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

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

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

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

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Irinotecan Plus Cisplatin for Therapy of Small-cell Carcinoma of the Esophagus: Report of 12 Cases from Single Institution Experience

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Background: Esophageal small-cell cancer is a rare disease, and standard therapy has not yet been established.
Methods: A total of 12 esophageal small-cell carcinoma patients were treated with CPT-11 (70 mg/m^2) on Days 1 and 15 and CPT-11 plus CDDP (80 mg/m^2) on Day 1 with each cycle repeated every 4 weeks at our institution.
Results: A total of 46 chemotherapy courses were given (median, 3.5). There were two complete responses and eight partial responses. The median survival time was 417 (97–1626) days, and three patients were still alive for >40 months. Grade 4 neutropenia was observed in two patients, Grade 4 anemia in one patient, Grade 3–4 diarrhea in three patients and Grade 3–4 hyponatremia in three patients. Other adverse reactions seen were mild with no treatment-related deaths observed.
Conclusions: To our knowledge, this is the first report of the series of more than 10 patients with small-cell carcinoma of the esophagus treated with the same chemotherapy regimen. The combination of CPT-11 and CDDP appears to be effective therapy of this disease with acceptable toxicity profile. We believe that this regimen is one of the options to be considered for treatment of esophageal small-cell carcinoma.

Key words: small-cell carcinoma – esophageal cancer – chemotherapy – CPT-11 – cisplatin

INTRODUCTION

Esophagus is one of the sites of extrapulmonary occurrence of the small-cell carcinoma. In the gastrointestinal (GI) tract, ~50% of tumors arise in the esophagus (1). Small-cell esophageal cancer (SCEC) is a rare disease with aggressive behavior and poor prognosis. Because of the rarity of this disease, standard therapy has not yet been established. Systemic chemotherapy is offered to patients with metastatic disease where chemoradiation or surgery is used to manage locoregional disease. Small-cell carcinoma is considered to be highly sensitive to chemotherapy. Since SCEC has similar histological and clinical characteristics to the small-cell lung cancer (SCLC), the same therapeutic strategies for both malignancies are recommended in the literature (2–5).

Irinotecan hydrochloride (CPT-11) has demonstrated activity against various tumor histologies. Marked synergism, lack of cross-resistance, different mechanisms of action, and different toxicity profiles make the combination of CPT-11 with cisplatin (CDDP), an attractive regimen (6). Phase II studies investigated this combination in therapy of SCLC and gastric cancer, demonstrating good efficacy with acceptable toxicity profile (7,8). Phase III evaluation of CPT-11 and cisplatin provided improved progression-free survival and overall survival (OS) in patients with metastatic SCLC compared with the etoposide and cisplatin combination regimen (9). Therefore, at our institution, we use CPT-11/CDDP combination to treat SCEC. We report here the results of our experience with 12 cases.

MATERIALS AND METHODS

Fifteen out of 631 esophageal cancer patients were diagnosed between June 1999 and May 2004 at the Cancer Institute Hospital of Japanese Foundation for Cancer

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Research as small-cell carcinoma pathologically (2.4%). We used immunohistochemical staining for neuron-specific enolase, CD56, chromogranin A, synaptophysin and so on in diagnosis for small-cell carcinoma of the esophagus. Out of these 15 patients, 12 were treated with CPT-11 plus CDDP. We conducted retrospective medical records review of the 12 cases. Staging evaluation included computed tomography (CT) of the chest, abdomen, barium esophagography and esophagoscopy with biopsy. We applied the tumor-node-metastasis (TNM) staging system to all cases according to the International Union against Cancer (UICC) classification. Since primary extrapulonary sites of the small-cell carcinoma are rare, a primary SCLC should be excluded. In our patients, primary SCLC was excluded in each case, using CT evaluation of the chest.

Treatment Schedule

Chemotherapy regimen was applied as follows: on Day 1, CPT-11 (70 mg/m^2) was administered by intravenous infusion over 90 min; this was followed by a 2-h interval after which, intravenous infusion of CDDP (80 mg/m^2) was administered over 2 h with adequate hydration. The same dose of CPT-11 was administered on Day 15. This regimen was repeated every 4 weeks until disease progression, patient refusal or unacceptable toxicity has occurred.

Response Evaluation

For measurable disease, responses were evaluated according to the World Health Organization (WHO) criteria (10). Response for the primary tumor was also evaluated according to the modified criteria of the Japanese Society for Esophageal Disease (11). Briefly, complete response (CR) for a primary tumor was consistent with disappearance of all visible tumors including ulceration and negative biopsy result on esophagoscopy that lasted more than 4 weeks. Partial response (PR) was assigned if the primary tumor was reduced by >50% on esophagography and lasted for >4 weeks. Progressive disease (PD) was consistent with an increase in the tumor area by >25%. Responses were evaluated using esophagography, esophagoscopy and CT of the chest and abdomen. The National Cancer Institute-Common Toxicity Criteria (NCI-CTC; version 2.0) was used to evaluate observed toxicity.

Statistics

Survival was measured from the date of the start of CPT-11/CDDP chemotherapy until death or the most recent follow-up visit. Survival data were estimated using Kaplan–Meier method.

RESULT

Patient Characteristics

Patient characteristics are listed in Table 1. Out of 12 patients, only one patient was female. The age ranged between 53 and 77 years with a median age of 66 years. Ten patients (83%) had performance status (PS) 0–1 with two treated patients with PS of 2. The tumor was located in the middle third of the esophagus in seven patients. The median size of the primary tumor was 6.0 cm. Histologically, four out of 12 (33%) tumors were of mixed small-cell and squamous cell histology with remaining eight tumors of only small-cell type (67%) by biopsy. Five patients had locoregional disease and remaining seven patients with either metastatic or recurrent tumor after surgical resection.

One patient had previous history of gastric adenocarcinoma 8 years prior to the diagnosis of small-cell cancer of the esophagus. Another patient had simultaneously detected advanced gastric adenocarcinoma and esophageal small-cell cancer.

Ten out of 12 patients (83%) had no prior treatment for their malignancy. One patient (Patient 6) received 2 Gy of radiation to esophageal tumor prior to chemotherapy. Radiation was started initially as he was thought to have squamous cell carcinoma of the esophagus. However, few days later his histology report was amended to add the small-cell component. In another patient (Patient 11), pharyngeal mass was noted 3 months after esophagectomy. Because, at first, it was clinically diagnosed as second primary-pharyngeal cancer, 4 Gy of radiation to pharyngeal tumor was applied.

Treatment

The total number of chemotherapy courses given was 46 (median, 3.5 courses per patient; range, 2–6 courses) (Table 2). In three patients, 20–25% dose reduction of both agents was needed at first cycle due to the old age (Patient 1), borderline PS (Patient 4) or proximity of the last radiotherapy session (Patient 11). Additional two patients required both omitting Day 15 of CPT-11 in the first course and dose reduction following the first cycle due to the diarrhea, neutropenia or hyponatremia. Seven out of 12 patients were able to receive planned full doses of chemotherapy for all cycles.

Response and Survival

There were two CRs and eight PRs achieved resulting in a response rate (RR) of 83%. The RR of primary esophageal lesion was 82% (nine of 11 patients) (Table 2). The median follow-up time was 462 days, and the median survival time of all patients was 417 days (range, 97–1626 days) (Figure 1). Three patients (Patients 2, 9 and 12) were still alive at the last follow-up, for over 40 months. Two had locoregional disease and one had metastatic disease. Two (Patients 2 and 9) of the three patients showed no evidence

Table 1. Patient characteristics

Patient	Gender	Age	PS	Gross type	Stage	Site of primary esophageal tumor	Tumor length (cm)	Metastatic site	Previous treatment
1	M	77	0	Polyploidy	4b	Middle third	9	Liver LN	No
2	M	69	1	Ulcerative	2	Lower third	5	No	No
3	M	62	1	Ulcerative	3	Middle third	6	mLN	No
4	M	59	2	Ulcerative	4b	Lower third	13	cLN, mLN, aLN, pleural effusion	No
5	M	66	1	Ulcerative	4a	Upper third	7	mLN, cLN	No
6	M	53	2	Ulcerative	4b	Middle third	5	cLN, mLN, pleural effusion	RT(2Gy)
7	M	66	1	Ulcerative	4b	Lower third	6	cLN, mLN, aLN	No
8	M	70	0	Polyploidy	3	Middle third	4	mLN	No
9	F	63	1	Ulcerative	4b	Middle third	8	cLN	No
10	M	71	0	Ulcerative	4b	Middle third	9	mLN, adrenal gland	No
11	M	61	1	NE	recurrence	NE	NE	Pharynx	Esophagectomy, RT(4Gy)
12	M	68	0	Polyploidy	1	Middle third	3	No	No

LN, lymph node; cLN, cervical LN; mLN, mediatsinal LN; aLN, abdominal LN; RT, radiation; NE, not evaluated; PS, performance status; M, male; F, female.

Table 2. Treatment course and results of treatment

Patient	Total course of Cx	Response	Oral food intake		PD site	Survival (days)	Subsequent therapy	Present status
			Before Cx	After Cx				
1	3	PR	Semi-solid	Solid	Esophagus, LN	325	RT	Dead of disease
2	3	CR	Solid	Solid	Non-PD	1465	5-FU+CDDP+RT	Alive with NED
3	6	PR	Semi-solid	Solid	Esophagus	417	RT	Dead of disease
4	4	PR	Liquid	Solid	LN	226	docetaxel	Dead of disease
5	3	PD	Semi-solid	Semi-solid	Esophagus	307	RT	Dead of disease
6	3	PR	Semi-solid	Semi-solid	Pleural effusion	97	none	Dead of disease
7	2	PD	Liquid	Semi-solid	Esophagus, LN, adrenal gland	220	RT	Dead of disease
8	4	PR	Semi-solid	Semi-solid	LN	714	MTX/5-FU	Dead of disease
9	6	CR	Semi-solid	Solid	Non-PD	1291	nedaplatin+5-FU	Alive with NED
10	4	PR	Solid	Solid	Pancreas	507	5-FU+CDDP+RT	Dead of disease
11	6	PR	NE	NE	LN	766	RT	Dead of disease
12	2	PR	Solid	Solid	Non-PD	1626	5-FU+CDDP+RT	Alive with disease

Cx, chemotherapy; NED, no evidence of disease; PR, partial response; CR, complete response; PD, progressive disease; 5-FU, 5-fluorouracil; CDDP, cisplatin; MTX, methotrexate.

of disease. One patient (Patient 9) developed recurrent disease at the primary site at 24 months after initial CR, but it disappeared again with chemotherapy (nedaplatin and 5-FU) followed by radiation. Since, initially, she had bulky lymph node metastasis in her neck, we performed enough chemotherapy again followed by radiation despite local recurrence only. Two (Patients 2 and 12) of the three alive patients underwent additional concurrent chemoradiotherapy following second and third course of irinotecan and cisplatin because residual tumor after this chemotherapy (Patient 12) and to ensure disease control in spite of disappearance the tumor (Patient 2). These subsequent therapies included a total of 50 and 60 Gy, respectively, of radiation and combination of cisplatin and 5-fluorouracil. One patient (Patient 12) achieved complete response after chemoradiation, and recurrent neuroendocrine carcinoma with squamous cell differentiation was detected in lung at 35 months from the start of chemotherapy. Because there was a possibility of primary lung cancer, it was surgically resected. At 40 months, metastasis was found again in the lung and pleura,

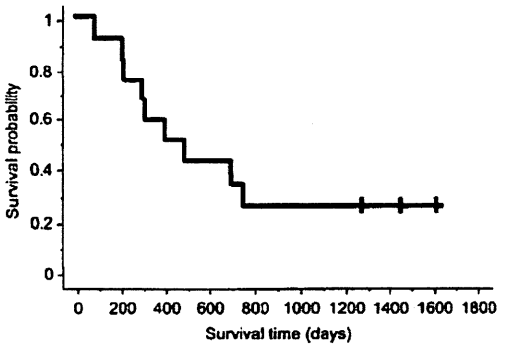

Figure 1. Survival curves of all patients.

and then he was treated with nedaplatin and 5-FU. There was no recurrence at the primary site at 4-year follow-up. A patient (Patient 3) with stage III SCEC obtained PR with CPT-11 plus CDDP, which was continued until PD in the primary site. He received radiation alone following CPT-11 plus CDDP, but did not get reduction of primary tumor or improvement of dysphagea and developed new lesion in abdominal lymph nods.

Assessment of Oral Intake

We also assessed oral intake in our patients which was categorized as follows: patient can ingest solid food, semi-solid food, only liquid or neither food nor liquid.

We evaluated 11 patients for changes in their oral intake before and after treatment (Table 2). After treatment, five out of these eight patients achieved improvement in oral intake.

Adverse Reactions

Toxicity of this regimen is summarized in Table 3. The most frequent adverse reaction was nausea/vomiting and diarrhea. Grade 3–4 nausea was observed in two patients (17%) with Grade 3–4 diarrhea noted in three patients (25%). Diarrhea was controlled with loperamide or other antidiarrheals, and supported with intravenous hydration.

Grade 3–4 hyponatremia was observed in three (25%) patients. One was thought to be due to the CDDP-induced syndrome of inappropriate ADH secretion (SIADH). Neutropenia occurred in 11 of 12 patients (92%) in the first course. Grade 3–4 neutropenia was observed in seven patients (58%) including one Grade 4 (8%) with Grade 3–4 infection documented in two patients (17%). Other hematologic adverse reactions were mild with no treatment-related deaths observed.

Table 3. Severe adverse reactions of all courses

Hematologic adverse reactions		Grade 4	Grade 4 (%)
Leukopenia		0	0
Neutropenia		2	17
Thrombocytopenia		0	0
Anemia		1	8
Non-hematologic adverse reactions	**Grade 3**	**Grade 4**	**Grades 3 and 4 (%)**
Nausea	2	0	17
Vomiting	0	0	0
Diarrhea	2	1	25
Infection	2	0	17
AST	1	0	8
ALT	1	0	8
Cr	0	0	0
T.Bil	0	0	0
Hyponatremia	2	1	25

AST, aspartate aminotransferase; ALT, alanine aminotransferase; Cr, creatinine; T.Bil, total bilirubin.

DISCUSSION

Since McKeown reported first two cases of small-cell carcinoma of the esophagus (12), there have been only <300 cases this disease described in the literature (1). It comprises only 0.8–2.4% of all esophageal malignancies (13). In our hospital, there were 15 patients diagnosed with this disease out of 631 of all identified esophageal malignancies between June 1999 and May 2004. This makes our institutional incidence rate of 2.4% that is consistent with the rate reported in the literature. Because of the rarity of this disease, the standard treatment has not yet been established. Many investigators recommend that SCEC should be managed similar to SCLC (2–5). A randomized phase III study was conducted in Japan comparing the combination of CPT-11 and CDDP with standard regimen for extensive stage SCLC: etoposide plus cisplatin. The median survival was 12.8 months in the CPT-11 plus CDDP arm and 9.4 months in the etoposide plus cisplatin group ($P = 0.002$ by the unadjusted log-rank test) (9). Those results demonstrated efficacy of CPT-11/CDDP in therapy of advanced SCLC.

Reports of a single case have suggested that CPT-11/CDDP combination was also effective in SCEC (14,15). In our experience of 12 cases, CPT-11 plus CDDP demonstrated RR of 83% (10 of 12 patients) with median survival of 417 days (13.9 months) and three patients were still alive for over 40 months. Three out of seven patients with metastatic or recurrent disease survived for >10 months.

Limited stage SCLC is usually treated with concurrent chemoradiotherapy. Because of aggressive behavior, we initially treated local disease of SCEC also with CPT-11 plus CDDP. After that, four of five patients with locoregional disease received radiation (including two concurrent chemoradiation). Two patients (Patients 3 and 5) received radiation without chemotherapy after failure in CPT-11 plus CDDP.

For another local disease patient (Patient 8), we did not use radiation due to progression of simultaneously detected advanced gastric cancer. Three long survivors (Patients 2, 9, 12) all received subsequent radiotherapy after this CPT-11 plus CDDP chemotherapy (Table 2). One (Patient 12) of them achieved complete response after chemoradiation, and there has been no evidence of recurrence at the primary site for >40 months. Another patient (Patient 9) developed recurrent disease at the primary site, and disappeared again using sequential chemotherapy followed by radiation. Therefore, it is thought that this chemotherapy alone is not enough and radiotherapy is needed to obtain CR in the primary site. Takada et al. showed that concurrent chemoradiotherapy group was superior to sequential group for limited stage SCLC (16). Two patients with local disease (Patients 3 and 5) who received radiation without chemotherapy after failure in CPT-11 plus CDDP did not get reduction of primary tumor. It is considered that concurrent chemoradiation is better than sequential in SCEC also and used before progression of the disease. The appropriate chemotherapy concurrently with radiotherapy for SCEC is unknown. We used combination of 5-FU plus cisplatin concurrently because some tumors were of mixed small-cell and squamous cell histology. Several studies demonstrated the promising efficacy of chemoradiotherapy concurrently with etoposide plus cisplatin (16,17), which is an attractive treatment for locoregional SCEC. Since there has been no adequate data on safety and efficacy of concurrent CPT-11 and radiation applied to the mediastinum, we did not use it in our patients. We would like to point out that CPT-11 plus CDDP chemotherapy used alone was able to induce CR in two patients. Nine out of 11 patients demonstrated CR or PR in primary esophageal tumor. Additionally, oral intake tolerance was improved in majority of treated patients (five of eight patients). These data suggest that CPT-11 plus CDDP chemotherapy is a good treatment as induction chemotherapy and subsequent chemoradiation are necessary for locoregional disease of SCEC.

Several retrospective reviews reported poor prognosis of SCEC. However, these patients were not treated with the same chemotherapy regimen and various initial treatments including surgery or radiation were applied. Casas et al. (18) reported literature review of 230 patients with SCEC (199 evaluable patients). In this report, median survival for patients with local disease was 8 months and extensive disease patients surviving only 3 months. Bennouna et al. (19) presented 10 cases of SCEC treated with various cisplatin-based chemotherapy regimens. Complete response was observed in eight patients. Seven of these patients received subsequent locoregional radiotherapy with endoesophageal brachytherapy applied in two patients. The overall median survival for all patients was 15.5 months (range, 2–36 months). In limited disease, the median survival was 18.5 months (range, 2–36 months) with 11 months (range, 6–19 months) median survival seen in patients with extensive disease.

Medgyesy et al. (20), at the University of Texas, M. D. Anderson Cancer Center, reported with eight cases of SCEC that four out of six patients with limited stage disease received combined modality treatment including esophagectomy and two received only radiotherapy. Two patients with extensive disease were treated with chemotherapy alone. Observed median OS in this report was 12.5 months (range, 5–57 months). Some authors suggested that surgery is a possible choice of treatment for SCEC (20,21). Surgery considered being also an alternative method for local control instead of chemoradiation.

In our experience, four out of seven patients with metastatic or recurrent disease survived for more than 10 months (range, 3–43 months). Four out of five patients with local disease survived for more than 1 year (range, 10–54 months). This statistics is comparable, or better, with data reported in the literature.

Diarrhea and neutropenia are major toxicities of CPT-11 and CDDP. Neutropenia occurred in 11 of 12 patients (92%) following the first cycle. Grade 4 neutropenia was observed in two of 12 patients (17%) and Grade 3 or 4 diarrhea occurred in three of 12 patients (25%) during all courses; however, both toxicities were well controlled with the use of G-CSF and loperamide, respectively. These observed side effects are comparable with toxicity data reported in the literature. SIADH was seen in one of our patients and it was of brief duration. All severe adverse reactions were manageable and did not recur after 20–25% dose reduction in subsequent courses. There was no treatment-related death observed. Therefore, we consider this regimen to be safe and tolerable in patients with SCEC.

To date, there are only few single-center, retrospective reports published in the literature on experience with therapy of the esophageal small-cell cancer. We believe our report is the first to comment on treatment of more than 10 small-cell esophageal carcinoma patients using the same chemotherapy regimen. Our overall RR achieved with this therapy was 83%, including two complete responses, with median survival time of 417 days. This is comparable with data reported in the literature. Although the small number of patients prohibits any firm conclusions, we believe that this regimen is one of the options to be considered for initial treatment of this disease.

Conflict of interest statement

None declared.

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●原 著●

高齢者進行・再発大腸癌症例に対するFOLFOX4療法の検討

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Safety and Efficacy Analysis of FOLFOX4 Regimen in Elderly Compared to Younger Colorectal Cancer Patients:

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Summary

The number of elderly patients with colorectal cancer is increasing in Japan. They have the opportunity to receive chemotherapy similar to non-elderly patients because of the development of new drug agents and improvement of supportive therapy. We analyzed retrospectively 184 patients (32 aged≧70, 75≦) with advanced and metastatic colorectal cancer with good performance status who received FOLFOX4 regimen between April 2005 and March 2006. We observed adverse events, time to treatment failure, response rate, reason to discontinue treatment, and dose intensity.

Age≧70 was associated with slightly higher rates of neutropenia but no other grade≧3 adverse events. The FOLFOX4 regimen maintains its efficacy/safety ratio in elderly patients with good performance status with colorectal cancer in Japan. **Key words:** Elderly patients, Colorectal cancer, Oxaliplatin (*Received Aug. 3, 2007/Accepted Oct. 26, 2007*)

要旨 現在，日本においても高齢者の大腸癌患者は増えている。以前は，抗癌剤治療は年齢のみで不適格とされることも多かったが，新規薬剤の開発や支持療法の進歩などによってPSのよい高齢者には治療を施すことが増えてきた。今回われわれは，2005年4月～2006年3月までにFOLFOX4療法を導入したPS 0～1の70歳以上75歳以下の高齢者大腸癌症例32例の治療効果や有害事象をまとめ，70歳未満の非高齢者大腸癌症例154例と比較して有効性と安全性の検討を行った。奏効率は31.3%，TTFは204日であり，非高齢者と有意な差は認めなかった。有害事象については，grade 3以上の好中球減少が53.1%と非高齢者より有意に多く認められたが，その他は差を認めなかった。relative dose intensityや治療中止理由についても非高齢者との差は認めなかった。FOLFOX4療法はPSが良好な75歳以下の高齢者についても安全かつ有効な化学療法であると考えられた。

はじめに

FOLFOX4療法（5-FU，LV，oxaliplatin（L-OHP）併用療法）は進行・再発大腸癌に対するfirst-lineの治療として2000年にde Gramontらによって開発され，奏効率は50%を超え，progression free survival（PFS）は8か月を超え，全生存期間は約16か月という画期的な治療方法である[1]。その後，GoldbergらによってIFL療法より優れていることが示され，FOLFOX4療法が欧米での進行・再発大腸癌の標準治療となった[2]。日本でも2005年にFOLFOX4療法が承認されて以降，進行・再発大腸癌の標準治療として定着しつつある。

一方，現在日本において大腸癌は，癌死亡数において第三位，罹患数において第二位を占めている。また，日本の男性の平均寿命は78.64歳，女性は85.59歳と世界一の長寿国であり，今後急速に高齢者大腸癌患者は増えることが予想される。進行・再発大腸癌に対する化学療法では5-FU/LV療法，UFT/LV療法は高齢者においても認容性があることは報告されている[3,4]。また，CPT-11を含むレジメンは，ハイリスクな症例については毒性が高まるという報告が多く，高齢者においても注意が必要である[5-7]。

多剤併用化学療法は加齢に伴う臓器機能の低下した高齢者において毒性が強まることが予想され，非高齢者と

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表1 患者背景

		高齢者（n=32例）	非高齢（n=152例）
年齢（中央値）		72（70～75）歳	57（28～69）歳
性別	男性	16	79
	女性	16	73
PS	PS 0	27	116
	PS 1	5	34
	PS 2	0	2
原発部位	結腸	21	85
	直腸	11	67
初発・再発	初発	25	106
	再発	7	46
原発の有無	あり	1	9
	なし	31	143
治療目的	first-line	11	63
	second-line 以降	21	89
施行サイクル数（中央値）		10（4～18）サイクル	9（1～19）サイクル

同様な化学療法を行うかどうかは議論の多いところである。これまで高齢者進行・再発大腸癌症例に対するFOLFOX4療法の認容性に関してはあまり検討されていない。今回われわれは，高齢者進行・再発大腸癌症例に対するFOLFOX4療法の治療成績および安全性について検討した。

Ⅰ．対象および方法

2005年4月～2006年3月までの1年間に当院にてFOLFOX4療法を導入した70歳以上75歳以下の高齢者進行・再発大腸癌32症例を対象とした。同時期にFOLFOX4療法を施行した70歳未満の非高齢者大腸癌症例152症例を比較対象とした。

対象症例の年齢は中央値72（70～75）歳であり，性別，治療開始前のEastern Cooperative Oncology Group Performance Status（PS），原発部位，初発・再発の割合，性別は非高齢者群との間に差はなかった。また初回治療症例は11例，二次治療以降の症例（治癒切除後の術後補助化学療法施行例で，その終了6か月以内に再発が確認されている症例も含む）が21例であり，これも非高齢者群との間に差はなかった（表1）。しかし，前治療にCPT-11を含む症例の割合は非高齢者群で多かった（高齢者群/非高齢者群は22/34%）。また32症例中18症例は併存症を有していた。併存症は高血圧13例，糖尿病4例，喘息3例，狭心症1例（重複例を含む）であった。

治療は高齢者，非高齢者ともに1日目にLV 100 mg/m^{2}とL-OHP 85 mg/m^{2}を2時間かけて経静脈投与し，その後5-FU 400 mg/m^{2}を急速静脈内投与にて行う。引き続き5-FU 1,200 mg/m^{2}を約22時間持続静注で施行，2日目に同様にLV 100 mg/m^{2}を2時間かけて経静脈投与し，その後5-FU 400 mg/m^{2}を急速静脈内投与し，5-FU 1,200 mg/m^{2}を約22時間持続静注で施行し終了する。これを2週間ごとに繰り返す。

当院では前投薬として1日目にdexamethasone 8 mgとgranisetron 3 mgを，2日目にgranisetron 3 mgを静注している。また4サイクル目以降では，アレルギー予防のためにdiphenhydramine 50 mgを投与前30分以内に内服してもらっている。初回治療導入は入院で行い，2回目以降は外来で行った。アレルギーが出現した場合は，Common Terminology Criteria for Adverse Events v3.0（CTCAE v3.0）にてgrade 2以下であれば次回治療は入院で，前投薬のdexamethasoneを20 mgに増量し，L-OHPの投与時間を4時間に延長して行い，アレルギーの再現なければ，以降外来で継続した。効果はResponse Evaluation Criteira in Solid Tumors（RECIST）に基づき約3か月ごとCTにて，有害事象についてはCTCAE v3.0に基づき評価した。観察期間は2006年4月1日から2007年9月30日までとし，後ろ向き調査にて解析，検討を行った。

Ⅱ．結　果

1．治療成績

奏効率はRECISTにより評価した。高齢者群は31.3%であり，非高齢者群は26.3%であった。初回治療は，高齢者群63.6%，非高齢者群41.3%であった。また二次治療以降は，高齢者群14%，非高齢者群15.7%であった（表2）。

観察期間内time to treatment failure（TTF）中央値は，高齢者群204日，非高齢者群169日であり，両群に有意な差は認めなかった（p=0.78）。初回治療症例は，高齢者群204日，非高齢者群236日であった。また二次治療以降の症例は，高齢者群210日，非高齢者群159日であ

表 2　効　果

		奏効率	
全体	(n=184)	27.1% (first-line: 44.6%	second-line 以降: 15.5%)
非高齢者	(n=152)	26.3% (first-line: 41.3%	second-line 以降: 15.7%)
高齢者	(n=32)	31.3% (first-line: 63.6%	second-line 以降: 14.0%)

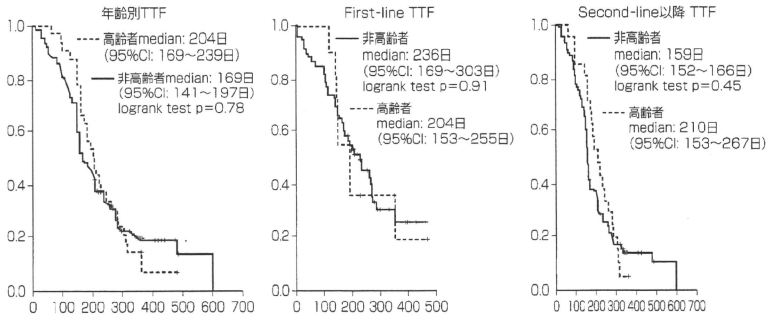

図 1　TTF

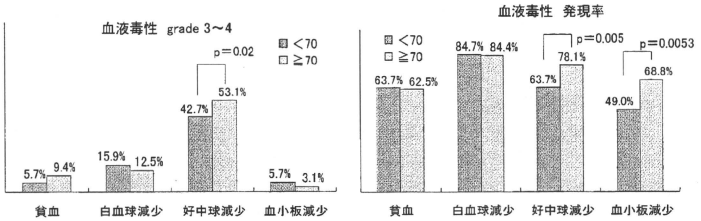

図 2　血液毒性

り，初回治療，二次治療以降いずれにおいても両群に有意な差は認めなかった（p=0.91，0.45）（図1）。

2．有害事象

血液毒性について，高齢者群においては白血球減少の発現率が最も多く認められたが，非高齢者群と比較して有意な差は認めなかった。また，貧血についても同様に非高齢者群と比較して発現率に差は認めなかった。しかしながら図2に示すように，好中球減少と血小板減少については非高齢者群と比較して多く認められた。また，grade 3 以上の好中球減少についても高齢者群は多く認められた。

非血液毒性については，高齢者群において悪心，食欲不振，疲労，末梢神経障害の発現率が90%以上に認められたが，非高齢者群と同程度であった。grade 3 以上の末梢神経障害については高齢者群において20.6%に認めたが，非高齢者群と同程度であった。また，その他の grade 3 以上の非血液毒性が問題となることはなかった（表3）。

dose intensity については，7サイクルまで完遂できた高齢者群 26 症例と非高齢者群 117 症例について relative dose intensity（RDI）を用いて比較検討した。高齢者群で RDI は 76.5%，非高齢者群で 79.8%と有意な差は認めなかった（Mann-Whitney's U test，p=0.36）。また，有害事象以外の理由で治療を延期した場合（祝日や症例自身の都合など）を，7日の allowance を設けて補正を行った。その補正 RDI については高齢者群で 81.0%，非高齢者群で 83.9%と，これも有意な差は認めなかった（p=0.61）。

治療を中止した理由としては増悪が最も多く，高齢者群 52.1%，非高齢者群 57.3%であった。末梢神経障害によって継続が不可能になった症例がそれぞれ 14.2%/15.5%，アレルギーによって中止になった症例がそれぞ

表 3 非血液毒性

	発現率（%）		grade 3 以上（%）	
	≧70	<70	≧70	<70
悪心	93.8	93.6	0	6.4
嘔吐	53.0	58	0	3.8
下痢	34.4	52.9	5.9	3.8
食欲不振	96.9	93.6	0	7.0
口内炎	25.0	20.4	0	0.6
疲労	96.9	94.3	0	0
手足症候群	44.1	39.5	3.0	2.0
総ビリルビン上昇	40.6	42.0	0	2.5
AST 上昇	65.7	74.3	3.0	1.3
ALT 上昇	46.9	55.8	0	1.3
sCr 上昇	6.3	10.8	0	0.6
末梢神経障害	93.8	91.7	20.6	17.0

れ 14.2%/21.8%であった。中止理由の分布は両群で有意な差は認めなかった（p=0.99）。

FOLFOX4 療法中止後の治療方法は，高齢者群では FOLFIRI 療法が 51.6%で最も多く，化学療法未施行症例が 45.2%であった。一方，非高齢者群では FOLFIRI 療法が 51.7%で，化学療法未施行症例は 36.4%であった。

Ⅲ．考　察

何歳からを高齢者と定義するかは議論の多いところである。WHO においては 65 歳以上を高齢者と定義している。一方，日本においては 75 歳までを前期高齢者，75 歳以上を後期高齢者と定義している。欧米では高齢者を 70 歳もしくは 71 歳以上としている報告が多い。FOLFOX4 療法については，de Gramont らの報告では 75 歳以下を対象としており，当院においても 75 歳までを上限として FOLFOX4 療法を導入している。今回われわれは，当院において FOLFOX4 療法を受けた症例のなかで 70 歳以上 75 歳以下を高齢者症例として後ろ向きに解析した。

従来，高齢者に対しては，一般的に造血器，心肺機能，肝，腎などの主要臓器機能が全体的に低下していることが多く，予想以上の有害事象を呈することがしばしば見受けられるため，有害事象により状態悪化を招くことを恐れ，治療効果の乏しい化学療法を行うか，化学療法を選択しないこともしばしばであった。しかし近年，大腸癌の領域においても新規抗癌剤の登場により治療成績は向上し，目覚ましい進歩を遂げ，また支持療法も進歩しており，全身状態に問題なければ高齢者においても非高齢者と同様の標準化学療法を積極的に考慮する時代となったといえるかもしれない。

海外においては，Goldberg らが FOLFOX4 療法の高齢者（70 歳以上）への適応について四つの臨床試験を集計解析し，高齢者群において grade 3 以上好中球減少（49%対 43%，p=0.04）と血小板減少（5%対 2%，p=0.04）が有意に高かったが，他の有害事象については差を認めなかったと報告している[8]。

当院での PS が 1 以下の 32 症例の解析においても，上記のように有害事象については高齢者で大きな問題となることはなかった。また，RDI は非高齢者と同様に保たれており，合併症は治療中および観察期間内においてもコントロール可能であり，治療経過に影響は認めなかった。さらに TTF も非高齢者と同程度であった。末梢神経障害については非高齢者と同程度認められており，日常の診察のなかでより注意して診ていく必要はあるが，主要臓器機能の保たれた PS が良好な 75 歳以下の日本人高齢者における FOLFOX4 療法の認容性は良好であり，有効な治療方法と考えている。75 歳を超える高齢者についても，米国で主張されているように，日本でも年齢制限を設けず積極的に FOLFOX4 療法を検討してもよいかもしれない。

しかし，FOLFOX4 療法は血液毒性が高齢者で有意に高いことも事実である。近年 bevacizumab や cetuximab などの分子標的治療薬が大腸癌領域でも有効性が確認されており，欧米ではすでに標準治療に組み込まれている[9,10]。Kabbinavar らは bevacizumab（5 mg/kg）と FL 療法の併用療法においては，年齢は安全性に影響を与えなかったと報告した[11]。効果についても PFS で 9 か月ほど，生存期間中央値で 16 か月ほどであり，FOLFOX4療法に劣らない治療方法であると考えられる。フッ化ピリミジン系薬剤と bevacizumab などの毒性のより少ない分子標的治療薬をうまく併用した化学療法が，高齢者における有用な治療方法になるかもしれない。

まとめ

PS が良好で主要臓器機能が保たれており，コントロール不良の合併症がない 75 歳以下の高齢者において，FOLFOX4 療法は安全かつ有効な治療方法の一つと考えられた。

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●原 著●

進行大腸癌に対するFOLFOX4療法による末梢神経障害の回復の解析

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Retrospective Analysis of FOLFOX4 Neurotoxicity for Recovery from Advanced Colorectal Cancer: Masanori Matsuda, Satoshi Matsusaka, Yasutoshi Kuboki, Takashi Itimura, Mariko Ogura, Mitsukuni Suenaga, Daigo Syouji, Chie Watanabe, Keisho Chin, Nobuyuki Mizunuma and Kiyohiko Hatake (*Division of Medical Oncology, Cancer Chemotherapy Center, Japanese Foundation for Cancer Research*)

Summary

Background: Oxaliplatin (L-OHP) in combination with infusional 5-fluorouracil/leucovorin (FOLFOX), has been established as a key drug for advanced colorectal cancer. Sensory neurotoxicity is its dose-limiting toxicity. No prior recovery from neurotoxicity data is available for Japanese patients treated by FOLFOX4 for advanced colorectal cancer.

Purpose: We performed a retrospective study on the recovery from chronic neurotoxicity and period for discontinuing FOLFOX4 therapy due to neurotoxicity.

Patients and method: One hundred eighty-seven patients with advanced or recurrent colorectal cancer were treated with FOLFOX4 regimen between April 2005 and March 2006. We evaluated chronic peripheral sensory neuropathy by National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0), and calculated the period of recovery from grade 3 and grade 2 neurotoxicity by the Kaplan-Meier method.

Result: Seventy-two patients had to discontinue FOLFOX4 due to grade 3 and grade 2 neurotoxicity. grade 2 and grade 3 neurotoxicity was observed in 39 (20.8%) and 33 (17.6%) patients, respectively. Patients with grade 2 and grade 3 neurotoxicity had a median age of 59 years (range, 35-75 years), and 62 years (range, 36-73 years), respectively. The median number of courses until expression of grade 2 neurotoxicity was ten (range, 2-23 courses) and that for grade 3 neurotoxicity was also ten (range, 4-14 courses). The period of reducing grade 2 neurotoxicity to grade 1 was 56 days, while that for reducing grade 3 neurotoxicity to grade 1 was 106 days. FOLFOX4 was reintroduced in 15 patients with grade 2 neurotoxicity and in 14 patients with grade 3 neurotoxicity. The main reason that patients could not have reintroduction FOLFOX4 was early progression before reducing neurotoxicity to grade 1. The period from discontinuation of FOLFOX4 to disease progression was 88.5 days in partial response (PR) cases and 58 days in stable disease (SD) cases. PR cases took longer until disease progression than SD cases.

Conclusions: The incidences of neurotoxicity were similar in Japanese patients compared with those reported in Western studies. These findings provide useful information for clinicians and patients using oxaliplatin. **Key words**: FOLFOX, Neuropathy, Oxaliplatin (*Received Jul. 2, 2007/Accepted Aug. 30, 2007*)

要旨 背景: FOLFOX4療法は進行大腸癌に対する標準療法である。oxaliplatinの用量規定因子は末梢神経障害である。目的: FOLFOX4療法での末梢神経障害による休薬，中止後の回復期間について検討する。対象と方法: 2005年4月～2006年3月までに当院でFOLFOX4療法を導入された切除不能転移・再発大腸癌に対して，慢性末梢神経障害をCommon Terminology Criteria for Adverse Events v3.0 (CTCAE v3.0) にて評価し，2006年7月31日までにgrade (G) 3にて休薬・中止となった症例について，2006年12月31日までの末梢神経障害の回復期間をKaplan-Meier法にてretrospectiveに解析する。結果: FOLFOX4療法を施行した患者は187例のうちG2以上の末梢神経障害で休薬，中止となった症例はG2: 39例 (20.8%)/G3: 33例 (17.6%) であった。発現までのサイクル数の中央値はG2: 10 (2～23)/G3: 10 (4～14) サイクルであった。G1への回復期間の中央値はG2からは56日で，G3からは106日であった。休薬された例で治療を再開できたのはG2で15例 (78.9%)，G3で14例 (51.9%) であった。再開ができなかった理由は休薬中の増悪が最も多かった。休薬から増悪までの期間はpartial response (PR) 例88.5日/stable disease (SD) 例58日で，PR例はSD例と比較して休薬から増悪までの期間が長かった。結語: FOLFOX4療法における機能障害を伴う末梢神経障害が海外の臨床試験と同様にみられた。今後，

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末梢神経障害への対策が必要であると考えられた。

Ⅰ. 背　景

進行大腸癌，進行結腸・直腸癌に対する leucovorin (LV) と fluorouracil (FU) に oxaliplatin (L-OHP) との併用療法（FOLFOX 療法）が国際的に標準療法とされており[1,2]，日本でも 2005 年 4 月より治癒切除不能の結腸・直腸癌に対して FOLFOX4 療法が承認され，保険適応となった。L-OHP の用量規定因子に四肢の感覚不全あるいは知覚異常を特徴とする末梢神経障害がある。FOLFOX4 療法の用量規定因子は骨髄抑制と L-OHP による可逆性の感覚性末梢神経障害とされている。末梢神経障害は日常生活に支障を来し，治療の中断を余儀なくされるため重大な有害事象といえるが，わが国における神経障害についての報告はまだない。L-OHP に特異的な神経障害に対して，glutathione[3]や carbamazepine[4]，カルシウム-マグネシウムなど[5,6]の薬剤による神経症状の軽減の可能性が検討されている。また de Gramont らの Stop and Go 戦略[7]があるが，これは重篤な神経症状の発現予測時期に L-OHP を休薬する投与方法である。

今回われわれは L-OHP の神経症状を軽減する方法を模索するため，当院における末梢神経障害の現状について検討したので報告する。

Ⅱ. 対象と方法

1. 症　例

2005 年 4 月～2006 年 3 月までに当院で病理学的・組織学的に診断が得られた切除不能および術後再発大腸癌，結腸および直腸癌で performance status 0～2 の全身状態が良好な例に対して FOLFOX4 療法を導入した。

FOLFOX4 療法は L-OHP を第 1 日目に 2 時間点滴静注，第 1 日目，2 日目にレボフォリナートカルシウム 100 mg/m^{2}を 2 時間点滴静注後，FU 400 mg/m^{2}を急速静注した後，600 mg/m^{2}を 22 時間で持続静注する投与方法を 2 週間ごとに行った。治療の中止基準は原病の進行が認められた場合，神経障害を含め忍容できない副作用が生じた場合とした。

2. 末梢神経毒性の評価

末梢神経障害の評価は FOLFOX4 療法の各 cycle の投与開始前に CTCAE v3.0 にて評価した。2006 年 7 月 31 日までに G2 以上で休薬・中止となった例について，2006 年 12 月 31 日までの末梢神経障害の回復について継続的に観察を行った。

G3 の末梢神経障害が発症した例については FOLFOX4 療法を休薬とし，神経障害が G1 に回復されるまでの期間を評価した。発症時に病勢のコントロールされている例については，休薬期間を G3 が発症する直前の治療から FOLFOX4 療法が再導入されるまでの期間とした。G2 の神経障害が発症した例では，休薬した例に対して休薬直前の治療から G1 までの回復および再導入までの期間をそれぞれ回復期間，休薬期間とした。

以上の回復期間，休薬期間について SPSS Ver. 11 を用いて Kaplan-Meier 法にて retrospective に解析を行った。

Ⅲ. 結　果

1. 患者背景

当院で FOLFOX を導入した 187 例のうち G2 の末梢神経障害が発症した例は 72 例，G2 以上の神経障害の発現頻度は 38.5%，72 例の内訳は G2 39 例 20.8%，G3 33 例 17.6%であった。このうち神経障害の回復時期が特定できなかった 1 例に関しては不適切症例として除外した。残りの 71 例（G2 38 例，G3 33 例）を末梢神経障害の回復の解析の対象例とした。神経障害の回復の解析例のなかで FOLFOX4 療法中断時に原病の増悪，オキサリプラチンアレルギーやその他の副作用により他の治療に変更となった 26 例を除外し，神経障害回復時に治療の再開を前提として FOLFOX4 療法を中断した 45 例を休薬の解析の対象例とした（図 1）。末梢神経障害で休薬した例は G3 27 例 10.1%，G2 19 例 14.4%であった。患者背景には G2，G3 および全体に差は認めなかった（表 1）。

2. 末梢神経障害の発現の解析

末梢神経障害について休薬・中止のサイクル数の中央値は 10 サイクルであった（表 2）。G3 症例での G2 神経障害は G1 から G3 に移行した症例があるため，症例数 n が少なくなっている。10 サイクル以上での G2，G3 の頻度は減少していた（図 2）。G3 の末梢神経障害では L-OHP の累積投与量が増えるに従い末梢神経障害の発症は多くなった（表 2，図 3）。

3. 末梢神経障害の回復についての解析

回復期間の観察期間の中央値は 63 日であった。Kaplan-Meier 曲線を示す（図 4）。末梢神経障害が G1 に回復する以前に原病の増悪により全身状態が悪化し，末梢神経障害の評価ができない場合には最終確認日，また休薬症例に関しては神経障害が回復しないまま再投与した時点で打ち切りとした。

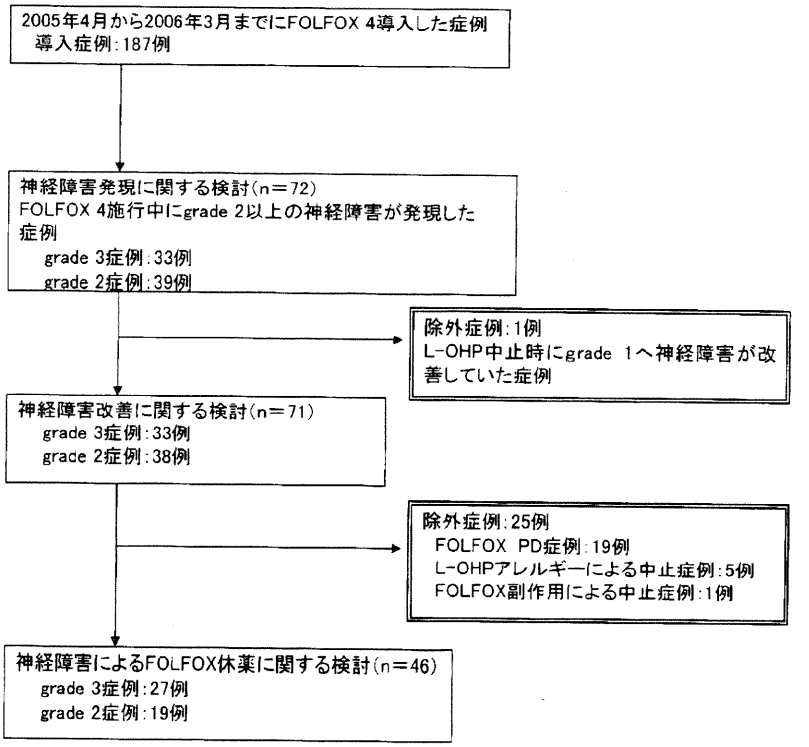

図1　症例選択

表1　患者背景

	grade 2	grade 3	全症例
症例数	39（20.8%）	33（17.6%）	187
性別			
男性	17（43.6%）	18（54.5%）	96（51.3%）
女性	22（56.4%）	15（45.5%）	91（48.7%）
年齢 中央値（範囲）	59（35～75）	62（36～73）	60（28～75）
PS			
0	29（74.4%）	29（87.9%）	145（77.5%）
1	10（35.6%）	4（12%）	40（21.4%）
2	0	0	2（1.1%）
前化学療法歴			
あり	28（71.8%）	26（78.8%）	135（72.2%）
なし	11（28.2%）	7（21.2%）	52（27.8%）

G2がG1に回復するまでの中央値は56日，G3がG1に回復するまでの期間は106日であった。G3の症例のほうがG2の症例に比べて回復まで時間を要した。

4．末梢神経障害による休薬

休薬された例で治療を再開できたのはG2で15例78.9%，G3で14例51.9%であった。再開ができなかった理由としては休薬中の増悪が最も多かった。休薬中の増悪がみられた例はG2で5例，G3で13例であった。休薬から増悪までの期間はG2で56日，G3で73日であった（表3）。

休薬中の増悪を最良治療効果で比較した。PR例はSD例と比較して休薬から増悪までの期間が長くなっていた。全休薬例での休薬から増悪までの期間はPR例88.5日，SD例で58日であった（表4）。

Ⅳ．考　察

2005年4月にL-OHPが承認され，当院では2005年4月～2006年3月までの期間で188例にFOLFOX4療法の導入を行った。当院でのFOLFOX4療法における遅発性末梢神経障害G2の末梢神経障害の発症は20.8%，休薬・中止までのサイクル数は10サイクル，回復期間は56日であった。G3の末梢神経障害の発症は17.6%，発症までのサイクル数の中央値は10サイクル，回復期間は106日であり，海外の臨床試験と同様である

表 2　神経障害の発現とサイクル数，累積投与量

	grade 2 症例 中央値（範囲）	grade 3 症例 中央値（範囲）	全体 中央値（範囲）
grade 1 神経障害	n=39	n=33	n=72
発現サイクル数（サイクル）	2（1～4）	1（1～5）	2（1～5）
L-OHP 累積投与量（mg/m^2*）	170（85～340）	85（85～425）	170（85～425）
発現までの日数（日）	19（0～74）	15（0～153）	16（0～153）
grade 2 神経障害	n=39	n=17	n=56
発現サイクル数（サイクル）	10（5～23）	9（2～12）	10（2～23）
L-OHP 累積投与量（mg/m^2*）	850（408～1,764）	765（170～1,020）	845.75（170～1,764）
発現までの日数（日）	180（62～424）	154（28～299）	174（28～424）
grade 3 神経障害		n=33	n=33
発現サイクル数（サイクル）	—	10（4～14）	10（4～14）
L-OHP 累積投与量（mg/m^2）		850（340～1,122）	850（340～1,122）
発現までの日数（日）		177（69～350）	177（69～350）

*：grade 3 症例での grade 2 神経障害は grade 1⇒grade 3 に移行した症例があるため n が少なくなっている

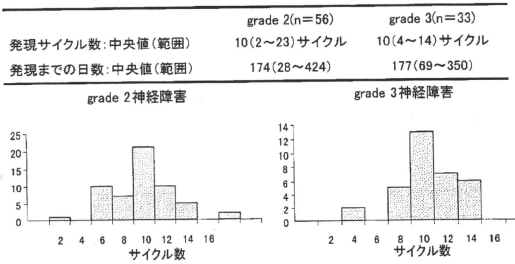

図 2　神経障害とサイクル数

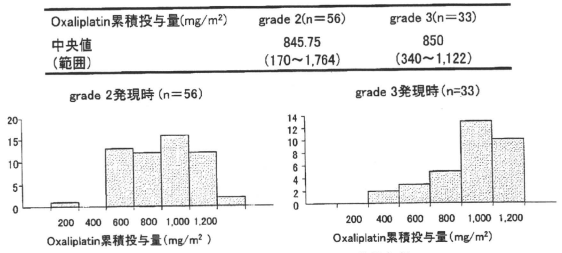

図 3　神経障害と oxaliplatin 累積投与量

と考えられた。

また，今回われわれの報告では G2 で休薬した症例では神経障害の回復期間が短く，休薬からの再導入率も高かった。このことは，より神経障害が軽度な段階で休薬を行ったほうがよい可能性が示唆された。

L-OHP による末梢神経障害は FOLFOX6 療法と irinotecan と FU 持続投与との併用療法である FOLFIRI 療法との比較試験である C97 試験[8]や L-OHP の用量を高めた FOLFOX7 療法での臨床試験でも認められ[9]，末梢神経障害は日常生活に支障を来し，治療の中断を余儀なくされるため重大な有害事象といえる。末梢神経障害の対策としてカルシウム-マグネシウム[6]や抗けいれん薬である carbamazepine，gabapentin などの試みがある[10,11]。近年，Cassidy らにより転移性大腸癌患者 649

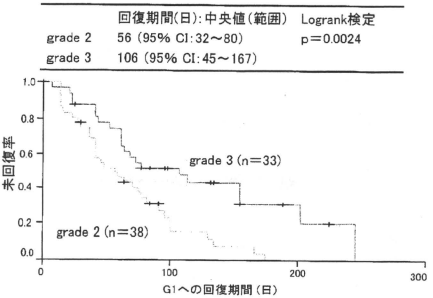

図 4 神経障害の回復

表 3 FOLFOX4療法の休薬

	grade 2	grade 3
休薬症例数	n=19	n=27
休薬後の転帰		
FOLFOX 再開例	15	14
(FOLFOX 再開率)	(78.9%)	(51.9%)
再開までの期間 (日):中央値	56(16～175)	77(28～266)
FOLFOX 非再開例	3	13
後治療開始	2	10
緩和ケアへの移行	0	3
観察期間中 (休薬中)	1	0

表 4 休薬中の増悪

		増悪までの期間		
		n	中央値 (日)	範囲 (日)
grade 2	全体	5	55	49～70
	SD	3	49	49～70
	PR	2	63	55～92
grade 3	全体	14	66	41～120
	SD	9	59	41～99
	PR	5	98	66～120
grade 2+grade 3	全体	19	66	41～120
	SD	12	58	41～99
	PR	7	85	55～120

例を対象に，筋萎縮性側索硬化症治療薬である xaliproden を併用する群と FOLFOX4 単独群でのランダム化比較試験の結果，G3 以上の重症の末梢性感覚神経障害は FOLFOX4 単独群では 16.7%，xaliproden 併用群で 11.1% であり，相対リスクは 39% 減少したと報告した[12]。しかし，いずれも末梢神経障害の予防としては確立したとはいえない。

de Gramont らによる OPTIMOX1 では Stop and Go 戦略に基づいた FOLFOX4 療法の継続療法と FOLFOX7 療法 6 サイクルと FU/LV 療法 12 サイクルの交替療法が比較された。両者は末梢神経障害，生存期間に差を認めなかった[7]。また，OPTIMOX 2 は mFOLFOX7 療法を 6 コース投与後，化学療法を中止し，ベースラインより腫瘍径が増大してから再度 mFOLFOX7 投与を行うものである。OPTIMOX1 と OPTIMOX2 との比較では，初回 mFOLFOX7 療法で disease control (CR+PR+SD) 以上の症例では完全休薬が可能で末梢神経症状の発現も少ない可能性を示唆された[13]。本検討結果から全休薬例での休薬から増悪までの期間は PR 例 88.5 日，SD 例で 58 日，PR 例は SD 例と比較して休薬から増悪までの期間が長い結果から，治療効果によって休薬期間を変更する必要があると考えられた。本研究は，日本における Stop and Go 戦略の導入に有益な情報になると考えられた。

今後，わが国における末梢神経障害に対する新規補助薬や Stop and Go 戦略を取り入れた治療戦略の確立が望まれる。

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6. 胃がん腹水例に全身化学療法は有効か？有効であれば何を選択すればよいのか？

1 序論

進行胃がんに伴う腹膜転移は腹水，腸管閉塞，尿管閉塞による水腎症（腎不全），胆管閉塞などの合併を伴うことが多く，これらによって腹満感，食物摂取不能，腹痛，悪心・嘔吐，浮腫，黄疸などの症状をしばしば引き起こす．またこのような病態は，急速な全身状態の悪化を引き起こすことから，胃がん腹膜転移例は予後不良とされてきた．加えて，腹膜転移例においては抗がん剤の毒性が遷延，重篤化するため，抗がん剤治療の開発は安全性の面からも治療開発に限界があり，胃がん腹膜転移例（特に腹水例）を対象とした臨床試験は非常に少ない．しかし近年になって，これら腹膜転移例を対象とした試験が本邦から少しずつ発信されるようになってきた．

本稿においては主に腹水を含む腹膜転移例におけるエビデンスを紹介しながら，胃がん腹水例における治療について考察したい．

2 コンセンサス

腹水量の多寡により化学療法の適応またはレジメン選択が議論されることが多いが，実際には腹水量に関する明確な定義はない．そこで本稿ではJCOG（Japan Clinical Oncology Group）試験である，胃がん腹膜転移を対象とした比較試験（JCOG0106）で用いた定義を参考に，腹膜転移の程度を軽度，中等度，高度の3つに分けて検討することとする（表1）．

表1

腹膜転移	軽度※	中等度	高度
腸管狭窄所見	認めない	認める	認める
腹水	なし	CTにて骨盤腔のみ，または上腹部のみに認める．	骨盤腔を越えて，上腹部方向へ連続的に存在する．

※術中所見のみで認識できる腹膜転移

(1) 軽度腹膜転移例におけるコンセンサス

腸管や胆管，尿管の狭窄を認めず，術中所見のみで診断された軽度腹膜転移例はその多くは腹膜転移による症状がなく，全身状態もよい．このような病態はJCOG9912，SPIRITS試験（後述）といった一般的な切除不能・再発胃がんを対象とした臨床試験の適格基準に合致するものであり，その他の一般的な投与基準を満たせば，安全性にも問題はないと考えられる．したがって，軽度腹膜転移例に対しては標準療法である，S-1＋CDDP（シスプラチン）療法も