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ORIGINAL ARTICLE

Docetaxel/cisplatin followed by FOLFIRI versus the reverse sequence in metastatic gastric cancer

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Abstract
Background Both docetaxel-based and irinotecan-based chemotherapy has been demonstrated as active combination regimen in either first-line or second-line setting for metastatic gastric cancer. The purpose of this trial was to evaluate the two active regimens, docetaxel/cisplatin and FOLFIRI, as first- and second-line chemotherapy and to compare the sequence of the two regimens in terms of efficacy and tolerability.
Patients and methods Eligible patients were randomized to receive one of the two treatment arms: Arm A-DP (docetaxel 75 mg/m^2 D1, cisplatin 75 mg/m^2 D1 repeated every 3 weeks) until progression or unacceptable toxicity as the first-line treatment which was followed by FOLFIRI (irinotecan 150 mg/m^2 D1, leucovorin 100 mg/m^2 D1, 5-fluorouracil 3,000 mg/m^2 D1-2 for 48 h every 2 weeks) upon disease progression as second-line chemotherapy; Arm B-FOLFIRI as the first-line treatment until disease progression or unacceptable toxicity then followed by DP as the second-line treatment upon documented disease progression.
Results Between April 2005 and Aug 2008, 58 patients were enrolled (Arm A, $n = 28$; Arm B, $n = 30$). Median follow-up was 38.2 months. The overall response rate (ORR) of the first-line chemotherapy was 25.0% with DP (Arm A1) and 13.3 with FOLFIRI (Arm B1) ($P = 0.322$). The tumor control rate (TCR) of first-line chemotherapy was 82.1% with DP and 66.7% with FOLFIRI ($P = 0.209$). The median first progression-free survival (1st PFS) was 4.3 months with DP and 3.4 months with FOLFIRI ($P = 0.547$). The overall response rate of second-line chemotherapy was 20.0% with FOLFIRI (Arm A2) and 27.2% with DP (Arm B2) ($P = 0.296$). The tumor control rate of second-line chemotherapy was 46.7% with FOLFIRI and 50.0% with DP. The median second progression-free survival (2nd PFS) was 8.1 months with Arm A and 6.7 months with Arm B ($P = 0.865$). The median overall survival was 12.5 months (95% CI 8.17–16.83) in Arm A and 13.4 months (95% CI 9.99–16.81) in Arm B ($P = 0.674$). In safety profile, the incidence of neutropenic fever was comparable among the 4 arms ranging from 0 to 3.9%.
Conclusions The ORR, TCR of Arm A (DP → FOLFIRI) were not different from those of Arm B (FOLFIRI → DP). There was no statistically significant difference in 1st PFS, 2nd PFS, and OS of both arms. Although the trial was terminated early due to poor patient accrual, we found that both DP and FOLFIRI regimens were tolerable with comparable efficacies regardless of the sequence administered.

Keywords FOLFIRI · Docetaxel · Advanced gastric cancer · DP

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Introduction

The relative incidence rate of gastric cancer among all cancer is 18.3% (2003–2005) and gastric cancer is the second most common cause of death from malignancy in Korea [1]. Currently, more than two-thirds of gastric cancers are still diagnosed at advanced or unrespectable stage requiring

systemic chemotherapy [4]. Currently, there is no globally accepted chemotherapy regimen for metastatic gastric cancer. One of the most widely used first- or second-line regimens are either docetaxel-based or irinotecan-based chemotherapy for gastric cancer. Several randomized trials incorporated docetaxel or irinotecan-based combination regimen as first- or second-line chemotherapy. One phase II/III trial compared docetaxel/cisplatin/5-FU (DCF) to cisplatin/5-FU (CF) and reported a significant superiority of DCF in terms of survival (9.2 vs. 8.6 months), TTP (5.6 vs. 3.7 months) and RR (37 vs. 25%) [19]. However, the incidence of neutropenia was considerably higher in DCF arm which limited its use as first-line chemotherapy worldwide. In another trial, DP (docetaxel/platinum) compared to ECF, which demonstrated lower response rate, poorer survival in the DP arm but not inferior to DCF in terms of toxicity [15].

Despite numerous clinical studies with irinotecan, another active chemotherapeutic agent in gastric cancer, there was no direct comparison between irinotecan- and docetaxel-based chemotherapy either in first- or second-line setting. In previous studies including ours, the combination regimen of irinotecan plus leucovorin with continuous infusion of 5-FU (FOLFIRI) has demonstrated acceptable toxicity and efficacy with overall survival of 5–10.9 months as second-line chemotherapy of gastric cancer [6, 8, 9, 17]. The purpose of this trial was to evaluate the two active regimens, docetaxel/cisplatin and FOLFIRI, as first- and second-line chemotherapy and to compare the sequence of the two regimens in terms of efficacy and tolerability.

Patients and methods

Patient eligibility

Eligible patients were required to have histologically confirmed recurrent or metastatic gastric cancer, no previous chemotherapy for metastatic gastric cancer, age $\geq$18 years, an Eastern Cooperative Oncology Group (ECOG) performance status $\leq$2, adequate hematologic parameters (hemoglobin $\geq$9.0 g/dl, absolute neutrophile count $\geq$1,500/μl; platelet count $\geq$100,000/μl), renal function (creatinine clearance by Cockroft formula $\geq$60 ml/min or creatinine $\leq$1.5 mg/dl), and liver parameters (aspartate aminotransferase (AST), alanine aminotransferase (ALT) $\leq 3 \times$ the upper limits of normal (ULN), total bilirubin <1.5 mg/dl). Patients who received adjuvant chemotherapy completed $\geq$6 months from the date of study entry were eligible for the study. Patients with metastasis to the central nervous system, history of another malignancy within 5 years of study entry except for basal cell carcinoma of the skin or carcinoma in situ of the uterine cervix, active infection required antibiotic therapy, history of radiotherapy within 2 weeks, and pregnant or breast-feeding woman were excluded from the study. Before patients entered the study, all participants provided a written informed consent according to the guideline provided by the institutional review board. The study has been approved by the Institutional Review Board at Samsung Medical Center.

Study design

Patients who provided informed consent were randomized to either Arms A or B. Patients in Arm A received docetaxel 75 mg/m^2 D1, cisplatin 75 mg/m^2 D1 which was repeated every 3 weeks (DP) until disease progression or unacceptable toxicity as first-line chemotherapy. Upon progression, patients randomized to Arm A received FOLFIRI (irinotecan 150 mg/m^2 D1, leucovorin 100 mg/m^2 D1, 5-fluorouracil 3,000 mg/m^2 D1-2 for 48 h every 2 weeks). For Arm B, patients received FOLFIRI as first-line treatment until disease progression or unacceptable toxicity. Upon disease progression, patients received DP as second-line chemotherapy. Second-line chemotherapy was delivered at physician's discretion after reevaluation of the disease status and medical condition.

Study protocol

DP regimen: Docetaxel 75 mg/m^2 was infused over 1-h which was followed by cisplatin 75 mg/m^2 as a 1-h infusion. This regimen was repeated every 3 weeks until disease progression, unacceptable toxicity or patient's refusal. For emesis prophylaxis, intravenous 5-HT3 antagonist was used once on day 1, and followed by oral 5-HT3 antagonist once on days 2–5. Oral dexamethasone was also given once at night of day 0, three times on day 1, and once on days 3,4. FOLFIRI regimen: Irinotecan 150 mg/m^2 was infused over 90-min, followed by leucovorin 100 mg/m^2 as a 2-h infusion, and then followed by 3,000 mg/m^2 as a 48-h continuous infusion. For emesis prophylaxis, 5-HT3 antagonists intravenously were given before irinotecan infusion, followed by oral 5-HT3 antagonists on days 1, 2. Atropine 0.3 mg subcutaneous was administered for prophylaxis of cholinergic syndrome. This regimen was repeated every 2 weeks until disease progression, unacceptable toxicity or patient's refusal.

Efficacy assessment

Pretreatment evaluation included history and physical examination, complete blood cell count with differentials, chemistry, chest X-ray, computed tomography (CT) scan of abdomen and pelvis, and any other diagnostic procedures as clinically indicated. During treatment, a history taking,

physical examination including toxicity assessment, complete blood cell count, and chemistry were performed before each cycle. Appropriate imaging studies including abdominal and pelvis CT scan were performed every two cycles (6 weeks) in Arm A and every three cycles (6 weeks) in Arm B to evaluate treatment response, or sooner if needed for documentation of disease progression. Patients were assessed every 2 months for disease progression after the completion of the chemotherapy. Responses were classified according to Response Evaluation Criteria in Solid Tumors (RECIST1.0) criteria. Tumor measurements were independently reviewed by a radiologist and an oncologist, who were blinded from the tumor assessments performed by investigators.

ORR and TCR were used to evaluate the response of chemotherapy. The ORR was the ratio of the number of patients with complete or partial response in terms of their best response for chemotherapy to the number of all enrolled patients. The TCR was the ratio of the number of patients with complete, partial response or stable disease in terms of their best response for chemotherapy to the number of all patients. The first progression-free survival (1st PFS) was calculated from the initial day of treatment to the first documented date of disease progression after the first-line chemotherapy or to the date of the last follow-up. The second progression-free survival (2nd PFS) was calculated from the initial day of chemotherapy to the day when disease progression occurred after second chemotherapy or to the day when disease progressed after first chemotherapy in patients who had not received the second chemotherapy. Treatment-free duration (TFD) was calculated from the last day of the treatment after first-line chemotherapy to the first day of second-line chemotherapy. Overall survival (OS) was calculated from the first day of treatment to the date of death or the last follow-up. Toxicity was monitored according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC) scale version 3.0.

Statistical considerations

The total number of patients in this trial was derived from the assumption that 6-month disease-free survival of both arms was over 50%. Sample size of 190 and total 77 events were required to accept the hypothesis that the 6-month disease-free survival rate (DFS rate) of one arm is 50% with 80% power (two sided test, alpha = 0.05, beta = 0.80) and the 6-month DFS rate of another arm is improved by 20%. Total 100 patients in each arm were needed to assume that 5% of patients were not assessable.

Analyses were performed using SPSS software on all patients who had received at least one infusion). Descriptive statistics were reported as proportions and medians. Kaplan–Meier estimates were used in the analysis of time-to-event variable and the 95% confidence interval (CI) for the median time-to-event was computed. The dose intensity (DI) was calculated as the ratio of the total dose in milligrams per square meter of the patient, divided by the total treatment duration expressed in days. The relative DI was calculated as the ratio of the DI actually delivered to the DI planned by the protocol.

Results

Patient characteristics

From April 2005 to August 2008, total 58 patients were enrolled. Twenty-eight patients of them were included in Arm A and the others in Arm B. The baseline characteristics are listed in Table 1. There were no significant differences of baseline characteristics between two groups. The median age of patients in Arm A was 51 (range, 31–68 years) and Arm B was 53 years (range, 32–68 years). All patients had histologically proven adenocarcinoma or signet ring cell tumor of the stomach. Twenty-two patients in Arm A and 24 patients in Arm B had metastatic disease at the time of study entry. Fifteen of 28 patients (53.6%) in Arm A had received second-line chemotherapy, and 22 of 30 patients (73.3%) in Arm B had received second-line chemotherapy.

Treatment and drug delivery

The delivered relative dose intensities of Arm A were 95.1% for docetaxel, 95.1% for cisplatin, 87.5% for irinotecan, and 87.5% for 5-FU. The delivered relative dose intensities of Arm B were 86.2% for irinotecan, 86.2% for 5-FU, 92.0% for docetaxel, and 92.0% for cisplatin.

Response

In total, 54 (93.1%) of 58 patients were assessable for treatment response, which was summerized on Table 2. The ORRs of Arms A1 (DP) and B1 (FOLFIRI) were 25.0% (95% CI, 13.9–36.1%) and 13.3% (95% CI, 4.6–22.0%) by intent-to-treat analysis, respectively ($P = 0.322$). The ORRs of Arms A2 and B2 were 20.0% (95% CI, 9.7–30.3%) and 27.2% (95% CI, 15.7–38.6%) by intent-to-treat analysis, respectively ($P = 0.296$). The rate of stable disease (SD) was similar in two arms: 16 in A1 (59.3%), 16 in B1 (55.2%), 4 in A2 (26.7%), and 5 in B2 (25.0%).

Survival

All patients were included in the survival analysis by ITT. The median follow-up duration was 35.7 months in Arm A and 40.8 months in Arm B. The median 1st PFS was

Table 1 Patient characteristics

	Total	Arm A DP → FOLFIRI (n = 28, 48.3%)	Arm B FOLFIRI → DP (n = 30, 51.7%)	P value
Median age (range)	53 (31–68)	51 (31–68)	53 (32–68)	0.418
Sex				
M (%)	32	15	17	
F (%)	26	13	13	0.813
ECOG PS				
0	14	10	4	
1	41	16	25	
2	3	1	2	0.133
Previous surgery				
TG or STG	12	5	7	0.534
O&C	8	5	3	
Palliative	16	7	9	
Adjuvant chemotherapy				
None	49	23	26	
Done	9	5	4	0.634
Primary site				
Antrum	20	8	12	
Body	33	16	17	
Cardia	3	2	1	
Omentum	1	1	0	0.542
Unknown	1	1	0	
Grade				
Well differentiated	4	2	2	
Moderately	11	7	4	
Poorly	30	11	18	
Unclassified	13	7	6	0.567
Histology subtype				
Tubular adenoca	25	11	14	
Mucinous adenoca	5	3	2	
Signet ring cell	18	9	9	
Adenocarcinoma	10	5	5	0.921
Disease status				
Local recurrence	6	3	3	
Metastatic	46	22	24	
Advanced	6	3	2	0.991

ECOG Eastern Cooperative Oncology Group

4.3 months (95% CI 0.80–7.80) in Arm A1 (DP) and 3.4 months (95% CI 0.00–6.87) in Arm B1 (FOLFIRI; $P = 0.547$; Fig. 1). For second PFS, there was no significant difference between the two arms (8.1 months in Arm A2, 6.7 months in Arm B2, $P = 0.865$; Fig. 2). There was no significant difference in survival between the two arms (12.5 months (95% CI 8.17–16.83) in Arm A, 13.4 month (95% CI 9.99–16.81) in Arm B, $P = 0.674$; Fig. 3).

Toxicity

All patients were assessable for safety. The hematological toxicities per cycle observed during the study are listed in Table 3. The most common hematological toxic effect was neutropenia. During the first-line chemotherapy, grade 3 or 4 neutropenia was similarly detected in 6.3% of cycles in Arm A1 (DP) ($n = 129$), 6.5% in Arm B1 (FOLFIRI) ($n = 212$). In the second-line chemotherapy, three cycles (4.0%) of grade 3 or 4 neutropenia occurred in Arm A2 ($n = 75$) and four cycles (4.8%) of grade 3 of 4 neutropenia in Arm B2 ($n = 83$). The incidence of grade 3 neutropenic fever was relatively low (Arm A2, 1.3%; Arm B2, 3.6%). The non-hematological toxicities per patients observed during the study are listed in Table 4. Most of non-hematological toxic effects were grade 1 or 2 which were manageable.

Table 2 Response to treatment

	First-line chemotherapy			Second-line chemotherapy		
	Arm A1 DP (n = 28)	Arm B1 FOLFIRI (n = 30)	P value	Arm A2 FOLFIRI (n = 15)	Arm B2 DP (n = 22)	P value
Measureable lesion, n (%)	10 (35.7)	14 (46.7)		6 (40.0)	10 (45.5)	
CR, n (%)	1 (3.7)	0 (0.0)		1 (6.7)	0 (0.0)	
PR, n (%)	6 (22.2)	4 (13.8)		2 (13.3)	6 (30.0)	
SD, n (%)	16 (59.3)	16 (55.2)		4 (26.7)	5 (25.0)	
PD, n (%)	4 (14.8)	9 (31.0)		8 (53.3)	9 (45.0)	
Not evaluable, n	1	1		0	2	
ORR (%)	25.0	13.3	0.322	20.0	27.2	0.296
95% CI	13.9–36.14	4.6–22.0		9.7–30.3	15.7–38.6	
TCR (%)	82.1	66.7	0.209	46.7	50.0	1.000
95% CI	72.1–91.9	54.6–78.8		33.9–59.5	37.1–62.9	

n number of total patients in each Arm; *CR* Complete response; *PR* Partial response; *SD* Stable disease; *PD* Progressive disease; *ORR* Overall response rate; *TCR* Tumor control rate

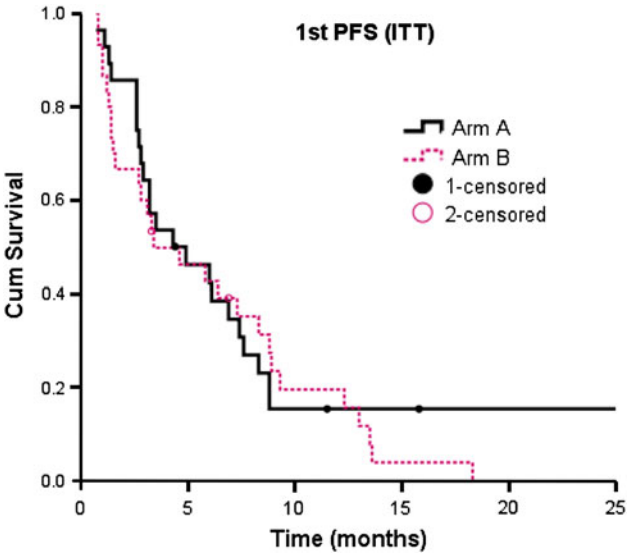

Fig. 1 First progression-free survival (1st PFS) of Arms A (*red line 1*) and B (*black line 2*). The first progression-free survival for Arms A (DP → FOLFIRI, n = 28) and B (FOLFILI → DP, n = 30) were 4.3 months (95% CI: 0.80–7.80) and 3.4 months (95% CI: 0.00–6.87) (P = 0.547), respectively (color figure online)

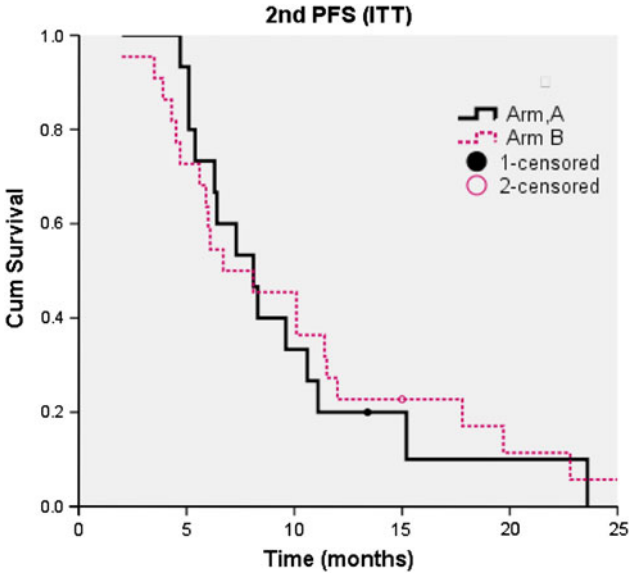

Fig. 2 Second progression-free survival (2nd PFS) of Arms A (*red line 1*) and B (*black line 2*). The second progression-free survival for Arms A (DP → FOLFIRI, n = 28) and B (FOLFILI → CP, n = 30) were 8.1 months (95% CI: 5.11–10.50) and 6.7 months (95% CI: 2.93–10.47) (P = 0.865), respectively (color figure online)

Discussion

This trial was terminated early due to poor patient accrual rate. After accrual of 58 patients over the period of 4 years, the study committee has decided to terminate the study. At the time of the study design, docetaxel-based chemotherapy was one of the widely used regimens as first-line chemotherapy. However, with the results from ML 17,032 trial that compared capecitabine/cisplatin (XP) versus 5-FU/cisplatin released in 2008, XP has become one of the most widely used regimens. Secondly, another large randomized study comparing ECF (epirubicin, cisplatin, 5-fluorouracil) or ECX (epirubicin, cisplatin, capecitabine) demonstrated that capecitabine could replace 5-fluorouracil, and anthracycline-containing regimen (ECX) is a promising regimen as first-line chemotherapy for gastric cancer.

In addition, we conducted a randomized phase II study comparing ECX vs. XP as first-line chemotherapy and found that XP was comparable to ECX with respect to the response rate (38 vs. 37%, respectively) and PFS (6.4 vs. 6.5 months) [21]. Although the results from meta-analysis

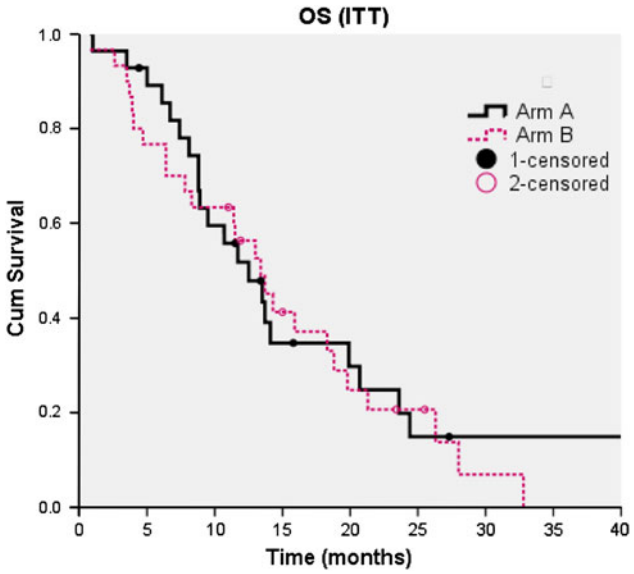

Fig. 3 Overall survival (OS) of Arms A (*red line 1*) and B (*black line 2*). The median overall survival for Arms A (DP → FOLFIRI, $n = 28$) and B (FOLFILI → CP, $n = 30$) were 12.5 months (95% CI: 8.17–16.83) and 13.40 months (95% CI: 9.99–16.81) ($P = 0.674$), respectively (color figure online)

showed a difference in survival of approximately 2 months in favor of the anthracycline-containing three-drug combination versus FP [20], 2-month survival benefit may be potentially misleading, since none of the studies that were included in the meta-analysis [2, 3, 10] demonstrated significant difference in OS between treatment arms. Given the results from large-scaled phase III trials in metastatic gastric cancer, we decided to terminate the study early.

Nevertheless, this study is the first randomized trial to directly compare DP versus FOLFIRI as first-line chemotherapy. Although it may not be conclusive due to limited number of enrolled patients, both regimens were active in metastatic gastric cancer, and the sequence of DP and FOLFIRI did not significantly influence treatment outcome in terms of PFS, OS, or toxicity in our study. The ORRs of first-line DP and FOLFIRI were 25.0% (95% CI, 13.9–36.1%) and 13.3% (95% CI, 4.6–22.0%), respectively. In our previous study, the ORR of first-line DP in patients with advanced gastric cancer was reported as 43.5% (95% CI, 33.4–53.6) [12]. In other group's studies, ORR of DPF as the first-line chemotherapy ranged from 27 to 56% [11, 18]. According to our present data, the ORR of the first-line DP is included lower limit. In present study, the ORR of first-line FOLFIRI is also similar to the result of previous phase II study in which ORR of first-line ILF was reported as 42% (95% CI, 28–57%) and PFS was 4.8 months [14].

The ORRs of second-line FOLFIRI and DP were 20.0% (95% CI, 9.7–30.3%) and 27.2% (95% CI, 15.7–38.6%), respectively, which were comparable to those reported in other studies. In other two phase II studies about DP in patients with recurred gastric cancer after 5-FU/platinum treatment, the ORR of second-line DP was reported 16.7–17.1% [5, 13]. The presented ORR of second-line FOLFIRI is very similar to our previous phase II study in which that obtained by second-line FOLFIRI for taxane and cisplatin refractory gastric cancer was 21% (95% CI, 10–32%) with favorable toxicity [8]. According to other study, ORRs of FOLFIRI as a second-line chemotherapy was reported about 18% [7, 16]. One of plausible explanations for relatively low response rate would be the proportion of patients with measurable lesion included in our study. Hence, PFS might be a better index of clinical outcome in our study. As illustrated in Fig. 2, the median PFS were similar between the two arms regardless of the sequence administered (DP → FOLFIRI, 4.3 months (95% CI 0.80–7.80); FOLFIRI → DP, 3.4 months (95% CI 0.00–6.87); $P = 0.547$).

In toxicity profile, six episodes of grade 3 or 4 neutropenic fever occurred in Arm A (DP → FOLFIRI) and three

Table 3 Hematological toxicity profile

Hematological toxicity per cycle	Arm A1 DP ($n = 129$)		Arm B1 FOLFIRI ($n = 212$)	
NCI-CTC grade	Grade 3	Grade 4	Grade 3	Grade 4
Febrile neutropenia	5 (3.9%)	–	–	–
Neutropenia	1 (0.8%)	2 (1.6%)	13 (6.1%)	1 (0.5%)
Thrombocytopenia	–	–	–	–
Anemia	3 (2.3%)	–	–	–
	Arm A2 FOLFIRI ($n = 75$)		Arm B2 DP ($n = 83$)	
Febrile neutropenia	1 (1.33%)	–	3 (3.6%)	–
Neutropenia	1 (1.33%)	1 (1.33%)	–	1 (1.2%)
Thrombocytopenia	–	–	–	–
Anemia	–	–	2 (2.4%)	–

NCI-CTC National Cancer Institute Common Toxicity Criteria

Table 4 Non-hematological toxicity profile

Non-hematological toxicity per patient	Arm A1 DP (n = 28) NCI-CTC grade (%)		Arm B1 FOLFIRI (n = 30) NCI-CTC grade (%)	
	Grade 3	Grade 4	Grade 3	Grade 4
Nausea/vomiting	2 (7.1%)	–	–	–
Peripheral neuropathy	1 (3.6%)	–	–	–
Fatigue	1 (3.6%)	–	–	–
Diarrhea	–	–	–	–
Elevated liver enzyme	1 (3.6%)	–	–	–
Mucositis	1 (3.6%)	–		–
Skin rash	–	–		–
	Arm A2 FOLFIRI (n = 14)		Arm B2 DP (n = 22)	
Nausea/vomiting	–	–	–	–
Peripheral neuropathy	–	–	–	–
Fatigue	–	–	–	–
Diarrhea	–	–	2 (9.1%)	–
Elevated liver enzyme	–	–	–	–
Mucositis	–	–		–
Skin rash	–	–		–

episodes in Arm B (FOLFIRI → DP). Grade 3, 4 non-febrile neutropenia occurred more frequently in Arm B than in Arm A. Therefore, the sequence of DP or FOLFIRI chemotherapy did not significantly influence neither the efficacy nor the dose intensity of the two treatments. In conclusion, although this study has been terminated early, the sequence of DP and FOLFIRI did not seem to influence of treatment outcome or tolerability in gastric cancer patients.

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