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Breast Cancer
DOI 10.1007/s12282-008-0073-9

ORIGINAL ARTICLE

Efficacy of S-1 in heavily pretreated patients with metastatic breast cancer: cross-resistance to capecitabine

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Received: 23 May 2008 / Accepted: 8 August 2008

Abstract
Background It is not clear what the optimal treatment of chemotherapy is for patients with heavily treated metastatic breast cancer (MBC). We have retrospectively examined the efficacy and safety of S-1 in patients with MBC who had been previously treated with anthracycline, taxane, and capecitabine.
Methods Patients with MBC who had been administered S-1, an oral modulated compound containing a fluoropyrimidine derivative, between November 2001 and June 2003 at the Cancer Institute Hospital were retrospectively reviewed. S-1 at a standard dose of 50 mg/body was administered twice daily for four weeks, followed by a two-week rest period. This was repeated every six weeks until disease progression or unacceptable toxicity.
Results Thirty-five patients were assessed. The patients were heavily pretreated with anthracycline (100%), taxane (paclitaxel or docetaxel) (100%), capecitabine (100%), vinorelbine (71%), and mitomycin (69%). Median follow-up time of patients was 9.6 months (range, 1.2–26.6). ORR was 3% (95% confidence interval: 0–9%), and CBR was 20% (95% confidence interval: 6–33%). Time to treatment failure was 2.8 months. Overall survival was 21.4 months. Grade 1 or 2 adverse events were observed in 17% and 13%, respectively. Grade 3 events occurred as anorexia (9%), nausea (9%), vomiting (9%), diarrhea (14%), fatigue (3%), and elevation of AST/ALT (3%). No grade 3 was seen as hand-foot syndrome. Neither grade 3 nor 4 was observed in bone marrow suppression.
Conclusions S-1 was fairly well tolerated, but demonstrated very limited activity in capecitabine-pretreated patients who had already been exposed to anthracycline and taxane. It was suggested that S-1 clinically exhibited cross-resistance to capecitabine.

Keywords S-1 · Capecitabine · Taxane · Anthracycline · Metastatic breast cancer

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Introduction

Many active agents have been used to treat metastatic breast cancer (MBC), which is defined as breast cancer with any distant metastasis. However, it is difficult to achieve an absolute cure. Endocrine treatment, chemotherapy or molecular targeted agents are useful for controlling MBC. Hormone-insensitive or life-threatening MBC favors chemotherapy. Anthracycline, taxane, and trastuzumab play a central role in the chemotherapy of MBC. A durable response with less toxicity may prolong survival with a better quality of life (QOL) [1]. However, prior exposure to anthracycline and taxane limits the chance of choosing subsequent treatments. In such cases, third-line agents such as capecitabine [2], vinorelbine [9–11], gemcitabine [12–14], irinotecan [15] and ixabepilone [16–18] may be tried. However, it is not clear from the data which drug is optimal.

Capecitabine, a fluoropyrimidine derivative, is a common third-line drug [2–8]. Capecitabine is an oral

fluoropyrimidine carbonate, which is converted to 5FU selectively in tumors through a cascade of three enzymes. Based on the differential distribution of these three enzymes in different tissues, this drug is designed to yield more 5FU in cancer cells than in bone marrow cells or gastrointestinal epithelial cells [19, 20]. Capecitabine produces a response rate of approximately 20% with a duration of 3–6 months [2–8]. The convenient oral delivery of capecitabine gives mild gastrointestinal toxicity and myelosuppression without hair loss. The major toxicity of capecitabine is hand-foot syndrome [2–8].

S-1 is also one of the derivatives and produces a response rate of approximately 20% in patients who did not receive capecitabine [21]. S-1 is an orally administered agent containing 1M tegafur (FT) and two classes of a modulator, 5-chloro-2,4-dihydroxypyrimidine (CDHP) and potassium oxonate (Oxo), at a molar ratio of FT:CDHP:Oxo = 1:0.4:1. One phase II study of S-1 for MBC patients in a heterogeneous population demonstrated that the response rate was 42% among 108 patients [21]. The common toxicities were neutropenia, anemia, stomatitis, or nausea/vomiting. Hand-foot syndrome was rarely seen. Another phase II study was conducted in patients with refractory MBC. In 55 patients who had received taxane, the response rate was 21.8%. The common toxic profile was similar to the previous study [22].

Since S-1 has the same final active metabolites in its mechanism of action as capecitabine, cross-resistance is presumed to exist between the drugs. However, there is no clinical data on the activity of S-1 in capecitabine-pretreated patients with MBC. Here we have retrospectively examined the usefulness of S-1 in patients who were pretreated with anthracycline, taxane and capecitabine. We have focused on whether S-1 is cross-resistant to prior treatment with capecitabine.

Materials and methods

Patients

Patients with MBC who had been given S-1 between November 2001 and June 2003 at the Cancer Institute Hospital were retrospectively reviewed. The eligibility criteria were: (1) histologically confirmed MBC; (2) prior treatment with anthracycline, taxane, and capecitabine; (3) absolute neutrophil count >2,000μ/L; (4) serum bilirubin <1.25 × upper normal limit (UNL) of range; (5) transaminase <2.5 × UNL (in cases of hepatic metastasis <5 × UNL); (6) serum creatinine <1.5 × UNL (7) measurable lesion(s) according to the *Response Evaluation Criteria in Solid Tumors* guidelines; (8) performance status of 0, 1, or 2 on the Eastern Cooperative Oncology Group scale; (9) written informed consent from each patient.

Treatment plan

When body surface area (BSA) was between 1.25 and 1.5 m^2, S-1 was administered orally at a dose of 50 mg/body, twice daily, for four weeks followed by a two-week rest period. This was repeated every six weeks until disease progression or unacceptable toxicity. S-1 was given 60 mg/body when BSA >1.5 m^2 and 40 mg/body for BSA <1.25 m^2. In patients with HER2-positive cancer (HER2 protein scored as 3+ in immunohistochemistry or HER2 gene was amplified twofold or greater in fluorescence in situ hybridization), trastuzumab was administered intravenously at an initial loading dose of 4 mg/kg, followed by 2 mg/kg weekly. Treatment interruption and/or individual dose adjustment of S-1 was considered when patients experienced any adverse events assessed at grade 2 or more as defined by the National Cancer Institute, Common Toxicity Criteria, version 3.0. Patients with an objective response or stable disease (SD) continued to receive treatment until progressive disease (PD) or unacceptable toxicity developed.

Evaluation of efficacy and safety

Efficacy was evaluated by intention-to-treat analysis. 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%. PD was defined as an increase of 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. Long SD was defined as SD lasting for more than 24 weeks.

Objective response rate (ORR) was defined as the sum of the CR and PR rates. Clinical benefit rate (CBR) was defined as the sum of the CR, PR, and long SD rates. Time-to-treatment failure (TTF) was defined as the period from the commencement of S-1 to the discontinuation of S-1 and/or trastuzumab due to PD or unacceptable toxicity.

All adverse events and laboratory parameters were graded according to the National Cancer Institute, Common Toxicity Criteria, version 3.0.

Statistical analysis

TTF were calculated by the Kaplan–Meier method, performed to analyze censored data. Confidence intervals (CI) were set at the 95% level.

Results

Patient characteristics

Thirty-five patients were assessed in the present study. Median follow-up time of patients was 9.6 months, and the range was 1.2–26.6 months. All patients were Japanese women. The demographic characteristics of the present study population are presented in Table 1. Median age was 54 years (range 31–83).

The patients in the present study had advanced disease. More than half of the patients (57%) had three or more metastatic organs, visceral metastasis of the lung (18%), or of the liver (19%). The patients were heavily pretreated with anthracycline (100%), taxane (paclitaxel or docetaxel) (100%), capecitabine (100%), vinorelbine (71%), and mitomycin (69%). More than five prior chemotherapie courses for MBC had been administered to 57% of the patients. In terms of hormonal status, 60% were positive to both estrogen and/or progesterone receptors. With regard to HER2 status, 17% of the patients were HER2 protein 3+ in immunohistochemistry or HER2 gene-amplified in FISH.

Table 1 Patient characteristics ($n = 35$)

Characteristics	No. of patients	Percentage (%)
Mean age (range)	54 (31–83)	
Performance status		
0	12	34
1	14	40
2	9	26
Estrogen receptor/progesterone receptor status		
+/+	19	54
+/−	2	6
−/−	12	34
Unknown	2	6
HER2 status		
Positive (IHC 3+ or FISH+)	6	17
Negative (IHC 0, 1+ or FISH−)	28	80
Unknown	1	3
Recurrent or stage IV		
Recurrent	26	74
Stage IV	9	26
No. of metastases		
Median (range)	3 (1–5)	
1	7	20
2	8	23
3	11	31
4	8	23
5	1	3
Sites of metastases		
Lymph node	23	25
Chest wall/skin	11	12
Lung	17	18
Pleura	8	9
Bone	16	17
Liver	18	19
No. of prior chemotherapy courses for MBC		
Median (range)	5 (1–8)	
1–2	5	14
3–4	10	29
5 onwards	20	57
Agents used in prior chemotherapy		
Anthracycline	35	100
Pre- or postoperative usage	11	31
Taxane (paclitaxel or docetaxel)	35	100
Pre-or postoperative usage	3	9
Capecitabine	35	100
Vinorelbine	25	71
Mitomycin	24	69

Efficacy

Out of 35 patients, the response was assessable in 28. One patient achieved PR (3%). Eight patients obtained SD (23%), and six of those eight patients were long SD (17%) Therefore, ORR was 3% (95% CI; 0–9%). CBR was 20% (95% CI; 6–33%) (Table 2). Median TTF was 2.8 months (Fig. 1). Median overall survival was 21.4 months (Fig. 2).

Among 21 patients in whom the disease progressed during treatment with capecitabine, one PR and five SD (four long SD) were obtained. ORR was 5% and CBR was 23%. A PR was observed after progression to capecitabine preceding stable disease for seven months. In seven patients who had discontinued capecitabine due to their toxicities (four hand-foot syndrome, one thrombocytopenia, one cystitis, one eruption), two SD (one long SD) was observed. In six patients with HER2-positive cancer who were treated with S-1 combined with trastuzumab, two long SD were obtained.

Safety

Grade 1 or 2 adverse events were observed in 17 or 13%, respectively (Table 3). Grade 3 was rarely seen (3% of patients). One grade 4 toxicity of anorexia was observed. Common toxicities at any grade were anorexia (54%), nausea (49%), vomiting (34%), diarrhea (52%), and hand-foot syndrome (35%). Grade 3 events occurred as anorexia (9%), nausea (9%), vomiting (9%), diarrhea (14%), fatigue (3%), and elevation of AST/ALT (3%). No grade 3 was seen as hand-foot syndrome. Neither grade 3 nor 4 was observed in bone marrow suppression. There was no serious organ toxicity.

Table 2 Response

	All ($n = 35$)		Capecitabine-resistant ($n = 21$)		Discontinued capecitabine due to toxicities ($n = 7$)	
	n	%	*n*	%	*n*	%
Response						
Partial response	1	3	1	5	0	0
Stable disease	8	23	5	24	2	28
Long stable disease	6	17	4	19	1	14
Progressive disease	19	54	13	62	2	28
Not evaluable	7	20	2	10	3	43
Objective response rate	1	3	1	5	0	0
Clinical benefit rate	7	20	5	23	1	14

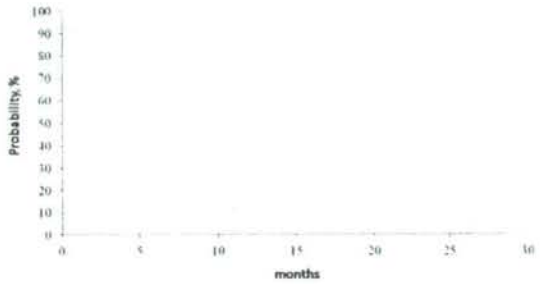

Fig. 1 Time to treatment failure ($n = 35$)

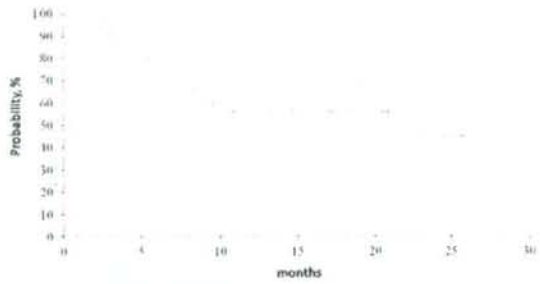

Fig. 2 Overall survival ($n = 35$)

In four patients who had discontinued capecitabine because of hand-foot syndrome, three patients experienced no hand-foot syndrome, but one patient had grade 2. One patient who had discontinued capecitabine due to hemorrhagic cystitis experienced grade 3 diarrhea without other gastrointestinal complaints. One patient who had discontinued capecitabine due to upper abdominal pain experienced grade 2 anorexia without pain. In ten patients (29%), S-1 was discontinued due to toxicities such as diarrhea (four cases), deterioration of PS (3), hand-foot syndrome (1), conjunctivitis (1), and enhancement neuropathy of concomitant phenytoin (1).

Table 3 Adverse events ($n = 35$)

	Total		Grade 1		Grade 2		Grade 3		Grade 4	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%
Anorexia	19	54	12	34	3	9	3	9	1	3
Fatigue	14	40	9	26	11	13	1	3	0	0
Nausea	17	49	6	17	8	23	3	9	0	0
Vomiting	12	34	1	3	8	23	3	9	0	0
Diarrhea	18	51	11	31	2	6	5	14	0	0
Hand-foot syndrome	9	35	4	11	5	14	0	0	0	0
Hair loss	0	0	0	0	0	0	NA	NA	NA	NA
Leukopenia	12	34	10	29	2	6	0	0	0	0
Neutropenia	8	23	5	14	3	9	0	0	0	0
Anemia	16	46	11	31	14	21	0	0	0	0
Thrombocytopenia	3	9	1	3	2	6	0	0	0	0
AST elevation	13	37	8	23	4	11	1	3	0	0
ALT elevation	10	29	5	14	4	11	1	3	0	0
Total bilirubin elevation	5	14	5	14	0	0	0	0	0	0
Creatinine elevation	2	6	2	6	0	0	0	0	0	0
All events	158	30	90	17	66	13	17	3	1	0.2

NA not applicable

Discussion

S-1 or capecitabine is active in MBC patients who have been previously treated with anthracycline and taxane. Both drugs may exhibit cross-resistance because of their shared final active metabolite. The present study showed that S-1 demonstrated 3% ORR and 20% CBR in patients who were heavily pretreated with anthracycline, taxane, and capecitabine. The median of 2.8 months TTF was relatively short (Fig. 1). These results suggest that S-1 has very limited activity in such heavily treated patients. However, for the minority, the disease may stabilize. It was suggested that S-1 demonstrated almost complete cross-resistance to capecitabine.

The safety profile was fairly good. Grade 4 toxicity was rare. Common toxicities were anorexia, nausea/vomiting, diarrhea, and hand-foot syndrome. All toxicities were manageable. However, several patients with poor PS could not continue treatment with moderate toxicities. No severe diarrhea (grade 4) was seen. Interestingly, it is likely that there is a lower incidence of hand-foot syndrome with S-1, even in patients who have suffered from hand-foot syndrome with capecitabine. In the majority, this well-tolerated profile may contribute to maintaining QOL in heavily treated patients.

In managing patients with MBC, it is still controversial as to whether a single agent or combination chemotherapy is superior. For instance, concurrent treatment with

docetaxel and capecitabine produced a longer survival than sequential treatment with each drug [23]. However, more patients receiving capecitabine plus docetaxel required dose reductions because of adverse events [24]. Recently, concurrent usage with capecitabine and ixabepilone was reported to give superior results in terms of progression-free survival than single administration of capecitabine, but overall survival data are not available [18]. There are no conclusive data on the superiority of concurrent treatment because of a lack of data comparing the sequential single usage of each agent. There is also no information on S-1 including other active agents such as vinorelbine, gemcitabine, or irinotecan. Sequential treatment has the potential advantage of yielding fewer adverse events. The strong safety profile with single usage of S-1 may be desirable in heavily treated MBC patients.

This study is both small and retrospective. There is no standard treatment in MBC pretreated with anthracycline, taxane and capecitabine. Well-designed clinical trials or palliative care would be recommended in this setting. It is not clear whether S-1 is active against HER2-positive MBC. Further investigations should be carried out on the clinical effectiveness of the upfront usage of S-1.

In conclusion, S-1 is fairly well tolerated but demonstrates very limited activity in capecitabine-pretreated patients who have already been exposed to anthracycline and taxane. It is suggested that S-1 clinically exhibits cross-resistance to capecitabine.

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Cancer Chemother Pharmacol (2008) 62:159–164
DOI 10.1007/s00280-007-0586-5

ORIGINAL ARTICLE

Efficacy and safety of trastuzumab plus capecitabine in heavily pretreated patients with HER2-positive metastatic breast cancer

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Received: 6 June 2007 / Accepted: 30 August 2007 / Published online: 20 September 2007

Abstract
Purpose We retrospectively evaluated the efficacy and safety of combination therapy of trastuzumab plus capecitabine in heavily pretreated patients with HER2-positive metastatic breast cancer (MBC).
Methods Patients with HER2-positive MBC who had been administered the combination therapy between July 2003 and July 2006 at the Cancer Institute Hospital, Tokyo, were retrospectively reviewed. Capecitabine (828 mg/m^2) was given twice daily for 3 weeks followed by a 1-week rest period; this was repeated every 4 weeks. Trastuzumab was given at 4 mg/kg as an initial loading dose intravenously, followed by 2 mg/kg weekly. We investigated objective response rate (ORR), clinical benefit rate (CBR), and time-to-treatment failure (TTF) according to the Response Evaluation Criteria in Solid Tumors guidelines. Adverse events were graded according to the National Cancer Institute, Common Toxicity Criteria, version 3.0.
Results A total of 49 patients were assessed and median follow-up time of patients was 16.2 months (1.4–43.5 months). ORR was 16% (95% confidence interval: 7–30%) and CBR was 47% (95% confidence interval: 32–62%). Median TTF was 5.4 months. Common adverse effects were hand–foot syndrome, liver dysfunction, and bone marrow suppression. Grade 3 adverse events were observed in nine patients (18%). One patient (2%) suffered from symptomatic chronic heart failure, which improved after discontinuation of trastuzumab.
Conclusions The combination therapy of trastuzumab plus capecitabine is effective and tolerable for heavily pretreated patients with HER2-positive MBC.

Keywords Capecitabine · Trastuzumab · HER2-positive · Metastatic breast cancer

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Introduction

HER2/neu is a surface membrane protein, member of the type I epidermal growth factor receptor family, encoded by the c-erb-b2 gene. In human breast cancer, c-erb-b2 gene amplification occurs in 25–30% of patients [1, 2]. The gene amplification induces HER2/neu protein overexpression. The overexpression results in a constitutive activation of the HER2/neu signaling pathways and an increase of cell proliferations [3]. Clinically, HER2/neu alteration is associated with an adverse prognostic profile, including shortened time to progression and overall survival in patients whose primary breast tumors contain the HER2/neu abnormality [1, 2, 4].

Trastuzumab is a humanized monoclonal antibody that binds with a specific epitope of the HER2 protein [1, 2, 4]. Trastuzumab as a single agent induced responses in 15–20% of patients with HER2-overexpressing breast cancer [5–7]. Furthermore, there is clear synergism between trastuzumab and several chemotherapeutic agents including cisplatin [8], docetaxel [9], paclitaxel [10], and vinorelbine [11, 12]. So, many clinicians continue trastuzumab therapy and change one chemotherapeutic agent for another sequentially in patients with HER2-positive metastatic

breast cancer (MBC), when the disease has progressed during treatment, in the hope of taking advantage of this possible synergy.

Capecitabine is an oral fluoropyrimidine carbonate, which is converted to 5FU selectively in tumors through a cascade of three enzymes [13]. Based on the differential distribution of these three enzymes in different tissues, this drug is designed to yield more 5FU in cancer cells than in bone marrow cells or gastrointestinal epithelial cells [13]. Capecitabine is effective and well tolerated for MBC patients who have failed anthracycline- and taxane-containing regimen [14–19]. Therefore, capecitabine is one of key drugs for patients with MBC.

However, for patients with HER2-positive MBC, there are not enough data about the efficacy and safety of the combination therapy of trastuzumab plus capecitabine. Therefore, the purpose of the present single-institute retrospective study is to evaluate efficacy and safety of combination therapy of trastuzumab plus capecitabine in heavily pretreated patients with HER2-positive MBC.

Materials and methods

Patients

Patients with HER2-positive MBC who had been administered combination therapy of trastuzumab plus capecitabine between July 2003 and July 2006 at the Cancer Institute Hospital, Tokyo, were retrospectively reviewed. The eligibility criteria were as follows: (1) trastuzumab plus capecitabine, (2) metastatic breast cancer, (3) HER2-positive cancer (HER2 protein scored as 3+ in immunohistochemistry or HER2 gene-amplified twofold or greater in fluorescence in situ hybridization), (4) lesion(s) measurable according to the Response Evaluation Criteria in Solid Tumors guidelines, (5) performance status of three or less according to the Eastern Cooperative Oncology Group's scale.

Treatment plan

Capecitabine was given orally at a dosage of 828 mg/m^2, twice daily for 3 weeks followed by a 1-week rest period. This was repeated every 4 weeks. The dose was calculated on the basis of body surface area at baseline (Table 1). The schedule of trastuzumab is 4 mg/kg as an initial loading dose intravenously, followed by 2 mg/kg weekly. This regimen was registered with the hospital.

Patients with an objective response or stable disease (SD) could continue to receive the combination treatment until progressive disease (PD) or unacceptable toxicity developed.

Table 1 Determination of capecitabine dose according to body surface area

Body surface area (m^2)	Dose (mg, twice daily)
<1.31	900
1.31–1.64	1,200
≥1.64	1,500

Treatment interruption and/or individual dose adjustment of capecitabine was considered when patients experienced any adverse events assessed at grade 2 or more as defined by the National Cancer Institute, Common Toxicity Criteria, version 3.0.

Evaluation of efficacy and safety

Tumor response was assessed according to the Response Evaluation Criteria in Solid Tumors guidelines by the investigators and the independent reviewers, with computed tomography scans at baseline and every 2 or 3 months. Complete response (CR) was defined as the disappearance of all known lesions for at least 4 weeks. Partial response (PR) was defined as a reduction of the sum of all measurable lesions by at least 30%. PD was defined as an increase of the sum of all measurable lesions by than greater 20% or as the appearance of a new lesion and stable disease (SD) was defined as neither CR, PR, nor PD. Long SD was defined as SD lasting for more than 24 weeks.

Objective response rate (ORR) was defined as the sum of CR and PR rates. Clinical benefit rate (CBR) was defined as the sum of CR, PR, and long SD rates. Time-to-treatment failure (TTF) was defined as the period from the commencement of capecitabine to discontinuation of capecitabine and/or trastuzumab due to PD or unacceptable toxicity.

All adverse events and laboratory parameters were graded according to the National Cancer Institute, Common Toxicity Criteria, version 3.0. Objective and subjective adverse events were assessed every week and laboratory parameters were assessed every 4 weeks.

Statistical analysis

Calculation of TTF was done by the Kaplan–Meier method, in order to analyze censored data. Confidence intervals (CI) were set at the 95% level.

Results

Patient characteristics

In the present study, 49 patients were assessed. Median follow-up time of patients was 16.2 months and the range was

1.4–43.5 months. All patients were Japanese women. The demographic characteristics of the present study population are presented in Table 2. Regarding hormonal status, 59% of patients were both estrogen and progesterone receptors negative. With regard to HER2 status, 86% of the patients were HER2 protein 3+ in immunohistochemistry and 14% were HER2-gene amplified in FISH.

The patients in the present study ailed from advanced disease. More than half of the patients (57%) had three or more metastatic organs. Approximately half of the patients had visceral metastasis of either the lung (49%) or liver (39%).

Table 2 Baseline patient and disease characteristics ($n = 49$)

Characteristics	No. of patients	%
Mean age (range)	54.3 (33–72)	
Performance status		
0	42	86
1	5	10
2	2	4
Estrogen receptor/progesterone receptor status		
+/+	9	18
+/–	9	18
–/+	2	4
–/–	29	59
HER2 status		
IHC 3+	42	86
FISH positive	7	14
No. of metastases		
Mean (range)	2.6 (1–5)	
1	8	16
2	13	27
3	28	57
Sites of metastases		
Lymph node	33	67
Lung	24	49
Bone	20	41
Liver	19	39
Chest wall/skin	19	39
Chemotherapeutic pretreatment	49	100
Adjuvant or neoadjuvant setting	24	49
Anthracyclines	20	41
Taxanes	12	24
Metastatic setting	47	96
1 prior regimen	8	16
2 prior regimens	17	35
Mean number of regimens (range)	2.7 (0–8)	
Anthracyclines	26	53
Taxanes	42	86
Trastuzumab	43	88

IHC Immunohistochemistry, *FISH* fluorescence in situ hybridization

Moreover, they had been heavily pretreated. Approximately 90% of the patients were pretreated with anthracyclines (42 of 49; 86%) and taxanes (43 of 49; 88%) in the adjuvant, neoadjuvant, and/or metastatic settings, and 88% (43 of 49) of the patients were pretreated with trastuzumab-containing regimens in the metastatic setting. The mean number of chemotherapeutic pretreatment regimens was 2.7 (range 0–8, median 2) in the metastatic setting.

Efficacy

Of the 49 patients, response was assessable in 44 patients. One patient achieved CR (2%), and seven patients achieved PR (14%). Therefore, ORR for capecitabine was 16% (95% CI: 7–30%). Moreover, 16 patients achieved SD, and of these, 15 achieved long SD (31%); hence, CBR for capecitabine was 47% (95% CI: 32–62%) (Table 3). Median TTF was 5.4 months (Fig. 1). Median overall survival (OS) has not been reached.

Safety (Table 4)

Grade 3 adverse events were observed in nine patients (18%). No grade 4 event was observed. Treatment interruption and/or individual dose adjustment of capecitabine was required in 15 patients (31%).

Table 3 Response to trastuzumab plus capecitabine ($n = 49$)

	No. of patients	%
Response		
Complete response	1	2
Partial response	7	14
Stable disease	16	33
(Long stable disease)	(15)	(31)
Progressive disease	21	43
Not evaluable	4	8
Objective response rate	8	16
Clinical benefit rate	23	47

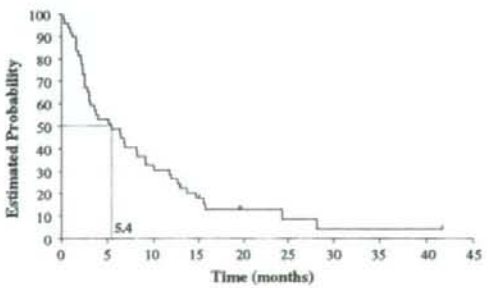

Fig. 1 Time-to-treatment failure ($n = 49$)

Table 4 Summary of adverse events worst by patient ($n = 49$)

	Total		Grade 1		Grade 2		Grade 3	
	No.	%	No.	%	No.	%	No.	%
Hand-foot syndrome	32	65	15	31	13	27	4	8
Fatigue	18	37	18	37				
Nausea	12	24	11	22	1	2		
Diarrhea	10	20	8	16	1	2	1	2
Anorexia	4	8	3	6	1	2		
Vomiting	4	8	4	8				
Interstitial pneumonia	1	2					1	2
Chronic heart failure	1	2					1	2
Leukopenia	27	55	20	41	7	14		
Neutropenia	13	27	7	14	6	12		
Anemia	14	29	8	16	4	8	2	4
Thrombocytepenia	1	2			1	2		
AST elevation	27	55	25	51	1	2	1	2
ALT elevation	15	31	10	20	4	8	1	2
Total bilirubin elevation	17	35	11	22	6	12		
Creatinine elevation	1	2	1	2				
All events	47	96	12	24	26	53	9	18

No grade 4 event was observed

Common adverse effects of the combination therapy were hand–foot syndrome, liver dysfunction, and bone marrow suppression. First, 32 patients had hand–foot syndrome (65%). This was classified as grade 3 in four patients (8%). Second, elevation of AST, ALT, and total bilirubin were noted in 27 (55%), 15 (31%), and 17 patients (35%), respectively. Grade 3 liver dysfunction occurred in one patient (2%). Third, effects of bone marrow suppression as leukopenia, anemia, and neutropenia were seen in 27 (55%), 14 (29%), and 13 patients (27%) at all grades; however grade 3 occurred in 2 patients (4%).

One patient suffered from grade 3 interstitial pneumonia, which improved after discontinuation of trastuzumab plus capecitabine.

Another patient without past medical history of cardiac dysfunction suffered symptomatic chronic heart failure (CHF), which improved after discontinuation of trastuzumab. She had been given doxorubicin in the neoadjuvant setting (total dose 300 mg/m^2). And also, she had been given trastuzumab in the metastatic setting for 1 year and 7 months. The interval between anthracycline and trastuzumab/capecitabine therapy was 2 year and 11 months.

Discussion

This retrospective study showed that the combination therapy of trastuzumab plus capecitabine is effective and safe for heavily pretreated patients with HER2-positive MBC. ORR was 16% and CBR was 47% (Table 3). Median TTF was 5.4 months (Fig. 1). Grade 3 adverse events were observed in 18% of the patients, but symptoms were improved after discontinuation of the therapy (Table 4).

Preclinical data investigating the combination of trastuzumab with 5FU showed that this combination was less effective than either drug alone, suggesting antagonism in vitro, whereas it may be synergic (cisplatin, thiopeta, etoposide) or additive (doxorubicin, paclitaxel, methotrexate, vinblastin) [20]. However, further studies indicated that trastuzumab and 5FU prodrug capecitabine had at least additive antitumor activity in in vivo models [21]. The reason for the discrepancy between the in vivo and in vitro results has not been clarified [21].

In the clinical setting, the combination therapy of trastuzumab plus capecitabine is effective for patients with HER2-positive MBC. In German multicenter phase II study of weekly trastuzumab with capecitabine (1,250 mg/m2 twice daily on days 1–14, tri weekly) in patients with pretreated MBC ($n = 27$), ORR was 45%, CBR was 68%, median progression-free survival time was 6.7 months, and median OS was 28 months [22]. Using the same treatment regimen as the German trial, this high ORR was mirrored in Chinese phase II study of the first-line therapy ($n = 43$), in which an ORR of 63% was recorded [23]. In Japanese phase II trial ($n = 27$), using the same regimen as the present study, ORR was 41%, median time to progression was 5.2 months, and median OS was 16.1 months [24]. In the present study, although ORR was inferior to these studies, tumor was

controlled for a relatively long time, considering the poor prognosis of the patients in the study population who had been heavily pretreated for the multiple metastases.

Furthermore, the combination therapy of trastuzumab plus capecitabine is well tolerated. The German trial showed that grade 3/4 adverse events were general pain (28%), motor dysfunction (16%), hand-foot-syndrome (16%), nausea (12%), anemia (8%), and leucopenia (4%) [22]. The Chinese trial showed that grade 3 hand–foot syndrome occurred in 9% and myelosupression occurred in 1% of patients [23]. The Japanese trial, same regimen as the present study showed no reports of grade 3/4 events [24]. Our results of adverse events are in the range of these prior studies.

The most clinically significant adverse event of trastuzumab was cardiac dysfunction. Patients ranging 2–5% who were treated with trastuzumab alone developed CHF [6, 7] and 0–2% of patients who were treated with trastuzumab plus non-anthracycline containing combination regimens developed CHF [9–11]. In the present study, grade 3 CHF was observed in one patient (2% Table 4), although approximately 90% of the patients pretreated with anthracycline (Table 2). Therefore, capecitabine added to trastuzumab does not increase CHF. Moreover, the clinically significant adverse events of capecitabine were hand-foot syndrome, liver dysfunction, and bone marrow suppression [14–18, 25, 26]. In the present study, the safety profile is not inferior to that seen in previous studies of capecitabine alone [14–18, 25, 26]. Therefore, trastuzumab added to capecitabine does not increase the adverse events of capecitabine.

In conclusion, the results of the present single-institute retrospective study confirm that the combination therapy of trastuzumab plus capecitabine is effective and tolerable in heavily pretreated patients with HER2-positive MBC.

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J Gastroenterol 2008; 43:842–848
DOI 10.1007/s00535-008-2242-1

Journal of Gastroenterology

Modified irinotecan plus bolus 5-fluorouracil/L-leucovorin for metastatic colorectal cancer at a single institution in Japan

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Background. The modified irinotecan plus bolus 5-fluorouracil/L-leucovorin (IFL) regimen (irinotecan plus bolus 5-fluorouracil/L-leucovorin) used to be one of the standard treatments for metastatic colorectal cancer until approval of oxaliplatin in Japan. We evaluated the efficacy of modified IFL therapy for Japanese patients. ***Methods.*** Forty-seven patients with metastatic colorectal cancer received irinotecan (100 mg/m^2) and bolus 5-fluorouracil (500 mg/m^2) plus L-leucovorin (10 mg/m^2) on days 1 and 8 every 3 weeks until progression or unmanageable toxicity occurred. The data on toxicity and tumor response were analyzed retrospectively. ***Results.*** All patients discontinued modified IFL therapy due to cancer progression, except for one patient who developed severe liver dysfunction. The overall response rate was 25%. The median progression-free survival time (PFS) was 6.1 months. The median overall survival time (OS) was 17.4 months for all patients, 28.8 months for patients receiving subsequent oxaliplatin therapy, and 8.9 months for patients without oxaliplatin (P = 0.0031). According to multivariate analysis results, good performance status, a normal white cell count, and absence of local recurrence were associated with a better PFS. Tumor response was a good prognostic factor for both PFS and OS. Gastrointestinal symptoms were the most common toxicities, including grade 3 diarrhea (8%) and grade 3 anorexia (10%). Grade 4 neutropenia occurred in 6% of patients. No other drug-related severe adverse events or deaths were observed. ***Conclusions.*** Modified IFL therapy is an effective and well-tolerated regimen for Japanese patients with metastatic colorectal cancer. Modified IFL therapy combined with biological agents might remain an option for some patients who refuse a central venous catheter.

Received: January 4, 2008 / Accepted: June 25, 2008
Reprint requests to: K. Hatake

Key words: irinotecan, 5-fluorouracil, colorectal cancer, IFL

Introduction

In Japan, approximately 326000 patients died of cancer in 2005.[1] The number of cancer deaths in men was 1.5 times that in women. Cancer of the colon and rectum combined was the fourth leading cause of death, accounting for 11% of all new cancer deaths in men, and was the leading cause of death (15%) in women.

In general, new treatments tend to be better than the previous standard treatment for colorectal cancer and promise to provide an improved outcome. However, we have not been able to use the standard chemotherapy available in Western countries for Japanese patients with metastatic colorectal cancer because of the delayed approval of key drugs. We started to perform treatment with folinic acid (leucovorin), 5-fluorouracil (5-FU), and oxaliplatin (FOLFOX) or leucovorin, 5-FU, and irinotecan (FOLFIRI) as new standard regimens in Japan, as in United States and the European Union, after approval of infusional 5-FU and oxaliplatin in 2005.[2,3]

Since Japanese studies of the modified irinotecan plus bolus 5-FU/L-leucovorin (IFL) regimen published in 2003 and 2004[4,5] revealed that it was well tolerated and effective for Japanese patients, modified IFL was the standard treatment in Japan until the approval of oxaliplatin. Because of the short duration of use of the modified IFL regimen, however, its efficacy for Japanese patients has not yet been reported.

The present study was performed to evaluate the efficacy of our regimen in Japanese patients, since it might remain an option for some patients in whom infusional 5-FU therapy is not appropriate. The study was not done with the aim of promoting this regimen as a

replacement for current standard treatment with FOLFOX or FOLFIRI.

Methods

Patients

Forty-seven patients with metastatic colorectal cancer received modified irinotecan plus bolus 5-FU and leucovorin (the modified IFL regimen) at our hospital between January and December 2004. Written informed consent was obtained from all patients.

Treatment

The modified IFL regimen involved administration of irinotecan (100 mg/m^2) intravenously as a 90-min infusion and 5-FU as an intravenous bolus of 500 mg/m^2 plus L-leucovorin (l-LV) at 10 mg/m^2 as an intravenous infusion on days 1 and 8 every 3 weeks.

Treatment was continued until there was disease progression, unmanageable toxicity, or patient refusal. Supportive care included intensive treatment with loperamide for late diarrhea. Atropine was given as needed for irinotecan-related cholinergic symptoms. Antiemetic agents were provided at the discretion of the treating physician. Prophylactic use of colony-stimulating factors was not permitted.

Evaluation of toxicity and efficacy

Data were retrieved from the tumor registry at our institution, and the patients' records were reviewed retrospectively.

Adverse effects were graded on a weekly basis by using National Cancer Institute Common Toxicity Criteria (version 2.0). Tumor response was assessed from computed tomography (CT) scans obtained every 12 weeks according to the response evaluation criteria for solid tumors (RECIST). Toxicity and tumor response were analyzed retrospectively from the medical records and CT scans of each patient.

The progression-free survival time (PFS) and overall survival time (OS) were defined as the time between the date of starting treatment and the date of confirmation of disease progression or death (or the date at which the patient was last confirmed to be alive), respectively, and were calculated by using the Kaplan-Meier method.[6] Stepwise regression analysis was done to identify subsets of factors associated with the PFS and OS by using the Cox proportional hazards model to calculate hazard ratios and confidence intervals (CIs). A P value of less than 0.05 was considered statistically significant for all comparisons of PFS and OS.

Results

Patient characteristics

The characteristics of all evaluated patients are listed in Table 1. The median age was 62 years (range, 34–75 years). Performance status scores were usually 0 or 1. The liver and lungs were the main sites of metastasis, followed by lymph node and peritoneal metastases. Most patients (89%) received modified IFL as first-line treatment. Twenty-two of the 47 patients switched to second-line FOLFOX4 (2-weekly cycles of oxaliplatin (85 mg/m^2) intravenously over 2 h on day 1, together with leucovorin (200 mg/m^2) over 2 h, 5-FU (400 mg/m^2) as a bolus, followed by a 22-h infusion of 5-FU (600 mg/m^2) on days 1–2, every 2 weeks) after disease

Table 1. Baseline characteristics (n = 47)

Characteristic	n	%
Median age (range) = 62 (34–75) years		
Sex		
Male	24	51
Female	23	49
ECOG performance status		
0	39	83
1	7	15
2	1	2
Site of primary tumor		
Colon	30	64
Rectum	17	36
No. of involved organs		
1	16	34
2	24	51
>2	7	15
Sites of metastasis		
Liver	27	57
Lung	20	43
Peritoneum	10	21
Nodes	14	30
Local recurrence	2	4
Other	1	2
Prior adjuvant fluorouracil	7	15
No. of regimens for metastatic disease before IFL		
None	42	89
One	4	9
Two or more	1	2
Prior radiotherapy		
Yes	1	2
No	46	98
Baseline laboratory abnormalities		
White cell count >8 × 103/mm3	12	26
Hemoglobin < 11 g/dl	11	23
Total bilirubin > upper normal limit	4	9
Lactate dehydrogenase > upper normal limit	42	89
Carcinoembryonic antigen > 100 ng/ml	17	36
Next chemotherapy with oxaliplatin		
Yes	22	47
No	25	53

ECOG, Eastern Cooperative Oncology Group; IFL, irinotecan plus bolus 5-fluorouracil/L-leucovorin

Table 2. Response rates

Status	No. of patients		
	Total ($n = 47$)	First-line ($n = 42$)	Second-line ($n = 4$)
Complete response	1 (2)	1 (2)	0
Partial response	11 (23)	11 (26)	0
Stable disease	23 (49)	19 (45)	4
Disease progression	8 (17)	7 (17)	0
Not evaluable for response	4 (9)	4 (10)	0

Values shown are *n* (%)

progression was detected during modified IFL therapy. The other patients received non-oxaliplatin-based chemotherapy, such as S-1 monotherapy, hepatic arterial infusion combined with low-dose 5-FU and cisplatin, or radiation therapy for local control if they did not want oxaliplatin or only needed local control.

The median duration of treatment with the modified IFL regimen was 6.1 months (range, 0.7–20.8 months). All patients discontinued treatment due to disease progression, except for one patient who developed grade 4 liver dysfunction on day 3 of the initial cycle without other hematologic or gastrointestinal toxicities. This patient recovered completely by day 25 after conservative therapy with administration of monoammonium glycyrrhizinate and ursodeoxycholic acid. However, modified IFL therapy was discontinued. Among all 47 patients, eight patients (17%) required a dose reduction of 20% for both cytotoxic drugs during the initial cycle of therapy. The reason was old age in four patients, ascites in two, liver dysfunction due to metastasis in two, and multiple prior treatments in one. There was no progression of liver dysfunction due to chemotherapy in either patient with baseline hepatic impairment. Adverse events led to a dose reduction of 20% for both cytotoxic drugs in another seven patients (14.9%) during the second cycle, except for one who needed it during the initial cycle. The toxicities were grade 3 neutropenia in three patients (6.4%), grade 3 diarrhea in one patient (2.1%), grade 3 anorexia in two patients (4.3%), grade 3 nausea in three patients (6.4%), grade 3 vomiting in one patient (2.1%), and grade 3 fatigue related to grade 3 gastrointestinal toxicity in one patient (2.1%). None of the patients required a further dose reduction.

Efficacy

All 47 patients were assessed for tumor response. The overall response rate achieved with modified IFL therapy was 25% (95% CI, 13%–37%), and the response rate was the same in patients receiving first-line treatment. No response was obtained when modified IFL therapy was used as a second-line treatment (Table 2).

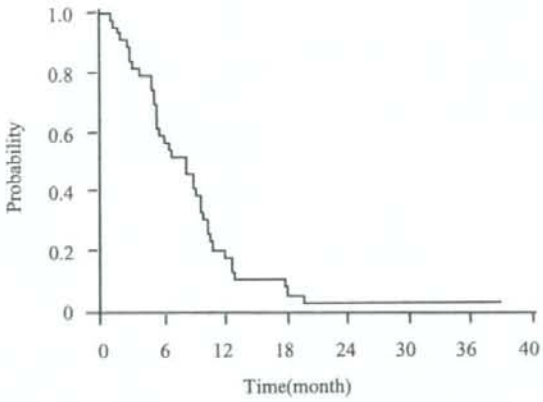

Fig. 1. Progression-free survival of patients treated with modified irinotecan plus bolus 5-fluorouracil/L-leucovorin (IFL) ($n = 47$)

The median PFS of the 47 patients was 6.1 months (95% CI, 6.0–9.9 months). The Kaplan-Meier curve for PFS is shown in Fig. 1. Multivariate analysis revealed five independent prognostic factors for an improved PFS: second-line FOLFOX4, a white cell count $< 8 \times 10^3/mm^3$, achieving a response, a good performance status, and no local recurrence (Table 3).

The median OS of the 47 patients was 17.4 months (95% CI, 15.9–22.9 months). For the 21 patients who received second-line FOLFOX4, the median OS was 28.8 months, while it was 8.9 months for the 26 patients who did not receive second-line FOLFOX4 (log-rank test $P = 0.0031$, Fig. 2).

Multivariate analysis showed that independent prognostic factors for an improved OS were second-line FOLFOX, a white cell count $< 8 \times 10^3/mm^3$, achieving a response, and a carcinoembryonic antigen (CEA) level < 100 ng/ml (Table 3).

Adverse events

The grade 3 or 4 toxicities are summarized in Table 4. Treatment with modified IFL was generally well toler

Table 3. Prognostic factors in multivariate analysis ($n = 47$)

Factor	Progression-free survival			Overall survival		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Second-line FOLFOX4						
No	1			1		
Yes	0.26	0.11–0.60	0.002	0.08	0.03–0.28	<0.0001
White cell count						
$\leq 8 \times 10^3/mm^3$	1			1		
$< 8 \times 10^3/mm^3$	0.37	0.14–0.95	0.04	0.2	0.07–0.6	0.004
Response						
Nonresponder	1			1		
Responder	0.27	0.12–0.62	0.002	0.103	0.03–0.34	0.0002
Carcinoembryonic antigen						
≤100 ng/ml	–	–	NS	1		
<100 ng/ml				0.2341	0.08–0.65	0.005
Performance status						
1 or 2	1			–	–	NS
0	0.27	0.10–0.71	0.008			
Local recurrence						
Yes	1			–	–	NS
No	0.03	0.002–0.31	0.004			

CI, confidence interval; FOLFOX4, folinic acid (leucovorin), 5-fluorouracil, and oxaliplatin

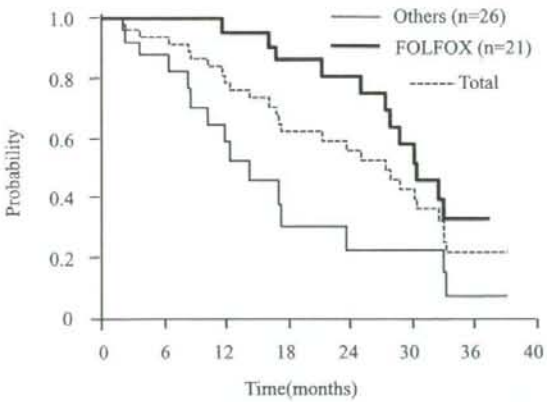

Fig. 2. Overall survival of patients treated with modified IFL followed by folinic acid (leucovorin) 5-fluorouracil, and oxaliplatin (FOLFOX) or another treatment

ated. Gastrointestinal symptoms were the most common toxicities, including diarrhea (8%), anorexia (10%), and nausea (8%), but there was no grade 4 gastrointestinal toxicity. Grade 3 and 4 neutropenia occurred in 27% and 6% of the patients, respectively. Grade 3 urticaria (not life-threatening) was observed in one patient on day 15 of the initial cycle, and this resolved completely with symptomatic treatment. No other allergic reactions occurred, and there were no other treatment-related severe adverse events or deaths.

Table 4. Grade 3/4 toxicity of modified IFL according to NCI-CTC grades ($n = 47$)

	NCI-CTC grade	
	3	4
Neutropenia	13 (27)	3 (6)
Anemia	1 (2)	0
Diarrhea	4 (8)	0
Anorexia	5 (10)	0
Nausea	4 (8)	0
Vomiting	1 (2)	0
Skin toxicity	1 (2)	0
Fatigue	1 (2)	0
Liver dysfunction	0	1 (2)

Values shown are *n* (%)
NCI-CTC, National Cancer Institute Common Toxicity Criteria

Discussion

In this study, we retrospectively assessed the efficacy and safety of a modified IFL regimen, which was the standard chemotherapy for metastatic colorectal cancer in Japan before approval of oxaliplatin (March 2005). The results obtained with modified IFL in Japanese patients have not been reported before, except for two phase I/II studies. In addition, different modified IFL regimens were used at each hospital in Japan.

In a phase I study that enrolled Japanese patients with metastatic colorectal cancer, irinotecan and bolus 5-FU plus l-LV were administered weekly for 3 weeks every 28 days (modified Saltz regimen).[4,7] Dose level 3

(irinotecan, 100 mg/m^2; 5-FU, 500 mg/m^2; and l-LV, 25 mg) was the recommended dose, causing frequent but manageable grade 3–4 neutropenia and well-tolerated nonhematological toxicities. There were no treatment-related deaths. The relative dose intensity was 87% and 84% for 5-FU and irinotecan respectively, at dose level 3. In the other phase I/II study, patients with untreated metastatic colorectal cancer received irinotecan (100 mg/m^2) as a 90-min intravenous infusion, followed by bolus 5-FU and l-LV (10 mg/m^2) on days 1 and 8 of a 21-day cycle. The recommended doses were 100 mg/m^2 for irinotecan, 500 mg/m^2 for 5-FU, and 10 mg/m^2 for l-LV. Grade 3–4 neutropenia occurred in 9% of the patients, but no grade 3–4 nonhematologic toxicities were observed and there were no treatment-related deaths. The relative dose intensity through the first five cycles was 86% for 5-FU and 93% for irinotecan at dose level 2. The response rates achieved in these two studies were 39% and 58%, respectively. In these Japanese phase I/II studies, the efficacy of therapy was consistent with that reported earlier, but a lower weekly dose of irinotecan than that in the original Saltz regimen[7] was recommended because the maximum approved weekly dose of irinotecan in Japan is 100 mg/m^2. Therefore, a good toxicity profile was achieved, and the modified IFL regimen with 100 mg/m^2 of irinotecan weekly became established for Japanese patients.

The present study retrospectively analyzed the clinical value of the modified IFL therapy. We followed the regimen employed in the latter Japanese study because of its simplicity and the better quality of life for the patients. The baseline number of involved organs and nonhepatic metastases were higher in this study than in previous reports,[4,5,7,8] which might have contributed to the lower response rate (28% vs. 31%–58%). The PFS achieved in our patients was similar to that reported by Saltz et al.[7] (6.1 vs. 7.0 months), but we achieved a 2.6-month longer survival benefit (17.4 vs. 14.8 months). It is possible that the low incidence (52%) of continuation of treatment in patients assigned to receive IFL after their study and the small number of patients receiving subsequent oxaliplatin-based regimens or investigational agents led to the difference in OS. In contrast, the OS of the subgroup who received second-line FOLFOX (44.7% of the patients in our study) was 28.8 months, which is probably the longest survival time reported so far except in studies of biological agents. The higher incidence of discontinuation related to adverse events in their study compared with ours (7.6% vs. 2%) was perhaps another reason for the shorter survival.

Comparison of our analysis of prognostic factors with that of Saltz et al.[7] shows that a good performance status was associated with a better PFS and OS in their study, but with PFS alone in our study. Also, a normal white cell count was associated with a better PFS and OS in our study, but only with OS in their report. Among other significant factors identified in our study, achieving a response was a good prognostic factor for both PFS and OS, local recurrence was an adverse prognostic factor for PFS, and CEA < 100 ng/ml was associated with better OS. Thus, a better prognosis might be predicted in patients receiving the modified IFL regimen who have metastases to organs other than the liver, no local recurrence, CEA < 100 ng/ml, and a good tumor response regardless of the number of metastatic sites. Obviously, subsequent treatment with FOLFOX had an important influence on survival.

The median survival time is approximately 12 months when 5-FU combined with LV is administered,[8,9], 14 to 16 months when either irinotecan or oxaliplatin is added to 5-FU,[2,7] and more than 20 months when all three drugs are used as sequential therapy or in combination with biological agents.[10,11] Comparisons of IFL with FOLFOX for the initial treatment of metastatic colorectal cancer has shown that patients receiving the FOLFOX regimen have a superior tumor response rate (45% vs. 31%, $P < 0.001$), time to progression (9.3 months vs. 7.0 months, $P = 0.002$), and OS (19.5 months vs. 15.0 months) than those receiving IFL.[10] Treatment with an antibody (bevacizumab) for vascular endothelial growth factor (VEGF) plus chemotherapy agents has been assessed in several clinical trials.[11] Compared with IFL therapy alone, the addition of bevacizumab to IFL leads to a significant increase in the response rate (45% vs. 35%, $P = 0.004$) and significant prolongation of PFS (10.6% vs. 6.2%, $P < 0.001$) and OS (20.3% vs. 15.6%, $P < 0.001$). A survival benefit of adding bevacizumab has also been demonstrated with other chemotherapy regimens.[12–15]

A valuable review of seven phase III trials[2,3,7,8,10,16–18] has revealed a positive correlation between improvement of OS and treatment with fluorouracil–leucovorin, irinotecan, and oxaliplatin, indicating that the percentage of patients receiving these three drugs had more influence on OS than the overall percentage of patients receiving second-line therapy. We administered the modified FOLFIRI regimen (administration of irinotecan (150 mg/m^2) intravenously over 1.5 h on day 1, together with leucovorin (400 mg/m^2 over 2 h) and 5-FU (400 mg/m^2 as a bolus), followed by a 46-h infusion of 5-FU at 1200 mg/m^2 on days 1–2, every 2 weeks) to seven patients after confirming disease progression during treatment with the FOLFOX regimen as second-line irinotecan-based chemotherapy. At that time, none of the biological agents had been approved in Japan, and these three key cytotoxic drugs were third-line treatment, so we hoped that a difference in the administration method between bolus dosing and infusion of 5-FU would improve survival, even though cross-resistance

might also be expected. Analysis of this subgroup demonstrated no tumor response, and five patients did not achieve disease control, even though all of them had shown disease control (with a partial response in three) during treatment with the modified IFL regimen. These results suggest that cycling the three key drugs and changing the administration method after disease progression might not be a useful strategy.

An intentional cycling strategy was assessed in a phase II trial (FIREFOX study), which involved alternating four cycles of FOLFOX6 with four cycles of FOLFIRI in patients with metastatic colorectal cancer[19] until progression or limiting toxicity occurred. The response rate was 46.1%, the median PFS and OS were 8.8 and 18.7 months, respectively, and there was less grade 3 sensory neuropathy due to oxaliplatin than in previous reports. Further investigation will be necessary to determine the efficacy and safety of this type of cycling strategy combined with biological agents as another way to reduce severe neuropathy due to oxaliplatin.[20]

Recently, a new regimen of irinotecan combined with an oral fluoropyrimidine (S-1), IRIS therapy, has been reported to be effective for patients with metastatic colorectal cancer in Japan, and it does not require implantation of a central venous catheter.[21] However, use of IRIS combined with biological agents has not been reported (and is not yet allowed in Japan), although IFL therapy combined with an anti-VEGF antibody (bevacizumab) achieves a good survival benefit.[11]

In conclusion, this study showed that modified IFL therapy is an effective and well-tolerated regimen for Japanese patients with metastatic colorectal cancer. IFL has lost popularity as standard chemotherapy due to the results of a randomized trial (N9741) that showed higher treatment-related mortality within the first 60 days in the IFL arm compared with the FOLFOX arm or irinotecan–oxaliplatin (IROX) arm.[10] However, in Japan, the combination of modified IFL therapy and biological agents might remain a viable option that can improve survival and the quality of life in patients who refuse implantation of a central venous catheter.

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