1 administration was interrupted and not resumed until the toxicity had resolved or improved to grade 1.

Evaluation of efficacy and safety. Responses were assessed according to the Response Evaluation Criteria in Solid Tumors guidelines. Complete response (CR) was defined as the disappearance of all known lesions for at least four weeks. Partial response (PR) was defined as a reduction of the sum of all measurable lesions by at least 30%. Progressive disease (PD) was defined as an increase in the sum of all measurable lesions by greater than 20% or as the appearance of a new lesion. Stable disease (SD) was defined as neither CR, PR, nor PD. The objective response rate (ORR) was defined as the sum of the CR and PR rates. The clinical benefit rate (CBR) was defined as the sum of the CR and PR rates. All adverse events and laboratory parameters were graded according to the National Cancer Institute, Common Toxicity Criteria, version 3.0. The time to progression (TTP) was calculated from the day of commencement of S-1 administration until the day of documented progression. Overall survival (OS) was calculated from the start date of S-1 treatment to the date of death from any cause. TTP and OS were analyzed using the Kaplan–Meier estimates.

Results

Patient characteristics. The characteristics of the present study population are presented in Table I. The median age was 50 (range: 34-78) years. The Eastern Cooperative Oncology Group (ECOG) performance statuses of the patients were all ≤3. The patients were pretreated with anthracycline and taxane (20%), taxane (paclitaxel or docetaxel) (10%), and CMF (20%). The median number of metastatic sites was 2 (range: 1-5). The sites of metastatic disease were the bone and/or soft tissue in 26 patients (65%) and visceral sites in 16 patients (40%).

Efficacy. The patients were evaluable for response and toxicity. Out of 40 patients, the response was assessable in 36. Ten patients (27.8%) achieved a partial response, 9 patients had stable disease, and 17 patients had progressive disease. Among the 10 patients who showed a partial response during treatment with S-1, six patients had received prior chemotherapy, and four patients had received no prior chemotherapy (Table II). In addition, among the same patients, three patients were hormone receptor negative, and seven patients were hormone receptor positive (Table III). The antitumor effect on each metastatic lesion was also evaluated. All patients had more than one metastatic lesion. The total numbers of metastatic foci were as follows: bone: 10, lung: 8, liver: 8, lymph nodes: 10, and skin: 6. A PR was observed in 2 of the lung foci, 4 of the liver foci, and 4 of the lymph node foci (Table IV).
The median time to PD was 186 (range: 130-335) days. The median OS from the start of S-1 treatment was 576 (range: 366-740) days, and six patients (17%) were still alive at the last follow-up. Those patients who showed a partial response during treatment with S-1 had a longer OS than those who did not respond to this treatment (SD+PD) (median OS: 630 days vs. 408 days, log-rank p<0.05) (Figure 1).

Safety. The most common treatment-related adverse events were grade 1/2 in intensity (Table V). Common toxicities were HFS (15%), nausea (15%), disorder of taste (7.5%), vomiting (7.5%), and diarrhea (5%). No grade 3 HFS was seen. Seven patients experienced a S-1-related gastrointestinal disorder and among them, they required dose modifications in 3 patients and the treatment was discontinued in 4 patients.

Discussion

The results of this multicenter retrospective study suggest that S-1 is highly active and well-tolerated among women with MBS who failed capecitabine-based chemotherapy. S-1 chemotherapy produced a 27.8% RR. The median TTP was 186 days and OS was 576 days. The results presented here are better than those recently reported (14, 15). In previous studies, S-1 demonstrated 3% ORR and 20% CBR in patients who were heavily pretreated with anthracycline, taxane, and capecitabine. The median of TTF was 2.8 months. This discrepancy is probably due to the fact that 18 patients had not received other chemotherapy prior to S1, the median order of S-1 administration was second-line (most of the patients received S-1 chemotherapy as their second treatment), and most of the patients had two metastatic sites in the present study.
On the contrary, in the current study, the majority of adverse events were mild to moderate in intensity and confirm the results of the previous studies in a similar patient population. Grade 3 toxicity was rare. Acute toxicities were quite mild and manageable. Gastrointestinal side-effects and HFS were common and was managed with S-1 dose modification. Furthermore, the toxicity profiles of S-1 and capecitabine seem to be different (14-16). S-1 is a fluoropyrimidine that consists of 1-(2-tetrahydrofuryl)-5-fluorouracil (FTO), a pro-drug of 5-FU, and two other compounds, 5-chloro-2,4-dihydroxy-pyrimidine (CDHP, gimestat) and potassium oxonate (OXO; otastat), in molar proportions of 1:0.4:1. CDHP is an inhibitor of dihydropirimidine dehydrogenase (DPD), which degenerates 80% of 5-FU in the liver and maintains the 5-FU level above the minimal effective concentration (14-16). On the other hand, capecitabine is converted to 5'-DFUR either by human carboxylesterase (CE) or cytidine deaminase (CD), which is mainly localized in the human liver. 5'-DFUR is converted to the active form of 5-FU by thymidine phosphorylase (dThdPase) in human tumors (14-16). Low CE and CD activity levels are thought to protect the digestive wall and skin from capecitabine toxicity (14-16). Interestingly, 6 of the 40 patients (15.0%) who received S-1 developed HFS, in comparison to 20 of the 40 patients (50.0%) who had received capecitabine (data not shown). Therefore, the toxicity of S-1 was mild, and S-1 is considered to be a feasible chemotherapy in MBC patients who have previously been treated with capecitabine.

Moreover, since the antitumor activity of capecitabine might be relatively low in tumor cells with high DPD levels, an evaluation of the efficacy of S-1 after the occurrence of progression during capecitabine treatment or in tumors with high DPD expression levels is warranted (14). Thus, this may be the reason why S-1 was active in MBC patients who had previously been treated with capecitabine in the present study. S-1 and capecitabine can be used as oral monotherapies, which are easy to administer, and thus representing a significant advance for patient-oriented therapy and the maintenance of patient QOL (17). RR were comparable to or better than those seen with other therapies for patients with capecitabine-resistant MBC. While this study is both small and retrospective, there is no standard treatment for MBC pretreated with anthracycline, taxane, and capecitabine. Thus, S-1 could be considered the reference treatment in this setting based on its consistently high efficacy and good tolerability.

In conclusion, our study indicates that S-1 is safe, well-tolerated, and effective in patients with capecitabine-resistant breast cancer. Additional trials are needed to clarify the predictive factors for drug selection, to establish the clinical role of S-1, and to perform a direct comparison of S-1 and capecitabine monotherapy.

Acknowledgements

The Authors are indebted to Mr. Kagawa in Taiho Pharmaceutical Co., Ltd.

References


Received March 16, 2010
Revised June 14, 2010
Accepted June 21, 2010