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ORIGINAL ARTICLE

Phase I/II study of a combination of docetaxel, capecitabine, and cisplatin (DXP) as first-line chemotherapy in patients with advanced gastric cancer

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Abstract
Background This study was conducted to determine the optimal dosage of the docetaxel-capecitabine-cisplatin (DXP) regimen and to evaluate its efficacy and safety in patients with advanced gastric cancer.
Methods Patients with advanced gastric or esophagogastric junctional adenocarcinoma received capecitabine (days 1–14) and intravenous docetaxel and cisplatin (day 1) every 3 weeks.
Results In the phase I study, 15 patients were treated with 4 different dose levels. Asthenia and neutropenic fever were the dose-limiting toxicities. For the phase II study, 1,125 mg/m^2 of capecitabine was initially recommended with 60 mg/m^2 docetaxel and 60 mg/m^2 cisplatin. However, frequent dose modifications at this dose level resulted in a final optimal dose of 937.5 mg/m^2 capecitabine. Among the 40 patients enrolled in the phase II study, 4 complete and 23 partial responses were observed, presenting objective response rate of 68%. Ten patients achieving good response with complete disappearance of distant metastases underwent surgery, and 4 pathologic complete responses were identified. After the median follow-up of 83.7 months (range, 20.2–86.5) in surviving patients, the median overall survival was 14.4 months and median progression-free survival was 7.6 months. The most frequent grade 3/4 adverse events were neutropenia (62.5%) and asthenia (37.5%). Ten per cent of the patients experienced neutropenic fever, with one case of sepsis-induced death.
Conclusion DXP displays considerable antitumor activity, and may thus present effective first-line treatment for advanced gastric cancer. Further investigation of the efficacy and safety of this regimen in both first-line and neoadjuvant settings is warranted.

Keywords Capecitabine · Docetaxel · Cisplatin · First-line chemotherapy · Advanced gastric cancer · Neoadjuvant therapy

Introduction

The prevalence of gastric cancer has declined dramatically over the past century in some countries, but the disease remains the second leading cause of cancer-related death on a global scale [1, 2]. Although the incidence of gastric cancer is relatively low in the US, Canada and Australia, it poses a serious health problem in Asia, South America and Eastern Europe [3]. A high proportion of patients present with unresectable locally advanced or metastatic disease at diagnosis, and local and distant relapses are common even after complete surgical resection. Palliative chemotherapy offers improved survival outcomes, compared with best supportive care alone, for advanced gastric cancer (AGC) patients, but response rates remain low (approximately 50% or less) and the duration of survival is disappointingly short (median of approximately 9–10 months) [4]. To improve these poor results, combination chemotherapy

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using established or novel cytotoxic agents has been the focus of many clinical trials, because combination regimens seemed to achieve better results than single-agent regimens [5].

Since promising efficacy of the fluorouracil–cisplatin (FP) regimen has been shown in phase II trials [6, 7], and confirmed in subsequent phase III trials [8, 9], this regimen has been taken as reference treatment for chemotherapy-naive patients with AGC. Combination therapy incorporating docetaxel into the FP regimen (DCF) was investigated in a randomized phase III V325 study, with the aim of improving the anti-tumor activity of FP. The data showed significantly increased time to progression, survival, and response rate [10]. However, substantial toxicities (82% grade 3/4 toxicities and 29% neutropenic fever) have limited the use of this drug combination as standard chemotherapy in daily clinical practice [10]. Thus, modification of DCF regimen was necessary to improve the safety profiles and to be applied to more patients.

On the other hand, the FP and DCF regimens involve the continuous infusion of fluorouracil, which requires placement of a central venous access device. This is an inconvenient process associated with additional costs and morbidity. Recently, capecitabine (Xeloda, F.Hoffmann-La Roche Ltd.), an oral fluoropyrimidine presenting 20–30% response rate and favorable tolerability in several phase II trials for AGC patients as a single agent [11–13], has been investigated as an alternative to intravenous fluorouracil. A previous phase II study on the capecitabine and cisplatin (XP) combination regimen revealed comparable efficacy (response rate, 54.5%, and overall survival, 10.1 months) and tolerability as first-line AGC therapy in relation to the FP regimen [14].

In this phase I/II study, we modified the DCF regimen by substituting capecitabine for intravenous fluorouracil and adjusting the doses of docetaxel and cisplatin. The purpose of this study was to determine the recommended dose (phase I), and further evaluate the efficacy and safety (phase II) of the docetaxel-capecitabine-cisplatin (DXP) combination regimen in chemotherapy-naive patients with AGC.

Materials and methods

Patient characteristics

Patients with histologically or cytologically documented gastric or esophagogastric junctional adenocarcinoma were considered eligible if they met the following inclusion criteria: age between 18 and 70 years, non-resectable disease owing to metastatic or recurrent disease after curative resection, Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, adequate bone marrow, renal and liver function, no prior chemotherapy or radiotherapy, and life expectancy of >3 months. Patients with gastric outlet or intestinal obstruction or evidence of gastrointestinal bleeding were excluded. For the phase II study, at least one measurable lesion was required, according to the Response Evaluation Criteria In Solid Tumors (RECIST) [15]. The protocol was approved by the institutional review board of Asan Medical Center, and all patients provided written informed consent before enrollment.

Treatment schedule

The predefined dose escalation scheme in the phase I part consists of 4 levels as follows; level 1, capecitabine (X) 937.5 mg/m^2 twice daily, docetaxel (D) 60 mg/m^2 on day 1 and cisplatin (P) 60 mg/m^2 on day1; level 2, X1,125 mg/m^2, D 60 mg/m^2 and P 60 mg/m^2; level 3, X1,125 mg/m^2, D 75 mg/m^2 and P 60 mg/m^2; level 4, X1,250 mg/m^2, D 75 mg/m^2, and P 60 mg/m^2, respectively. Standard 3 + 3 method was used and a minimum of 3 patients were treated at each dose level.

Capecitabine was administered orally twice daily with a standard intermittent schedule (14 days of treatment, followed by a 7-day rest period every 3 weeks). The first dose was administered after infusion of both cisplatin and docetaxel (i.e., on the evening of day 1). Docetaxel was provided as a 1-hour intravenous infusion on day 1 of each cycle, repeated every 3 weeks. As prophylaxis for potential docetaxel hypersensitivity reactions, 8 mg of oral dexamethasone was administered twice daily (or equivalent) for 3 days, prior to docetaxel infusion at day 1. Cisplatin was administered 3 h after the completion of docetaxel infusion as a 1-hour intravenous infusion in 500 mL of saline with a standard hydration method, repeated every 3 weeks. Patients additionally received antiemetic therapy consisting of intravenous ondansetron (8 mg) and dexamethasone (10 mg). Prophylactic use of colony-stimulating factors was not permitted. Treatment was continued at the discretion of the investigator until evidence of progression, unacceptable toxicity, or patient request for withdrawal. A maximum of 12 cycles of treatment was provided.

Maximum tolerated dose (MTD) was determined based on toxicity data from the first cycle. Dose-limiting toxicities (DLTs) were defined as follows: granulocytes $<0.5 \times 10^9$/L for more than 5 days, granulocytes $<1.0 \times 10^9$/L with fever, grade 4 thrombocytopenia or any other non-hematological grade 3/4 toxicity (excluding alopecia) that did not improve to at least grade 1 within 2 days of instituting the appropriate therapy or leading to the interruption of capecitabine or delayed docetaxel and cisplatin treatment for more than 2 weeks. If one of three patients experienced DLT, three additional patients were entered for treatment at that dose level. Dose escalation was continued until two or

more of six patients experienced DLTs. This dose level was defined as MTD. We employed the dose level below MTD for the phase II study. Patients not previously subjected to surgery showing good response (i.e., disappearance of all the metastatic lesions in imaging studies) were offered resection of the primary tumor in the stomach.

Evaluation of safety and dose modifications

Adverse events were evaluated before each treatment cycle according to the National Cancer Institute Common Toxicity Criteria, version 2.0. Hand-foot syndrome (HFS) was assessed using the previously described 3-grade system [14]. All patients were reviewed approximately 1 month after the last cycle to document any late adverse effects.

For commencement of each treatment cycle, patients were required to have a white blood cell count of $\geq 3.0 \times 10^9$/L, absolute neutrophil count of $\geq 1.0 \times 10^9$/L, platelet count of $\geq 100 \times 10^9$/L and resolution of non-hematological toxicities to grade 1 or better. A treatment delay of up to 1 week was permitted without dose reduction. Doses were modified in the phase II study based on the predefined guideline. Briefly, capecitabine and docetaxel were reduced by 25% at neutrophil counts of $1.0–1.5 \times 10^9$/L or platelet counts of $75–100 \times 10^9$/L. Docetaxel and cisplatin were reduced by 25% for grade 2 neuropathy, and discontinued in case of grade 2 neuropathy lasting more than 3 weeks or grade 3/4 neuropathy. Cisplatin was reduced by 50% in case of serum creatinine 1.5–2.0 mg/dL, and discontinued at >2.0 mg/dL, following treatment delay of 1 week with hydration. Capecitabine was reduced by 25% for grade 3 stomatitis or diarrhea. Patients with HFS were managed according to the schedule outlined by Kim et al. [14].

Evaluation before and during treatment

Prior to participation in the study, patients underwent a number of assessments, including history, physical examination, complete blood count with differential counts, serum chemistry, electrolytes, determination of coagulation parameters, urinalysis, electrocardiography, chest X-ray, and computed tomography (CT) scanning of the abdomen and pelvis. Other investigations, such as bone scan and chest CT scan were performed if clinically indicated metastatic disease. Physical examinations, chest X-rays, complete blood count with differential counts, and chemistry tests were repetitively performed prior to each chemotherapy cycle. Patients with documented progressive disease were monitored every 3 months until death.

Tumor response, the primary end-point for the phase II study, was evaluated every 2 cycles according to RECIST criteria using the same imaging technique as at baseline [15]. Complete or partial responses (PR) were confirmed at least 4 weeks later. Secondary endpoints included overall and progression-free survival (PFS). PFS was measured from the start of treatment to documented tumor progression or death from any cause, whichever occurred first. Overall survival (OS) was calculated from the start of treatment to the date of last follow-up or death. Response duration was measured from the initiation of treatment to documented tumor progression.

Statistical analysis

The phase II study was conducted using the one-sample two-stage testing design of Fleming and Simon [16, 17]. At the first stage, if there were fewer than five responses out of the initial 16 patients, the anticipated response rate was expected to be less than 30%, and the study was consequently terminated. Therefore, the probability of accepting therapy with a real response rate of less than 30% and the risk of rejecting treatment with a response rate of more than 40% would be less than 10% in both cases. Assuming a dropout rate of 20% (due to protocol non-compliance), a total of 41 patients were required. PFS, overall survival and duration of response were estimated using the Kaplan–Meier method.

Results

Phase I study

In total, 15 patients were recruited for the phase I study. Groups comprising 3 patients each received DXP at dose levels I, II and IV, and 6 patients were administered DXP at dose level III. The baseline characteristics of these patients are presented in Table 1.

The primary dose-limiting toxicities for the DXP regimen were asthenia and neutropenic fever (Table 2). During the 1st cycle, no DLT was observed at dose level I and II. At dose level III, a DLT was noted in 1 patient out of 3. So, three more patients were enrolled at dose level III but no more DLT was observed. Dose was escalated to level IV, and DLT was observed in 2 patients out of 3 enrolled at dose level IV. So, according to the protocol, dose level IV was MTD, and thus dose level III should become recommended dose. However, during the 2nd cycle of chemotherapy, 3 patients experienced DLTs at dose level III, which made us redefine dose level III as the MTD. And, finally, dose level II (capecitabine 1,125 mg/m^2 twice daily for 14 days, docetaxel 60 mg/m^2 and cisplatin 60 mg/m^2 on day 1) was recommended for the phase II study.

Table 1 Baseline patient characteristics

Characteristic	Phase I		Phase II	
	N (total = 15)	%	*N* (total = 40)	%
Median age, years (range)	55 (24–64)		53 (33–68)	
Male gender	9	60.0	28	70.0
ECOG performance status				
0	0	0	4	10.0
1	14	93.0	30	75.0
2	1	7.0	6	15.0
Disease location				
Cardia	1	7.0	1	2.5
Corpus	6	40.0	13	32.5
Antrum	8	53.0	24	60.0
Diffuse	0	0	2	5.0
Extent of disease				
Metastatic	15	100	32	80.0
Recurrent	0	0	4	10.0
Locally advanced	0	0	4	10.0
Metastatic sites				
Liver	6	40.0	20	50.0
Lung	1	7.0	2	5.0
Cervical lymph node	2	13.0	8	20.0
Abdominal lymph node	10	67.0	28	70.0
Peritoneum	6	40.0	8	20.0
Previous surgery	3	20.0	5	12.5

Table 2 Grade 3/4 adverse events in phase I portion (n = 15)

Grade	Dose level [no. of patients]							
	I		II		III		IV	
	(937.5/60/60)[a]		(1125/60/60)[a]		(1125/75/60)[a]		(1250/75/60)[a]	
	[n = 3]		[n = 3]		[n = 6]		[n = 3]	
	3	4	3	4	3	4	3	4
Neutropenia	2 (2)	0 (1)	1 (1)	0 (1)	2 (1)	0 (2)	0	0
Neutropenic fever	0 (1)	0 (0)	0 (0)	0 (0)	0 (3)	1 (0)	0	0
Thrombocytopenia	0	0	0	0	0	0	0	0
Asthenia	0	0	0	0	1 (2)	0	2 (1)	0

[a] Capecitabine/docetaxel/cisplatin doses in mg/m^2; capecitabine given twice daily

() number of patients experiencing adverse events at 2nd cycle

Phase II study

The baseline characteristics of the 40 patients enrolled in the phase II trial are presented in Table 1. Although level II was determined as the recommended dose based on the phase I study, many patients required dose modifications owing to toxicities during subsequent cycles, and the actual dose intensity of capecitabine at this level was approximately 80%, equivalent to that for dose level I. Accordingly, we decided to modify the recommended dose to level I (capecitabine 937.5 mg/m^2 twice daily for 14 days, docetaxel 60 mg/m^2 and cisplatin 60 mg/m^2 on day 1). As a result, dose level II was used to treat 17 patients and the subsequent 23 patients received dose level I. Median 6 (range, 1–11) cycles of chemotherapy were administered. Ten patients (25%) underwent surgery after achieving complete disappearance of distant metastatic lesions with median 6 chemotherapy cycles (range, 4–9).

Efficacy and survival

In total, 36 patients were evaluable in terms of treatment efficacy, and 4 patients could not be evaluated (3 withdrew consent and the 1 was lost to follow-up after one cycle of chemotherapy) (Table 3). Four complete and 23 PR were observed with DXP, providing an overall response rate of 68% (95% confidence intervals [CI], 53–83%) according to intention-to-treat analysis. And, there was no significant difference in response rate between patients treated at dose level I and II (69.6 and 64.7%, respectively). The median follow-up duration of surviving patients was 83.7 months (range, 68.7–86.5). Median overall survival was determined as 14.4 months (95% CI, 7.3–21.5) and median PFS as 7.6 months (95% CI, 6.9–8.4) (Fig. 1). In 27 patients showing response, the median response duration was 8.9 months (95% CI, 6.7–11.1). Details and survival curves of the 10 patients subjected to surgery after achieving complete response of distant metastasis are presented in Table 4; Fig. 2. Following surgery, the surgical specimens of 4 patients revealed pathologic complete response (CR). Among these 4 patients achieving pathologic CR, 3 patients are alive for 66–79 months without evidence of tumor. Another one patient with pathologic PR is also disease free and alive for 69 months. The patients who underwent surgical resection of primary gastric tumor after DXP chemotherapy had significantly superior PFS ($P = 0.002$) and OS ($P = 0.006$) to those who had DXP chemotherapy alone.

Table 3 Antitumor efficacy in the phase II study ($n = 40$)

	No. of patients	%	95% CI
Overall response rate	27	68	52–83
Complete response (confirmed)	4	10	0–20
Partial response (confirmed)	23	58	41–74
Stable disease	8	20	7–33
Progressive disease	1	3	0–8
Not evaluable	4	10	0–20

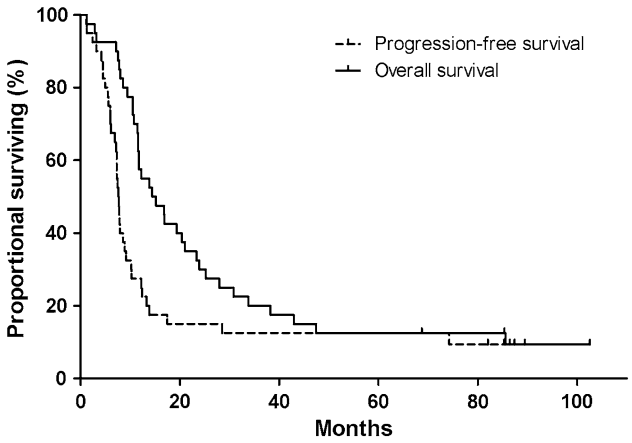

Fig. 1 Progression-free survival and overall survival in the phase II study

Adverse events

The frequencies of treatment-related hematological and non-hematological adverse events are summarized in Table 5. The most common treatment-related grade 3 clinical adverse events were asthenia, vomiting and constipation occurring in 37.5, 17.5 and 17.5% patients, respectively. Despite frequent development of HFS (82.5%), grade 3 HFS was observed only in one patient (2.5%). Grade 3 or 4 neutropenia was reported in 62.5% patients. Four (10%) patients experienced neutropenic fever, and one neutropenia-related death was recorded. Severe anemia and thrombocytopenia occurred in 10 and 7.5% of patients, respectively (grade 3). Among the 36 patients continuing treatment for more than 1 cycle, dose reduction was required for 28 (78%) individuals and treatment was interrupted over 7 days in 17 (47%) patients.

Discussion

Our results suggest that the DXP regimen in this study is highly active as first-line treatment in AGC patients. This regimen showed good efficacy, with an objective response rate of 68%, median PFS of 7.7 months, and median OS of 14.4 months. The efficacy of DXP may be due to the additive antitumor activity of the constituent agents reported in preclinical and early clinical studies [14, 18–20].

These findings are pertinent in view of data obtained from a large phase III trial comparing the efficacy of DCF with FP in chemotherapy-naïve AGC patients [10]. The earlier study reported a statistically superior response rate (37%) and time to progression (5.6 months) as well as clinically significant prolongation of overall survival (9.2 months) with the docetaxel-containing regimen. Although it is difficult to compare directly, DXP triplet seem to induce an improved response rate (68 vs. 55%) and median OS (14.4 vs. 10.1 months), compared with XP doublets [14], suggestive of a significant contribution by docetaxel. Consistent with previous trials showing that oral capecitabine is similar or superior to intravenous fluorouracil [21–23], the efficacy data obtained with DXP in the present study seem to be superior to those generated with DCF reported by Van Cutsem et al. [10], in terms of overall response rate (68 vs. 39%) and overall survival (14.4 vs. 10.2 months). Although these results require further confirmation in a larger group of patients, they clearly support the theory that the infused fluorouracil component of DCF can

Table 4 Overview of patients who received DXP followed by surgery ($n = 10$)

Age (years)/ sex	Initial clinical stage	Cycles of DXP prior to surgery	Response to DXP	Pathological stage at surgery	Postoperative status
47/F	M1:PA LN	6	PR	pT2N0M0	NED for 69 mo
35/F	M1:PA LN	4	PR	pT4N2M0	PD after 3 mo
60/M	M1:PA LN	7	PR	pT2N1M0	PD after 23 mo
49/F	M1:PA LN	8	CR	NED	NED for 79 mo
64/M	LA:HD LN	6	CR	NED	PD after 2 mo
71/M	M1:Liver	7	PR	pT2N1M0	PD after 9 mo
45/F	M1:PA SC LN	9	PR	NED	NED for 74 mo
38/M	M1:Liver PA LN	6	PR	pT4N0M0	PD after 3 mo
59/M	M1:PA LN	5	PR	M1:peritoneum	PD after 3 mo
61/M	LA:GC LN	4	PR	NED	NED for 66 mo

GC greater curvature, *F* female, *HD* hepatoduodenal, *LA* locally advanced, *LN* lymph node, *M* male, *M1* metastasis, *mo* months, *NED* no evidence of disease/residual disease, *PA* paraaortic, *PD* progressive disease, *SC* supraclavicular

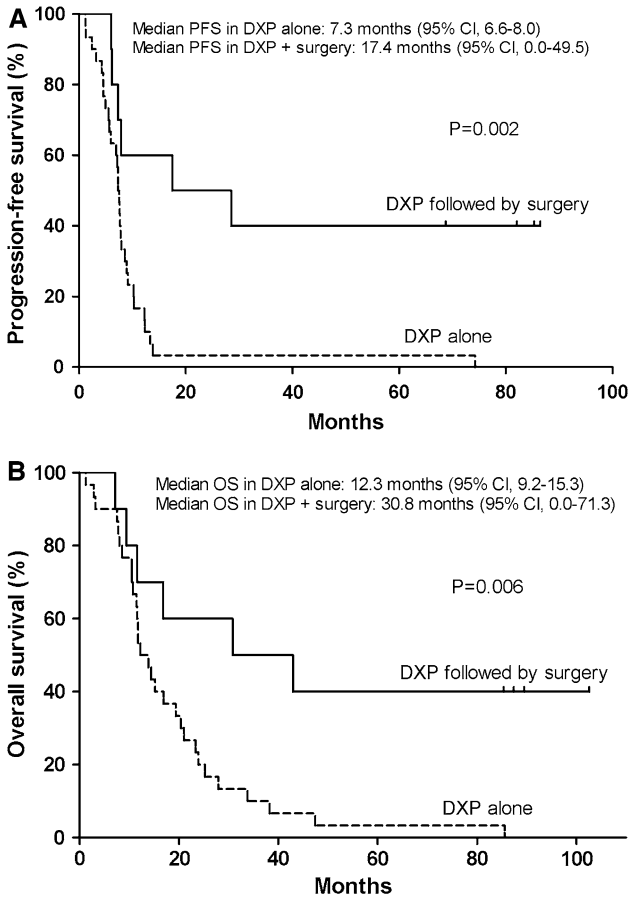

Fig. 2 Progression-free survival (**a**) and overall survival (**b**) in patients receiving DXP alone ($n = 30$) and DXP followed by surgery ($n = 10$)

be effectively replaced with capecitabine, similar to the case of epirubicin-cisplatin-fluorouracil (ECF) [21].

Despite the more severe toxicity profile of DXP than XP in terms of grade 3/4 neutropenia (62.5 vs. 32.5%) and neutropenic fever (10 vs. 0%) [14], the DXP regimen presented more favorable hematologic toxicity compared with the DCF regimen. Specifically, grade 3/4 neutropenia was observed in 62.5% and neutropenic fever in 10% patients, compared to 82 and 29% patients, respectively, in the V325 study with DCF [10]. This reduced risk of infection is of course attributed to reduced dose of docetaxel and cisplatin employed in DXP regimen. In addition to DXP, several regimens have been evaluated to improve the safety profile and maintain the efficacy of DCF, including the use of oral fluoropyrimidine or oxaliplatin for infusional fluorouracil or cisplatin, modified form of DCF at reduced dosages [24, 25], docetaxel-capecitabine-oxaliplatin (DXO) [26], and docetaxel-S1-oxaliplatin (DSO) [27].

Interestingly, compared to a previous study in which patients were administered XP alone [14], the higher response rate achieved in the present study by adding docetaxel to the XP regimen enabled a higher proportion of patients to undergo gastrectomy (25 vs. 5%). Although this was not a predefined objective of the phase II study, it is important to acknowledge the improved survival outcomes observed in the 10 patients who received DXP followed by surgery, compared with those administered DXP alone. Among these individuals, pathologic CR was achieved in 4 patients and long-term disease-free survival over 5 years in 4 patients (3 pathologic CR), implying cure of disease. Based on these findings, which strongly support the value of the DXP regimen in a neoadjuvant setting, we performed a phase II study involving DXP therapy for patients with locally advanced disease, isolated para-aortic lymph node, and limited peritoneal metastasis. In this study, a complete resection rate of 71% was found for patients with locally advanced disease who had been administered DXP [28]. Furthermore, a complete resection rate of 70% was obtained for patients with isolated para-aortic lymph node involvement (categorized as distant metastasis) who received DXP [28]. This result, together with previous findings indicating that patients with isolated para-aortic lymph node metastasis have a more favorable prognosis compared with those with metastases to other sites [28, 29], suggests that triplet regimens with high anti-tumor activity could be

Table 5 Adverse events in the phase II study ($n = 40$)

Adverse event	Grade 1		Grade 2		Grade 3		Grade 4	
	No. of patients	%	No. of patients	%	No. of patients	%	No. of patients	%
Hematologic toxicity								
Leukopenia	5	12.5	14	35.0	14	35.0	2	5.0
Neutropenia*	2	5.0	7	17.5	14	35.0	11	27.5
Anemia	14	35.0	20	50.0	4	10.0	0	0.0
Thrombocytopenia	6	15.0	6	15.0	3	7.5	0	0.0
Non-hematologic toxicity								
Asthenia	7	17.5	16	40.0	15	37.5	0	0.0
Nausea	18	45.0	12	30.0	5	12.5	0	0.0
Vomiting	9	22.5	10	25.0	7	17.5	0	0.0
Stomatitis	13	32.5	17	42.5	3	7.5	0	0.0
Diarrhea	21	52.5	9	22.5	1	2.5	0	0.0
Constipation	10	25.0	10	25.0	7	17.5	0	0.0
Neuropathy	15	37.5	9	22.5	4	10.0	0	0.0
Hand-foot syndrome	21	52.5	11	27.5	1	2.5	0	0.0
Nail toxicity	10	25.0	11	27.5	0	0.0	0	0.0
Edema	11	27.5	5	12.5	0	0.0	0	0.0
Abdominal pain	3	7.5	8	20.0	5	12.5	0	0.0

* Neutropenia includes neutropenic fever (10%)

recommended for this patient group with locally advanced tumor or isolated paraaortic lymph node metastasis at the expense of the associated toxicities.

At present, the issue of whether the DXP triplet regimen is more effective than the fluoropyrimidine-platinum doublet regimen for the general AGC population in a palliative setting is unclear, because DXP presents considerable disadvantages in terms of safety. A previous phase II study shows that docetaxel is effective in patients displaying treatment failure outcome with a fluoropyrimidine and platinum combination regimen (disease control rate of 57.1%, median TTP of 2.5 months, and median OS of 8.3 months) [30]. Thus, one reasonable option may be to reserve docetaxel for patients who fail to respond to doublet therapy. Sequential treatment (i.e., XP → docetaxel) may compensate for the inferior activity of the doublet and reduce safety concerns, compared to the triple combination regimen. In view of the large numbers of patients receiving second-line chemotherapy in Asian countries, particularly Korea [31] and Japan [32], this approach may be more suitable for this geographic area, compared with Western countries. However, this proposal should be considered cautiously, as to date no studies have compared the triple combination and sequential therapies.

On the other hand, in the era of targeted therapy, the ToGA trial disclosed significantly improved outcomes in HER2-overexpressing gastric cancer [33]. Moreover, several clinical trials on targeted agents are ongoing for AGC [34]. Current trials selectively focus on doublet regimens as partners for targeted agents, mainly due to possible additional toxicities. However, DXP as well as other triplets may be useful as combination regimens with targeted agents in a neoadjuvant setting, which requires greater activity for downstaging.

The recommended dose of DXP regimen, which was originally defined in phase I part, was modified right after phase I and during phase II study, because of cumulative toxicities during subsequent cycles such as asthenia and neutropenic fever. This modification was inevitable to maintain the relative dose intensities of chemotherapy and treatment compliance. The efficacy and tolerability of DXP dose, which was finally determined in this study, was verified in the other phase II study [28]. Because phase I studies usually define MTD after first cycle of chemotherapy, cumulative toxicities which limit tolerability during whole treatment period might not be definite at this point. Therefore, this should be considered in conducting the phase I dose-finding study. Based on this experience, we assessed toxicities of first two treatment cycles for determination of MTD in several phase I studies [26, 35].

In conclusion, data from our phase I/II study strongly suggest that DXP is an active regimen that can be effectively applied as first-line treatment for advanced gastric cancer. However, further clinical trials to evaluate the efficacy and safety of this regimen in both first-line therapy and the neoadjuvant setting are clearly warranted.

Conflict of interest Yoon-Koo Kang: Consultant for Roche and Sanofi-Aventis and honoraria for Roche and Sanofi-Aventis.

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