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ORIGINAL ARTICLE

Phase I study of 3-weekly docetaxel, capecitabine and oxaliplatin combination chemotherapy in patients with previously untreated advanced gastric cancer

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Abstract
Purpose Adding docetaxel to cisplatin and 5-fluorouracil (5-FU) (DCF) significantly improved clinical efficacy in advanced gastric cancer (AGC). To further improve the efficacy and tolerability, we substituted oxaliplatin for cisplatin and capecitabine for 5-FU in the DCF regimen and performed a phase I study to determine the recommended dose (RD) and dose-limiting toxicity (DLT) of docetaxel, capecitabine and oxaliplatin (DXO) combination in patients with AGC.
Materials and methods Previously untreated patients with histologically proven metastatic AGC and ECOG performance status 0–2 were enrolled. Docetaxel and oxaliplatin were administered i.v. on day 1. Capecitabine was administered orally bid on days 1–14. Each cycle was repeated every 3 weeks. DLTs were evaluated during the first two cycles of treatment.
Results Twenty-one patients were enrolled: 15 patients in dose-escalation phase and 6 patients in the extension at the RD. Median age was 50 years (range 21–65 years). At dose level 3 (60 mg/m^2 docetaxel, 1,000 mg/m^2 capecitabine, 100 mg/m^2 oxaliplatin), 1 diarrhea (DLT) was found among 6 patients while at dose level 4 (60 mg/m^2 docetaxel, 800 mg/m^2 capecitabine, 130 mg/m^2 oxaliplatin), 2 DLTs (febrile neutropenia and diarrhea) were observed among 3 patients. Therefore, the dose level 3 was determined as RD. DLTs include grade 3 diarrhea and febrile neutropenia. Cumulative (all cycles) grade 3/4 toxicity included neutropenia (75%), leucopenia (50%), febrile neutropenia (25%), diarrhea (17%), and neuropathy (17%). Of 14 patients with measurable lesions, 11 achieved partial response and 3 showed stable disease.
Conclusion The RD of the DXO regimen in patients with AGC is capecitabine 1,000 mg/m^2 twice daily on days 1–14, in combination with decetaxel 60 mg/m^2 (day 1) and oxaliplatin 100 mg/m^2 (day 1) repeated every 3 weeks. The DXO regimen seems to have promising activity and offers an easy alternative to DCF. The toxicities appear to be still substantial, but manageable.

Keywords Oxaliplatin · Docetaxel · Capecitabine · Chemotherapy · Gastric cancer

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Introduction

Despite the general decreasing trend in incidence, gastric cancer is the second most common cause of cancer death worldwide [1]. In Korean, gastric cancer is the most common cancer (24%) and the second leading cause of cancer-related deaths (19%) [2]. Many patients present initially with locally advanced disease or distant metastases. Even after complete resection, local and distant relapse rates are still high. For these patients, combination chemotherapy

has been found to improve quality of life and overall survival when compared with best supportive care alone [3–5]. Of the available regimens in this setting, such regimens containing 5-fluorouracil (5-FU) and cisplatin as CF (cisplatin and 5-FU) and ECF (epirubicin, cisplatin, and 5-FU) have been widely used [6–10]. However, the administration of infusional 5-FU in the CF regimen or protracted infusional 5-FU in the ECF regimen require hospitalization or central venous access with ambulatory infusion devices, which is associated with frequent outpatient visits or significant morbidity, particularly venous thrombosis and sepsis, requiring line removal in up to 15% of patients [9]. In addition, extensive time spent for intravenous (i.v.) hydration required for cisplatin is another inconvenience. Therefore, more effective and convenient systemic therapy is needed to improve the management of AGC patients.

The oral fluoropyrimidine capecitabine (Xeloda®) was designed to generate 5-FU preferentially in tumor tissue and to mimic a continuous infusion of 5-FU while minimizing systemic 5-FU exposure. Following absorption, capecitabine is bioactivated by a three-enzyme process, the final step being conversion to 5-FU by thymidine phosphorylase (TP): tumor selectivity results from the significantly greater TP activity in tumor tissue compared with healthy tissue [11]. This tumor-specific generation of 5-FU could potentially lead to an improved therapeutic index. Capecitabine at the dose of 1,250 mg/m^2 twice daily on days 1–14 every 3 weeks has demonstrated superior response rate and improved safety profile as well as improved convenience compared with i.v. bolus 5-FU/LV in the treatment of colorectal cancer [12].

Moreover, non-inferiority in substitution of capecitabine for i.v. 5-FU in the CF and ECF regimen in the treatment of AGC has been proven, without jeopardizing the efficacy or the safety in recent two phase III trials [13, 14].

Oxaliplatin is a newer generation platinum compound. Oxaliplatin is less emetogenic and nephrotoxic potential and eliminate the need for pre- and post-chemotherapy hydration, which also translates to patient convenience. Oxaliplatin, when combined with capecitabine every 3 weeks, has demonstrated significant activity in patients with AGC. Previous phase II studies had response rate ranging 63–65% with median progression-free survival (PFS) 5.8–7.5 months [15, 16]. The REAL-2 study also showed that oxaliplatin was as effective as cisplatin in patients with previously untreated AGC [14].

Docetaxel has significant activity against AGC. In the recent TAX 325 phase III trial, the addition of docetaxel to 5-FU and cisplatin (DCF) significantly improved the efficacy in terms of time to progression (5.6 vs. 3.7 months, $p < 0.001$), overall survival (OS) (9.2 vs. 8.6 months, $p = 0.02$), and response rate (37 vs. 25%, $p = 0.01$) when compared with 5-FU and cisplatin. However, it resulted in significant increase in toxicity with grade 3/4 leucopenia (65 vs. 31%), grade 3/4 neutropenia (82 vs. 57%), febrile neutropenia and/or neutropenic infection (29 vs. 12%), grade 3/4 diarrhea (19 vs. 8%), and grade 3/4 neurosensory toxicity (19 vs. 14%) [17], which may contribute to the limitation of using DCF regimen as first-line treatment in patients with AGC.

Considering the established non-inferiority and more favorable toxicity profile of capecitabine to infusional 5-FU and oxaliplatin to cisplatin and the additional benefit of docetaxel to fluoropyrimidine and cisplatin combination, we have performed a dose-finding study of docetaxel in combination with capecitabine and oxaliplatin in patients with previously untreated AGC.

Materials and methods

This study was an open-label, prospective, phase I study at Asan Medical Center, Seoul, Korea. This study was approved by the institutional review board of the Asan Medical Center, and all patients gave written informed consents before enrollment.

Eligibility criteria

All patients entered into this study were aged between 18 and 70 years and had histologically or cytologically confirmed unresectable or metastatic gastric adenocarcinoma. Eligibility criteria also included estimated life expectancy ≥ 12 weeks; adequate bone marrow function (absolute neutrophil count [ANC] ≥ 1.5 × 10^9/L and platelet count ≥ 100 × 10^9/L); adequate renal function (serum creatinine < 1.5 mg/dl or calculated creatinine clearance ≥ 60 ml/min by the Cockcroft and Gault formula); adequate hepatic function (total bilirubin level ≤2 times institutional upper limit of normal [ULN], and serum transaminases levels ≤3 times institutional ULN). Patients who had received prior chemotherapy were excluded. Patient's performance status was assessed using the Eastern Cooperative Oncology Group (ECOG) criteria, and those patients with performance status ≤2 were considered eligible. Eligibility also included the ability to reliably tolerate and to comply with oral medication, and patients with gastro-intestinal obstruction or evidence of ongoing serious gastro-intestinal bleeding were excluded. Patients also were excluded if they had evidence of central nervous system metastasis, peripheral neuropathy ≥grade 2, serious uncontrolled concomitant disease, other primary malignancy (except squamous or basal cell skin caner or cervical carcinoma in situ) within 5 years, or if they were pregnant or breastfeeding.

Chemotherapy

Cohorts of three patients were treated at each of five predetermined dose levels (Table 1) and no intra-patient dose escalation was permitted. Dose escalation was performed after all three patients in the previous dose level had completed at least two cycles of treatment.

Docetaxel was given as a 1-h i.v. in 200 ml of 5% dextrose water on day 1. After the completion of the docetaxel infusion, oxaliplatin was administered i.v. in 5% dextrose water 500 ml for 2 h without hydration methods for cisplatin on day 1. Capecitabine was administered orally at a pre-planned dose from the evening on day 1 to the morning on day 15 according to the standard intermittent schedule (14 days of treatment followed by a 7-day rest period). The capecitabine daily dose was 'rounded-up' and given equally divided twice-daily doses. The 'rounding-up' of doses was based on body surface area and total daily dose in accordance with the manufacturer's recommendation. Prior to starting docetaxel, the protocol dictated that patients be prescribed dexamethasone 4 mg orally twice a day for three doses with the first dose given 12-h before chemotherapy. All of which were given as part of a 21-day cycle for up to a maximum of nine cycles, until disease progression or unacceptable toxicity.

Dose-limiting toxicity (DLT) and recommended dose (RD)

Toxicity was graded using the National Cancer Institute Common Toxicity Criteria (NCI CTC) version 3.0. Complete blood count (CBC) with differential counts was examined weekly for all treatment cycles. Full medical history, physical examination including evaluation of ECOG PS, and biochemistry profiles were assessed prior to each treatment cycle. If grade IV neutropenia occurred, the complete blood count was repeated daily for the first two cycles of treatment to determine its duration.

DLT was determined during the first two cycles of treatment. The definitions of DLTs were as follows: (1) grade 4 neutropenia lasting for more than 5 days, or grade 3/4 neutropenia with fever; (2) grade 4 thrombocytopenia; (3) any other grade 3 non-hematological toxicity (excluding alopecia); or (4) treatment delay of more than 2 weeks following the time of planned treatment. A minimum of three patients was enrolled at each dose level. If no excessive toxicity was observed following the two cycles of treatment, the dose was escalated in successive cohorts. If a DLT was observed in one patient out of three, the dose level was expanded. The RD was defined as one dose level below the dose in which DLTs were observed in two or more patients from a cohort of two to six patients. An additional six patients were accrued at the defined RD to fully evaluate any toxicity encountered. Cumulative toxicity was also recorded for subsequent treatment cycles at all dose levels in all patients.

Table 1 Dose level

Dose level	Docetaxel (mg/m^2)	Capecitabine (mg/m^2, twice daily)	Oxaliplatin (mg/m^2)
1	45	800	100
2	60	800	100
3	60	1,000	100
4	60	800	130
5	60	1,000	130

Dose modification and delays

Dose modifications were performed based on toxicity. During the first two cycles of treatment, each drug was administered without intra-cycle interruption until the DLTs occurred. After the first two cycles of treatment, each drug was administered according to the dose modification method below.

Administration of all three agents was delayed until the adequate hematological recovery (ANC $\geq 1.5 \times 10^9$/L and platelet count $\geq 100 \times 10^9$/L). Non-hematologic toxicities, excluding alopecia, were required to be grade 1 or better prior to initiation of each cycle. If the event did not resolve for more than 3 weeks following the time of planned treatment, a patient was withdrawn from the study.

In the event of the first occurrence of grade 4 neutropenia lasting for more than 5 days, grade 4 thrombocytopenia, or febrile neutropenia, the doses of all three drugs were reduced by 25% for all subsequent cycles of the treatment. With the second occurrence of those hematologic toxicities, the doses of all three drugs were reduced by 50%. With the third occurrence of those hematologic toxicities, the patients were withdrawn form the study.

Capecitabine administration was interrupted immediately if patients developed grade ≥ 2 diarrhea, stomatitis or hand–foot syndrome, and resumed after the resolution of the toxicity to grade ≤ 1. Doses of capecitabine omitted for toxicity were not replaced or restored, but the patient could resume the planned treatment cycle with appropriate dose modification on resolution of the toxicity to grade ≤ 1. Subsequent treatment cycles were also given at the appropriate dose adjustment. No dose reductions or interruptions were performed for anemia, or for any grade 1 or less toxicity. The daily dose of capecitabine was reduced by 25% at the first occurrence of grade 3 or the second occurrence of grade 2 non-hematologic toxicities, by 50% at the second occurrence of grade 3 non-hematologic toxicities or the first occurrence of grade 4 non-hematologic toxicities.

In the event of the first occurrence of grade 2 peripheral sensory neuropathy, the doses of docetaxel and oxaliplatin were reduced by 25% for all subsequent cycles of

chemotherapy. In case of the second occurrence of grade 2 neuropathy, or the first occurrence of grade 3/4 neuropathy, both docetaxel and oxaliplatin was discontinued permanently. In case of the permanent discontinuation of docetaxel and oxaliplatin, capecitabine monotherapy was allowed. Docetaxel or oxaliplatin was reinstituted at 75% of the original dose with recovery of toxicities to grade 1 or less in case of other grade 3 non-hematologic toxicities, and discontinued with grade 4 non-hematologic toxicities.

Evaluation of response and survival

As screening assessment, tumor assessment by computed tomography (CT) scan was performed within 3 weeks before starting the treatment. Response was evaluated by CT scan every 2 cycles until the tumor progressed, with each assessment using the same imaging technique as at baseline. Tumor responses were classified according to the response evaluation criteria in solid tumor (RECIST) guidelines. Patients with complete response (CR) or partial response (PR) required a confirmatory disease assessment at least 4 weeks later. Patients with no confirmed tumor response were not regarded as responders. PFS was recorded from the start of chemotherapy until documented disease progression or death and the OS was determined from the start of chemotherapy until death (all causes). Survival curves were estimated using Kaplan–Meier techniques. All analyses were on an intention-to-treat basis. Statistical calculations were preformed using SPSS Version 15.0 (Chicago, IL, USA).

Table 2 Patient characteristics

Characteristic	No.	%
Total	21	100
Age (years)		
Median	50	
Range	21–65	
Sex		
Male	16	76
Female	5	24
ECOG performance status		
0	6	29
1	15	71
Histology		
Well/moderately differentiated	6	29
Poorly differentiated or signet-ring cell type	15	71
Primary tumor		
Cardia	1	5
Body and antrum	18	85
Diffuse	2	10
Metastatic sites		
Abdominal lymph node	13	62
Peritoneum	10	48
Liver	9	43
Other (e.g. ovary, bone, and spleen)	3	14
No. of metastatic sites		
1	8	38
≥2	13	62

ECOG Eastern Cooperative Oncology Group

Results

Patient characteristics

Between April 2006 and May 2007, 21 patients were enrolled in the study; their demographic and clinical characteristics are summarized in Table 2. The median age of patient was 50 years (range 21–65 years) and male was predominant (76%). All patients had good performance status (ECOG 0-1). All patients had metastatic disease and 14 patients had measurable lesions.

DLT and RD

No DLT was noted among 6 patients enrolled to cohort 1 at dose level 1 (docetaxel 45 mg/m^2, along with capecitabine 800 mg/m^2, twice daily and oxaliplatin 100 mg/m^2) and cohort 2 at dose level 2 (decetaxel 60 mg/m^2, along with capecitabine 800 mg/m^2, twice daily and oxaliplatin 100 mg/m^2). A further cohort of three patients was enrolled at dose level 3 (decetaxel 60 mg/m^2, along with capecitabine 1,000 mg/m^2, twice daily and oxaliplatin 100 mg/m^2). One of these three patients experienced DLT (grade 3 diarrhea). This cohort was therefore expanded to six patients. No patients from the expanded cohort experienced DLT.

A further cohort of 3 patients was enrolled at dose level 4 (decetaxel 60 mg/m^2, along with capecitabine 800 mg/m^2, twice daily and oxaliplatin 130 mg/m^2). Two of three patients experienced DLT (grade 3 febrile neutropenia, which was accompanied by grade 3 diarrhea in one patient) (Table 3). As a result, subsequent dose escalation was halted and no patient was treated at dose level 5. Therefore, a dose of docetaxel 60 mg/m^2, along with intermittent capecitabine 1,000 mg/m^2, twice daily (14 days' treatment followed by a 7-day rest period) and oxaliplatin 100 mg/m^2 administered on day 1 of each 21-day cycle was determined as the RD for further development.

Safety profile

During the study, a total of 151 treatment cycles were administered, with a median of 8 treatment cycles (range

Table 3 Treatment-related toxicity during the first two treatment cycles at each dose level (worst toxicity per patient)

	Dose level											
	I (n = 3)			II (n = 3)			III (n = 3)			IV (n = 3)		
Grade	1–2	3	4	1–2	3	4	1–2	3	4	1–2	3	4
Anemia	3	0	0	3	0	0	5	0	0	3	0	0
Leucopenia	1	0	0	3	0	0	1	2	0	2	1	0
Neutropenia	0	0	0	1	2	0	1	2	0	0	0	2[a]
Thrombocytopenia	0	0	0	0	0	0	0	0	0	0	0	0
Febrile neutropenia	–	0	0	–	0	0	–	0	0	–	2[a]	0
Asthenia	2	0	0	3	0	0	6	0	0	3	0	0
Nausea	3	0	0	3	0	0	4	0	0	1	0	0
Vomiting	0	0	0	2	0	0	3	0	0	1	0	0
Stomatitis	0	0	0	1	0	0	1	0	0	0	0	0
Diarrhea	1	0	0	0	0	0	3	1[a]	0	1	1[a]	0
Nail tocixity	0	0	0	0	0	0	2	0	0	0	0	0
Neuropathy	1	0	0	2	0	0	1	0	0	2	0	0
Hand–foot syndrome	1	0	0	0	0	0	0	0	0	0	0	0

[a] Dose-limiting toxicity

1–9 cycles) administered per patients. 10 (48%) patients in this study completed 9 cycles of treatment with no disease progression. Of 12 patients entered at the RD, a total of 77 treatment cycles was administered, with a median of 7 treatment cycles (range 1–9 cycles); 5 (42%) of 12 patients completed nine cycles of treatment with no disease progression. The remaining seven patients discontinued therapy due to withdrawal of consent (two), disease progression (two), dose-limiting toxicity (one), oxaliplatin-associated cumulative peripheral neuropathy (one), and surgery for curative intent after four cycles of treatment (one). Table 4 lists the cumulative toxicity experienced by patients treated at the RD during all treatment cycles. Eighteen grade 3 toxicities were reported in 10 patients (of 12 patients at the RD). Two patients developed grade 3 diarrhea. The onset of the grade 3 diarrhea was in days 7 and 10 in these two patients. Grade 3 peripheral sensory neuropathy was developed in two. The first patient developed a grade 3 neuropathy after completing the nine cycles of chemotherapy. A second patient after completing the eight cycle of chemotherapy and was withdrawn from further treatment. Grade 3 febrile neutropenia was observed in three patients (at cycle 2, 4, and 7, respectively) but was not associated with documented infection. Eight grade 4 toxicities which were limited by only hematologic toxicity (two grade 4 leucopenia and six grade 4 neutropenia) were reported in 6 patients. The median cycle at the onset of grade 4 neutropenia was 3 (range, 1–7 cycles). There were neither grade 4 non-hematologic toxicities nor deaths that were attributed to toxicity of the chemotherapy treatment.

Table 4 Incidence of cumulative toxicity during all treatment cycles at the recommended dose (worst toxicity per patient)

	n (%) of all patients (n = 12)				
	Grade 1	Grade 2	Grade 3	Grade 4	All grades
Anemia	1 (8)	8 (67)	2 (17)	0	11 (92)
Leucopenia	1 (8)	3 (25)	4 (33)	2 (17)	10 (83)
Neutropenia	1 (8)	1 (8)	3 (25)	6 (50)	11 (92)
Thrombocytopenia	4 (33)	4 (33)	0	0	8 (76)
Febrile neutropenia	–	–	3 (25)	0	3 (25)
Asthenia	10 (83)	2 (17)	0	0	12 (100)
Nausea	9 (75)	1 (8)	0	0	10 (83)
Vomiting	2 (17)	3 (25)	0	0	5 (42)
Stomatitis	6 (50)	1 (8)	0	0	7 (58)
Diarrhea	6 (50)	0	2 (17)	0	8 (76)
Nail toxicity	2 (50)	5 (42)	2 (17)	0	9 (75)
Neuropathy	6 (50)	2 (17)	2 (17)	0	8 (67)
Hand–foot syndrome	5 (42)	3 (35)	0	0	8 (67)

Of 12 patients entered at RD, chemotherapy was delayed in 6 cycles in 5 patients. Capecitabine dose was reduced in four patients, and docetaxel and oxaliplatin doses in four patients, respectively.

The median relative dose intensity of capecitabine, docetaxel, and oxaliplatin for the first six treatment cycles at the RD was 0.89 (range 0.39–1.0), 0.94 (range 0.45–1.0) and 0.94 (range 0.45–1.0), respectively.

Response and survival

Fourteen patients had measurable disease, and seven had evaluable disease at baseline.

In 14 patients with measurable lesions, all patients were assessable for response. One patient who experienced partial response after cycle 2, however, was not confirmed by a second imaging procedure due to the withdrawal of consent. Overall, 11 patients experienced confirmed partial responses, and 2 patients had stable disease (for 9.6 and 2.7 months, respectively). The objective response rate was 78.6% (95% CI, 57.1–100%) in intent-to-treat population (Table 5). Among 11 patients who experienced confirmed partial response during treatment, two patients with para-aortic lymph nodes metastasis at the RD were enable to proceed to potentially curative surgical resection after the complete resolution of distant metastatic sites after completion of cycle 4 and 9, respectively. In addition, among seven patients who had only evaluable disease, two patients with peritoneal metastasis (in dose level 1 and dose level 2, respectively) underwent exploratory laparotomy on investigator's decision after cycle 9 and 8, respectively. Interestingly, of those 4 patients, who underwent surgical resection, all patients achieved a R0 resection including one pathologic complete response.

At the time of writing, three of those 4 patients (two peritoneal metastasis and one para-aortic lymph node metastasis) were still alive with no disease progression for 29, 27, and 23 months from the start of treatment, respectively. The other one patient had died from disease 13 months after the start of treatment.

With a median follow-up of 27 months for the all patients, 6 patients are still alive. The median PFS and OS of all patients were 10.6 months (95% CI, 6.7–14.5 months) and 15.7 months (95% CI, 10.3–21.2 months), respectively. The median PFS and OS of patients treated with RD were 6.0 months (95% CI, 1.3–10.1 months) and 13.2 months (95% CI, 10.8–15.6 months), respectively (Fig. 1).

Table 5 Objective response rate (ORR) at different dose levels

Dose level	Assessable patients	Objective response				ORR (%)
		CR	PR	SD	PD	
1	0	–	–	–	–	NA
2	2	0	2	0	0	100
3	10	0	9	1	0	90
4	2	0	0	2	0	0
Overall	14	0	11	3	0	78.6*

CR complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease, *NA* not assessable

* The 95% confidence interval is 57.1–100%

Discussion

This study has demonstrated that the principal DLTs associated with docetaxel, along with capecitabine and oxaliplatin were diarrhea and febrile neutropenia. The following regimen of capecitabine 1,000 mg/m^2, twice daily (14 days' treatment followed by a 7-day rest period), in combination with decetaxel 60 mg/m^2 and oxaliplatin 100 mg/m^2, each administered on day 1 of a 21-day cycle was determined as the RD for further investigation.

The combination of docetaxel, cisplatin, and 5-FU (DCF) has demonstrated a significant activity in the treatment of gastric cancer [17–19]. In the meantime, significant toxicities counterbalance the high efficacy of this triplet regimen. In addition, the hospitalization requirement and the hydration procedures required for continuous i.v. infusion of 5-FU and for cisplatin, respectively, limit the application of this regimen.

The substitution capecitabine for 5-FU and oxaliplatin for cisplatin results in simpler and less invasive schedule of administration, while potentially maintaining a high degree of the activity [13, 14, 20]. We designed this phase I trial to seek a regimen that would maintain the equivalent activity as DCF, while reducing the degree of toxicity and simplifying the outpatient administration. At the level of

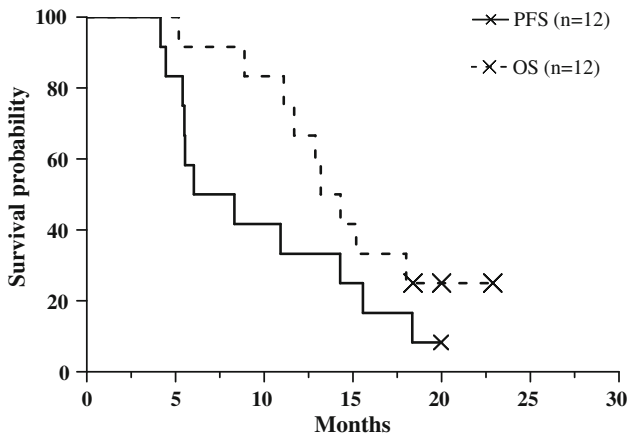

Fig. 1 Progression-free survival (*PFS*) and overall survival (*OS*) of patients treated with recommended dose

RD in the present study, during the 77 treatment cycles with a median 7, cumulative (all cycle) grade 3/4 toxicities included neutropenia in 75%, leucopenia in 50%, febrile neutropenia in 25%, diarrhea in 17%, and neuropathy in 17% of patients. This pattern of toxicity was at least comparable with data for DCF [17]. However, the hematologic monitoring strategy was different between the two studies [(every 3 weeks in DCF vs. every week in docetaxel, capecitabine and oxaliplatin (DXO)] which likely led to the similarly high incidence of hematologic toxicities of DXO regimen in our study to DCF regimen in V325 study. Myelotoxic complications, such as leucopenia and neutropenia showed the tendency of cumulative effects, mainly after three or more cycles of the therapy. However, neutropenia did not require withdrawal from the treatment in any patients, and neutrophil levels typically returned to the baseline by the end of the 3-week regimen. Grade 3 febrile neutropenia was observed in three patients receiving RD (at cycle 2, 4, and 7, respectively). However, it was not associated with documented infection and through appropriate dose reduction in subsequent cycles in these patients, no patients experienced febrile neutropenia for all subsequent cycles of the treatment. Severe diarrhea was the most frequent non-hematological toxicities and was observed in two patients at first treatment cycle. With appropriate dose modification of capecitabine, however, no patients experienced further severe diarrhea for all subsequent cycles of the treatment. Although toxicities appear to be frequent with DXO regimen partially due to more frequent monitoring, the toxicities such as neutropenia and diarrhea were transient and easily manageable with appropriate dose adjustment, and there was no treatment-related mortality in this study.

Evans et al. reported a phase I study of DXO combination in a variant intermittent weekly schedule of docetaxel and oxaliplatin. The regimen of docetaxel 30 mg/m^2 and oxaliplatin 50 mg/m^2 day 1 and 8, in combination with orally capecitabine 750 mg/m^2, twice daily for 10 days, in a 21-day cycle was set as RD in patients with metastatic gastroesophageal cancer [21]. The planned dose intensity in this study is comparable to that of our 3-weekly regimen except for the planned capecitabine dose intensity, which was much higher in our study than that of Evans's study. DLTs including nausea, diarrhea, fatigue, and febrile neutropenia, during the first 2 cycles reported by Evans were similar to our study. The cumulative toxicity of all dose level during the 52 treatment cycles, with a median of 3, of this study dose however distinguish from our 3-weekly regimen. Myelotoxic complications were mild as expected and gastrointestinal toxicity, including nausea/vomiting (19%), and diarrhea (12%) was predominant. Caution should be exercised, however, when comparing toxicities between the two studies, due to the considerable difference patients' population enrolled in each study, the limited numbers, the different treatment duration, and the different toxicity monitoring strategies.

As expected with the regimen containing oxaliplatin and docetaxel, there was a high frequency of grade 2/3 neuropathy at the RD, being reported in 33% of the population; and the severe (grade 3) was reported in 17%. Nonetheless, the peripheral neuropathy occurred only in patients benefiting from the treatment. Indeed, the four patients with a median cumulative oxaliplatin dose of 863 mg/m^2 (range 800–900 mg/m^2) experienced grade 2/3 neuropathy but achieved a partial response lasting a median 8.2 months (range 4.3–11.6 month). In particular, the risk of functional impairment was estimated in 10% of the patients receiving a cumulative oxaliplatin dose of 780 mg/m^2 [22].

The DXO regimen requires only a 1 h infusion of docetaxel, a 2 h infusion of oxaliplatin without hydration methods for cisplatin, and twice daily oral administration of capecitabine for 14 days every 3 weeks, making this regimen much more simpler and less invasive schedule of administration than the DCF regimen, requires a 5-day, continuous infusion of 5-FU and hydration for cisplatin. Therefore, the DXO regimen was more convenient for patients receiving treatment through an outpatient clinic.

The DXO combination also demonstrated a high antitumor activity. The objective response rate was 78.6% (intent-to-treat population) (95% CI, 57.1–100%) and median PFS and OS of all patients were 10.6 months (95% CI, 6.7–14.5 months) and 15.7 months (95% CI, 10.3–21.2 months), respectively. These results compare favorably with those of the previous triplet regimen, which have demonstrated response rates of 37% to 67% as first-line therapy in patients with AGC [17, 23].

Furthermore, the potential for a curative surgical approach in responders is noteworthy, four responders had surgical treatment, and three of them were still alive without evidence of disease progression at the time of analysis. These findings suggest that an effective chemotherapy can lead to long-term survival and even cure in some patients with distant metastasis, if complete resection of primary gastric tumor is attempted after the complete resolution of distant metastatic sites [23, 24].

Given the encouraging preliminary antitumor activity and the tendency of cumulative effects of severe toxicity, this regimen may be a reasonable treatment option in the neoadjuvant setting in patients with good performance status, where high antitumor activity resulting in down staging is required.

In conclusion, the 3-weekly regimen of capecitabine 1,000 mg/m^2, twice daily (14 days' treatment followed by a 7-day rest period), in combination with decetaxel 60 mg/m^2 and oxaliplatin 100 mg/m^2, each administered on day 1 renders not only the encouraging antitumor activity but also

the simpler and less invasive administration schedule. Therefore, this regimen warrants further evaluation in phase II/III trials in advanced gastric cancer.

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Conflict of interest statement None.

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