Table 3 Findings associated with asymptomatic thrombosis ($n = 21$)

Findings	Initial DUS	Follow-up DUS
Location, *n* (%)		
Distal (not extended to SVC)	21 (100)	18 (85.7)
Central (extended to SVC)	0	0
Comparison	Improved (disappeared) in 3 patients (14.3)	
Maximum size, *n* (%)		
0–<10 mm	14 (66.7)	12 (57.1)
10–<20 mm	2 (9.5)	4 (19)
20–<30 mm	3 (14.3)	3 (14.3)
>30 mm	2 (9.5)	2 (9.5)
Comparison	Improved in 5 patients (23.8) (disappeared in 3 and reduced in 2)	
	Progressed in 4 patients (19)	
Vascular flow, *n* (%)		
Adequate	18 (85.7)	13 (61.9)
Inadequate	3 (14.3)	5 (23.8)
Comparison	Improved in 3 patients (14.3)	
	Progressed in 2 patients (9.5)	
Collateral vascular flow, n (%)		
Adequately increased	2 (9.5)	2 (9.5)
Inadequately increased	1 (4.8)	3 (14.3)
Comparison	Progressed in 2 patients (9.5)	
Overall evaluation[a]	Improved in 5 patients (23.8)	
	Stable in 12 patients (57.1)	
	Progressed in 4 patients (19)	

[a] Overall improvement was defined as at least one improved finding without progression in location, maximum size, or (collateral) vascular flow and progression as at least one progressed finding; those fitting neither category were defined as the remainder. One patient receiving anticoagulant therapy after initial DUS showed a thrombus 45 mm in diameter that developed into the brachiocephalic vein; no progression was noted. One patient with thrombus progression experienced a symptomatic pulmonary embolism after the sixth cycle, and one progressed patient experienced an asymptomatic pulmonary embolism after the sixth cycle

SVC superior vena cava

Table 4 Correlation between vascular flow and other findings of asymptomatic thrombosis ($n = 21$)

Findings on DUS	Initial DUS ($n = 21$)		Follow-up DUS ($n = 18$)	
	Adequate ($n = 18$)	Inadequate ($n = 3$)	Adequate ($n = 13$)	Inadequate ($n = 5$)
Location, *n* (%)				
SCV–ECV–SSV junction[a]	1 (5.6)	2 (66.7)	0	4 (80)
P value	0.0414		0.0016	
Maximum size, *n* (%)				
<30 mm	18(100)	1 (33.3)	13 (100)	3 (60)
≥30 mm	0	2 (66.7)	0	2 (40)
P value	0.0143		0.0654	

[a] Thrombi extended into junction of SCV, ECV, and SSV in two inadequate patients at initial DUS; both thrombi sizes were ≥30 mm

DUS Doppler ultrasound imaging, *SCV* subclavian vein, *ECV* external jugular vein, *SSV* suprascapular vein, *N.A* not applicable

an increased risk for VTE and PE [8–10]. According to a review by Vescia et al. [19], the incidence of catheter-related thrombosis varied from 12 to 64% in four retrospective studies [20–24]. In a recent prospective trial using phlebography in patients with a CVAS, Verso et al. [25] found that the incidence of thrombosis in two groups receiving low molecular weight heparin (LMWH) or placebo for 6 weeks was 14.1 and 18%, respectively (95% CI 0.47–1.31; $P = 0.35$), with symptomatic upper limb thrombosis seen only in 1.0% of the LMWH group and 3.1% of the placebo group (hazard ratio 0.32; 95% CI 0.07–1.66). In another trial by Couban et al. [12], the rate of symptomatic thrombosis in a group received 1-mg warfarin for 9 weeks was 4.6% when compared with 4.0% in the placebo group (hazard ratio 1.20; 95% CI 0.37–3.94).

We summarized thromboembolic events reported in nine pivotal studies of bev plus chemotherapy [1–4, 17, 18, 26–28]. According to the results, the incidence of thromboembolism ranged from 3 to 26% in these studies, and PE was reported in 1–4% of cases. Prophylactic anticoagulant treatment was not permitted in any study, except for maintenance of CVAS in four studies [1, 2, 4, 18].

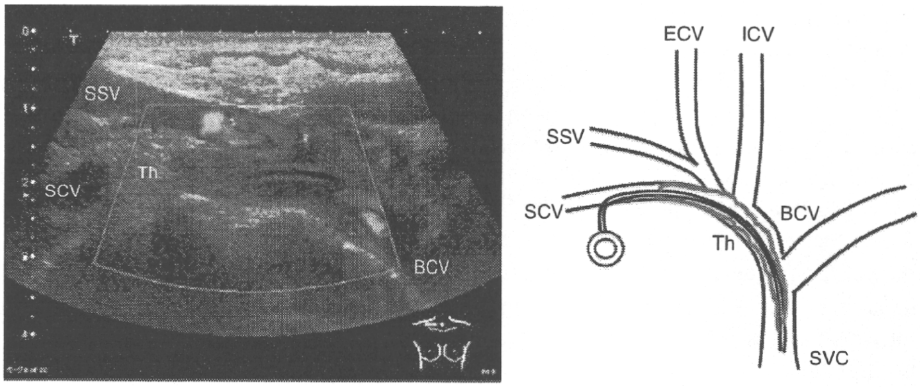

Fig. 2 Findings of DUS image and illustration in symptomatic case. This thrombus (Th) extended into superior vena cava (SVC) through brachiocephalic vein (BCV), was >40 mm in diameter, and resulted in clearly decreased vascular flow

Table 5 Comparison between patients with and without thrombus formation

	With thrombus ($n = 22$)	Without thrombus ($n = 19$)	P value
Sex: male/female	9/13	8/11	>0.9999
Mean age (range), years	62 (16–69)	60.1 (47–69)	0.9896
ECOG performance status, *n* (%)			
0	22 (100)	17 (89.5)	0.2308
1	0	2 (10.5)	
Chemotherapy regimen, *n* (%)			
FOLFOX4 + bev	20 (90.9)	9 (47.4)	0.0047
FOLFIRI + bev	2 (9.1)	10 (52.6)	
Prior treatment, *n* (%)			
FOLFOX	2 (9.1)	10 (52.6)	0.0047
Hepatic arterial infusion	3 (13.6)	4 (21.1)	0.6847
Radiation	3 (13.6)	0	0.2354
No. of involved organs, *n* (%)			
1/2/3/4	10/10/2/0	6/9/3/1	0.3899
≥3	2 (9.1)	4 (21.1)	
Baseline laboratory data, mean ± SD			
Platelets ($\times 10^4$ μl)	22.6 ± 5.68	18.89 ± 6.84	0.0652
INR	1.05 ± 0.49	1.05 ± 0.12	0.9811
D-dimer	1.15 ± 1.52	1.21 ± 0.83	–
Acquired risk factors, *n* (%)			
Anticardiolipin antibody IgG	3 (13.6)	2 (10.5)	>0.9999
Lupus anticoagulants	1 (4.5)	0	>0.9999
Median length (range), *n* (%)			
IP-CVAS—induction of bev	5 days (2–252)	107.5 days (2–695)	0.0048
IP-CVAS—initial DUS	13.5 days (7–259)	116 days (7–700)	0.0059

ECOG Eastern Cooperative Oncology Group, *bev* bevacizumab, *INR* international normalized ratio, *IP-CVAS* implantation of central venous access system, *DUS* Doppler ultrasound imaging, *SD* standard deviation

According to these studies, the incidence of thromboembolic events was not high and routine prophylactic anticoagulant treatment for thromboembolism did not appear necessary.

Patient characteristics in our study were similar to those in previous reports, and no specific characteristics related to thrombus formation were seen. However, we observed a higher rate of thrombi than expected using DUS and almost all of them were asymptomatic. Indeed, this study was designed to detect diagnostic findings, not clinical findings.

This study had a number of limitations. First, there was no control population (with no administration of bev). In other words, thromboembolic events may have been due to prior chemotherapy rather than bev, as only small doses of bev had been given at first screening. Second, the study protocol did not provide true baseline DUS at pre-treatment, as the time to treatment from implantation of the CVAS was usually just 2 days or more. Therefore, it was difficult to establish whether there was a correlation between the treatment drugs and catheter-related thrombosis, or when

thrombus formation occurred, as a CVAS itself is a risk factor for VTE.

However, we did perform DUS at pre-treatment between implantation of the CVAS and induction of bev in a limited number (17) of the patients. The characteristics of these 17 patients showed no differences to those of the other enrolled patients. Of these 17 patients, asymptomatic thrombosis was detected in 5 (29.4%). Of the other 12 patients, 5 showed asymptomatic thrombosis on initial DUS. Treatment with bev was probably associated with thrombus formation in these 5 patients, with incidence lower than that in the total study population (41.7 vs. 53.7%). The characteristics of these 5 patients were also similar to those of the general study population, and their outcomes consisted of a stable thrombus in 3 and asymptomatic progression in 2. The results indicate that a CVAS-associated thrombus prior to induction of bev was not necessarily a significant risk factor for severe thromboembolism.

When comparing the thrombus group with the non-thrombus group, the shorter the time between implantation of CVAS and induction of bev, the greater the risk of thrombus formation, regardless of whether it was symptomatic or asymptomatic. Moreover, a statistically significant difference in thrombus formation was observed between FOLFOX and FOLFIRI (90.9 vs. 9.1%; $P = 0.0047$). However, we do not believe that variation of drugs in FOLFOX versus FOLFIRI was associated with incidence of catheter-related thrombosis, as FOLFOX was used as first-line therapy with implantation of the CVAS, and FOLFIRI as second-line therapy in patients who already had a CVAS. No significant difference in laboratory data was observed between patients receiving FOLFOX and those receiving FOLFIRI; moreover, a shorter time between implantation of the CVAS and induction of bev showed no correlation with poor prognosis of thromboembolism. This point is of particular importance for the physician in treating patients with a bev-based regimen. Therefore, we hypothesized as follows: inhibition of either VEGF or cyclooxygenase (COX)-2-dependent prostacyclin (PGI2) biosynthesis associated with bev may have abolished a tonic protective pathway, thereby increasing the risk of thrombosis. VEGF binds to its major endothelial receptor, kinase insert domain-containing receptor (KDR) or VEGF receptor-2, triggering activation of endothelial nitric oxide synthase (eNOS) and COX-2, enzymes that mediate production of nitric oxide (NO) and PGI2. Bev would interrupt the pathway by which NO and PG12 inhibit platelet aggregation and proliferation of vascular smooth muscle cells, thus increasing risk of thrombosis and arterial wall thickening [29, 30]. Fibroblast growth factor (FGF-2) is quickly released during the wound-healing process, providing an early stimulus for endothelial cell proliferation in the acute phase immediately after injury. FGF-2 appears to be able to up-regulate VEGF production and acts synergistically in stimulating angiogenesis. Platelet-derived growth factor, transforming growth factor-3 and local hypoxia may also regulate VEGF production. Consequently, VEGF increases gradually from the third day after injury onward, providing a sustained stimulus for endothelial cell migration and differentiation into new capillary tubes [31]. Based on these previous reports, we believe that induction of bev in the early phase after implantation of a CVAS may be associated with high risk of thrombus formation due to a low level of VEGF production.

The strength of this study is its prospective assessment of catheter-related thrombus formation using DUS, a highly sensitive and non-invasive strategy. Routine prophylactic anticoagulant treatment at baseline, or if asymptomatic thrombosis was detected, was not permitted; this provided us with the opportunity to evaluate asymptomatic thrombus formation without the influence of prophylactic drugs. The results showed that outcomes in patients with asymptomatic thrombosis mainly depended on changes in thrombus size, as well as decreased vascular flow. In addition, vascular flow appeared to deteriorate with increase in thrombus size.

Our findings indicate that an enlarging thrombus, or large thrombus (>40 mm in diameter), along with decreased venous flow, is a risk factor for symptomatic thromboembolism or PE. Accordingly, we have started to administer prophylactic anticoagulant treatment in such patients at this facility. Further examination of venous flow revealed that thrombi extending into the junction of the SCV, ECV, or SSV strongly affected vascular flow. This finding may furnish an indirect marker of decreased vascular flow.

The American Society of Clinical Oncology provides guidelines on the prevention of recurrent VTE in oncology patients [14]. LMWH is the preferred initial approach for established VTE, and is also preferred in long-term prevention (>6 months). Vitamin K antagonists are an option when LMWH is not available. In Japan, LMWH has not been approved, and unfractionated heparin is used as initial therapy, followed by long-term warfarin therapy with a targeted INR of 2–3.

In conclusion, we propose that routine prophylactic anticoagulant treatment should not be used in patients treated with bev, as bev can increase the risk of bleeding. Therefore, it is important to assess eligibility for bev before treatment and during routine follow-up using available strategies to prevent severe thromboembolism. The results of this study indicate that a period of 1 week or more should be left between introduction of an IP-CVAS to administration of bev to reduce thrombus formation. DUS may offer the optimum strategy for detection of asymptomatic thrombosis in the early cycles of treatment. Moreover,

detection of an enlarging asymptomatic thrombosis developing into the superior vena cava along with decreased vascular flow or extending into the junction of the SCV, ECV, or SSV by DUS may be predictive of subsequent severe symptomatic thromboembolism. Large randomized controlled trials are needed to investigate the mechanism of VTE associated with bev and optimal management of this problem.

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Management of Allergic Reactions to Oxaliplatin in Colorectal Cancer Patients

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Abstract Allergic reactions to oxaliplatin (Eloxatin) may be sufficiently severe to prevent patients from continuing treatment. Oxaliplatin is a key drug that improves the survival of colorectal cancer patients; however, a uniform approach to prevent allergic reactions in patients using this drug has not been established. We investigated the safety and efficacy of our own preventive strategy in colorectal cancer patients receiving the 5-fluorouracil/leucovorin plus oxaliplatin (FOLFOX4) regimen. Each patient received the primary prevention regimen before oxaliplatin infusion during the first cycle and diphenhydramine after cycle 4. Patients who experienced grade 1 or 2 allergic reactions subsequently received the secondary prevention regimen with a higher dose of dexamethasone and prolonged oxaliplatin infusion to allow continued treatment. Oxaliplatin was discontinued in patients with grade 3 or 4 allergic reactions. Forty-eight patients (17.6%) developed allergic reactions, and 30 patients underwent retreatment with the secondary prevention regimen. Nineteen patients (63.3%) showed no reactions during at least 2 cycles; most could be treated for 4 months longer than could patients who did not respond to secondary prevention. This preventive strategy was both safe and effective, allowing patients to continue treatment without detriment to their quality of life.

Oxaliplatin (Eloxatin) is a third-generation platinum compound that is widely used to treat colorectal cancer. The drug usually is given in combination with 5-fluorouracil (5-FU) and leucovorin (LV) as one part of the FOLFOX regimens, which have shown efficacy in several large-scale clinical trials.[1–5] Allergic reactions and hypersensitivity to oxaliplatin are chronic adverse events that usually manifest as type I reactions and that are characterized by cutaneous, respiratory, and digestive symptoms. Such allergic reactions have been reported in 2%–15% of treated patients; in 2%–3% of cases, these reactions are severe to life-threatening.[6–9]

Allergic reactions to other platinum compounds (eg, cisplatin, carboplatin) have been reported mainly in the gynecology field; the role of type I allergy in such reactions has been suggested. According to the literature, hypersensitivity to cisplatin and carboplatin occurs in 5%–27% of treated patients and increases as more courses are given.[10–19] Reactions occur within several minutes of starting administration. In contrast to prevention of taxane allergy, prophylaxis of hypersensitivity reactions to platinum compounds using steroids and/or antihistamines is not very effective.[10–19]

The number of Japanese clinical reports about allergic reactions to oxaliplatin is not large, because the incidence of such reactions is not high; further, the drug was introduced in Japan only a few years ago. Allergic reactions account for approximately 10% of all adverse events, and just 5% of related grade 3/4 events, reported for this platinum drug. They rarely occur after the first dose of oxaliplatin; generally, they develop after about 6 cycles.[6,7,20] In the Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer (MOSAIC) trial,[8,9] allergic reactions occurred in 10.6% of treated patients, although only 2.9% suffered grade 3/4 events.

The pathophysiology of these allergic reactions has not been clarified. However, a role of immunoglobulin E-mediated, type I allergy resulting from sensitization during previous cycles often has been suggested, along with some reports of type II allergy.[21–23] Oligo- or polyclonal T-cell expansion induced by the platinum salt targets a superan-

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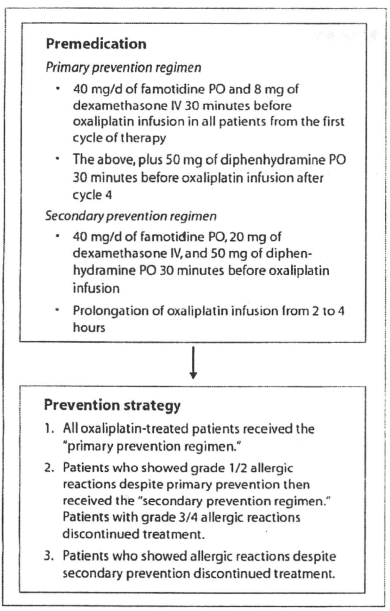

Figure 1 Preventive Strategy Against Allergic Reactions in Patients Receiving 5-Fluorouracil/Leucovorin Plus Oxaliplatin (FOLFOX4) Therapy

Abbreviations: PO = orally; IV = intravenously

tigen on peripheral blood mononuclear cells, leading to the release of pro-inflammatory cytokines. The existence of other unknown binding proteins also has been suggested.[24,25]

The incidence of neurotoxicity, the dose-limiting toxicity of oxaliplatin, increases in a cycle-dependent manner, and severe symptoms and allergic reactions may necessitate discontinuation of the drug.[26] Tumor progression also may be a factor that promotes allergic reactions, since cytokines or binding proteins may be released and may stimulate the immune system.

The onset of most allergic reactions occurs within several minutes after the start of oxaliplatin infusion, and the reaction usually resolves within 2 hours. Cutaneous symptoms are most common, followed by respiratory symptoms, digestive reactions, and generalized reactions. The majority of reactions are grade 1/2, although a few severe reactions (eg, anaphylactic shock) and, rarely, death may occur.

Treatment of allergic reactions usually involves stopping the oxaliplatin infusion and administering antihistamines and/or steroids. Subsequent management is more controversial. Discontinuation of oxaliplatin therapy may be the appropriate approach, but an alternative is discontinuation of therapy in patients with severe allergic reactions; therapy may be continued if a mild-to-moderate reaction occurs and if the patient is expected to benefit from further treatment.[6,7,9,11] When treatment is continued, patients receive prophylactic therapy (ie, antihistamines and steroids) and/or a longer duration of oxaliplatin infusion. Desensitization may allow continuation of therapy; however, the large number of patients who receive oxaliplatin makes this strategy impractical.[27]

After oxaliplatin was approved in Japan in March 2005, we encountered allergic reactions, including some severe cases, in approximately 18% of our patients. The occurrence of severe reactions prompted us to monitor our patients carefully for all allergic reactions, particularly during ambulatory therapy.

This research was designed to evaluate the safety and efficacy of two regimens given to prevent allergic reactions in colorectal cancer patients receiving oxaliplatin at our hospital. We also investigated possible risk factors for allergic reactions, including advanced neurotoxicity and tumor progression.

Methods

PARTICIPANTS

The enrollment criteria for this study follow: histologically confirmed colorectal cancer, advanced metastatic disease, age up to 75 years, Eastern Cooperative Oncology Group performance status of 0–2, and no prior use of oxaliplatin. The treatment protocol was approved by the Institutional Review Board, and written informed consent was obtained from all patients.

TREATMENT REGIMEN

From April 2005 to August 2006, patients were treated with the oxaliplatin-based 5-FU/LV plus oxaliplatin (FOLFOX4) regimen as first-line or subsequent therapy. The regimen involved biweekly cycles. On day 1, patients received 85 mg/m^2 of oxaliplatin infused intravenously (IV) over 2 hours in 250 mL of 5% glucose plus a bolus dose of 400 mg/m^2 of 5-FU IV and 100 mg/m^2 of l-leucovorin (l-LV) IV over 2 hours, followed by 600-mg/m^2 of 5-FU via IV infusion for 22 hours. The same 5-FU plus l-LV regimen was used on day 2.

PREVENTIVE STRATEGY

Our preventive strategy is outlined in Figure 1. The primary regimen involved administration of 40 mg/d of the histamine-2-receptor antagonist famotidine orally (PO) and 8 mg of dexamethasone IV 30 minutes before the oxaliplatin infusion began. This regimen was given to all oxaliplatin-treated patients from the first cycle of therapy; 50 mg of the histamine-1-receptor antagonist diphenhydramine was given PO after cycle 4.

Patients having any allergic reactions in spite of receiving primary prevention then received the secondary prevention regimen, which entailed 40 mg/d of famotidine PO plus 20 mg

Table 1

Baseline Patient Characteristics (n = 48)

CHARACTERISTIC	VALUE
Gender, n	
Male	27
Female	21
Mean age, years	58
Range, years	34–75
Incidence, n (%)	48/272* (17.6)
Prior chemotherapy, n (%)	
Yes	30 (62.5)
5-Fluorouracil	29 (60.4)
Irinotecan	11 (22.9)
No	18 (37.5)
Allergy history, n (%)	
Yes	17 (35.4)
Iodine	4 (8.3)
Ethanol (for disinfection)	2 (4.2)
Asthma	5 (10.4)
Others	9 (18.8)
No	31 (64.6)
Antitumor effect, n (%)†	
Partial response	12 (25.0)
Stable disease	31 (64.6)
Progressive disease	4 (8.3)
Not evaluable	1 (2.1)
Partial response plus stable disease	43 (89.6)
Neurotoxicity, n (%)†	
Grade 0	1 (2.1)
Grade 1	38 (79.2)
Grade 2	9 (18.8)

*272 patients treated with FOLFOX4 (5-fluorouracil/leucovorin plus oxaliplatin)
†Antitumor effect and neurotoxicity were evaluated when allergic reactions occurred.

Table 2

Features of Allergic Reactions (n = 48)

FEATURE	VALUE
Median number of cycles	9
Range	4–16
Median total dose of oxaliplatin (mg/m²)	680
Range	255–1,275
Time to onset of symptoms, n (%)	
< 30 min	16 (33.3)
> 30 min	32 (66.7)
Symptoms, n (%)	
Cutaneous reaction	
Redness	41 (85.4)
Pruritus	36 (75.0)
Urticaria	19 (39.6)
Respiratory symptoms	
Dyspnea	7 (14.6)
Decreased arterial oxygen saturation	8 (16.7)
Digestive symptoms *	5 (10.4)
Generalized reaction	
Hypotension	7 (14.6)
Sweating	5 (10.4)
Fever	4 (8.3)
Chills	1 (2.1)
Grade, n (%)	
1	34 (70.8)
2	7 (14.6)
3/4	7 (14.6)
Treatment of allergic reactions, n (%)	
Stopped oxaliplatin infusion	43 (89.6)
Steroids †	26 (54.2)
Antihistamine‡	17 (35.4)
Rapid fluid infusion	7 (14.6)
Duration of allergic reaction, n (%)	
< 120 min	47 (97.9)
120 min to 24 h	1 (2.1)
> 24 h	0

*Vomiting, nausea, abdominal pain
†100 mg of hydrocortisone intravenously
‡Diphenhydramine or chlorpheniramine

of dexamethasone IV and 50 mg of diphenhydramine PO 30 minutes before the oxaliplatin infusion began. In addition, the duration of oxaliplatin infusion was increased from 2 hours to 4 hours for patients within mild (grade 1) to moderate (grade 2) allergic reactions. Oxaliplatin was discontinued in patients with severe (grade 3) or potentially life-threatening/disabling (grade 4) allergic reactions.

EVALUATION OF TOXICITY/EFFICACY

Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.[28] Data on toxicity and tumor responses were obtained from electronic medical records and examination of films for each patient. The safety of premedication also was assessed from electronic medical records, laboratory results, and vital sign data.

Neurotoxicity and tumor progression were re-evaluated at the time of allergic reaction as possible risk factors for such reactions. Tumor response was assessed by the Response Evaluation Criteria in Solid Tumors[29]; this assessment was based mainly upon computed tomography scans obtained every 3 months.

STATISTICAL ANALYSIS

The chi-square test and Fisher's exact probability test were used to compare categorical data. Differences between the mean values of continuous variables were assessed by the Student's *t*-test and confirmed by the Mann-Whitney *U*-test. In all analyses, a *P* value of less than 0.05 indicated statistical significance.

Results

Among the 272 patients (140 men, 132 women) who were treated with oxaliplatin and the primary-prevention regimen, 48 (17.6%) developed allergic reactions. Their gender, age, prior chemotherapy, and history of allergy were not risk factors for such events. Tumor progression and neurotoxicity also were not related to development of allergic reactions (Table 1).

Table 3

Comparison of Grade 3/4 and Grade 1/2 Reactions (n = 48)

CHARACTERISTIC	GRADE 3/4 (n = 7)	GRADE 1/2 (n = 41)	P VALUE
Gender			
Male	7	20	0.013
Female	0	21	
Mean age, years	55	58	0.554
Range, years	40–75	34–75	
Median cycle number	8	9	
Range	5–12	4–16	0.288
Symptoms, n (%)			
Cutaneous	5 (71.4)	39 (95.1)	0.038
Respiratory	4 (57.1)	7 (17.1)	0.021
Digestive	3 (42.9)	2 (4.9)	0.002
Generalized*	7 (100.0)	4 (9.8)	< 0.001
Hypotension	7 (100.0)	0	< 0.001
Sweating	4 (57.1)	1 (2.4)	< 0.001
Fever	1 (14.3)	3 (7.3)	0.479
Chills	0	1 (2.4)	> 0.999

*Generalized reactions included fever, sweating, chills, malaise, and hypotension.

Features of the allergic reactions are summarized in Table 2. Allergic reactions occurred after a median of 9 cycles (range, 4–16 cycles); the median total dose of oxaliplatin was 680 mg/m^2 (range, 255–1,275 mg/m^2). All allergic reactions were detected within 2 hours of infusion; in 33.3% of patients, they were detected in less than 30 minutes. Skin reactions were observed most frequently, followed by respiratory symptoms. In all, 41 reactions (85.4%) were grade 1 or 2 events, whereas the other 7 reactions (14.6%) were severe, including 1 grade 4 event. Infusion of oxaliplatin was discontinued immediately, except when symptoms were detected initially at the end of the scheduled infusion. Administration of antihistamines or a steroid (eg, hydrocortisone) or rapid fluid infusion was given, as appropriate. Most patients recovered completely within 2 hours. Oxaliplatin infusion was resumed on the same day at the previous rate in two patients and at a slower rate in an additional two patients without recurrence.

Comparison of clinical features between patients with severe allergic reactions and those with grade 1/2 reactions showed that severe reactions only occurred in men ($P = 0.013$); no other significant risk factors were apparent. Respiratory and digestive symptoms and more generalized reactions (eg, hypotension, fever) were more common among patients experiencing severe reactions than among those having grade 1/2 reactions (Table 3).

A total of 30 patients underwent retreatment with oxaliplatin using the secondary prevention regimen. We defined success as prevention of allergic reactions during at least 2 cycles and failure as any lesser outcome. The results obtained with secondary prevention are summarized in Table 4. Allergic reactions occurred in 11 patients (36.7%) within 2 cycles; 3 patients (27.3%) were so affected during the second cycle. Prevention

Table 4

Outcome of the Secondary Prevention Regimen (n = 30)

ALLERGIC REACTION	n (%)
Effective*	19 (63.3)
Ineffective	11 (36.7)
Episodes of prevention in ineffective patients†	11
1	8 (72.7)
2	3 (27.3)
Episodes of prevention until discontinuation due to re-allergic reaction in effective patients‡	6
< 4	3 (15.8)
4 to < 8	3 (15.8)
8 to < 12	0
12 to < 16	0
> 16	0§
Episodes of prevention until discontinuation due to disease progression in effective patients	11
< 4	5 (26.3)
4 to < 8	4 (21.1)
8 to < 12	1 (5.3)
12 < 16	0
> 16	1§
Comparison of second allergic reaction with first in effective patients	6
Equivalent	6
Worse	0
Better	0
Comparison of second allergic reaction with first in ineffective patients¶	11
Equivalent	9 (81.8)
Worse	2 (18.2)
Better	0

*Successful prevention for at least two courses was defined as effective.

†Almost all additional reactions occurred during the first course among ineffective cases.

‡In effective patients, prevention usually was successful for at least 4 courses (2 months). Two patients have continued treatment for over 16 courses.

§Continuing treatment in 2

¶Serious reactions occurred in 2 patients, and 1 had a grade-3 reaction.

was successful for at least 2 cycles in the other 19 patients. Eleven patients discontinued FOLFOX4 due to tumor progression, and 6 patients discontinued therapy after experiencing allergic reactions during courses 3–6. The other two patients were successfully treated a total of 16 and 22 times, respectively. In the 11 patients for whom prophylaxis failed, a comparison of the reactions occurring during primary and secondary prophylaxis showed that two patients had worse reactions after secondary prophylaxis, and one had a grade-3 reaction.

The safety of the premedications is summarized in Table 5. Drowsiness due to diphenhydramine was observed in two patients (4.2%), and a mild/moderate increase of blood pressure associated with 8 mg or 20 mg of dexamethasone occurred in three patients (6.3%) and 2 patients (6.7%), respectively. There was no cytopenia nor neurologic or digestive manifestations caused by famotidine in any of the patients. No other severe reactions occurred, and there were no other treatment-related severe adverse events or deaths.

We evaluated the benefit of our secondary prevention

regimen by comparing the 19 effective cases with the 11 ineffective cases, as shown in Figure 2. The median number of cycles until the first allergic reaction was 9 in the group for which prevention was effective and 10 in the other group ($P = 0.349$). The median treatment time was 285 days in the effective group versus 164 days in the ineffective group (95% confidence interval: 76–250; $P = 0.0006$).

Discussion

The safety and efficacy of our preventive approach using two regimens for oxaliplatin allergy were evaluated. Comparing our experience with that of previous reports,[6–9,20] the median number of cycles during which allergic reactions developed and symptoms reported were similar, but the incidence (17.6%) was higher in our patients than in those of previous studies (2%–15%). The overall incidence of allergic reactions was higher in our study than in the MOSAIC trial[8] (17.6% vs 10.3%, respectively); the same was true for severe reactions (14.6 vs 2.9%, respectively).

Our analysis failed to reveal any risk factors for allergic reactions (eg, history of allergy, occurrence of tumor progression) among patient characteristics. However, there was a significant difference between genders with respect to the risk of severe allergic reactions; this finding must be investigated further in a larger number of patients. In our series, seven patients experienced severe reactions, and they suffered from more symptoms (except cutaneous reactions) than did patients having grade 1/2 reactions. However, these severe reactions all were managed with immediate treatment, and no secondary complications or deaths occurred. To our knowledge, there has been no previous examination of the incidence of grade 3/4 allergic reactions resulting from continued oxaliplatin exposure in patients receiving a specific preventive regimen after experiencing grade 1/2 reactions. Some clinicians at other institutions use preventive methods that are similar to our schemes, but the safety and efficacy of such methods have not been confirmed. Therefore, none of our grade 1/2 patients was assigned to continue FOLFOX4 therapy without prophylaxis because of the risk of complications.

We chose a preventive strategy that included two regimens to promote continuation of therapy, and 63% of our patients showed some benefit. When secondary prevention was successful, most patients (excluding those with tumor progression) could continue FOLFOX4 for 4 or more cycles without experiencing further allergic reactions; these patients were able to receive an additional 4 months of treatment as compared with patients who did not benefit from the strategy.

The outcome of re-exposure to oxaliplatin after a grade-1/2 reaction with or without premedication has been described by several other authors. Brandi et al[7] reported that 6 of 17 patients having mild allergic reactions were re-exposed to oxaliplatin after receiving premedication with steroids and antihistamines, and 5 of the 6 developed further reactions. Maindrault-Goebel et al[8] studied 42 patients who had allergic reactions to oxaliplatin, and 8 of 15 patients (53.3%) who underwent retreatment with an increased duration of oxaliplatin infusion could continue therapy. Siu et al[20] reported that 14 oxaliplatin-allergic patients were re-exposed to the drug after receiving a steroid and chlorpheniramine as premedication; four patients (28.6%) had further reactions, including two patients (14.3%) who had grade 3/4 reactions. According to these studies, both administration of steroids plus antihistamines and prolongation of oxaliplatin infusion were moderately effective in preventing further reactions. However, previous strategies were not uniform, and the details of each protocol and its outcome were not clarified.

When compared with these other studies, our preventive strategy was similarly effective. The strengths of our study included a uniform premedication strategy and a defined prevention plan, which allowed us to evaluate our strategy easily. These results suggested that our strategy allows continued oxaliplatin treatment—therefore, it should be considered an option for preventing allergic reactions to this drug. However, this study also demonstrated that prolonged oxaliplatin treatment

Table 5

Safety of the Premedications

DRUG*	SYMPTOMS	n (%)
Diphenhydramine, 50 mg (n = 48)	Headache	2 (4.2)
	Drowsiness	2 (4.2)
	Fatigue	1 (2.1)
	None	44 (91.7)
Dexamethasone, 8 mg for primary prevention (n = 48)	Facial flushing	4 (8.3)
	Insomnia	4 (8.3)
	Increased blood pressure	3 (6.3)
	Fever	3 (6.3)
	Headache	2 (4.2)
	None	36 (75)
Dexamethasone, 20 mg, for secondary prevention (n = 30)	Facial flushing	1 (3.3)
	Increased blood pressure	2 (6.7)
	Fever	2 (6.7)
	None	23 (76.7)

*No symptoms related to famotidine were observed

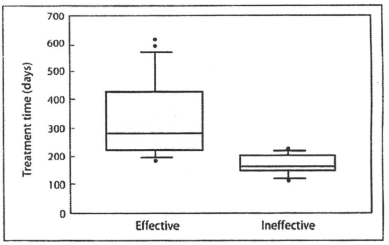

Figure 2 Benefit of the Secondary Prevention Regimen

The median treatment time for the effective and ineffective groups was 285 days and 164 days, respectively (95% confidence interval: 76–250; $P = 0.0006$).

resulted in a continued increase in the risk of allergic reactions. Therefore, to lessen the risk of allergic reactions to oxaliplatin, it seems prudent to limit the treatment period to 4–4.5 months (8 or 9 cycles of FOLFOX4; total dose, 680–765 mg/m^2). This recommendation allows patients enough time to achieve the maximum tumor response, as it helps them to avoid severe neurotoxicity[26] and diminishes the risk of allergic reactions.

In previous studies, the median time to tumor response was 9 weeks in patients treated with FOLFOX4[2]; patients receiving oxaliplatin experienced severe neurotoxicity after a cumulative dose of 780–850 mg/m^2. In our study, nine patients developed grade 2 neurotoxicity after a median of 4 months (8 cycles of FOLFOX4) and a median total dose of 676 mg/m^2 (range, 340–1,105 mg/m^2) without experiencing any severe allergic reactions. We still are investigating predictors of allergic reactions to oxaliplatin that may enable us to avoid severe reactions.

In conclusion, severe reactions to oxaliplatin generally are manageable if appropriate treatment is provided immediately. Oxaliplatin-based chemotherapy will continue to be first-line treatment for various cancers. Therefore, an appropriate strategy to prevent such allergic adverse reactions should be devised and assessed in a larger trial.

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Chemotherapy for Small-Bowel Adenocarcinoma at a Single Institution

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Abstract

Purpose. Small-bowel adenocarcinoma (SBA) is rare. No standard chemotherapy for this type of cancer has yet been established. At Cancer Institute Hospital (CIH), the chemotherapy regimen used for colorectal cancer is initially used for patients with SBA, followed by that used for gastric cancer.

Methods. Patients with advanced or recurrent SBA who had been treated with chemotherapy in CIH were retrospectively analyzed. The first-line treatments were fluoropyrimidines used alone or in combination with other drugs, such as 5-fluorouracil plus leucovorin (FL), UFT-E, or TS-1. The second-line treatment was irinotecan (CPT-11) monotherapy.

Results. Fluoropyrimidine-based regimens, mainly FL, were used for 10 patients. Seven patients received the second-line CPT-11 regimen. Disease control was seen in five patients (50%) with the first-line chemotherapy and in three (43%) with the second-line. The median overall survival time was 12 months (range 3–39). The treatments were generally tolerated. Gastrointestinal symptoms were the most common adverse effects.

Conclusions. Fluoropyrimidines as the first-line and CPT-11 as the second-line chemotherapy yielded low response, although the adverse effects were mild. The FOLFOX and FOLFIRI regimens such as those used for metastatic colorectal cancer are potential alternative strategies. Extensive trials are needed to develop standard chemotherapy with new drugs.

Key words Small bowel · Adenocarcinoma · Chemotherapy · 5-Fluorouracil · Irinotecan

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Introduction

Small-bowel adenocarcinoma (SBA) is a rare cancer. Patients suffering from this type of tumor are likely to have a poor prognosis.[1–3] No efficacious standard chemotherapy has been developed that can prolong survival. No aggressive large-scale clinical trial has been undertaken in Japan because of the rarity of this cancer in comparison to other forms of gastrointestinal cancer. In general, empirical chemotherapy regimens established for gastric and colorectal cancer have been used for SBA, with unsatisfactory results.

Patients and Methods

Patients

Patients diagnosed with unresectable or recurrent SBA were treated with chemotherapy between August 2001 and March 2006. The patients' data were retrieved from the tumor registry at Cancer Institute Hospital and the extracted patients' records were reviewed retrospectively.

Chemotherapy

The chemotherapeutic strategy of SBA was discussed and fluoropyrimidine-based chemotherapies were chosen as the first-line, followed by irinotecan (CPT-11) monotherapy as the second-line in the regular Digestive Cancer Board Meeting.

Toxicity and Efficacy Evaluation

Adverse effects were evaluated and graded according to the National Cancer Institute Common Toxicity Criteria.[4] The response was assessed using computed tomography (CT) according to the RECIST criteria,

every 12 weeks. The data of toxicity and tumor evaluation were analyzed retrospectively from the medical records and the examination films of each patient.

The progression-free survival time and overall survival time were defined as the time between the date of treatment initiation and the date of diagnosis of disease progression or death with the date at which the patient was last confirmed to be alive, respectively, using the Kaplan–Meier method.[5]

Results

Study Population

Ten patients with advanced SBA received chemotherapy between August 2001 and March 2006. The characteristics of all evaluated patients are detailed in Table 1. The median age was 60 years (range 37–77). The performance status scores varied from 0 to 2. The locations of the primary small-bowel adenocarcinoma were 7 in the duodenum, 1 in the jejunum, and 2 in the ileum. The metastatic or recurrent sites when chemotherapy for SBA was begun were 4 in the local region, 4 in the liver, 4 in the peritoneum, and 4 in the para-aortic lymph nodes. Six patients underwent a noncurative operation as the primary treatment followed by chemotherapy, and one patient underwent chemotherapy immediately.

Table 1. Patient characteristics ($n = 10$)

Characteristics	No. of patients
Median age, years (range)	60 (37–77)
Male/female	6/4
ECOG performance status: first-line/second-line	
0	7/3
1	1/1
2	2/3
Primary site	
Duodenum (papilla of Vater)	7 (3)
Jejunum	1
Ileum	2
Metastatic sites	
Liver	4
Nodal (Para-aortic lymph node)	4
Peritoneum	4
Locoregional	4
Histological differentiation	
Adenocarcinoma	10
Well-differentiated	1
Moderately differentiated	1
Poorly differentiated	1
Unknown	7
Operation method ($n = 9$)	
Bypass	3
Partial resection	4
Pancreatoduodenectomy	2
Tumor size (mm)	
< 40/40–80/unknown	2/2/6
Depth of invasion	
SS/SE/SI/unknown	2/1/1/6
Extent of lymph node metastasis	
N0/N1/N2/N3/N4/Nx	3/1/0/1/4/1
Lymphatic invasion	
Positive/negative/unknown	1/1/8
Venous invasion	
Positive/negative/unknown	1/1/8
Curability of surgery ($n = 9$)	
A/B/C	2/1/6

ECOG, Eastern Cooperative Oncology Group

Response and Survival

Fluoropyrimidine-based regimens were carried out on 10 patients. A 5-fluorouracil plus leucovorin (FL) regimen was used as the first-line treatment for seven patients: four of those received the Mayo Clinic regimen; 5-fluorouracil (5-FU), 500 mg/m^2 of body-surface area and leucovorin (LV), 20 mg/m^2 for 5 days; three received the Roswell Park Memorial Institute (RPMI) regimen, weekly for 6 weeks followed by a 2-week rest period; D,L-leucovorin (D, L-CF; 500 mg/m^2 in a 2-h infusion) with 5-FU (600 mg/m^2 i.v. bolus) 1 h after the D, L-CF infusion began and the others were treated with oral drugs: UFT-E 300 mg/body, twice daily every day; TS-1 40 mg/m^2 twice daily on days 1 through 28 every 42 days. Seven patients received the second-line CPT-11 regimen, 150 mg/m^2, given biweekly, after a confirmed diagnosis of disease progression during the first-line chemotherapy (Table 2).

The antitumor response to the first-line chemotherapy was partial response (PR) in one patient, stable disease (SD) in four patients, and progressive disease (PD) in four patients. The response to the second-line chemotherapy was three patients in SD and four in PD (Tables 3 and 4). The median progression-free survival following the first-line fluoropyrimidine-based regimen and the second-line CPT-11 was 81 days (range 27–666) and 71 days (range 14–935), respectively. The median overall survival time was 12 months (range 3–39). Six patients succumbed to tumor progression with systemic disease, three are still alive, and one was transferred to another hospital for supportive care (Fig. 1).

Safety

The adverse effects are summarized in Tables 5 and 6. Both treatments were generally tolerated. Gastrointestinal symptoms were the most common in both regimens; two patients had grade 3 nausea. Grade 3 neutropenia was only seen in one patient undergoing the CPT-11 regimen and no other severe hematologic toxicity occurred.

Table 2. Treatment and survival

Patient	Age (years)/Sex	Primary site	Regimens	PFS (days)	Survival time (months)
1	42/M	Jejunum	FL (Mayo)	63	12 (dead)
			CPT-11	52	
2	68/F	Papilla Vater	FL (Mayo)	27	3 (dead)
			CPT-11	14	
3	38/F	Duodenum	FL (Mayo)	34	39 (dead)
			CPT-11	935	
4	37/M	Duodenum	FL (Mayo)	226	12 (dead)
			CPT-11	82	
5	54/M	Papilla Vater	UFT-E	49	7*
			CPT-11	216	
6	77/F	Ileum	S-1	666	28 (alive)
7	67/F	Jejunum	FL (RPMI)	164	16 (dead)
			CPT-11	21	
8	66/M	Papilla Vater	FL (RPMI)	248	12 (dead)
9	70/M	Ileum	FL (RPMI)	377	19 (alive)
10	47/M	Duodenum	FL (RPMI)	81	6 (alive)
			CPT-11	71	

*This patient was transferred to another hospital for supportive care
PFS, Progression-free survival; FL, 5-fluorouracil plus leucovorin; RPMI, the Roswell Park Memorial Institute

Table 3. Response rates to the fluoropyrimidine-based regimen ($n = 10$)

Status	*N* (%)
Complete response	0 (0)
Partial response	1 (10)
Stable disease	4 (40)
Progressive disease	4 (40)
Not evaluable for response	1 (10)

Table 4. Response rates to the CPT-11 regimen ($n = 7$)

Status	*N* (%)
Complete response	0 (0)
Partial response	0 (0)
Stable disease	3 (42.9)
Progressive disease	4 (57.1)
Not evaluable for response	0 (0)

Table 5. Toxicity profile for the fluoropyrimidine-based regimen

Toxicity	All grades (%)	Grade 3/4 (%) ($n = 9$)
Diarrhea	3 (33.3)	0 (0)
Stomatitis	0 (0)	0 (0)
Alopecia	0 (0)	0 (0)
Nausea	6 (66.7)	1 (11.1)
Infection	0 (0)	0 (0)
Hand-foot syndrome	0 (0)	0 (0)
Fever	0 (0)	0 (0)
Fatigue	3 (33.3)	0 (0)
Anemia	2 (22.2)	0 (0)
Neutropenia	0 (0)	0 (0)
Thrombocytopenia	0 (0)	0 (0)

Table 6. Toxicity profile for the CPT-11 regimen

Toxicity	All grades (%)	Grade 3/4 (%) ($n = 7$)
Diarrhea	3 (42.9)	0 (0)
Stomatitis	0 (0)	0 (0)
Alopecia	2 (28.6)	0 (0)
Nausea	4 (57.1)	1 (14.3)
Infection	0 (0)	0 (0)
Hand–foot syndrome	0 (0)	0 (0)
Fever	0 (0)	0 (0)
Fatigue	2 (28.6)	0 (0)
Anemia	3 (42.9)	0 (0)
Neutropenia	1 (14.3)	1 (14.3)
Thrombocytopenia	0 (0)	0 (0)

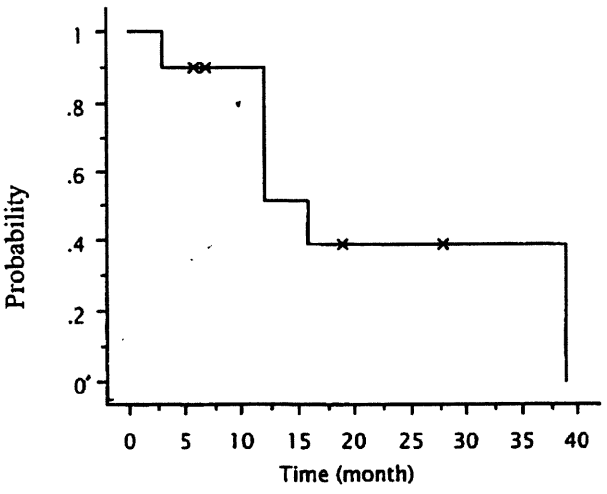

Fig. 1. The overall survival of 10 patients treated with chemotherapy against small-bowel adenocarcinoma

Discussion

Small-bowel tumors are often difficult to diagnose preoperatively. Adenocarcinoma is the most common histology, with a poor prognosis in comparison to carcinoid tumors.[6-8]

Surgery is the usual primary treatment for small-bowel tumors.[6,9,10] For malignancies, standard segmental resections or, if necessary, an extended radical resection including the adjacent organs or as much of the mesentery as is reasonable are recommended. Palliative operations are performed in oncologic emergencies such as gastrointestinal bleeding, obstruction, or perforation. Frost et al. reviewed 30 years of experience with small-bowel adenocarcinoma in their institute and reported the 10-year survival rates of all stages — stage I, II, III and a subgroup of 10 patients (one stage I, seven stage II, two stage III) — undergoing a pancreaticoduodenectomy to be 24%, 75%, 25%, 0%, and 30%, respectively.[9] Talamonti et al. reported their review of 129 surgically treated patients with small-bowel cancer and the prognostic factors for this rare cancer. The 5-year survival rate for an adenocarcinoma was 37%, in which the median survival of patients treated with a curative resection was better than patients with palliative surgery (37 months and 10 months, respectively).[10] According to the reports, late stage was a prognostic factor, while tumor location, size, and patient age were not significant. In addition, aggressive achievement of a sufficient surgical margin and if necessary, extended surgery such as a pancreaticoduodenectomy, are recommended to reduce the risk for local or peritoneal recurrence.

Of the three patients receiving a curative resection in the current study, two underwent a pancreaticoduodenectomy. However, intraoperative extended lymph node metastases were seen in one patient, resulting in para-aortic lymph node metastases. The other patient underwent a partial duodenectomy and the tumor microscopically invaded the serosa, concluding with peritoneal metastases and bilateral ovarian metastases.

In previous reports, few instances of effective chemotherapy and only a small number of large-scale clinical trials have been reported. Gibson et al. administered the FAM regimen (5-FU, mitomycin C, doxorubicin, 5-FU, 600 mg/m^2 on days 1, 8, 29, and 36; mitomycin C, 10 mg/m^2 on day 1; and doxorubicin, 30 mg/m^2 on days 1 and 2) in 38 patients with SBA. In that study, the response rate was 18.4%, including two complete responses; the median survival time was 8 months.[11] Jigyasu et al. also reported their experience using FAM-based regimens at the M.D. Anderson Cancer Center for 14 patients; the MST was 9 months, which was also inadequate.[12] Crawley et al. reported the Royal Marsden experience with protracted venous infusion of 5-FU administration in eight SBA patients with a response rate of 37.5%, including one complete response (CR). The MST and PFS were 13 and 7.8 months, respectively.[13] Polyzos et al. reported the use of irinotecan as salvage chemotherapy for SBA, mentioning irinotecan as a potentially key drug for metastatic SBA similar to metastatic colorectal cancer.[14] Locher et al. assessed the efficacy of 5-FU and either platinum compounds (cisplatin, carboplatin, oxaliplatin) or irinotecan in patients with advanced SBA. Using a combination of 5-FU and platinum compounds, the overall response rate was 21% and median progression-free and overall survival 8 and 14 months, respectively, with tolerable toxicity. The combination of 5-FU and irinotecan as a second-line treatment resulted in 50% disease stabilization with 5 months as the median progression-free survival. But no response was seen in the second-line 5-FU and cisplatin chemotherapy, and the need to try a 5-FU–irinotecan combination chemotherapy as the first-line treatment was indicated.[15] Onodera et al. reported a case of small-bowel adenocarcinoma with extensive lymph node metastases, which showed CR for 10 months after palliative surgery by use of 5-FU and methotrexate sequential chemotherapy.[16] The regimen is generally used for advanced gastric cancer patients who have poor performance status or are unable to receive the current intensive chemotherapy regimens such as S-1 combined regimens.[17-19]

In the current study, an oral fluoropyrimidine agent or bolus 5-FU/LV as the first-line and CPT-11 monotherapy as the second-line, such as the regimen used for metastatic colorectal cancer, were chosen for almost all of the patients. For that reason, no standard chemotherapy against gastric cancer has been established in recent years though both 5-FU and irinotecan were approved and bolus 5-FU/LV had been the standard treatment for first-line metastatic colorectal cancer (mCRC) and CPT-11 monotherapy for the second line until 2004 in Japan, which was applied to SBA patients. This study revealed this strategy to be insufficient against SBA. The FOLFOX or FOLFIRI regimens, which have been the new standard for mCRC in Japan since the approval of infusion of 5-fluorouracil and oxaliplatin in early 2005, are being considered for the treatment of SBA.[20,21] In the present cases, fluoropyrimidines as the first-line chemotherapy produced low response, but S-1 showed some potential, although the treatment was used in only one patient. The efficacy of S-1 or S-1 combined chemotherapy against gastric cancer was demonstrated in 2007, which also provides another indication for application to SBA.[18,19]

Therefore, more intensive chemotherapy is required against this rare malignancy to improve its present poor prognosis. In addition, aggressive surgery to achieve a sufficient surgical margin, followed by adjuvant chemo-

therapy in the later stages, is essential to reduce recurrence. Extensive trials to develop a standard chemotherapy regimen for SBA using capecitabine, oxaliplatin, CPT-11, or S-1 with new drugs such as vascular endothelial growth factor (VEGF) antibodies and epidermal growth factor receptor (EGFR) antibodies, which have been initiated for colorectal cancer, should therefore be started for SBA.[22,23]

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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.

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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 x 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).

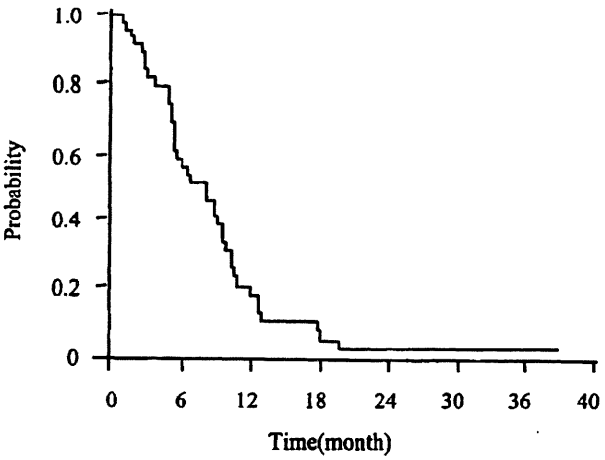

Fig. 1. Progression-free survival of patients treated with modified irinotecan plus bolus 5-fluorouracil/L-leucovorin (IFL) ($n = 47$)

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						
≤8 × 10^3/mm^3	1			1		
<8 × 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

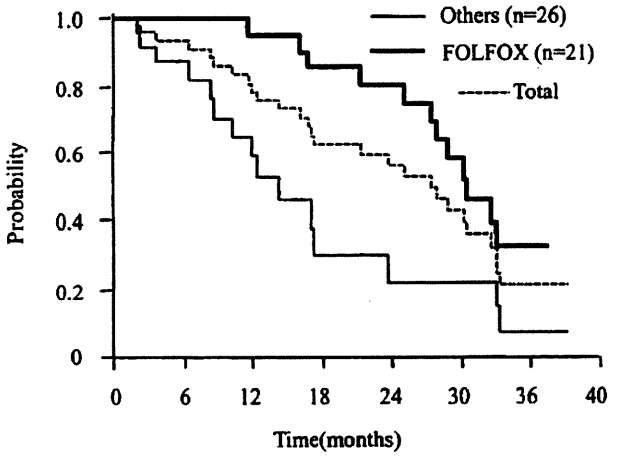

Fig. 2. Overall survival of patients treated with modified IFL followed by folinic acid (leucovorin) 5-fluorouracil, and oxaliplatin (FOLFOX) or another treatment

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

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.

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