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FOLFOX as First-line Therapy for Gastric Cancer with Severe Peritoneal Metastasis

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Abstract. *Background/Aim: Severe peritoneal metastasis (PM) from advanced gastric cancer (AGC) causes massive ascites and inadequate oral intake. Because patients with severe PM are often not included in clinical trials, little is known regarding the efficacy and safety of oxaliplatin with l-leucovorin and bolus/continuous infusion of 5-fluorouracil (FOLFOX) for them. Patients and Methods: We retrospectively studied AGC patients with massive ascites and/or inadequate oral intake due to severe PM treated with FOLFOX as the first-line treatment. Results: Only 39 (10%) of 378 AGC patients had severe PM; 10 received FOLFOX. The median progression-free and overall survivals were 7.5 and 13.2 months, respectively. Ascites decreased in seven of nine patients with ascites, and oral intake improved in four of seven patients with an inadequate oral intake. Common grade 3-4 adverse events included neutropenia and anemia. Conclusion: This study suggests that FOLFOX is effective and manageable for AGC patients with severe PM.*

In 2012, an estimated 951,000 new cases of gastric cancer occurred worldwide (the fifth most common malignancy), resulting in an estimated 723,000 deaths (the third leading cause of cancer death) (1). Standard treatment for advanced or recurrent gastric cancer (AGC) is chemotherapy based on fluoropyrimidine plus platinum, sometimes with a taxane or anthracycline depending on the patient or country (2). In Japan, S-1 or capecitabine, in combination with cisplatin or oxaliplatin, is the first-line standard regimen based on pivotal phase III trials such as the S-1 plus cisplatin *versus* S-1 alone for first-line treatment of advanced gastric cancer (SPIRITS) trial, ML17032 trial comparing capecitabine/cisplatin *versus* 5-fluorouracil (5-FU)/cisplatin, The Randomized ECF for Advanced and Locally Advanced Esophagogastric Cancer (REAL-2) trial, and The Randomized Phase III Study Comparing Oxaliplatin plus S-1 with Cisplatin plus S-1 in Chemotherapy-naïve Patients with Advanced Gastric Cancer (G-SOX) trial (3-6). Even if patients with AGC received these treatments, the prognosis of AGC remains poor with a median overall survival (OS) of 13.0-14.1 months (3, 6, 7).

Peritoneal metastasis is the most common metastatic pattern and often causes bowel obstruction or paralytic ileus. Patients with severe peritoneal metastasis, defined as massive ascites and/or inadequate oral intake, have poor prognosis and quality of life (8). Because they often do not meet the eligibility criteria for clinical trials, there are no standard regimens for this group of patients. In addition, treatment with oral fluoropyrimidine plus platinum cannot be successfully applied to this patient population due to inadequate oral intake. Therefore, we need to establish a beneficial treatment for them.

In two retrospective studies of 5-FU/methotrexate (MTX), 5-FU/l-leucovorin (LV), or 5-FU alone as first-line treatment for patients with severe peritoneal metastasis, the median progression-free survival (PFS) and OS were 1.9-4.2 months and 4.6-8.4 months, respectively, and efficacies of 5-FU/MTX, 5-FU/LV, and 5-FU alone were modest (8, 9). In the phase I/II study of 5-FU/LV plus paclitaxel (FLTAX) for the same population, the median PFS and OS were 6.2 months and 9.5 months, respectively (10). Based on these results, the phase III JCOG1108/WJOG7312G trial comparing FLTAX with 5-FU/LV for the same population is ongoing in Japan.

5-FU/LV plus oxaliplatin (FOLFOX) is one of the standard regimens for AGC globally. This regimen can be utilized effectively for patients with severe peritoneal metastasis because it comprises intravenous infusions and does not need hydration like cisplatin-based regimens. Additionally, FOLFOX is effective and feasible in heavily

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treated AGC patients or in patients with performance status (PS) 2. The frequency of grade 3 or more neutropenia related with FOLFOX was 15%-57% in heavily treated AGC patients (11-14) and 17% in patients with PS 2 (15), which were comparable to 29%-45% in patients with PS 0 or 1 (16-18). Response rates of FOLFOX were 21%-27% in heavily treated AGC patients and 32% in patients with PS 2. Therefore, postulating that FOLFOX is a promising regimen for patients with severe peritoneal metastasis who have typically poor PS, we conducted a retrospective analysis to evaluate its efficacy and safety for this population.

Patients and Methods

Patients. Patients who received first-line therapy for AGC at Aichi Cancer Center Hospital from December 2010 to December 2014 were included in this study according to the following eligibility criteria: (1) histologically confirmed gastric or gastroesophageal adenocarcinoma, (2) unresectable or recurrent disease, (3) massive ascites and/or inadequate oral intake due to peritoneal metastasis, (4) treated with FOLFOX, (5) no previous chemotherapy, except for adjuvant chemotherapy finished more than six months before the starting date of FOLFOX, (6) adequate bone marrow, hepatic, and renal function, and (7) no previous treatment with oxaliplatin. Peritoneal metastasis was defined in this study as follows: induration detected by digital rectal examination; gastrointestinal stenosis or obstruction proven by gastrointestinal series; peritoneal nodule, ascites, hydronephrosis, or obstruction of the extrahepatic bile duct detected by computed tomography (CT) scan, which was not due to factors other than peritoneal metastasis; and pathologically confirmed malignant ascites or peritoneal metastasis. Massive ascites was defined as continuous ascites spreading throughout the abdominal cavity. Inadequate oral intake was defined as the requirement for daily intravenous infusion to supply water and nutrition. These definitions were the same as those in the phase I/II study of FLTAX. All patients provided written informed consent for receiving chemotherapy. This study was reviewed and approved by the Institutional Reviewed Board of Aichi Cancer Center Hospital.

Treatments. FOLFOX consisted of oxaliplatin 85 mg/m^2 and *l*-leucovorin 200 mg/m^2 administered simultaneously as a two-hour intravenous infusion followed by a 5-FU bolus 400 mg/m^2 and then 5-FU 2,400 mg/m^2 as a continuous infusion over 46 h. Treatments were continued every two weeks until disease progression, death, unacceptable toxicities, or patient's refusal. Patients in whom the dose of FOLFOX was reduced due to old age or poor European Cooperative Oncology Group (ECOG) PS were also included in this study.

Assessments and statistical analysis. Tumor response was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. The response rate (RR) was presented as the proportion of patients with complete response (CR) or partial response (PR) among patients with target lesions. Confirmation of CR, PR, or stable disease (SD) was not required for this study. PFS was defined as the duration from the first administration of chemotherapy to the first radiological or clinical observation of disease progression or death from any cause. Time to treatment failure (TTF) was defined as the duration from the first administration of chemotherapy to the discontinuation of any drugs from any cause. OS was defined as the duration from the first administration of treatment to death from any cause or the last follow-up date. Median PFS, TTF, and OS were estimated by the Kaplan–Meier method. Improvement in oral intake was defined as keeping sufficient oral intake for seven or more days without daily intravenous drip infusion. This definition was the same as in the two abovementioned retrospective studies (8, 19). The levels of ascites were defined by CT as follows: massive, continuous ascites from the pelvic cavity to the upper abdomen; moderate, not massive, or mild ascites; mild ascites limited to the pelvic cavity or upper abdomen;

Table I. *Patient characteristics*.

Characteristic	N=10	%
Age (years)		
Median (range)	64.5	(40-94)
Gender		
Male	8	80
Female	2	20
ECOG PS		
0	0	0
1	5	50
2	3	30
3 or 4	2	20
Histological type		
Diffuse type	8	80
Intestinal type	2	20
Disease status		
Unresectable	9	90
Recurrent	1	10
Prior gastrectomy		
Yes	2	20
No	8	80
Number of metastatic sites		
1	5	50
≥2	5	50
ALP (ULN=339)		
<ULN	4	40
≥ULN	6	60
LDH (ULN=231)		
<ULN	9	90
≥ULN	1	10
Albumin (LLN=3.8)		
<LLN	10	100
≥LLN	0	0
Severe peritoneal metastasis		
Massive ascites	3	30
Inadequate oral intake	5	50
Both of the above factors	2	20
Ascites		
None	1	10
Mild	3	30
Moderate	1	10
Massive	5	50

ECOG: Eastern Cooperative Oncology Group; PS: performance status; ALP: alkaline phosphatase; LDH: lactate dehydrogenase; ULN: upper limits of normal; LLN: lower limits of normal.

Table II. *Dose reduction and dose intensity.*

Case	Age	PS	Ascites	OI	Initial dose (mg/m^2)			Dose interruption or reduction after the first course				Total course	Relative dose intensity (%)		
								Interruption	Reduction						
					FU b	FU c	OX		Course	Drug	Reason		FU b	FU c	OX
1	56	1	No	Inadequate	400	2400	85	yes	6th	All 80%	Fatigue G2	21	59	64	30
2	93	2	Massive	Inadequate	260	1600	60	no	No reduction			1	65	67	71
3	65	1	Mild	Inadequate	320	2240	85	yes	13th	FU b 70%		15	70	87	39
4	39	1	Massive	Adequate	400	2400	85	yes	7th	All 80%	Nausea G2	10	66	68	67
5	46	1	Mild	Inadequate	400	2400	85	no	3rd	FU b 0%	Neutropenia G4	9	20	92	61
6	76	4	Massive	Inadequate	0	2400	85	yes	2nd	All 80%	Neutropenia G4	5	0	71	66
7	68	3	Moderate	Inadequate	0	2400	65	no	No reduction			23	38	96	45
8	62	2	Mild	Inadequate	0	2400	85	yes	No reduction			10	0	95	95
9	69	2	Massive	Adequate	400	2400	85	yes	No reduction			15	83	83	83
10	63	1	Massive	Adequate	400	2400	85	yes	No reduction			21	70	70	27

PS: Performance status (Eastern Cooperative Oncology Group); OI: oral intake; FU b: 5-FU bolus; FU c: 5-FU continuous infusion; OX: oxaliplatin; G: grade.

no ascites that was undetectable. The ascites response by CT scan was defined as follows: CR, disappearance of ascites; PR, decreased levels of ascites; SD, same level of ascites as that before treatment; and progressive disease (PD), increased levels of ascites or drainage frequency. These definitions were the same as those in the phase I/II study of FLTAX. Adverse events were assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. All statistical analyses were performed using JMP version 10 (SAS Institute, Cary, N.C., USA).

Results

Patient characteristics. Among the 378 patients with gastric cancer who received first-line therapy, 39 (10.3%) had severe peritoneal metastasis. Of these 39 patients, 10 received FOLFOX. Among them, peritoneal metastasis was diagnosed with histopathology of peritoneal metastasis in three patients, with cytology of ascites in three patients, with obstruction of the extrahepatic bile duct detected by CT scan in two patients, with hydronephrosis by CT scan in one patient, and with massive ascites by CT scan in one patient. All of them fulfilled other eligibility criteria for this study. Patient characteristics are shown in Table I. Among all the patients, five (50%) had ECOG PS of 2 or more, six (60%) had higher than normal levels of alkaline phosphatase, eight (80%) had diffuse-type adenocarcinoma and primary lesion, and nine (90%) had ascites. All patients had lower than normal levels of serum albumin. Two patients had both massive ascites and inadequate oral intake. No patient had human epidermal growth receptor 2 (HER2)-positive tumors, defined as immunohistochemical staining (IHC) of 3+ or IHC of 2+ with gene amplification according to *in situ* hybridization.

Treatment exposure. The median number of treatment cycles was 11.5 (range=1-23 cycles). Dose modification for the first course was performed in five patients. Because of PS 2 or more, the initial doses of oxaliplatin, bolus 5-FU, and continuous infusion 5-FU were reduced in two, two, and one patient, respectively, and bolus 5-FU was not administered in three patients. The median relative dose intensity was 64% (27 mg/m^2/week; range=11-40 mg/m^2/week) for oxaliplatin, 62% (123 mg/m^2/week; range=0-166 mg/m^2/week) for 5-FU bolus infusion, and 77% (921 mg/m^2/week; range=762-1157 mg/m^2/week) for 5-FU continuous infusion. Dose modification was required in five patients due to adverse events. Four patients discontinued oxaliplatin due to peripheral neuropathy. Seven patients had a delay of seven or more days due to adverse events (Table II). All patients had discontinued FOLFOX at the time of analysis. The median duration of follow-up was 13.2 months (range=1.1-29.2 months), and the median TTF was 6.5 months (95% CI=0.5-12.0). Reasons for discontinuation included disease progression in seven patients, treatment-related death in one patient, and changing to S-1-containing regimens due to improved oral intake in two patients.

Efficacy. Among the three patients with measurable lesions, one and two patients achieved CR and PR, respectively, with a response rate of 100%. However, this was not confirmed (Table III). All but one patient experienced disease progression at the time of analysis. Among all 10 eligible patients, the median PFS and OS were 7.5 months (95% CI=0.5-12.8) and 13.2 months (95% CI=1.1–not reached), respectively (Figures 1 and 2). Of the nine patients with ascites, five and two

Table III. *Baseline characteristics and efficacies among study patients.*

Case	Age	Gender	PS (Pre)	PS (Best)	His	Metastatic sites	Ascites	Ascites Res	Alb (Pre)	Alb (Best)	OI	Imp OI	Tumor Res	TTF	PFS	OS
1	56	M	1	0	Por		No	-	3.4	4.3	Inadequate	Yes	-	12.8	12.8	17.2+*
2	93	M	2	2	Por	ple	Massive	NE	2.7	2.6	Inadequate	No	-	0.49	0.49	1.1
3	65	M	1	0	Por	LN, liver	Mild	CR	3	4.7	Inadequate	Yes	PR	7	7	16.2
4	39	M	1	0	Por		Massive	PR	1.8	4.4	Adequate	-	-	5.9	5.9	11.6
5	46	M	1	1	Por		Mild	SD	2.8	4	Inadequate	No	-	4.7	4.7	9.7
6	76	M	4	0	Mod	Liver	Massive	CR	2.6	2.8	Inadequate	Yes	CR	3.7	29.2+	29.2+
7	68	F	3	1	Por		Moderate	CR	3.5	4.1	Inadequate	No	-	12	12	14.8
8	62	M	2	1	Well	LN, liver, lung, ple	Mild	CR	3.4	3.9	Inadequate	Yes	PR	5	5	5
9	69	M	2	1	Por	ple	Massive	PR	2.6	3.7	Adequate	-	-	7.5	8	8.1
10	63	F	1	1	Por		Massive	CR	1.9	3.9	Adequate	-	-	14.3	14.3	18.4+
Res/ Imp rate			70%				78%		90%		57%		100%			

PS: Performance status (Eastern Cooperative Oncology Group); Pre: pre-treatment; His: histology; Res: response; OI: oral intake; Imp: improvement; TTF: time to treatment failure; PFS: progression-free survival; OS: overall survival; Por: poorly; Mod: moderately; ple: pleura; LN: lymph node; RR: response rate; *+: censored data.

achieved CR and PR, respectively, with an ascites response rate of 78% (Table III). In two patients who required abdominal paracentesis before receiving FOLFOX, survival time without abdominal paracentesis was 0.69 and 6.3 months, respectively. Among the seven patients with inadequate oral intake, four (57%) showed improved oral intake (Table III). The median duration from initiation of chemotherapy to obtaining adequate oral intake was 2.1 months (range=0.95-3.4 months). Among patients who achieved adequate oral intake, median survival time with adequate oral intake was 13.8 months (range=1.5-27.8+ months). Receiving FOLFOX, an improvement of PS was observed in seven patients (Table III). All but one patient (case 2), who had early progression on FOLFOX, could be discharged and FOLFOX was continued (Table III). All but one patient (case 2) showed improvements in the serum albumin level (Table III).

Subsequent treatment. Of the nine patients who had disease progression, seven (78%) received second-line treatment, four of whom received paclitaxel, two had irinotecan, and one had intraperitoneal cisplatin. One of the six patients who had measurable lesions achieved SD. The median PFS and OS on second-line treatment were 2.8 months (95% CI=0.6-4.6) and 4.7 months (95% CI=0.6-8.8), respectively. Of the six patients with disease progression, three (50%) received third-line treatment such as paclitaxel, docetaxel, or irinotecan plus cisplatin.

Adverse events. Adverse events in all ten patients are shown in Table IV. The common grade 3 or 4 adverse events were neutropenia (30%), increased ALT (30%), anemia (30%), thrombocytopenia (20%), and increased aspartate aminotransferase (AST) (20%). None of the patients had grade 3 or 4 gastrointestinal toxicities or febrile neutropenia. Treatment-related serious adverse events defined as adverse events with hospital care were recorded in two patients. One patient with hyperglycemia due to antiemetic dexamethasone received insulin and quickly recovered. Although the other patient who had bacterial pneumonia received antibacterial drug, he deceased within 30 days of the last FOLFOX dose.

Discussion

The results of this study suggest that FOLFOX is effective and manageable as first-line treatment for AGC patients with massive ascites and/or inadequate oral intake due to severe peritoneal metastasis. To our knowledge, this is the first report evaluating the efficacy and safety of FOLFOX for this population.

For symptomatic patients in this population, both survival prolongation and symptom improvement are important. It has been suggested that the median PFS and OS observed in the present study were superior to those in FLTAX or 5-FU/MTX, 5-FU/LV, or 5-FU alone (other 5-FU-based chemotherapies) (8-10). Furthermore, the rates of improvement in ascites and oral intake in the present study (78% and 57%, respectively) are higher than those in patients treated with other 5-FU-based chemotherapies (27-54% and 21-33%, respectively) (8, 9). Therefore, the present study suggests the usefulness of FOLFOX for AGC

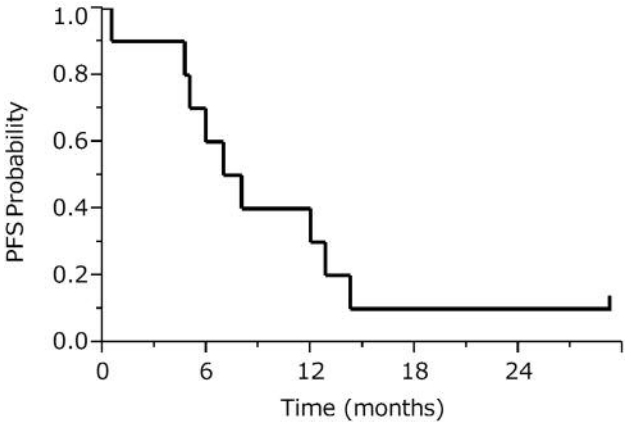

Figure 1. *Kaplan–Meier survival curves of progression-free survival (PFS).*

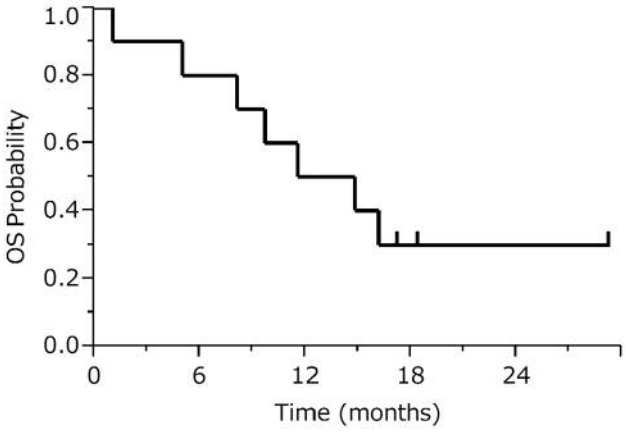

Figure 2. *Kaplan–Meier survival curves of overall survival (OS).*

Table IV. *Adverse events.*

	N=10				Grade 3-4
	Grade 1	Grade 2	Grade 3	Grade 4	(%)
Hematological					
Neutropenia	3	2	1	2	30
Leukopenia	1	6	1	0	10
Anemia	1	4	3	0	30
Thrombocytopenia	4	0	1	1	20
Non-hematological					
Nausea	5	4	0	0	0
Vomiting	5	0	0	0	0
Diarrhea	3	1	0	0	0
Fatigue	4	0	0	0	0
Anorexia	4	4	0	0	0
Mucositis oral	3	1	0	0	0
AST	5	1	2	0	20
ALT	6	0	3	0	30
Total bilirubin	3	0	1	0	10
Creatinine	4	0	0	0	0
Febrile neutropenia	-	-	0	0	0
Peripheral neuropathy	6	2	1	0	10

AST: Aspartate aminotransferase; ALT: alanine aminotransferase.

patients with severe peritoneal metastasis who could not receive an oral fluoropyrimidine- or cisplatin-containing chemotherapy.

In three randomized phase II and one phase III studies excluding patients with severe peritoneal metastasis, the response rate, median PFS, and median OS of FOLFOX were 30%-57%, 6.7-8.0 months, and 11.3-14.9 months, respectively. The frequencies of grade 3 or 4 common adverse events in these studies were neutropenia (29%-45%), febrile neutropenia (5%), anemia (10%), and peripheral neuropathy (1%-13%) (16, 17). Oh *et al*. conducted a phase II study to evaluate FOLFOX for AGC patients with malignant ascites. Although this study included 46% patients with PS 2, all drugs except for *l*-LV were administered at a regular dose and FOLFOX was feasible with grade 3 or 4 neutropenia rates of 19% per cycle, febrile neutropenia rates of 3% per cycle, and nausea and vomiting rates of 6% per person (20). However, because AGC patients with severe peritoneal metastasis typically have worse PS and are expected to have a higher rate of adverse events than those in the abovementioned previous studies, we performed initial dose modification in half of the patients (n=5). In addition, the other five patients needed dose reduction or interruption because of adverse events of FOLFOX. Therefore, we must carefully manage adverse events along with dose reduction or interruption.

There are several limitations in the present study. First, it was a retrospective analysis in a single institution and the sample size was very small. Therefore, a prospective multicenter study involving more patients with severe peritoneal metastasis must be conducted to clarify the efficacy and safety of FOLFOX for this population. Second, none of our patients had HER-2-positive tumors. Because adding trastuzumab to 5-FU or capecitabine plus cisplatin improved overall survival in the ToGA study (21), patients with HER-2-positive tumors might benefit from a trastuzumab-containing regimen.

This study suggests that FOLFOX is effective and manageable as first-line treatment for AGC patients with massive ascites and/or inadequate oral intake due to severe peritoneal metastasis. However, we must carefully manage adverse events along with initial dose modification, or dose reduction or interruption.

References

1 Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D and Bray F: Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer *136*: E359-386, 2015.

2 NCCN guidelindes. Gastric Cancer 31-41, 2016.

3 Koizumi W, Narahara H, Hara T, Takagane A, Akiya T, Takagi M, Miyashita K, Nishizaki T, Kobayashi O, Takiyama W, Toh Y, Nagaie T, Takagi S, Yamamura Y, Yanaoka K, Orita H and Takeuchi M: S-1 plus cisplatin *versus* S-1 alone for first-line treatment of advanced gastric cancer (SPIRITS trial): a phase III trial. Lancet Oncology *9*: 215-221, 2008.

4 Kang YK, Kang WK, Shin DB, Chen J, Xiong J, Wang J, Lichinitser M, Guan Z, Khasanov R, Zheng L, Philco-Salas M, Suarez T, Santamaria J, Forster G and McCloud PI: Capecitabine/cisplatin *versus* 5-fluorouracil/cisplatin as first-line therapy in patients with advanced gastric cancer: a randomised phase III noninferiority trial. Ann Oncol *20*: 666-673, 2009.

5 Cunningham D, Starling N, Rao S, Iveson T, Nicolson M, Coxon F, Middleton G, Daniel F, Oates J and Norman AR: Capecitabine and oxaliplatin for advanced esophagogastric cancer. N Engl J Med *358*: 36-46, 2008.

6 Yamada Y, Higuchi K, Nishikawa K, Gotoh M, Fuse N, Sugimoto N, Nishina T, Amagai K, Chin K, Niwa Y, Tsuji A, Imamura H, Tsuda M, Yasui H, Fujii H, Yamaguchi K, Yasui H, Hironaka S, Shimada K, Miwa H, Hamada C and Hyodo I: Phase III study comparing oxaliplatin plus S-1 with cisplatin plus S-1 in chemotherapy-naive patients with advanced gastric cancer. Ann Oncol *26*: 141-148, 2015.

7 Ryu MH, Baba E, Lee KH, Park YI, Boku N, Hyodo I, Nam BH, Esaki T, Yoo C, Ryoo BY, Song EK, Cho SH, Kang WK, Yang SH, Zang DY, Shin DB, Park SR, Shinozaki K, Takano T, Kang YK and investigators SOSs: Comparison of two different S-1 plus cisplatin dosing schedules as first-line chemotherapy for metastatic and/or recurrent gastric cancer: a multicenter, randomized phase III trial (SOS). Ann Oncol *26*: 2097-2101, 2015.

8 Iwasa S, Nakajima TE, Nakamura K, Takashima A, Kato K, Hamaguchi T, Yamada Y and Shimada Y: First-line fluorouracil-based chemotherapy for patients with severe peritoneal disseminated gastric cancer. Gastric Cancer *15*: 21-26, 2012.

9 Imazawa M, Kojima T, Boku N, Onozawa Y, Hironaka S, Fukutomi A, Yasui H, Yamazaki K and Taku K: Efficacy of sequential methotrexate and 5-fluorouracil (MTX/5FU) in improving oral intake in patients with advanced gastric cancer with severe peritoneal dissemination. Gastric Cancer *12*: 153-157, 2009.

10 Iwasa S, Goto M, Yasui H, Nishina T, Takahari D, Nakayama N, Taira K, Kusaba H, Fuse N, Hironaka S, Shimada Y and Nakajima TE: Multicenter feasibility study of combination therapy with fluorouracil, leucovorin and paclitaxel (FLTAX) for peritoneal disseminated gastric cancer with massive ascites or inadequate oral intake. Jpn J Clin Oncol *42*: 787-793, 2012.

11 Tsuji K, Yasui H, Onozawa Y, Boku N, Doyama H, Fukutomi A, Yamazaki K, Machida N, Todaka A, Taniguchi H, Tsushima T and Yokota T: Modified FOLFOX-6 therapy for heavily pretreated advanced gastric cancer refractory to fluorouracil, irinotecan, cisplatin and taxanes: a retrospective study. Jpn J Clin Oncol *42*: 686-690, 2012.

12 Suh SH, Kwon HC, Jo JH, Cho YR, Seo BG, Lee DM, Kim SH, Kim JS and Kim HJ: Oxaliplatin with biweekly low dose leucovorin and bolus and continuous infusion of 5-fluorouracil (modified FOLFOX 4) as a salvage therapy for patients with advanced gastric cancer. Cancer Res Treat *37*: 279-283, 2005.

13 Kim YS, Hong J, Sym SJ, Park SH, Park J, Cho EK, Lee JH, and Shin DB: Oxaliplatin, 5-fluorouracil and leucovorin (FOLFOX-4) combination chemotherapy as a salvage treatment in advanced gastric cancer. Cancer Res Treat *42*: 24-29, 2010.

14 Seo HY, Kim DS, Choi YS, Sung HJ, Park KH, Choi IK, Kim SJ, Oh SC, Seo JH, Choi CW, Kim BS, Shin SW, Kim YH and Kim JS: Treatment outcomes of oxaliplatin, 5-FU, and leucovorin as salvage therapy for patients with advanced or metastatic gastric cancer: a retrospective analysis. Cancer Chemother Pharmacol *63*: 433-439, 2009.

15 Kim HS, Kim JH, Kim HJ, Jang HJ, Kim JB, Kim JW, Jung SY, Kim BC, Yang DH, Park S, Kim KJ, Lee SI and Zang DY: Oxaliplatin, 5-fluorouracil and leucovorin (modified FOLFOX-6) as first-line chemotherapy for advanced gastric cancer patients with poor performance status. Oncol Lett *3*: 425-428, 2012.

16 Cohen DJ, Christos PJ, Kindler HL, Catenacci DVT, Bekaii-Saab TB, Tahiri S, Janjigian YY, Gibson MK, Chan E, Rajdev L, Urba S, James Wade L, Kozuch P, Love E, Vandris K, Takebe N, Hochster HS and Sparano JA: Vismodegib, a hedgehog pathway inhibitor, combined with FOLFOX for first-line therapy of patients with advanced gastric and gastroesophageal junction carcinoma: A New York Cancer Consortium led phase II randomized study. J Clin Oncol *31*: abstr 4011, 2013.

17 Shah MA, Cho JY, Tan IB, Tebbutt NC, Yen CJ, Kang A, Shames DS, Bu L and Kang YK: A randomized phase II study of FOLFOX with or without the MET inhibitor onartuzumab in advanced adenocarcinoma of the stomach and gastroesophageal junction. Oncologist *21*: 1085-1090, 2016.

18 Yoon HH, Bendell JC, Braiteh FS, Firdaus I, Philip PA, Cohn AL, Lewis N, Anderson DM, Arrowsmith E, Schwartz JD, Gao L, Hsu Y, Xu Y, Ferry D, Alberts SR and Wainberg ZA: Ramucirumab combined with FOLFOX as front-line therapy for advanced esophageal, gastroesophageal junction, or gastric adenocarcinoma: a randomized, double-blind, multicenter Phase II trial. Ann Oncol *27*: 2196-2203, 2016.

19 Iwasa S, Nakajima TE, Nakamura K, Takashima A, Kato K, Hamaguchi T, Yamada Y and Shimada Y: Systemic chemotherapy for peritoneal disseminated gastric cancer with inadequate oral intake: a retrospective study. Int J Clin Oncol *16*: 57-62, 2011.

20 Oh SY, Kwon HC, Lee S, Lee DM, Yoo HS, Kim SH, Jang JS, Kim MC, Jeong JS and Kim HJ: A Phase II study of oxaliplatin with low-dose leucovorin and bolus and continuous infusion 5-fluorouracil (modified FOLFOX-4) for gastric cancer patients with malignant ascites. Jpn J Clin Oncol *37*: 930-935, 2007.

21 Bang YJ, Van Cutsem E, Feyereislova A, Chung HC, Shen L, Sawaki A, Lordick F, Ohtsu A, Omuro Y, Satoh T, Aprile G, Kulikov E, Hill J, Lehle M, Ruschoff J and Kang YK: Trastuzumab in combination with chemotherapy *versus* chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. Lancet *376*: 687-697, 2010.

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