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Pilot Study of Irinotecan and S-1 (IRIS) for Advanced and Metastatic Breast Cancer

TOSHIHIRO TANAKA[1], MAKI TANAKA[2], HIDEMI FURUSAWA[3], YOSHIHIKO KAMADA[4], YOSHIAKI SAGARA[5], KEISEI ANAN[6], KYUICHIROU MIYARA[7], YUICHIROU KAI[8], TATSUYA UGA[9], KAZUO TAMURA[1], SHOSHU MITSUYAMA[6] and KBC-SG (Kyushu Breast Cancer-Study Group)

[1]Division of Oncology, Hematology, and Infectious Diseases, Department of Internal Medicine, Fukuoka University, Fukuoka, Japan;
[2]Department of Surgery, JCHO Kurume General Hospital, Fukuoka, Japan;
[3]Department of Breast Surgical Oncology, Breastopia Namba Hospital, Miyazaki, Japan;
[4]Department of Surgery, Nahanishi Clinic, Okinawa, Japan;
[5]Department of Radiology, Sagara Hospital, Kagoshima, Japan;
[6]Department of Surgery, Kitakyushu Municipal Medical Center, Fukuoka, Japan;
[7]Department of Surgery, Miyara Clinic, Okinawa, Japan;
[8]Department of Surgery, Ueo Breast Surgery Clinic, Oita, Japan;
[9]Department of Surgery, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan

Abstract. *Background/Aim: Irinotecan is rarely used on the metastatic breast cancer (MBC) setting. S-1 is an oral mixture of tegafur, gimeracil and oteracil. We conducted this pilot study to assess efficacy and safty of chemotherapy with combined irinotecan and S-1 (IRIS). Patients and Methods: Irinotecan was given intravenously at 80 mg/m^2 on days 1 and 8 and S-1 was given orally at 80-120 mg/day depending on body surface area for 2 weeks, repeating the cycle every 3 weeks. Results: Twenty-two patients were enrolled in the study. Median age was 50.5 years (range=26-72). Nineteen patients were evaluable for response. Median overall survival and progression-free survival were 672 days (95% CI=420-967) and 166 days (95% CI=76-814), respectively. Conclusion: The IRIS regimen has an acceptable safety profile and modest efficacy against MBC in patients previously heavily treated with chemotherapy. This regimen has potential to treat MBC.*

Patients with advanced and metastatic breast cancer (MBC) are not usually curable and are instead treated with various regimens to control symptoms when the disease recurs and to prolong survival time (1, 2). It is not uncommon to see such patients who have already received treatment with more than five regimens and physicians are stuck with few anticancer agents left to use although patients are still young with good performance status (PS).

Irinotecan, a topoisomerase-1 inhibitor, has a different mechanism of action from drugs (3) that are frequently used in breast cancer such as anthracyclines and taxanes and has a modest anti-tumor activity (4-6). However, it has never been studied extensively in breast cancer. S-1 is an oral fluorouracil derivative widely used to treat solid tumors in Japan. S-1 is based on a 5-FU prodrug, tegafur, and two biochemical modulators gimeracil (CDHP), and oteracil (oxonic acid), in a molar ratio of 1: 0.4: 1.8 (7, 8). Tegafur is converted to 5-FU by hepatic cytochrome P-450s and cytosolic enzymes, and CDHP is a competitive, reversible DPD (dihydropyrimidine dehydrogenase) inhibitor that prolongs the half-life of 5-FU (9). Oxonic acid is a pyrimidine phosphoribosyl-transferase inhibitor that is intended to mitigate 5-FU-related GI toxicity by preventing the phosphorylation of 5-FU in the digestive tract.

It has been reported that S-1 may be effective for patients with high DPD activity but may not be effective in thymidylate synthase (TS) elevated cases. However, irinotecan/S-1 combination therapy (IRIS) can target both high-DPD cases and unexpected TS high-value cases at the same time in daily practice where enzyme activity cannot be measured (10, 11). In addition, the toxicities of IRIS have already been reported in gastric cancer and colon cancer, and it is considered to be highly tolerable. There are also many

Correspondence to: Toshihiro Tanaka, MD, Ph.D, Division of Oncology, Hematology, and Infectious Diseases, Department of Internal Medicine, Fukuoka University 7-45-1 Nanakuma, Jonan-ku, Fukuoka, 814-0180, Japan. Tel: +81 928011011 (Ext. 3345), Fax: +81 928655656, e-mail: totanaka@fukuoka-u.ac.jp

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opportunities to administer microtubule-related drugs such as paclitaxel, docetaxel, vinorelbine or eribulin following treatment with an anthracycline-containing regimen. These agents act as a mechanism to promote or inhibit the polymerization of tubulin, and although the IRIS regimen does not cause cross-resistance to tubulin-modulating anticancer drugs, they are considered to be one of the important treatment options to target different action preferences. We report here the results of a pilot study of an IRIS regimen to assess the safety and tumor response in patients with MBC.

Patients and Methods

Study design. This was an open-label, non-randomized, multicenter study. The step I portion was designed to determine the safety, tolerability and recommended dose in patients with MBC. The step II portion was designed to evaluate the efficacy and safety of the recommended dose identified in step I. The primary endpoint was determination of safety in step 1 and tumor response in step 2. Secondary endpoints were progression-free survival (PFS) and overall survival (OS) in patients who could be evaluated for tumor response in both steps 1 and 2. The study was carried out in accordance with the Declaration of Helsinki and Ordinance on Good Clinical Practice. The protocol was reviewed and approved by the institutional review board of each participating center, and written informed consent was obtained from all patients. Patients with histologically-proven MBC who had been previously treated with anthracyclines and taxanes were enrolled between February 2007 and January 2010.

Patients. Patients were eligible for this study if they fulfilled the following eligibility criteria: age 20-75, PS of 0-2 by ECOG criteria and acceptable bone marrow, liver and kidney functions, *i.e.* white cell counts ≥3,000/μl, neutrophil counts ≥1,500/μl, platelet counts ≥100,000/μl, hemoglobin 9.0 g/dl, serum total bilirubin levels ≤2.0 mg/dl, serum values of aspartate transaminase, alanine transferase and alkaline phosphatase ≤2.5 times the institutional upper normal limits, and serum creatinine levels ≤1.5 mg/dl. They must be free of active infection or grave disorders which made the primary care physician feel they were unsuitable for the study. The main exclusion criteria were prior treatment with irinotecan or S-1 and significant comorbid conditions; pregnancy; previous blood transfusion or treatment with granulocyte colony-stimulating factor (G-CSF) within 7 days prior to study entry; history of cancers within 5 years; psychiatric diseases; brain tumors or brain metastases; ineligible for this protocol according to the attending physician's discretion. This study was approved by the local Ethics Committee at each Institution, and patients were informed of the investigational nature of the study and provided their written informed consent before registration in the study.

Drug administration. In step 1, the safety profile of the regimen was determined in 6 patients, and in step 2, tumor response was evaluated if the safety profile in step 1 was considered acceptable. Irinotecan was given intravenously at a dose of 80 mg/m^2 by 90 min infusion on days 1 and 8 and S-1 orally at 80-120 mg/day depending on body surface area for 2 weeks. Treatment was repeated every 21 days. Prophylactic anti-emetics, 5-HT$_3$ receptor antagonist and 8 mg of dexamethasone, were given 30 min before the administration of irinotecan. The use of G-CSF was permitted if a patient experienced G4 leukopenia, neutropenia or febrile neutropenia (FN). The dose of irinotecan in subsequent cycles was reduced by 65 mg/m^2 if any of the following toxicities or conditions was observed: G4 neutropenia that lasted more than 7 days; G3 or G4 FN that lasted more than 72 h; G3 or G4 thrombocytopenia, diarrhea, non-hematological toxicity except for nausea, vomiting and asthenia; serum creatinine >1.5 mg/dl; an 8 day interruption of drug administration. A patient was removed from this study when disease progression and/or G4 non-hematological toxicity were experienced or due to the patient's refusal to continue.

Dose-limiting toxicity criteria. Dose-limiting toxicity (DLT) was defined as follows: G4 neutropenia lasting more than 7 days; G3 FN for 3 days or more; G3 thrombocytopenia; G3 diarrhea; G3 or G4 non-hematological toxicity except nausea, vomiting, anorexia and alopecia; delay of more than 8 days in day 8 or initiating the second cycle of therapy; serum creatinine exceeds 1.5 mg/dl. To determine the maximum tolerated dose (MTD), only DLTs occurring during the first cycle of therapy were considered. Six patients were entered at step 1. The MTD was defined as the dose level that resulted in at least two of six patients developing DLTs.

Safety and response criteria. The safety profiles were evaluated according to Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 and tumor response was determined by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0. An objective response rate (ORR) is the sum of patients with a complete response (CR) + partial response (PR). The clinical benefit rate (CBR) is the sum of CR + PR, together with stable disease (SD). Laboratory variables in complete blood cell counts, biochemistry and urinalysis were assessed on days 1, 8 and 15 during the first course, and on day 1 from the second through to the sixth course. CT scans were repeated to evaluate lesions every two months, and tumor markers were measured at the same time. CR and PR required subsequent confirmation of response after an interval of at least 4 weeks. The OS was defined as the time from registration to any death. The PFS was defined as the time from the date of registration to the first confirmation of disease progression or death from any cause, and it was censored at the last tumor assessment if a patient withdrew before progression.

Statistical analysis. The efficacy data were assessed in the eligible population who received at least one dose of the study drug and had evaluable efficacy data. The final data cut-off date was September 2, 2010. PFS was defined from the registration date to disease progression or death from any cause. OS was defined from the registration date to death from any cause. PFS and OS (estimated median with 95% CI) were calculated using Kaplan-Meier methods. The safety data were assessed in the eligible population who received at least one dose of the study drug and are presented in a descriptive manner. Probability values of $p<0.05$ were considered statistically significant.

Results

Patient characteristics. A total of 22 patients were registered for the study. The baseline characteristics of patients are summarized in Table I. The median age was

Table I. *Patient characteristics*.

	Step 1 (n=6)	Step 2 (n=16)	Step 1+2 (n=22)
Median age (range)	49.5 (26-64)	54 (39-72)	50.5 (26-72)
PS (ECOG) 0/1	5/1	14/2	19/3
HR status			
Positive	5 (83.3)	8 (50.0)	13 (59.1)
Negative	1 (16.7)	8 (50.0)	9 (40.9)
HER2 status			
(IHC3+ or 2+ and FISH+)			
Positive	0 (0.0)	1 (6.3)	1 (4.5)
Negative	5 (83.3)	15 (93.7)	20 (90.9)
Unknown	1 (16.7)	0	1 (4.5)
No. of Metastases			
1/2/3/4 or more	4/1/1/0	4/4/5/3	8/5/6/3
Metastatic site			
Local	0	1	1
Skin	1	2	3
Lymph node	1	8	9
Bone	1	6	7
Lung/Pleura	4	11	15
Liver	2	9	11
Prior chemotherapy regimens			
Anthracyclines	6 (100.0)	16 (100.0)	22 (100.0)
Taxanes	6 (100.0)	16 (100.0)	22 (100.0)
Cyclophosphamide	6 (100.0)	16 (100.0)	22 (100.0)
Fluoropyrimidine	4 (66.7)	14 (87.5)	18 (81.8)
Vinorelbine	0 (0.0)	8 (50.0)	8 (36.4)
Trastuzumab	0 (0.0)	1 (6.3)	1 (4.5)
Methotrexate	0 (0.0)	2 (12.5)	2 (13.6)
Endocrine therapy	5 (83.3)	8 (50.0)	13 (59.1)

PS: Performance status; ECOG: Eastern Cooperative Oncology Group; HER2: human epidermal growth factor receptor 2; HR: hormone receptor; IHC: immunohistochemistry; FISH: fluorescence *in situ* hybridization.

50.5 years (range=26-72 years). PS was 0 and 1 in 19 and 3 patients, respectively. Three patients had stage IV disease and 19 patients had postoperative recurrent disease. Pathology-based subtype distributions were as follows: 13 (59.1%) HR+/HER2–, 0 (0.0%) HR+/HER2+, 1 (4.5%) HER2 type, and 8 (36.4%) triple negative (TN). The most common metastatic sites were lungs: 15 (68.2%), liver: 11 (50.0%), lymph nodes: nine (40.9%), bone: seven (31.8%), skin: three (13.6%) and local: one (4.5%). The median number of prior chemotherapy regimens including adjuvant therapy was three (range=2-10), wherein all patients had been previously treated with anthracycline- and taxane- and cyclophosphamide-based agents. Endocrine therapy was administered to 13 patients and the median number of regimens was two (range=1-4). For one patient with HER2 positivity, trastuzumab and an anticancer drug were used in combination. All patients received at least one cycle of treatment.

Table II. *The state of implementation of chemotherapy*.

	Median (range)
Cycles	5.5 (1-8)
Median DI	
Irinotecan	40.7 (23.3-53.3)
S-1	402.1 (248.3-538.3)
Relative DI (%)	
Irinotecan	76.3% (46.9-100.0)
S-1	80.7% (53.2-100.0)

DI: Dose intensity (mg/m^2/week).

Dose determination in step 1. Six patients were enrolled in step 1. G3 fatigue and vomiting were observed in one patient, G3/4 neutropenia in four and G3 anemia in one. The MTD was not reached, and we determined that an irinotecan dose of 80 mg/m^2 with an S-1 dose of 80 mg/m^2 was suitable. The safety profile in step 1 was deemed acceptable to move on to step 2 according to predefined criteria.

IRIS therapy in step 2. A total of 106 cycles of IRIS therapy were administered, with a median of 5.5 cycles (range=1-8 courses). The median dose intensity (DI) of irinotecan and S-1 was 40.7 mg/m^2/week (range=3.3-53.3) and 402.1 mg/m^2/week (range=248.3-538.3 mg/m^2/week), respectively, which corresponds to RDIs of 76.3% (range=46.9-100.0) and 80.7% (range=53.2-100.0), respectively (Table II).

Efficacy. The median observation period was 382 days (range=70-1,115 days). Nineteen patients were evaluated for responses as shown in Table III, but three patients were not evaluable. PR was obtained in five patients (26.3%), including in one patient who had a history of five previous treatments. In addition, SD was obtained in eight patients (42.1%), among whom two patients experienced SD for longer than 6 months. The CBR for patients who underwent two to four regimens were 68.4%. Kaplan–Meier survival curves for median OS and PFS are shown in Figure 1a and b). The median OS and PFS of IRIS therapy was 672 days (95% CI=420-967) and 166 days (95% CI=76-814), respectively. There were 18 patients who discontinued the protocol within the observation period. Reasons for the discontinuation were as follows (Table IV): PD in 10 (55.6%) patients, offering withdrawal from this study to patients for reasons related to adverse events in three (16.7%) patients and non-adverse events in two (11.1%) patients. Interruption of the administration due to delays in recovery of neutropenia occurred in only three (16.7%) patients.

Safety. The overall incidences of hematological and nonhematological toxicities are listed in Table V. G3/4 neutropenia was the most common adverse event and

Table III. *Overall response*.

Response	No. of patients (%)
CR	0 (0.0)
PR	5 (26.3)
SD	8 (42.1)
PD	6 (31.6)
CR+PR	5 (26.3)
CR+PR+SD	13 (68.4)

Treated cycles; median 5.5 (1-8), n=19. CR: Complete response; PR: partial response; SD: stable disease; PD: progressive disease.

occurred in 54.5% of all the courses, but no patient had FN. Major non-hematological toxicities were fatigue, anorexia, diarrhea, nausea, liver dysfunction, constipation and alopecia. G3 non-hematological toxicities were diarrhea (13.6%), fatigue (9.1%), anorexia (4.5%) and vomiting (4.5%). There were no serious unexpected adverse events and no treatment-related deaths.

Discussion

Numerous randomized studies have shown that second-line and subsequent lines of chemotherapy are effective in patients with MBC who developed resistance to first-line chemotherapy (12). Irinotecan is an anticancer drug whose utility and safety against various cancers, such as colon and lung cancers, have been proved; thus, its indications are expanding. However, very few studies have reported the use of irinotecan against breast cancer. In terms of irinotecan monotherapy against MBC in a second- and subsequent-line chemotherapy setting, a randomized phase II study (n=103) took place between a weekly administration group [100 mg/m^2; repeating a 6-week cycle (weekly administration over 4 weeks followed by 2 weeks off)] and an every 3-week administration group (240 mg/m^2) (13). The response rates, response duration, and OS of the weekly group *vs*. every 3-week group were 23% *vs*. 14%, 4.9 months *vs*. 4.2 months, and 9.7 months *vs*. 8.6 months, respectively, indicating that the efficacy of the weekly group was superior to that of the every 3-week group. Regarding safety, G3/4 diarrhea was observed in 17% of patients in the weekly group and 12% in the every 3-week group. Neutropenia was observed in 29% of patients in the weekly group and 36% in the every 3-week group, indicating a low incidence of neutropenia in the weekly group.

Two studies on IRIS therapy against MBC have been reported from Japan in patients who were previously treated with anthracyclines and taxanes. The doses and schedules of these studies were slightly different from those used in the present study. In a single-institutional phase II study for 34 patients, Otsuka *et al*. (14) used irinotecan (60 mg/m^2) on days 1, 8, and 15, and S-1 (80 mg/m^2/day) on days 3-7, 10-14, and 7-21, over a 4-week cycle. The response rate, median PFS, and OS were 47%, 14 months, and 26 months,

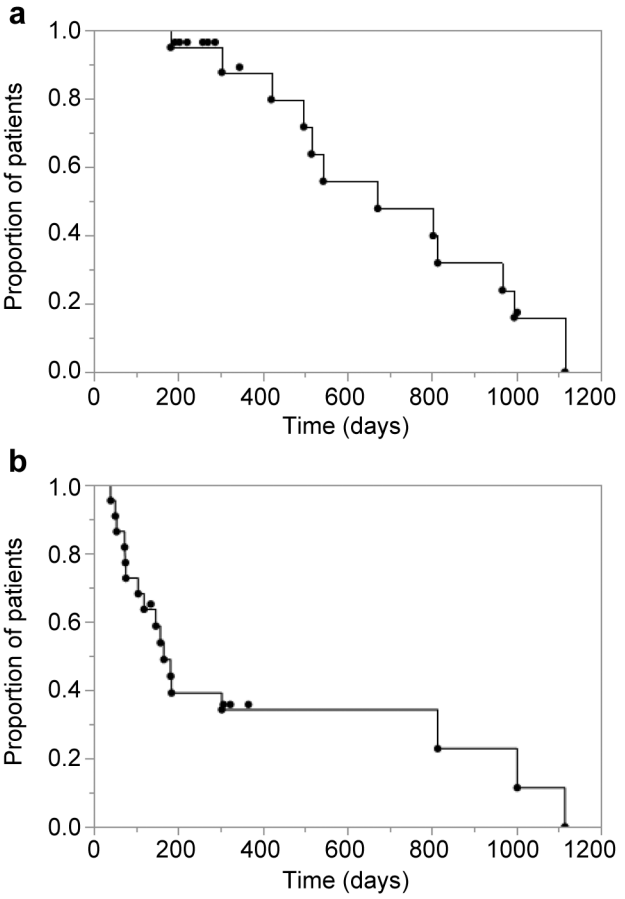

Figure 1. *Kaplan–Meier curves of overall survival (OS) (a) and progression-free survival (PFS) (b) in the overall patient population.*

Table IV. *Reasons for protocol*.

n=106 cycles	On schedule
Continuation	4 (18.2)
Discontinuation	18 (81.8)
Reasons	**n=18**
Progression	10 (55.6)
Grade 4 non-hematological toxicity	0 (0.0)
More than14 days delay due to hematological toxicity	3 (16.7)
Patient's request for reasons relating to toxicity	3 (16.7)
Patient's request for non-toxicity reasons	2 (11.1)

DI: Dose intensity (mg/m^2/week).

Table V. *Toxicities*.

Toxicity (n=22)	Grade 1	Grade 2	Grade 3	Grade 4	All grades	Grade 3/4
Hematologic toxicity						
Leukopenia	4 (18.2)	9 (40.9)	5 (22.7)	0 (0.0)	18 (81.8)	5 (22.7)
Neutropenia	1 (4.5)	1 (4.5)	9 (40.9)	3 (13.6)	14 (63.6)	12 (54.5)
Anemia	7 (31.8)	6 (27.3)	1 (4.5)	0 (0.0)	14 (63.6)	1 (4.5)
Thrombocytopenia	3 (13.6)	1 (4.5)	0 (0.0)	0 (0.0)	4 (18.2)	0 (0.0)
Febrile neutropenia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Non hematologic toxicity						
Fatigue	6 (27.3)	7 (31.8)	2 (9.1)	0 (0.0)	15 (68.2)	2 (9.1)
Diarrhea	4 (18.2)	5 (22.7)	3 (13.6)	0 (0.0)	12 (54.5)	3 (13.6)
Constipation	7 (31.8)	2 (9.1)	0 (0.0)	0 (0.0)	9 (40.9)	0 (0.0)
Anorexia	9 (40.9)	3 (13.6)	1 (4.5)	0 (0.0)	13 (59.1)	1 (4.5)
Nausea	10 (45.5)	2 (9.1)	0 (0.0)	0 (0.0)	12 (54.5)	0 (0.0)
Vomiting	1 (4.5)	2 (9.1)	1 (4.5)	0 (0.0)	4 (18.2)	1 (4.5)
Mucositis	2 (9.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (9.1)	0 (0.0)
Pigmentation	5 (22.7)	1 (4.5)	0 (0.0)	0 (0.0)	6 (27.3)	0 (0.0)
Rash	2 (9.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (9.1)	0 (0.0)
Skin reaction	1 (4.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.5)	0 (0.0)
Alopecia	6 (27.3)	2 (9.1)	0 (0.0)	0 (0.0)	8 (36.4)	0 (0.0)
Test value abnormality						
Bilirubin increased	1 (4.5)	1 (4.5)	0 (0.0)	0 (0.0)	2 (9.1)	0 (0.0)
ALT increased	8 (36.4)	1 (4.5)	0 (0.0)	0 (0.0)	9 (40.9)	0 (0.0)
ALP increased	8 (36.4)	0 (0.0)	0 (0.0)	0 (0.0)	8 (36.4)	0 (0.0)
AST increased	6 (27.3)	1 (4.5)	0 (0.0)	0 (0.0)	7 (31.8)	0 (0.0)
Creatinine increased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
BUN increased	1 (4.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.5)	0 (0.0)

respectively. The incidence rates of G3 or 4 neutropenia and diarrhea were 15% and 7.5%, respectively. Meanwhile Ishiguro *et al*. (15) conducted multi-institutional phase I/II studies in 37 patients. The recommended dose of irinotecan was set at 100 mg/m^2 based on the phase I portion. Irinotecan was administered on days 1 and 8, and S-1 (80 mg/m^2/day) was administered for 14 consecutive days, over a 3-week cycle. The efficacy and incidence of adverse events were examined with respect to *UGT1A1* polymorphisms. The response rates, median PFS, and OS of *UGT1A1 wt/wt vs. wt/mu* were 7% *vs*. 21%, 8 months *vs*. 12 months [hazard ratio (HR) 0.47, p=0.060], and 17 months *vs*. 23 months (HR=0.74, p=0.56), respectively. The median OS tended to be longer in heterozygous patients with *UGT1A1 wt/*6* and *wt/*28* than in those with *UGT1A1 wt/wt*. In addition, the median PFS was significantly prolonged (p=0.039) in patients whose median area under the curve of SN-38, an active metabolite of irinotecan, was larger. The incidence rate of diarrhea tended to be lower in the *UGT1A1 wt/wt* group than in the *wt/mu* group (25% *vs*. 46%). The overall efficacy was reported as follows: response rate, 14%; disease control rate, 31%; median PFS, 10 months; and median OS, 20 months. Comparing the present study and the two IRIS studies discussed above in terms of efficacy, although the median PFS of the present study was slightly shorter, the response rate, disease control rate, and median OS of this study were comparable to those studies. The incidence rates of G3 and G4 neutropenia tended to be higher in the present study than in the study of Otsuka *et al*. Although 16.7% of patients in the present study had to interrupt the treatment owing to hematotoxicity, none of the patients developed FN.

Only one clinical study compared S-1 with other drugs in a second- or subsequent-line treatment. That was capecitabine, which is also an oral pyrimidine fluoride (16). Although both these drugs showed comparable OS and PFS, their toxicological profiles were different, *i.e*., S-1 had a high incidence of gastrointestinal toxicities such as nausea, while capecitabine-treated patients developed hand-foot syndrome (HFS) at a higher frequency. IRIS therapy is a combination of drugs that cause similar gastrointestinal toxicities, but treatment discontinuation due to G4 non-hematological toxicity did not occur in this study. In contrast, when taxanes or eribulin are used over a prolonged period, HFS due to capecitabine may hamper the treatment.

The present study has some limitations. First, the number of registered patients was low. Only 22 patients enrolled within the registration period. Although the sample size was small, this study demonstrated that treatment with a combination of irinotecan 100 mg/m^2 on day 1, 8 and S-1 80 mg/m^2/day for 14 days can be conducted safely, with maintenance of high DI and

RDI. Second, we did not measure *UGT1A1* polymorphism to predict adverse reactions of irinotecan. This is because measurement of polymorphism was not commercially available in Japan in 2007 when the present study was started. Inter-individual differences in UGT activity may be one of the causes of interpersonal differences in adverse reactions of irinotecan. However, a consensus regarding dose setting based on polymorphism has not yet been reached in the oncology field. Therefore, information other than that of homozygous or double-heterozygous patients with respect to such as UGT1A1*6/*6, UGT1A1*28/*28 or UGT1A1*6/*28 is not useful in clinical practice.

In summary, we demonstrated that the IRIS regimen has an acceptable safety profile and modest efficacy against breast cancer in patients who have previously been heavily treated with chemotherapy including anthracyclines and taxanes for MBC. We believe the patients responded to the IRIS regimen because irinotecan has a different mechanism of action to other drugs commonly used for breast cancer and, when used in combination with S-1, it is possible to simultaneously target high-DPD value cases and unexpected TS high-value cases. IRIS therapy, however, frequently causes grade 3/4 neutropenia, and therefore, careful observation is necessary because it is feared that bone marrow function may have been impaired in patients who have been received chemotherapy for a long time. We conclude that this regimen has potential to treat breast cancer and can be used as an option in the late phase of treatment for MBC.

Conflicts of Interest

The Authors declare that no conflicts of interest exist with regard to the present study.

Authors' Contributions

All Authors have contributed to the study design and data collection. Toshihiro Tanaka wrote the manuscript. All other Authors interpretation and critically reviewed the manuscript. All Authors approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

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References

1 Pagani O, Senkus E, Wood W, Colleoni M, Cufer T, Kyriakides S, Costa A, Winer EP and Cardoso F: International guidelines for management of metastatic breast cancer: can metastatic breast cancer be cured? J Natl Cancer Inst *102*: 456-463, 2010. PMID: 20220104. DOI: 10.1093/jnci/djq029

2 Saghir N, Tfayli A, Hatoum HA, Nachef Z, Dinh P and Awada A: Treatment of metastatic breast cancer: state-of-the-art, subtypes and perspectives. Crit Rev Oncol Hematol *80*: 433-449, 2011. PMID: 21330148. DOI: 10.1016/j.critrevonc.2011.01.010

3 Shike M, Winawer SJ, Greenwald PH, Bloch A, Hill MJ and Swaroop SV: Primary prevention of colorectal cancer. The WHO Collaborating Centre for the Prevention of Colorectal Cancer. Bull World Health Organ *68*: 377-385, 1990. PMID: 2203551

4 Hortobagyi GN: Treatment of breast cancer. N Engl J Med 339: 974-984, 1998. PMID: 9753714. DOI: 10.1056/NEJM199810013391407

5 Valero V and Hortobagyi GN: Are Anthracycline-Taxane regimens the new standard of care in the treatment of metastatic breast cancer? J Clin Oncol *21*: 959-962, 2003. PMID: 12637456. DOI: 10.1200/JCO.2003.11.071

6 Bernard-Marty C, Cardoso F and Piccart MJ: Facts and controversies in systemic treatment of metastatic breast cancer. Oncologist *9*: 617-632, 2004. PMID: 15561806. DOI: 10.1634/theoncologist.9-6-617

7 Malet-Martino M and Martino R: Clinical studies of three oral prodrugs of 5-fluorouracil (capecitabine, UFT, S-1): a review. Oncologist *7*: 288-323, 2002. PMID: 12185293. DOI: 10.1634/theoncologist.7-4-288

8 Fujii T, Horiguchi J, Yanagita Y, Koibuchi Y, Ikeda F, Uchida N and Kimura M: Phase II Study of S-1 plus trastuzumab for HER2-positive metastatic breast cancer (GBCCSG-01). Anticancer Res *38*: 905-909, 2018. PMID: 29374719. DOI: 10.21873/anticanres.12301

9 Peters GJ: From 'targeted therapy' to targeted therapy. Anticancer Res *39*: 3341-3345, 2019. PMID: 31262854. DOI: 10.21873/anticanres.13476

10 Ichikawa W, Uetake H, Shirota Y, Yamada H, Nishi N, Nihei Z, Sugihara K and Hirayama R: Combination of dihydropyrimidine dehydrogenase and thymidylate synthase gene expressions in primary tumors as predictive parameters for the efficacy of fluoropyrimidine-based chemotherapy for metastatic colorectal cancer. Clin Cancer Res *9*: 786-791, 2003. PMID: 12576451.

11 Ichikawa W, Uetake H, Shirota Y, Yamada H, Takahashi T, Nihei Z, Sugihara K, Sasaki Y and Hirayama R: Both gene expression for orotate phosphoribosyltransferase and its ratio to dihydropyrimidine dehydrogenase influence outcome following fluoropyrimidine-based chemotherapy for metastatic colorectal cancer. Br J Cancer *89*: 1486-1492, 2003. PMID: 14562021. DOI: 10.1038/sj.bjc.6601335

12 Gianni L, Munzone E, Capri G, Villani F, Spreafico C, Tarenzi E, Fulfaro F, Caraceni A, Martini C, Laffranchi A, Valagussa P and Bonadonna G: Paclitaxel in metastatic breast cancer: a trial of two doses by a 3-hour infusion in patients with disease recurrence after prior therapy with anthracyclines. J Natl Cancer Inst *87*: 1169-1175, 1995. PMID: 7674322. DOI: 10.1093/jnci/87.15.1169

13 Perez EA, Hillman DW, Mailliard JA, Ingle JN, Ryan JM, Fitch TR, Rowland KM, Kardinal CG, Krook JE, Kugler JW and Dakhil SR: Randomized phase II study of two irinotecan schedules for patients with metastatic breast cancer refractory to an anthracycline, a taxane, or both. J Clin Oncol *22*: 2849-2855, 2004. PMID: 15254052. DOI: 10.1200/JCO.2004.10.047

14 Otsuka H, Fujii T, Toh U, Iwakuma N, Takahashi R, Mishima M, Takenaka M, Kakuma T, Tanaka M and Shirouzu K: Phase II clinical trial of metronomic chemotherapy with combined irinotecan and tegafur–gimeracil–oteracil potassium in metastatic and recurrent breast cancer. Breast Cancer *22*: 335-342, 2015. PMID: 23827973. DOI: 10.1007/s12282-013-0483-1

15 Ishiguro H, Saji S, Nomura S, Tanaka S, Ueno T, Onoue M, Iwata H, Yamanaka T, Sasaki Y and Toi M: A phase I/II pharmacokinetics/pharmacodynamics study of irinotecan combined with S−1 for recurrent/metastatic breast cancer in patients with selected UGT1A1 genotypes (the JBCRG-M01study). Cancer Med *6*: 2909-2917, 2017. PMID: 29131533. DOI: 10.1002/cam4.1258

16 Yamamoto D, Iwase S, Tsubota Y, Ariyoshi K, Kawaguchi T, Miyaji T, Sueoka N, Yamamoto C, Teramoto S, Odagiri H, Kitamura K, Nagumo Y and Yamaguchi T: Randomized study of orally administered fluorinated pyrimidines (capecitabine *versus* S-1) in women with metastatic or recurrent breast cancer: Japan Breast Cancer Research Network 05 Trial. Cancer Chemother Pharmacol *75*: 1183-1189, 2015. PMID: 25862350. DOI: 10.1007/s00280-015-2738-3

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