Fucoidan reduces the toxicities of chemotherapy for patients with unresectable advanced or recurrent colorectal cancer

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Received September 27, 2010; Accepted January 4, 2011

DOI: 10.3892/ol.2011.254

Abstract. Combination chemotherapy with oxaliplatin plus 5-fluorouracil/leucovorin (FOLFOX) or irinotecan plus 5-fluorouracil/leucovorin (FOLFIRI) has become a standard regimen for advanced or recurrent colorectal cancer. Numerous studies have reported that long-term use of FOLFOX or FOLFIRI leads to better survival for these patients. Thus, control of the toxicity of these drugs may be crucial to prolonging survival. Fucoidan is one of the major sulfated polysaccharides of brown seaweeds and exhibits a wide range of biological activities. In the present study, we analyzed the effect of fucoidan on suppressing the toxicity of anti-cancer drugs. A total of 20 patients with unresectable advanced or recurrent colorectal cancer scheduled to undergo treatment with FOLFOX or FOLFIRI were randomly allocated into a fucoidan treatment group (n=10) and a control group without fucoidan treatment (n=10). Results showed that fucoidan regulated the occurrence of fatigue during chemotherapy. Chemotherapy with fucoidan was continued for a longer period than chemotherapy without fucoidan. Additionally, the survival of patients with fucoidan treatment was longer than that of patients without fucoidan, although the difference was not significant. Thus, fucoidan may enable the continuous administration of chemotherapeutic drugs for patients with unresectable advanced or recurrent colorectal cancer, and as a result, the prognosis of such patients is prolonged.

Introduction

To prolong the survival of patients with unresectable advanced or recurrent colorectal cancer, it is essential to continue effective chemotherapy for as long as possible. Since the introduction of oxaliplatin for use in Japan in April 2005, combination chemotherapy with oxaliplatin plus 5-fluorouracil (5-FU)/leucovorin (LV) (FOLFOX) or irinotecan plus 5-FU/LV (FOLFIRI) has become the standard regimen for advanced or recurrent colorectal cancer, and a high response rate has been reported (1-3). However, FOLFOX and FOLFIRI are associated with severe toxicity, such as nausea, vomiting, stomatitis, diarrhea, fatigue, neutropenia, anemia, thrombocytopenia and liver dysfunction. A number of patients discontinue these effective chemotherapies due to toxicity. Thus, the prognosis of patients with unresectable advanced or recurrent colorectal cancer remains low despite advances in chemotherapeutic drugs.

To reduce the toxicity of chemotherapeutic drugs, various types of drugs or dietary supplements have been introduced (4-6). Among these supplements, fucoidan has been reported to exhibit anti-inflammatory, antiviral and anti-tumor activities (7-9). Fucoidan is a sulfated polysaccharide found mainly in various species of brown seaweeds such as kombu, wakame, mozuku and hijiki. Subsequently, fucoidan has become the focus of substantial pharmaceutical research.

The present study investigated whether fucoidan reduces the toxicity of chemotherapeutic drugs in patients with unresectable advanced or recurrent colorectal cancer.

Materials and methods

Patients. Between April 2008 and June 2009, 20 patients were diagnosed with unresectable advanced or recurrent colorectal cancer and were scheduled to undergo FOLFOX or FOLFIRI chemotherapy at our hospital. The Eastern Cooperative Oncology Group performance status of these patients was 0 or 1, and they had adequate bone marrow (platelet count ≥100,000/l, white blood cell count ≥4,000/l, granulocyte count ≥1500/l, hemoglobin level of ≥10.0 mg/dl), renal (serum creatinine concentration ≤2.0 mg/dl), and hepatic (serum bilirubin level ≤2.0 mg/dl) functions. Adjuvant chemotherapy using 5-FU plus LV was administered to 9 of the 20 patients prior to enrollment in this study. The Ethics Committee of Tottori University approved treatment with fucoidan to reduce the toxicity of chemotherapeutic drugs in 2008 (approval no. 1223).

Informed consent was obtained from the 20 patients, who were randomly allocated to a fucoidan treatment group (n=10) and a control group without fucoidan treatment (n=10). The patients were followed up until July 2010. The patient details are shown in Table I.

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Key words: fucoidan, colorectal cancer, chemotherapy, fatigue

Table I. Patient characteristics.

	+ Fucoidan	- Fucoidan	P-value
No. of patients	10	10	
Age (mean ± SD, years)	71.3±7.5	69.6±8.8	0.762
Male/Female	6/4	7/3	0.639
ECOG			0.653
PS 0/1	5/5	4/6	
Tumor			0.653
Primary/Recurrent	4/6	5/5	
Primary tumor			0.639
Colon/Rectum	6/4	7/3	
Previous chemotherapy			0.653
Yes/No	4/6	5/5	
Site of disease			0.953
Liver	5	4	
Lung	2	2	
Pelvis	1	1	
Peritoneum	1	1	
Lymph node	1	1	
Primary tumor	0	1	

ECOG, The Eastern Cooperative Oncology Group; PS, performance status.

Table II. Major adverse events.[a]

	+ Fucoidan	- Fucoidan	P-value
No. of patients	10	10	
Leukocytopenia	1	0	0.305
Neutropenia	3	4	0.639
Anemia	2	1	0.531
Thrombocytopenia	0	2	0.136
Nausea	1	1	1.000
Diarrhea	1	2	0.531
Stomatitis	3	1	0.264
Fatigue	1	6	0.019
Peripheral neuropathy	3	5	0.361
Liver dysfunction	0	2	0.136

[a]Adverse events ≥2.

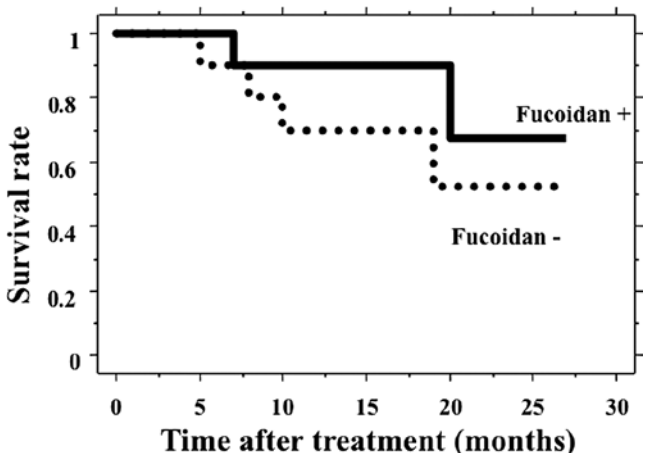

Figure 1. Survival curves of advanced or recurrent colorectal cancer patients. Solid line, survival curve of 10 patients who received fucoidan treatment. Dotted line, survival curve of 10 patients who did not receive fucoidan treatment. The difference was not significant (P=0.314).

Chemotherapy. A number of versions of FOLFOX therapy exist, of which modified FOLFOX6 (mFOLFOX6) allows for more convenient administration and has been adopted by various medical institutions in association with popularization of outpatient chemotherapy. Thus, mFOLFOX6 has been the first-line therapy for patients with unresectable advanced or recurrent colorectal cancer at our hospital (10). A 2-h intravenous infusion of oxaliplatin (85 mg/m^2) plus l-LV (200 mg/m^2) was followed by a bolus intravenous injection of 5-FU (400 mg/m^2), after which 5-FU (2,400 mg/m^2) was administered by continuous infusion for 46 h. However, 4 of the 20 patients requested FOLFIRI as first-line therapy. In the FOLFIRI regimen, on day 1, 180 mg/m^2 of irinotecan and 200 mg/m^2 of l-LV were administered as a 2-h infusion, prior to a 400 mg/m^2 5-FU intravenous bolus injection. Subsequently, 2,400 mg/m^2 of 5-FU was administered as a 46-h continuous infusion. The duration of one cycle of mFOLFOX6 was the same as that of FOLFIRI (2 weeks). Details of the chemotherapy regimens have been previously described (10).

Fucoidan treatment. Fucoidan is a sulfated polysaccharide that is extracted from brown seaweed, such as mozuku. In the present study, a high-molecular-weight product of fucoidan was used, which was derived from *Cladosiphon okamuranus* (Okinawamozuku) by Marine Products Kimuraya Co., Ltd. (Tottori, Japan). In the fucoidan group, each patient received 150 ml/day of liquid that contained 4.05 g fucoidan for 6 months from the initial day of chemotherapy.

Clinical assessment. All toxicities, with the exception of peripheral neuropathy, were graded according to the National Cancer Institute Common Toxicity Criteria (NCI CTC) (11). Peripheral neuropathy was graded according to the specific grading system (12). Hematological variables and clinical status were recorded every 2 weeks during the chemotherapy period. The drug dose level was reduced in the case of severe or persistent toxicity according to our protocol (10). In the case of persistent grade 3 toxicity or when grade 4 toxicity was recorded, chemotherapy was terminated.

Endpoints. The incidence and severity of adverse events were assessed as the primary endpoints, and patient survival, measured from the date of the first treatment until the patient succumbed to the disease, was assessed as the secondary endpoints.

Statistical analysis. The Chi-square test for independence, Fisher's exact probability test and the Mann-Whitney U test were used to compare patient characteristics, treatment status,

adverse events and the anti-tumor effect. The survival rates of the two groups were estimated by the Kaplan-Meier method, and the statistical differences between survival curves were examined by the log-rank test. $P<0.05$ was considered to be statistically significant.

Results

It was noted that fucoidan exhibited no side effects, such as allergic dermatitis. All 20 patients completed the 6 months of fucoidan therapy safely. Additionally, no patients succumbed due to chemotherapeutic toxicity. A total of 307 cycles of mFOLFOX6 or FOLFIRI were administered during the study, with a median of 15.4 cycles per patient (range 7-38). The average number of treatment cycles (19.9) in the fucoidan group was significantly greater than that in the control group (10.8 cycles, $P=0.016$).

The observed toxicities of the chemotherapeutic drugs are listed in Table II. No patients presented with severe toxicity (grade 4) in either group. The occurrences of diarrhea and neurotoxicity were not suppressed by fucoidan. Myelosuppression was found to be similar in the fucoidan and control groups. In contrast, general fatigue was detected in 60% of the control group, but was significantly suppressed to 10% in the fucoidan group (Table II).

Patients were followed up at our hospital. The median follow-up period of the 20 patients was 15 months (range 5-27). During the follow-up period, 6 patients (2 in the fucoidan group and 4 in the control group) succumbed due to colorectal cancer progression. The survival of the 10 patients receiving fucoidan treatment was longer than that of the 10 patients in the control group, but the difference was not significant ($P=0.314$, Fig. 1).

Discussion

Fucoidan is one of the major sulfated polysaccharides of brown seaweeds, and it has a wide range of biological activities. Choi *et al* (13) found that fucoidan protects gastric mucosa from inflammatory cytokine-mediated oxidative damage in rats. Hayashi *et al* (7) reported that fucoidan reduces CCl_4-induced acute and chronic liver failure with hepatic fibrosis. The anti-inflammatory activity of fucoidan was demonstrated in rats (14), and fucoidan conferred no toxicity in rats at high doses (15). Thus, fucoidan is anticipated to improve human health, and has been widely distributed as a foodstuff but not as a drug. However, the detailed mechanism of action of fucoidan remains to be verified, and its effects in humans have yet to be determined.

In the present study, we analyzed whether fucoidan protects patients from the toxicity of anti-cancer drugs. Nausea, vomiting, diarrhea, general fatigue and bone marrow suppression are well-known common adverse effects of anti-cancer drugs. Peripheral neuropathy is specific for oxaliplatin. We found that fucoidan suppressed the occurrence of general fatigue in colorectal cancer patients during chemotherapy. It has been demonstrated that fatigue reduces the individual resources of patients, affects their nutritional status, increases morbidity and can have a negative impact on the dose intensity of cancer therapy (16). Iop *et al* (16) reported that fatigue, which was graded using NCI CTC, was detected in almost 30% of patients receiving chemotherapy. In the present study, grade 2 and 3 fatigue was detected in 60% of colorectal cancer patients during chemotherapy. The use of antidepressants may also play a role in the treatment of fatigue, and a number of patients are administered chemical supplements of unproven efficacy. However, no published data exist to confirm this hypothesis. In our study, patients who received fucoidan were able to endure prolonged chemotherapy without fatigue. However, fucoidan did not have an impact on other adverse effects of anti-cancer drugs. The mechanisms that explain chemotherapy-induced fatigue remain to be determined, and no general treatment is currently available to alleviate the symptoms.

Fucoidan has also been found to play a significant role in tumor suppression (17-20). Yamasaki-Miyamoto *et al* (8) and Hyun *et al* (21) showed that fucoidan activates caspase-8 or extracellular signal-regulated kinase and induces apoptosis in tumor cells. These pro-apoptotic effects of fucoidan have not been detected in normal cells. However, no indisputable evidence exists that fucoidan prolongs the survival of cancer patients, even in animal models with human tumor implants. In the present study, although the number of patients was limited and the results were not statistically significant, the prognosis of patients with unresectable advanced or recurrent colorectal cancer was more favorable upon treatment with fucoidan than without. This may be explained by the fact that fucoidan prolonged the duration of the chemotherapy by suppressing the toxicity of the anti-cancer drugs or through an anti-cancer effect of fucoidan itself. Therefore, large controlled studies are required to evaluate the therapeutic effect of fucoidan for unresectable advanced or recurrent colorectal cancer.

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