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Efficacy and Safety of FOLFOX in Advanced Gastric Cancer Initially Presenting With Disseminated Intravascular Coagulation

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Abstract. *Background/Aim: Advanced gastric cancer (AGC) rarely presents with disseminated intravascular coagulation (DIC) at the time of diagnosis. Chemotherapy should be selected in consideration of hematological toxicities because these patients are at high risk of hemorrhagic complications. The leucovorin, fluorouracil, and oxaliplatin (FOLFOX) regimen is an effective and less toxic regimen for patients with AGC and poor performance status. Patients and Methods: The present study assessed overall survival of all patients receiving first-line chemotherapy with and without DIC using Kaplan-Meier methods and examined the clinicopathological factors, DIC parameters, response, and survival of five patients with AGC and DIC who received FOLFOX in the first-line setting between February 2017 and February 2020. Results: Among the patients, four patients (80%) recovered from DIC after a median of 12 days of FOLFOX therapy (range=12-25), and their platelet count gradually increased within 1 week after the start of chemotherapy. The median progression-free survival and overall survival were 46 (range=22-296) and 115 days (range=83-324), respectively. No patients experienced adverse events necessitating treatment discontinuation, including gastrointestinal bleeding and thrombocytopenia. Moreover, all patients received second-line treatment after progression, and one patient exhibited improvement of DIC symptoms following nab-paclitaxel and ramucirumab treatment. Conclusion: FOLFOX therapy is well tolerated and effective in patients with AGC initially presenting with DIC and subsequent second-line treatment might be crucial for better prognosis.*

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Gastric cancer is the fifth most commonly diagnosed cancer and the third most deadly cancer, with an estimated 1,089,103 new cases and 768,793 deaths annually (1). Advanced gastric cancer (AGC) rarely presents with disseminated intravascular coagulation (DIC) at the time of diagnosis, and the prognosis of AGC with DIC is extremely poor (2).

DIC is characterized by systemic intravascular coagulation activation and the simultaneous consumption of coagulation proteins and thrombocytes. It is caused by infection, solid cancers, hematological malignancies, obstetric diseases, trauma, aneurysms, and liver diseases (3). Eventually, DIC can lead to the exhaustion of platelets and coagulation factors; therefore, bleeding may be the first clinical symptom (4). Recently, the efficacy of anticoagulants such as recombinant human soluble thrombomodulin has been reported in cancer-associated DIC (5, 6); however, the principle of DIC treatment is treating the underlying disease (4). In particular, chemotherapy for DIC associated with solid tumors can prolong overall survival (7).

In patients with gastric cancer initially presenting with DIC, several reports illustrated that chemotherapy, including 5-fluorouracil (5-FU)/leucovorin and 5-FU/methotrexate, improved DIC parameters (8-10). Recently, fluoropyrimidine plus platinum-based chemotherapy, which is the standard

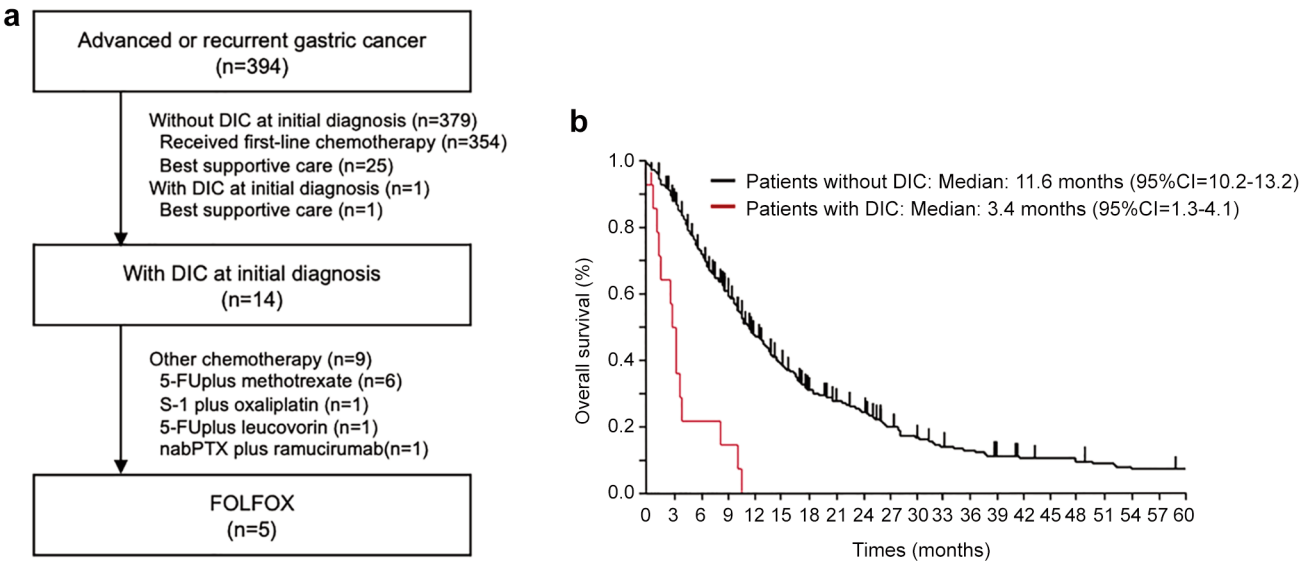

Figure 1. *(a) Treatment in advanced gastric cancer with disseminated intravascular coagulation (DIC). (b) Overall survival (OS) of patients with disseminated intravascular coagulation (DIC) and without DIC. OS in patients with DIC was extremely poor.*

regimen for AGC, was reported to be effective against DIC (10). However, the reports used different fluoropyrimidines including 5-FU, S-1, and capecitabine, and the incidence of hematological toxicities differed between 5-FU- and oral fluoropyrimidine-based regimens (11). In patients with DIC, the regimen should be selected in consideration of both hematological toxicities and efficacy because these patients have a high risk of gastrointestinal bleeding. Recently, a phase II study of FOLFOX reported an incidence of grade 3 or higher thrombocytopenia of only 3% even in heavily pretreated patients with gastric cancer (12). However, little is known about the outcome of FOLFOX treatment in patients with AGC and DIC. Therefore, we analyzed the efficacy and safety of FOLFOX as a first-line treatment for this population with a focus on DIC parameters.

Patients and Methods

Patient selection. The medical records of 394 patients who were diagnosed with metastatic or recurrent gastric cancer between January 2007 and February 2020 at four institutions (University of Toyama, Toyama Red Cross Hospital, Joetsu General Hospital, and University of Miyazaki), were reviewed. Overall survival of all patients receiving first-line chemotherapy with and without DIC were assessed using Kaplan-Meier method. Detailed data were collected from patients that fulfil the following criteria: 1) a histologically confirmed diagnosis of AGC; 2) DIC present at the initial diagnosis of metastatic or recurrent gastric cancer; 3) DIC score ≥7 points according to Japanese Ministry of Health, Labor and Welfare (JMHLW) criteria; and 4) receipt of FOLFOX as first-line chemotherapy. All patients received chest-pelvic computed tomography to evaluate the extent of disease. Additionally, bone marrow biopsy was performed to diagnose disseminated carcinomatosis of the bone marrow based on the physician's judgement.

Data collection and statistical analysis. The patient baseline characteristics, including age, sex, and performance status, as well as clinical stage of the disease, history of chemotherapy, and parameters of DIC, were retrospectively obtained from their medical charts. DIC was considered to recover when a patient's DIC score was decreased to <5. Toxicity was evaluated according to the Common Terminology Criteria for Adverse Events (CTCAE) v4.0. Progression-free survival (PFS) was measured from the day of the start of FOLFOX treatment to the day on which disease progression was confirmed or the final day of follow-up without disease progression. Overall survival (OS) was measured from the day of initiation of FOLFOX treatment until the day of death or the final day of follow-up. This study was approved by the Institutional Review Board of each institution.

Treatment regimens. Four patients received mFOLFOX6, and one patient received FOLFOX4. mFOLFOX6 consisted of oxaliplatin (85 mg/m^2 on day 1) as a 2-h infusion followed by a 5-FU bolus (400 mg/m^2 on day 1) and then a 46-h infusion of 5-FU (2,400 mg/m^2) concurrently with 200 mg/m^2 leucovorin. FOLFOX4 consisted of oxaliplatin (85 mg/m^2 on day 1) as a 2-h infusion, a 400 mg/m^2 5-FU bolus and a 600 mg/m^2 5-FU infusion over 22 h on days 1 and 2, respectively, and 100 mg/m^2 leucovorin on days 1 and 2. Cycles were repeated at 2-week intervals until disease progression. Adverse events were graded according to CTCAE v4.0.

Ethics approval. The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Review Board of University of Toyama (approval number R2020210, date of approval 21 January 2021).

Table I. *Baseline characteristics of patients with advanced gastric cancer with disseminated intravascular coagulation.*

Patient No	1	2	3	4	5
Age (years)	39	71	67	39	70
Sex	Female	Female	Male	Male	Male
ECOG-PS	2	2	3	2	2
Histology	Mixed	Diffuse	Mixed	Intestinal	Diffuse
HER2 status	Negative	Negative	Negative	Negative	Negative
Metastatic sites	Bone	Bone	Bone, liver, lymph node	Bone	Bone, liver, lymph node
Carcinomatosis of bone marrow	Yes	NA	Yes	Yes	Yes
DIC score	7	7	7	9	10
Platelet count ($\times 10^4/\mu l$)	11.2	14	8.9	9	1.8
Fibrinogen (mg/dl)	474	74	298	81	NA
FDP (μg/ml)	25.3	246.2	116	174.8	216.9
Treatment before chemotherapy	–	rTM	rTM	rTM, FFP	rTM

ECOG-PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth factor 2; NA, not assessed; DIC, disseminated intravascular coagulation; FDP, fibrinogen degradation product; rTM, recombinant thrombomodulin; FFP, fresh frozen plasma.

Table II. *Clinical outcomes including disseminated intravascular coagulation (DIC) improvement, progression-free survival (PFS), and overall survival (OS) of leucovorin, fluorouracil, and oxaliplatin (FOLFOX) treatment.*

Patient No	1	2	3	4	5
First-line therapy					
Treatment cycle	3	2	18	3	3
DIC improvement	Yes	Yes	Yes	Yes	No
Time to recovery of DIC (days)	12	12	13	25	–
PFS	53	22	296	46	41
Tumor response	PD	PD	PR	PD	PD
Recurrence of DIC	Yes	No	No	Yes	–
Second-line therapy					
Chemotherapy regimen	nabPTX/ram	nabPTX/ram	nabPTX/ram	PTX	PTX
DIC improvement	Yes	–	–	No	–
Tumor response	PD	SD	NE	PD	PD
OS after FOLFOX (days)	115/dead	251/dead	324/dead	102/dead	83/dead

nabPTX, Nanoparticle albumin-bound paclitaxel; ram, ramucirumab; PTX, paclitaxel; PD, progressive disease; PR, partial response; SD, stable disease; NE, not evaluable for response.

Results

Prognosis of AGC with DIC. Among a total of 394 patients with unresectable or recurrent gastric cancer, DIC occurred in 15 (3.8%) before chemotherapy between January 2007 and February 2020. Five patients received FOLFOX (aged 39-71 years, three males and two females), and the others received 5-FU plus methotrexate (n=6), S-1 plus oxaliplatin (n=1), nab-paclitaxel plus ramucirumab (n=1) and 5-FU plus leucovorin (n=1). One patient received best supportive care due to poor general condition (Figure 1a). In all patients receiving first-line chemotherapy, median OS was 3.4 months (range=1.3-4.1 days) and 11.6 months (range=10.2-13.2 days) in patients with and without DIC, respectively. OS was extremely poor in patients with DIC (Figure 1b).

Patient baseline characteristics. Since the Japanese insurance system covered FOLFOX in March 2015, five of ten patients received FOLFOX treatment, and patient characteristics are summarized in Table I. All patients had metastatic disease including bone metastasis, and carcinomatosis of bone marrow was confirmed *via* bone marrow biopsy in four patients. Endoscopic biopsy revealed intestinal, diffuse, and mixed histology without human epidermal growth factor 2 expression in one, two, and two patients, respectively. The median DIC score based on JMHLW criteria was 9 (range=7-10). The median platelet count, serum fibrinogen level, and

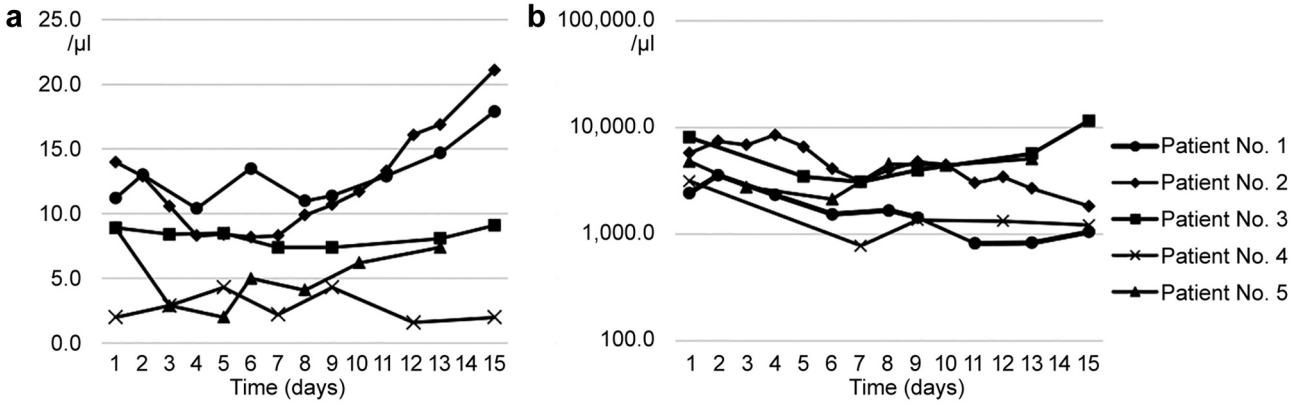

Figure 2. *Platelet (a) and neutrophil counts (b) during the first cycle of leucovorin, fluorouracil, and oxaliplatin (FOLFOX) treatment. Four patients (Patients 1-4) recovered from disseminated intravascular coagulation (DIC) after the initiation of FOLFOX treatment.*

fibrinogen degradation product level were 9.0×10^4/μl (range=1.8-14.0), 81 mg/dl (range=74-298), and 174.8 μg/ml (range=25.3-246.2), respectively. Therefore, thrombomodulin was administered as anticoagulant therapy in four patients, whereas Patient 4 received fresh frozen plasma as an additional treatment before chemotherapy.

DIC parameters during chemotherapy. The clinical course of each patient is summarized in Table II. The median number of FOLFOX cycles was three (range=2-18). Finally, four patients (80%) recovered from DIC after a median of 12 days of FOLFOX therapy (range=12-25). Indeed, the platelet count increased in all but one patient (Patient 4) within 1 week after the start of chemotherapy, suggesting improvement of DIC (Figure 2a). DIC recurred in patients 1 and 4 during FOLFOX treatment, and recovery was observed after second-line chemotherapy only in Patient 1. Patient 5 did not recover from DIC despite FOLFOX and subsequent second-line treatment, and his OS was 83 days.

Clinical outcome. The median PFS and OS were 46 (range=22-296) and 115 days (range=83-324), respectively. A tumor response was observed only in Patient 3, and his PFS was 296 days. Moreover, all patients received second-line treatment after progression following FOLFOX treatment, and Patient 2 had stable disease (PFS=209 days) after second-line treatment. Patients 2 and 3 survived for more than 8 months after achieving disease control following first- or second-line treatment, but the survival of all patients was generally poor.

Adverse events. The AEs of FOLFOX treatment are summarized in Table III. Hematological grade 4 AEs included neutropenia, thrombocytopenia, and anemia in two patients (Patient 2 and 4). Although the neutrophil count gradually decreased in all patients after the start of FOLFOX treatment, no patients experienced febrile neutropenia (Figure 2b). Grade 3 or higher non-hematological AEs occurred in only three patients (Patient 1, 2 and 3). There were no treatment-related deaths.

Table III. *Hematological and non-hematological adverse effects of leucovorin, fluorouracil, and oxaliplatin (FOLFOX) treatment.*

Factors	Any grade (%)	Grade ≥3 (%)
Hematological		
Leukopenia	5 (100)	2 (40)
Neutropenia	4 (80)	3 (60)
Anemia	5 (100)	5 (100)
Thrombocytopenia	5 (100)	2 (40)
Non-hematological		
Anorexia	3 (60)	1 (20)
Nausea	3 (60)	0
Vomiting	2 (40)	0
Fatigue	3 (60)	2 (40)
Mucositis	2 (40)	0
Sensory neuropathy	2 (40)	0
Febrile neutropenia		0

Discussion

DIC is a rare complication of solid tumors, and AGC is one of its most frequent causes. The short-term prognosis remains extremely poor, although palliative chemotherapy might prolong patient survival (10, 13). Indeed, the survival of patients presenting with hematological complications such as DIC was markedly shorter than that of patients free of hematological complications in a Japanese retrospective series of patients with gastric adenocarcinoma and bone marrow metastases (14). The poor prognosis of DIC is associated with impairment of the general condition and hemorrhagic complications. Myelosuppressive chemotherapy in the context of coagulopathy and thrombocytopenia is usually poorly tolerated, and it may worsen patient prognosis

through hemorrhagic or infectious complications. From this viewpoint, this study identified FOLFOX as a feasible regimen, and the rate of recovery from DIC was high in patients with AGC initially presenting with DIC.

First-line FOLFOX4 and mFOLFOX6, in addition to S-1– and capecitabine containing regimens, are standard regimens for patients with AGC, and several phase II and III clinical trials revealed the good safety profile of FOLFOX even in patients with an impaired general condition (1, 15, 16). Indeed, a meta-analysis comparing efficacy and safety between S-1 and 5-FU revealed significant increases of the rate of grade 1-4 hematological toxicities such as neutropenia [risk ratio (RR)=1.22, 95% confidence interval (CI)=1.08-1.37, p=0.001] and thrombocytopenia (RR=1.71, 95% CI=1.22-2.41, p=0.002) in patients who received S-1–containing regimens, especially in Asian patients (11). Moreover, the efficacy and safety of FOLFOX4 or mFOLFOX6 were reported in several retrospective phase II clinical trials, including studies of heavily pretreated patients with AGC (12, 17-20). In prospective trials, the most common grade 3-4 hematological AEs were neutropenia (36%) and thrombocytopenia (3%), and the most common non-hematological toxicity was fatigue (6%). These results suggest that FOLFOX is an effective and less toxic regimen for patients with gastric cancer and poor performance status. Indeed, no patients in our study experienced AEs necessitating treatment discontinuation, including gastrointestinal bleeding and thrombocytopenia even though patients with gastric cancer presenting with DIC have a high risk of hemorrhagic complications.

A recent meta-analysis evaluating phase III trials of gastric cancer clearly demonstrated that the receipt of post-progression chemotherapy was correlated with better post-progression survival and OS following first-line chemotherapy (21, 22). Indeed, several clinical trials revealed the efficacy of second-line chemotherapy consisting of taxanes and ramucirumab, an antibody targeting human vascular endothelial growth factor 2. The RAINBOW phase III trial of second-line therapy reported that the response rate and median PFS of paclitaxel and ramucirumab were 28% and 4.4 months, respectively (23). Moreover, a phase II trial of nab-paclitaxel and ramucirumab as second-line chemotherapy recorded a response rate and median PFS of 54.8% and 7.6 months, respectively (24). In this study, all patients received second-line treatment following disease progression, including recurrence or a lack of response of DIC. One of two patients with DIC at the time of progression following FOLFOX treatment recovered from DIC following nab-paclitaxel and ramucirumab treatment. This suggested that second-line chemotherapy might prolong OS despite the lack of reports describing the efficacy of salvage chemotherapy in this situation.

There are several limitations to this study. First, this study was a retrospective analysis of data sourced from a small number of cases. Therefore, statistical analysis seemed to be not robust due to the small sample size. Second, the chemotherapy regimen (oxaliplatin, 5-FU, and leucovorin) for one patient was made with different dosages and dissimilar infusion times, which may have led to differences in treatment outcomes. In our study, nevertheless, four in five patients received FOLFOX therapy recovered from DIC. In addition, all patients could receive second-line chemotherapy even after progression to first-line FOLFOX treatment. This strongly suggested that FOLFOX was a feasible regimen for patients with DIC.

In conclusion, our case series suggested that FOLFOX is well tolerated and effective in patients with AGC initially presenting with DIC. This treatment should be considered in the first-line treatment of AGC with DIC. Additionally, subsequent second-line treatment might be crucial for better prognoses.

Conflicts of Interest

The Authors declare that they have no competing interests.

Authors' Contributions

Data analysis and interpretation, N.T.; drafting manuscript, N.T. and T.A.; data collection, M.I., M.S., Y.U., S.K., K.N., A.H., A.U., N.S., and A.N.; supervision and revising manuscript, I.Y. All Authors have read and agreed to the published version of the manuscript.

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References

1 Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A and Bray F: Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin *71(3)*: 209-249, 2021. PMID: 33538338. DOI: 10.3322/caac.21660

2 Sallah S, Wan JY, Nguyen NP, Hanrahan LR and Sigounas G: Disseminated intravascular coagulation in solid tumors: clinical and pathologic study. Thromb Haemost *86(3)*: 828-833, 2001. PMID: 11583315.

3 Wada H, Matsumoto T and Yamashita Y: Diagnosis and treatment of disseminated intravascular coagulation (DIC) according to four DIC guidelines. J Intensive Care *2(1)*: 15, 2014. PMID: 25520831. DOI: 10.1186/2052-0492-2-15

4 Levi M: Disseminated intravascular coagulation in cancer patients. Best Pract Res Clin Haematol *22(1)*: 129-136, 2009. PMID: 19285279. DOI: 10.1016/j.beha.2008.12.005

5 Kashiwagi S, Asano Y, Takahashi K, Shibutani M, Amano R, Tomita S, Hirakawa K and Ohira M: Clinical outcomes of recombinant human-soluble thrombomodulin treatment for disseminated intravascular coagulation in solid tumors. Anticancer Res *39(5)*: 2259-2264, 2019. PMID: 31092417. DOI: 10.21873/anticanres.13342

6 Tamura K, Saito H, Asakura H, Okamoto K, Tagawa J, Hayakawa T and Aoki N: Recombinant human soluble thrombomodulin (thrombomodulin alfa) to treat disseminated intravascular coagulation in solid tumors: results of a one-arm prospective trial. Int J Clin Oncol *20(4)*: 821-828, 2015. PMID: 25385713. DOI: 10.1007/s10147-014-0768-1

7 Ouchi K, Takahashi S, Chikamatsu S, Ito S, Takahashi Y, Kawai S, Okita A, Kasahara Y, Okada Y, Imai H, Komine K, Saijo K, Takahashi M, Shirota H, Takahashi M, Gamoh M and Ishioka C: Retrospective analysis on the clinical outcomes of recombinant human soluble thrombomodulin for disseminated intravascular coagulation syndrome associated with solid tumors. Int J Clin Oncol *23(4)*: 790-798, 2018. PMID: 29511940. DOI: 10.1007/s10147-018-1261-z

8 Takashima A, Shirao K, Hirashima Y, Takahari D, Okita NT, Nakajima TE, Kato K, Hamaguchi T, Yamada Y and Shimada Y: Sequential chemotherapy with methotrexate and 5-fluorouracil for chemotherapy-naive advanced gastric cancer with disseminated intravascular coagulation at initial diagnosis. J Cancer Res Clin Oncol *136(2)*: 243-248, 2010. PMID: 19727819. DOI: 10.1007/s00432-009-0655-8

9 Huang TC, Yeh KH, Cheng AL and Hsu CH: Weekly 24-hour infusional 5-fluorouracil as initial treatment for advanced gastric cancer with acute disseminated intravascular coagulation. Anticancer Res *28(2B)*: 1293-1297, 2008. PMID: 18505068.

10 Rhee J, Han SW, Oh DY, Im SA, Kim TY and Bang YJ: Clinicopathologic features and clinical outcomes of gastric cancer that initially presents with disseminated intravascular coagulation: a retrospective study. J Gastroenterol Hepatol *25(9)*: 1537-1542, 2010. PMID: 20796152. DOI: 10.1111/j.1440-1746.2010.06289.x

11 Chen XD, He FQ, Chen M, Tang LC and Tang XL: Can S-1 replace fluorouracil for advanced gastric cancer? A PRISMA-compliant systematic review and meta-analysis. Medicine (Baltimore) *95(24)*: e3916, 2016. PMID: 27310997. DOI: 10.1097/MD.0000000000003916

12 Mitani S, Kadowaki S, Komori A, Kondoh C, Oze I, Kato K, Masuishi T, Honda K, Narita Y, Taniguchi H, Ando M, Tanaka T, Tajika M and Muro K: A phase II study of modified FOLFOX6 for advanced gastric cancer refractory to standard therapies. Adv Ther *37(6)*: 2853-2864, 2020. PMID: 32378071. DOI: 10.1007/s12325-020-01358-2

13 Pasquini E, Gianni L, Aitini E, Nicolini M, Fattori PP, Cavazzini G, Desiderio F, Monti F, Forghieri ME and Ravaioli A: Acute disseminated intravascular coagulation syndrome in cancer patients. Oncology *52(6)*: 505-508, 1995. PMID: 7478440. DOI: 10.1159/000227520

14 Etoh T, Baba H, Taketomi A, Nakashima H, Kohnoe S, Seo Y, Fukuda T and Tomoda H: Diffuse bone metastasis with hematologic disorders from gastric cancer: clinicopathological features and prognosis. Oncol Rep *6(3)*: 601-605, 1999. PMID: 10203599. DOI: 10.3892/or.6.3.601

15 De Vita F, Orditura M, Matano E, Bianco R, Carlomagno C, Infusino S, Damiano V, Simeone E, Diadema MR, Lieto E, Castellano P, Pepe S, De Placido S, Galizia G, Di Martino N, Ciardiello F, Catalano G and Bianco AR: A phase II study of biweekly oxaliplatin plus infusional 5-fluorouracil and folinic acid (FOLFOX-4) as first-line treatment of advanced gastric cancer patients. Br J Cancer *92(9)*: 1644-1649, 2005. PMID: 15856038. DOI: 10.1038/sj.bjc.6602573

16 Masuishi T, Kadowaki S, Kondo M, Komori A, Sugiyama K, Mitani S, Honda K, Narita Y, Taniguchi H, Ura T, Ando M, Mishima H and Muro K: FOLFOX as first-line therapy for gastric cancer with severe peritoneal metastasis. Anticancer Res *37(12)*: 7037-7042, 2017. PMID: 29187492. DOI: 10.21873/anticanres.12174

17 Kondoh C, Kadowaki S, Komori A, Narita Y, Taniguchi H, Ura T, Ando M and Muro K: Salvage chemotherapy with the combination of oxaliplatin, leucovorin, and 5-fluorouracil in advanced gastric cancer refractory or intolerant to fluoropyrimidines, platinum, taxanes, and irinotecan. Gastric Cancer *21(6)*: 1050-1057, 2018. PMID: 29658055. DOI: 10.1007/s10120-018-0825-y

18 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(8)*: 686-690, 2012. PMID: 22693245. DOI: 10.1093/jjco/hys084

19 Kim DY, Kim JH, Lee SH, Kim TY, Heo DS, Bang YJ and Kim NK: Phase II study of oxaliplatin, 5-fluorouracil and leucovorin in previously platinum-treated patients with advanced gastric cancer. Ann Oncol *14(3)*: 383-387, 2003. PMID: 12598342. DOI: 10.1093/annonc/mdg106

20 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(1)*: 24-29, 2010. PMID: 20369048. DOI: 10.4143/crt.2010.42.1.24

21 Shitara K, Matsuo K, Muro K, Doi T and Ohtsu A: Progression-free survival and post-progression survival in patients with advanced gastric cancer treated with first-line chemotherapy. J Cancer Res Clin Oncol *139(8)*: 1383-1389, 2013. PMID: 23708301. DOI: 10.1007/s00432-013-1452-y

22 Iizumi S, Takashima A, Sakamaki K, Morita S and Boku N: Survival impact of post-progression chemotherapy in advanced gastric cancer: systematic review and meta-analysis. Cancer Chemother Pharmacol *81(6)*: 981-989, 2018. PMID: 29600386. DOI: 10.1007/s00280-018-3569-9

23 Wilke H, Muro K, Van Cutsem E, Oh SC, Bodoky G, Shimada Y, Hironaka S, Sugimoto N, Lipatov O, Kim TY, Cunningham D, Rougier P, Komatsu Y, Ajani J, Emig M, Carlesi R, Ferry D, Chandrawansa K, Schwartz JD, Ohtsu A and RAINBOW Study Group: Ramucirumab plus paclitaxel *versus* placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): a double-blind, randomised phase 3 trial. Lancet Oncol *15(11)*: 1224-1235, 2014. PMID: 25240821. DOI: 10.1016/S1470-2045(14)70420-6

24 Bando H, Shimodaira H, Fujitani K, Takashima A, Yamaguchi K, Nakayama N, Takahashi T, Oki E, Azuma M, Nishina T, Hironaka S, Komatsu Y and Shitara K: A phase II study of nab-paclitaxel in combination with ramucirumab in patients with previously treated advanced gastric cancer. Eur J Cancer *91*: 86-91, 2018. PMID: 29353164. DOI: 10.1016/j.ejca.2017.11.032

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