Clinical Outcomes of FOLFOX/FOLFIRI for the Japanese Patients with Far Advanced or Recurrent Colorectal Cancer

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Original Articles

Clinical Outcomes of FOLFOX/FOLFIRI for the Japanese Patients with Far Advanced or Recurrent Colorectal Cancer

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Abstract Purpose : Oxaliplatin, Irinotecan, 5-fluorouracil and leucovorin are commonly used to treat advanced colorectal cancer in Western countries. Here, we investigated the efficacy and safety of FOLFOX/FOLFIRI in Japanese colorectal cancer patients. Methods : FOLFOX4, modified FOLFOX6 and FOLFIRI was administered to a total of 23 patients with far advanced or recurrent colorectal cancer in our institute. Tumor response rate and toxicity were analyzed with these patients. Results : Partial response and stable disease was observed in 28.6% of patients, respectively. There was no therapy-related death. Neutropenia was observed in 12 cases (52.2%), anemia was in 12 cases (52.2%) and thrombocytopenia was in 6 cases (26.1%), respectively ; among them, 9 patients (39.1%) experienced a Grade 3 of bone marrow suppression. Fatigue was observed in 8 cases (34.8%), nausea/vomiting was in 4 cases (17.4%), diarrhea was in 4 cases (17.4%) and neurotoxicity was in 8 cases (34.8%), respectively. All non-hematological toxicities were Grade 1 or 2. Conclusion : FOLFOX/FOLFIRI can contribute to efficacy and safety in cases of advanced colorectal cancer. In order to evaluate the long-term clinical results in Japanese patients, prospective controlled studies are urgently called for.

Key words : Colorectal adenocarcinoma, Novel chemotherapy, Japanese patients

Introduction

Chemotherapy for metastatic colorectal cancer proved to be more effective than the best supportive care at prolonging survival and improving quality of life[1]. In Western countries, two new chemotherapeutic agents, oxaliplatin and irinotecan, have recently demonstrated survival improvement, when given in combination with 5-fluorouracil (5-FU)+leucovorin (LV), in first- or second-line chemotherapy[2)~4)].

In Japan, the government approved the use of oxaliplatin and continuous infusion of 5-FU + LV for colorectal cancer patients on April, 2005. Since that, FOLFOX/FOLFIRI regimen, consists of oxaliplatin or irinotecan infusion and simultaneous LV infusion, followed by a bolus and a continuous 5-FU, began to be widely applied for the patients with advanced colorectal cancer. We herein report the short-term clinical results of FOLFOX/FOLFIRI undertaken in our institute.

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Patients and Methods

In the Department of Surgery, Nippon Steel Yawata Memorial Hospital, FOLFOX/FOLFIRI regimen started to be applied on May, 2005. Table 1 shows 23 patients with far advanced or recurrent colorectal cancer who received the therapy until August, 2006 (observation term : 3-18 months). There were 17 men and 6 women, with a median age of 67.3 years old. Primary sites were colon in 13 patients and rectum in 10 cases ; those were histologically proven adenocarcinoma. Resection of primary site +/− metastatic site was performed in 20 cases. All cases were in WHO performance status 0 or 1 and life expectancy of more than 3 months at the beginning of FOLFOX/FOLFIRI treatment. Twenty patients had received previous chemotherapy ; 4 patients had postoperative adjuvant chemotherapy, 10 patients had other first-line chemotherapy for metastatic lesions, 6 patients had both of them. Sites of metastasis were ; liver in 8 cases, local in 3 cases, peritoneal dissemination in 5 cases, distant metastasis in 2 cases and combined metastasis in 5 cases ; simultaneous metastasis in 12 cases and metachronous in 11 cases.

Table 1 Patient characteristics

Factor		No. of patients
Sex	Men	17
	Women	6
Age	50-81 (mean 67.3)	
First regimen	FOLFOX4	7
	mFOLFOX6	8
	FOLFIRI	8
Origin	Ascending colon	2
	Transverse colon	4
	Sigmoid colon	7
	Rectum	10
Resection	Yes	20
	No	3
Previous therapy	Yes	20
	No	3
Site of metastasis	Liver	8
	Local	3
	Dissemination	5
	Distant	2
	Combined	5
Mode of metastasis	Synchronous	12
	Metachronous	11

Three kinds of regimen performed in our institute were as follows (Fig 1) ; FOLFOX4, a 2-hour infusion of leucovorin isomers l-LV (100mg/m²) followed by a 5-FU bolus (400mg/m²) and 22-hour infusion (600mg/m²) for 2 consecutive days every 2 weeks, with oxiliplatin (85mg/m²) as a 2-hour infusion on day 1 ; modified FOLFOX6 (mFOLFOX6 : FOLFOX6 modified for Japanese patients), oxiliplatin (85mg/m²) as a 2-hour infusion on day 1, l-LV (200mg/m²) as a 2-hour infusion during oxiliplatin, followed by a 5-FU bolus (400mg/m²) and 46-hour continuous infusion of 5-FU (2400mg/m²) every 2 weeks ; FOLFIRI, irinotecan (100-150mg/m²) as a 2-hour infusion on day 1, l-LV (200mg/m²) as a 2-hour infusion during irinotecan, followed by a 5-FU bolus (400mg/m²) and 46-hour continuous infusion

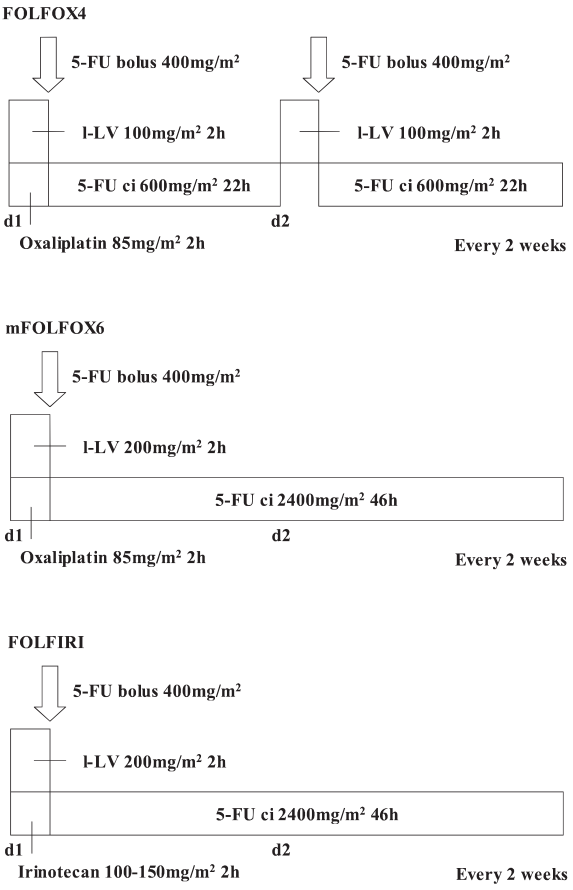

Fig. 1 Chemotherapy regimens

of 5-FU (2400mg/m²) every 2 weeks. Evaluation of measurable lesions was performed based on the RECIST guideline[5]. Toxicity was assessed using the National Cancer Institute-Common Toxicity Criteria (NCI-CTC)[6]. Neurotoxicity criteria of DEBIOPHARM (DEB-NTC) was applied for evaluation of neurotoxicity[7].

Statistically significant differences were determined using Student's t test and chi-square test. A p value less than 0.05 was considered to be statistically significant.

Results

Objective tumor response rates are listed in Table 2. Two cases were not assessable because of inadequate duration of follow up. Among 21 cases assessed, partial response (PR) and stable disease (SD) was observed in 6 cases (28.6%), respectively, although no complete response (CR) was observed. The PRs were 50.0% with FOLFOX4, 14.2% with mFOLFOX6 and 25.0% with FOLFIRI (p=0.35). PR was observed in 3 (50.0%) of 6 patients who received FOLFOX/FOLFIRI as first-line chemotherapy, while in 3 (20.0%) of 15 patients received as second-line chemotherapy (p=0.17). Time to progression was 4.0 months with FOLFOX4, 2.4 months with mFOLFOX6 and 5.2 months with FOLFIRI (mean: 4.0 months).

Survival times, at the point on November, 2006, were shown in Table 3. In all 23 cases, mean survival time from the first therapy for metastatic lesions and from the beginning of FOLFOX/FOLFIRI therapy was 14.6+ months (2.5-30.6+ months) and 8.0+ months (2.5-13.9+ months), respectively.

Table 2 Objective tumor response rates

Response	FOLFOX4 (n=6)	mFOLFOX6 (n=7)	FOLFIRI (n=8)	total (n=21)
PR	3 (50.0)	1 (14.2)	2 (25.0)	6 (28.6)
SD	1 (16.7)	1 (14.2)	4 (50.0)	6 (28.6)
PD	2 (33.3)	5 (71.4)	2 (25.0)	9 (42.9)

PR, partial response; SD, stable disease; PD, progressive disease; Parentheses are percentages.

Table 3 Survival times after chemotherapy for metastasis

	Time from first-line chemotherapy	Time from FOLFOX/FOLFIRI therapy
FOLFOX 4 (n=7)	2.5-25.6+ (14.6+)	2.5-13.9+ (9.4+)
mFOLFOX 6 (n=8)	2.9-30.6+ (16.4+)	2.9-10.8+ (5.8+)
FOLFIRI (n=8)	7.5-26.5+ (12.8+)	6.7-12.6+ (9.0+)
Total (n=23)	2.5-30.6+ (14.6+)	2.5-13.9+ (8.0+)

Values are months. Parentheses are mean values.

Table 4 Frequency of common toxicities

Toxicity	FOLFOX4 (n=7)	mFOLFOX6 (n=8)	FOLFIRI (n=8)	total (n=23)
Neutropenia	4 (57.1)	3 (37.5)	5 (62.5)	12 (52.2)
Anemia	5 (71.4)	2 (25.0)	5 (62.5)	12 (52.2)
Thrombocytopenia	3 (42.9)	1 (12.5)	2 (25.0)	6 (26.1)
Fatigue	3 (42.9)	3 (37.5)	2 (25.0)	8 (34.8)
Nausea/vomiting	0	3 (37.5)	1 (12.5)	4 (17.4)
Diarrhea	0	1 (12.5)	3 (37.5)	4 (17.4)
Mucositis	1 (14.3)	1 (12.5)	2 (25.0)	4 (17.4)
Cutaneus	1 (14.3)	0	1 (12.5)	2 (8.7)
Neurogic	3 (42.9)	2 (25.0)	3 (37.5)	8 (34.8)

Parentheses are percentages.

Toxicities observed during FOLFOX/FOLFIRI treatment are shown in Table 4. There was no therapy-related death during the treatment. All toxicities were manageable and acceptable, except for one patient who had to stop the FOLFOX4 therapy as a result of severe pneumonitis. Neutropenia was observed in 12 cases (52.2%), anemia was in 12 cases (52.2%) and thrombocytopenia was in 6 cases (26.1%), respectively. Among them, 9 patients (39.1%) experienced a Grade 3 of bone marrow suppression, while all of them were recovered without receiving any special therapies, such as G-CSF administration. As for non-hematological toxicities, general fatigue was found in 8 cases (34.8%), nausea/vomiting was in 4 cases (17.4%), diarrhea was in 4 cases (17.4%) and neurotoxicity was in 8 cases (34.8%), respectively. All non-hematological toxicities were Grade 1 or 2. Concerning frequency of toxicities, there is no significant difference

among three regimen groups.

Clinical courses of all patients were summarized in Figure 2. Among 23 cases, 10 patients had received postoperative adjuvant chemotherapy, such as S-1, UFT/LV and 5-FU/LV, before metachronous metastasis was found. Sixteen patients had received other chemotherapy than FOLFOX/FOLFIRI even after metastasis was recognized. Three patients who had synchronous metastasis received FOLFOX/FOLFIRI as a first-line chemotherapy. Nine patients received FOLFIRI followed by FOLFOX or the reverse sequence. Eight patients died because of cancer progression. Seven patients received other chemotherapy, such as S-1 and UFT, after the failure of FOLFOX/FOLFIRI.

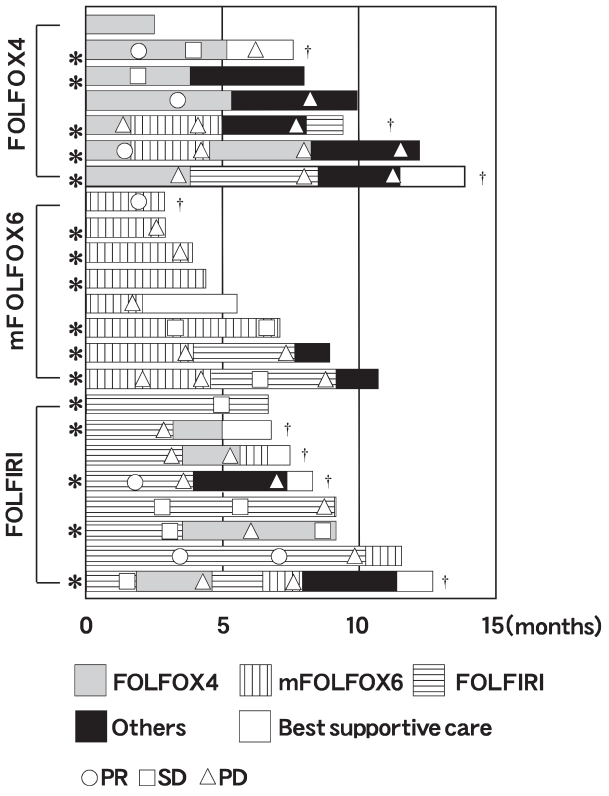

Fig. 2 Clinical course of each case
Asterisks indicate the patient who received other chemotherapy for metastatic lesion before FOLFOX/FOLFIRI.

Discussion

Combination of oxaliplatin or irinotecan with 5-FU and leucovorin has significantly increased response rates, time to progression, and survival compared with previous chemotherapies, such as 5-FU + LV[3)8)], oxaliplatin alone[9)] and IFL[10)], for colorectal cancer. In Japan, the delay of governmental approval to administer oxaliplatin and continuous infusion of 5-FU + LV to advanced colorectal cancer patients resulted in interference of clinical development in colorectal cancer therapy. Therefore, original clinical investigations concerning FOLFOX/FOLFIRI for patients in the Japanese are a matter of great urgency.

In this retrospective study, the objective tumor response rate of FOLFOX/FOLFIRI was 28.6%. Taking account that FOLFOX/FOLFIRI was introduced as a salvage chemotherapy (after failure of other chemotherapy) in 16 cases, our results were considered to be comparable with previous report[9)]. de Gramont et al[8)] reported that FOLFOX/FOLFIRI treatment tends to be more effective for liver metastasis than other disease sites. Although the objective tumor response was investigated by disease sites, no features were identified with regard to tumor sites in our small series of patients (data not shown). The results in this study do not make it possible to draw any conclusions concerning long-term survivals. Thus, prospective studies to elucidate the long-term effects of FOLFOX/FOLFIRI, as a first-line and second-line chemotherapy for Japanese patients, are needed.

Bone marrow suppression was the most common toxic effects in present cases. A Grade 3 of bone marrow suppression was observed in many cases compared with

previous reports[3)4)], provably because most patients in this study had received previous chemotherapy. We may need to monitor hematological data frequently when FOLFOX/FOLFIRI is given as a second-line chemotherapy. The frequency of non-hematological toxicities, such as nausea/vomiting, diarrhea, mucositis, cutaneous change and neuropathy, were relatively low. However, for instance, neuropathy was reported to occur in a dose-dependent manner[11)]. Further observation to evaluate the late event toxicities and regimen-related toxic events is thought to be necessary.

Sixteen patients had received other chemotherapy than FOLFOX/FOLFIRI even after metastasis was recognized, because FOLFOX/FOLFIRI was still unavailable when they had diagnosed to have metastasis, at least in some cases. Among 23 patients, 9 patients received FOLFIRI followed by FOLFOX or the reverse sequence after failure of first-line therapy. Tournigand et al[4)] reported that both sequences achieved a prolonged survival and similar efficacy, which support that the sequence therapy is recommended unless the patient is in poor general condition. Indeed most patients who had failure of first-line therapy receive the sequence therapy in our institute. Other chemotherapy, such as S-1 and UFT, was done in 9 cases after failure of FOLFOX/FOLFIRI. Whether or not such therapies are significant for those patients requires further investigation. Bevacizumab[12)], monoclonal antibody against vascular endothelial growth factor, might be one of the choices for the therapy of refractory colorectal cancer near in the future.

Other problems we have to solve are involved in management of patients. FOLFOX/FOLFIRI regimens can be administered on an outpatient basis. Outpatient based chemotherapy is thought to allow individuals to maintain everyday living and social activities, that contributes to enhanced quality of life among patients. On the other hand, it is needed to pay a special attention in order to keep safety of treatment on outpatient management. In many hospitals, including our institute, surgeons usually perform FOLFOX/FOLFIRI, because clinical oncologists are markedly insufficient to cover these patients in Japan. It is easily predicted that FOLFOX/FOLFILI hereafter will be introduced to many patients with advanced colorectal cancer. In order to achieve safe and efficient treatment, outpatient based chemotherapy should be systematized and performed by trained special medical staff.

In conclusion, FOLFOX/FOLFIRI can contribute to efficacy and safety, and probably to prolongation of survival time in cases of far advanced and recurrent colorectal cancer. In order to assess the long-term clinical results of FOLFOX/FOLFIRI, prospective controlled studies with Japanese patients are eagerly required.

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（和文抄録）

日本人進行，再発大腸癌患者に対する FOLFOX/FOLFIRI の臨床成績

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今村　秀[1]，安蘓正和[1]，加藤秀典[1]，掛地吉弘[2]，前原喜彦[2]

要旨【目的】Oxaliplatin，Irinotecan を用いた FOLFOX/FOLFIRI は，欧米においては進行大腸癌に対する標準治療である．我々は日本人の進行大腸癌患者に対する FOLFOX/FOLFIRI の効果と安全性について検討した．【方法】当施設において FOLFOX4，modified FOLFOX6，FOLFIRI が 23 人の高度進行，再発大腸癌患者に対して行われた．それらの腫瘍縮小効果，副作用について解析した．【結果】PR と SD はそれぞれ 28.6％ずつに認めた．治療関連死は認めなかった．好中球減少は 12 人（52.2％），貧血は 12 人（52.2％），血小板減少は 6 人（26.1％），うち Grade 3 の骨髄抑制は 9 人（39.1％）に認めた．全身倦怠感は 8 人（34.8％），悪心，嘔吐は 4 人（17.4％），下痢は 4 人（17.4％），神経毒性は 8 人（34.8％）に認めた．すべての非血液毒性は Grade 1 か 2 であった．【結論】FOLFOX/FOLFIRI は高度進行，再発大腸癌患者に対して有効で，かつ安全に投与できると考えられた．日本人患者における長期成績を検証するための臨床試験が急務である．