Clinical Efficacy of S-1 in Pretreated Metastatic Breast Cancer Patients

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Background: S-1, an oral fluoropyrimidine carbamate, is an active and well-tolerated agent against solid cancer. However, the clinical efficacy of S-1 in patients with metastatic breast cancer has not been determined.

Methods: We retrospectively evaluated the efficacy of S-1 and identified its adverse effects in patients with metastatic breast cancer who had failed to respond to prior chemotherapy regimens. All the patients were treated at the National Cancer Center Hospital and received S-1 twice daily at a dose of 80 mg/m² for 4 weeks, followed by a 2-week rest interval.

Results: Between 2003 and 2007, 37 women with metastatic breast cancer received S-1 as a third line or greater chemotherapy regimen. All the patients had been previously treated with both anthracyclines and taxanes prior to S-1 chemotherapy. The median order of S-1 administration was as a fifth-line treatment, and 23 patients (62%) received S-1 as their final anticancer drug. One (3%) partial response and two (5%) stable diseases were observed. The median time to progression (TTP) was 84 days. Grade 2 adverse events, such as diarrhea, stomatitis and neutropenia occurred in 5 (16%), 1 (3%) and 1 (3%) patients, respectively.

Conclusions: S-1 was safety administered to heavily treated metastatic breast cancer patients with limited efficacy. Further evaluation of S-1 is necessary to elucidate its clinical role in breast cancer treatment.

Key words: S-1 — metastatic breast — cancer — chemotherapy

INTRODUCTION

Treatment of patients with metastatic breast cancer (MBC) aims to prolong survival while relieving symptoms and maintaining a good quality of life (QOL).

Capecitabine is an orally administered fluoropyrimidine that has been reported to be effective in both monotherapy and combination therapy regimens. 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 in taxane-pretreated MBC patients (1–3). 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 cancers. 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; S-1 has been approved in Japan as a salvage chemotherapy for patients who have received anthracycline and taxane (4,5). In addition, S-1 has been used mainly for the treatment of cancers of the digestive tract (6–8), and its efficacy is well known. However, the clinical usefulness of S-1 in patients with MBC is uncertain. Here, we describe the efficacy and tolerability of S-1 in a clinical setting.

PATIENTS AND METHODS

Patients

A retrospective analysis was performed on patients with MBC who received S-1 monotherapy between January 2003 and December 2006 at the National Cancer Center Hospital (NCCH). The patient population was identified from a
database at the NCCH. All the patients had received che-
motherapy previously. They were followed up until death or,
if they were still alive, to their last visit prior to March 2007.

The best response for each patient was assessed according
to the WHO criteria (8). A complete response (CR) was
declared as the disappearance of all clinical and radiographic
evidence during two observations performed at least 4 weeks
apart. A partial response (PR) was defined as a decrease of
30% or more in the sum of the products of the biperpendicular
diameters of measurable lesions. Stable disease (SD) was
declared as a <30% decrease and a <25% increase in the
sum of the products of the biperpendicular diameters of
measurable lesions and no appearance of new lesions; these
conditions had to be maintained for at least 12 weeks.
Progressive disease was defined as a greater than 25%
increase in the sum of the products of the biperpendicular
diameters of measurable lesions or the appearance of new
lesions. The clinical benefit rate was defined as the pro-
portion of patients who achieved either a CR, PR or SD. The
National Cancer Institute common toxicity criteria (9) were
adopted to determine toxicity.

TREATMENT
S-1 was administered orally twice daily (80 mg/m²) for 28
days followed by 14 days of rest. Treatment was continued
until disease progression, unacceptable adverse effects or
withdrawal of the patient’s consent. 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.

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 calcu-
lated from the start date of S-1 to the date of death from any
cause. TTP and OS were analysed according to the Kaplan–
Meier estimates.

RESULTS
Thirty-seven patients received S-1 as a greater than second-
line chemotherapy for MBC between January 2003 and
December 2006 at NCCH. Table 1 shows the patient’s characteris-
tics. The median age was 49 (28–70) years. The
Eastern Cooperative Oncology Group (ECOG) performance
status of the patients were all ≤2. The sites of metastatic
disease were the bone and/or soft tissue in only six patients
(16%) and involved visceral sites in 31 patients (84%).
Table 2 shows the chemotherapy regimens that were admi-
nistered prior to S-1. The median number of chemotherapy
regimens used before the administration of S-1 including
adjuvant and neoadjuvant treatments, was 4, and 23 patients
(62%) received S-1 as their final chemotherapy regimen. All
the patients had previously received both anthracyclines and
taxanes, 13 patients (35%) had received vinorelbine and

11 patients (30%) had received oral 5FU-derivatives prior
to the administration of S-1. All the patients who had
responded to treatment had exhibited adequate progression-
free intervals from the prior taxane administration until the
subsequent taxane administration. Three patients received the
same taxane regimen twice, once as adjuvant chemotherapy
and the second time in combination with Trastuzumab
after recurrence. Prior oral 5FU-derivatives included in other
regimens were CMF (five patients), UFT (five patients),
5’DFUR (five patients) and CPT-11 (one patient). Sixteen
patients (43%) with ER-positive diseases had received
hormone therapy, and 13 patients (35%) with HER2-positive
diseases had received Trastuzumab as a monotherapy or in
combination with taxane or vinorelbine.

Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. of patients</th>
<th>% of patients</th>
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<tbody>
<tr>
<td>Median age (years; range)</td>
<td>49 (28–70)</td>
<td></td>
</tr>
<tr>
<td>Metastatic sites involved</td>
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<td></td>
</tr>
<tr>
<td>Bone/Soft tissue</td>
<td>6</td>
<td>16</td>
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<tr>
<td>Visceral</td>
<td>31</td>
<td>84</td>
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<tr>
<td>Oestrogen receptor</td>
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<td></td>
</tr>
<tr>
<td>Positive</td>
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<td>43</td>
</tr>
<tr>
<td>Negative</td>
<td>21</td>
<td>57</td>
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<tr>
<td>Progesteren receptor</td>
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<tr>
<td>Positive</td>
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<td>46</td>
</tr>
<tr>
<td>Negative</td>
<td>20</td>
<td>54</td>
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<td>HER2/neu status</td>
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<td></td>
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<tr>
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<td>35</td>
</tr>
<tr>
<td>Negative</td>
<td>24</td>
<td>65</td>
</tr>
</tbody>
</table>

Table 2. Prior chemotherapy

<table>
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<th>Prior chemotherapy</th>
<th>No. of patients (n = 37)</th>
<th>% of patients</th>
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</thead>
<tbody>
<tr>
<td>Anthracycline</td>
<td>37</td>
<td>100</td>
</tr>
<tr>
<td>Taxane</td>
<td>37</td>
<td>100</td>
</tr>
<tr>
<td>Vinorelbine</td>
<td>13</td>
<td>35</td>
</tr>
<tr>
<td>Capecitabine</td>
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<td>3</td>
</tr>
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</table>

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The median number of administration days was 70 (6–415 days). The RR was 3%, with no cCR and 3% (1/37) PR. The overall clinical benefit rate (CR, PR and SD for more than 6 months) was 8% (3/37). The median TTP was 84 days (range, 6–415) (Fig. 1; note that a colour version of this figure is available as supplementary data at http://www.jjco.oxfordjournals.org). The median OS from the start of S-1 treatment was 284 days (range, 14–1511), and six patients (16%) were still alive at the last follow-up. Nine patients (24%) received S-1 for more than 100 days. Six out of these nine patients had visceral involvement. Two out of seven patients had oestrogen receptor-positive diseases and four of them were HER2-positive.

Overall, S-1 was well tolerated. Table 3 shows the adverse events in response to S-1 chemotherapy. Toxicities of Grade 3 or more were not reported. The most common toxicities arising from S-1 administration were diarrhea (33%) and nausea (30%). Most of the adverse events were Grade 1, and none of the S-1-related adverse events were fatal. The most frequent reasons for treatment discontinuation were disease progression (30 patients, 81%) and adverse event (seven patients, 19%). The adverse events that were encountered were Grade 2 diarrhea (five cases), Grade 2 stomatitis (one case) and Grade 2 neutropenic fever (one case).

### DISCUSSION

The number of patients with MBC who have been pretreated with anthracyclines and/or taxanes are increasing. However, the optimal chemotherapy for patients with MBC who have been pretreated with both anthracyclines and taxanes has not been determined. These patients require palliative therapy that offers a chance of prolonging life with minimal toxicity according to the antitumor response and the alleviation of tumor-related symptoms.

In this study, S-1 chemotherapy produced a 3% RR and an 8% rate of clinical benefit in previously treated patients with MBC who were refractory to both anthracyclines and taxanes. The median TTP was 84 days, and 24% of the patients received S-1 for more than 100 days. These results were worse than those reported in clinical trials. This discrepancy is probably because 11 patients had received other 5FU-derivatives prior to S1, the median order of S-1 administration was fifth line (most of the patients received S-1 chemotherapy as their final treatment), and most of the patients had multiple metastatic sites (84% had visceral metastases).

The toxicity of S-1, however, was mild in these heavily treated patients, and S-1 is considered to be a feasible palliative chemotherapy in heavily treated MBC patients.

Several oral 5FU-derivatives have been used to treat MBC, but only S-1 and capecitabine have been tested in taxane-refractory MBC patients (10). The treatments were administered based upon physicians’ decisions, but the reason why S-1, and not capecitabine, was selected in this study population is unclear. 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-dihydroxypyrimidine (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 a minimal effective concentration level. On the other hand, capecitabine is converted to 5’-DFUR either by human carboxyesterase (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. Low CE and CD activity levels are thought to protect the digestive wall and bone marrow from capecitabine toxicity.

Clinically, the reported RRs of capecitabine and S-1 in taxane-pretreated MBC patients are similar, but the toxicity profile seems to be different. Relatively severe diarrhea (14%, Grade 3) and hand-foot syndrome (10%, Grade 3) were observed in a phase II study for capecitabine (2,3), whereas the incidence of Grade 3 or severe diarrhea was relatively low (0.9%) and no hand-foot syndrome was observed in a phase II study of S-1 for MBC (4). A direct comparison of capecitabine and S-1 monotherapy is surely necessary, and 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 progression with...
capecitabine or in tumors with high DPD expression levels is warranted.

Moreover, while the efficacy of capecitabine in combination therapy with other cytotoxics (11–16) or as first-line chemotherapy (17) has already been reported, few evidence of the efficacy of S-1 in combination therapy or first-line chemotherapy is available (18,19). The efficacy and safety of S-1 in combination with molecular-targeted drugs, such as antibodies and small molecule tyrosine kinase inhibitors, are also unknown. Further studies are thus required to elucidate the clinical role of S-1 in the management of breast cancer patients.

Conflict of interest statement
None declared.

References