RESEARCH ARTICLE

Modified Docetaxel and Cisplatin in Combination with Capecitabine (DCX) as a First-Line Treatment in HER2-Negative Advanced Gastric Cancer

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Abstract

<u>Background</u>: Docetaxel and cisplatin in combination with fluorouracil (DCF) regimen is accepted to be one of the standard regimens in the treatment of advanced gastric cancer. However, substantial toxicity has limited its use in daily clinical practice. Therefore, modification of DCF regimens, including introduction of capecitabine has been investigated to improve the safety profiles. In the present study, the efficacy and toxicity of a regimen with a modified dose of docetaxel and cisplatin in combination with oral capecitabine (DCX) was evaluated in untreated patients with HER2-negative advanced gastric cancer. <u>Materials and Methods</u>: Fifty-four patients with HER2-negative locally advanced or metastatic gastric cancer were included in this cohort. Patients received docetaxel 60 mg/m2 plus cisplatin 60 mg/m2 (day 1) combined with capecitabine 1650 mg/m2 (days 1–14) every 3 weeks. Treatment response, survival, and toxicity were retrospectively analyzed. <u>Results</u>: The median age was 54 years (range: 24–76). The majority of patients (70%) had metastatic disease, while 11 patients (21%) had recurrent disease and underwent curative gastrectomy, and 5 patients (9%) had locally advanced disease (LAD). The median number of DCX cycles was 4. There were 28 partial responses and 11 complete responses, with an overall response rate of 72%. Curative surgery could be performed in four patients among five with LAD. At the median follow-up of 10 months, the median progression-free survival (PFS) and overall survival (OS) of the entire cohort of patients were 7.4 and 12.1 months, respectively. Dose modification was done in 12 patients due to toxicity in 8 and noncompliance in 4 patients. The most common hematological toxicity was neutropenia, which occurred at grade 3-4 intensity in 10 of 54 patients (27.7%). Febrile neutropenia was diagnosed only in two cases. <u>Conclusions</u>: DCX regimen offers prominent anti-tumor activity and considered to be effective first-line treatment with manageable toxicity for patients with HER2-negative advanced gastric cancer.

Keywords: Docetaxel - cisplatin - capecitabine - advanced gastric cancer - HER2-negative - first-line chemotherapy

Introduction

Despite improvement in the diagnosis and treatment of gastric cancer, it is the second most common cause of cancer death worldwide and remains a major health problem (Crew and Neugut, 2006; Siegel, 2013). Two-thirds of patients present with inoperable locally advanced or metastatic disease at diagnosis as well as local and distant recurrence after curative gastrectomy. In this setting, prognosis is only a few months and systemic palliative chemotherapy or best supportive care (BSC) are the only options for these patients. Although palliative chemotherapy including fluoropyrimidine, platinum compounds, docetaxel, and epirubicin prolongs survival and improves quality of life compared with BSC, no standard palliative chemotherapy regimen has been accepted for patients with advanced gastric cancer (AGC) (Field et al., 2008; Wager et al., 2010).

Single agents provide low response rates of 20-30% and short survival time. Therefore, many trials have investigated the efficacy of combination chemotherapy including known and novel cytotoxic agents (Wagner et al., 2006). After the efficacy of the combination of cisplatin plus fluorouracil (CF) was confirmed in phase III trials, this regimen has been considered the standard reference regimen for patients with AGC, with a better response rate and survival times compared with older regimens (Vanhoefer et al., 2000; Kim et al., 1993). Thereafter, the randomized multinational phase III V325 trial evaluated the combination of docetaxel with CF regimen (DCF) in patients with untreated AGC against the reference CF regimen (Van Cutsem et al., 2006). The DCF arm

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showed statistically superior time-to-progression (TTP; 5.6 months *vs* 3.7 months; p<0.001). Moreover, the median overall survival (OS) time was significantly worse for patients who received CF compared with patients who received DCF (8.6 months *vs* 9.2 months, respectively; p=0.02). However, high toxicity rates were reported in the DCF arm (82% grade 3-4 toxicity), such as febrile neutropenia (29% *vs* 12% in CF), and this toxicity profile has limited the use of DCF regimen in daily clinical practice. As the DCF regimen has been associated with high toxicity profiles, several clinical trials have tested modifications of the DCF regimen utilizing capecitabine and dose modifications , with the aim of reducing toxicity and improving tolerability (Koizumi et al., 2003; Ozdemir et al., 2010; Kang et al., 2011; Kos et al., 2011; Polyzos et al., 2012; Alici et al., 2013). In addition, substitution of capecitabine, an orally administered fluoropyrimidine, for the continuous infusion of fluorouracil prevents the inconvenience of additional cost and morbidity with no negative impact on efficacy and safety in both early and advanced gastric cancer (Hong et al., 2004; Kang et al., 2009: Yoney and Isikli, 2013).

Kang et al. (2009) compared the combination of cisplatin and capecitabine (CX) with CF in AGC patients in the first-line setting in ML17032 trial. They showed that both response rate and median OS time were superior for patients treated with the CX regimen [overall response rate (RR): 41% *vs* 29%; OS: 10.5 *vs* 9.3 months], although the median progression-free survival (PFS) time was found to be similar for both regimens. A recent meta-analysis of the REAL-2 (Cunningham et al., 2008) and ML17032 trials demonstrated that OS was superior in the 654 patients who received capecitabine-based regimens compared with the 664 patients treated with fluorouracil-based combinations, but there was no significant difference between treatment groups with respect to PFS (Okines et al., 2009).

The number of clinical investigations utilizing targeted agents has recently increased. Trastuzumab was the first targeted drug developed, and pivotal phase III trials showed improved overall survival when trastuzumab was integrated into cisplatin/fluoropyrimidine-based chemotherapy in patients with HER2-positive AGC (Bang et al., 2010). In this current study, we aimed to evaluate the efficacy and toxicity of a modified dose docetaxel and cisplatin in combination with capecitabine (DCX), in chemotherapy-naïve patients with HER2-negative AGC.

Materials and Methods

Between 2011 and 2013, a total of 54 patients with previously untreated and histologically confirmed locally advanced or metastatic gastric cancer as well as local or distant relapses after radical surgery were retrospectively analyzed. Eligibility criteria were patients with HER2-negative disease, a life expectancy of at least 3 months, age >18 years, Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0-2, absolute neutrophil count >1500 mm3, platelet count >100,000 mm3, adequate hepatic (total serum bilirubin <1.5 times the upper normal limit [UNL]; ALT, AST <2.5 or <5 times the UNL in patients with liver metastasis) and renal function (serum creatinine level <1.25 mg/dl or creatinine clearance >60 ml/min), and having had no previous chemotherapy except for adjuvant treatment. Patients who had received prior treatment with taxanes or a platinum compound, had known hypersensitivity to a platinum, HER2-positive disease (immunohistochemistry [IHC] score 3+ or score 2+ and FISH-positive), central nervous system involvement, were pregnant or lactating, had active serious infections, or intestinal obstruction were excluded from the study. Patients with a history of other malignancies except for basal cell skin carcinoma or in situ carcinoma of the uterine cervix were not included. The Ethics Committees of participating centers approved the study.

Clinical information of the patients such as age at diagnosis, gender, performance status, and other histological parameters such as tumor stage, histopathological type, the presence of resection and resection type, primary tumor location, initial tumor stage at diagnosis, treatment with primary adjuvant chemotherapy and radiation therapy, primary metastatic sites, responses to treatment, and survival were obtained from patients' charts after informed written consent was obtained from each subject included in the study.

Treatment plan

Patients received the chemotherapy regimen on an outpatient basis. The DCX regimen consisted of docetaxel 60 mg/m^2 as a 1-hour i.v. infusion plus cisplatin 60 mg/m2 as a 1-hour i.v. infusion on day 1, followed by oral capecitabine 1650 mg/m^2, divided into two daily doses on days 1-14 of the cycle. DCX was administered every 3 weeks for a maximum of nine cycles, unless there was disease progression, unacceptable toxicity, or patient refusal. The patients received premedication with dexamethasone 16 mg i.v., diphenhydramine 50 mg i.v., and granisetron 3 mg i.v. on day 1 and aprepitant on days 1-3 to prevent emesis of each chemotherapy course. Before and after cisplatin infusion, hydration was administered with an i.v. infusion of 1000 ml sodium chloride 0.9% with 30 mmol potassium chloride and 18 mmol magnesium sulfate. An oral dose of dexamethasone 8 mg was given at 24 hours before and 24 and 48 hours after infusion for prevention of docetaxel hypersensitivity and fluid retention. Granulocyte colony-stimulating factor (G-CSF) was not routinely given, but it was used for secondary prophylaxis and in subsequent courses if severe neutropenia or febrile neutropenia developed.

Toxicity evaluation and dose modifications

During treatment, toxicity was defined as hematological or non-hematological and was graded as 1 to 4 based on the National Cancer Institute Common Toxicity Criteria (NCI-CTC) Version 3.0 at all visits. Required dose modifications were performed if grade 2-4 toxicity occurred. Both docetaxel and cisplatin were reduced by 25% for grade 4 hematological toxicity and grade 2 or higher neuropathy. The dose of cisplatin was reduced by 25% in the event of grade 2 nephrotoxicity. In addition, capecitabine was also reduced by 25% for grade 3 toxicity. A treatment delay of up to 1 week was permitted without dose reduction.

Patient assessments

The initial evaluations included a complete medical history, physical examination, complete blood count (CBC), and hepatic and renal function tests. Moreover, baseline tumor evaluations were performed using abdomino-pelvic CT or MRI scans and chest X-ray or CT scan of the chest. Additional investigations including bone scan and MRI scan of the brain were carried out if clinically indicated in metastatic disease. CBC and blood chemistry were monitored at each cycle and CBC was also assessed on a weekly during cycles. During treatment, imaging modalities were repeated after every two courses and at the end of treatment. Treatment responses were evaluated according to RECIST criteria (Eisenhauer et al., 2009). ORR was defined as a complete response (CR) plus partial response (PR).

Statistical analysis

All data were analyzed using SPSS 17.0 (SPSS Inc., Chicago, IL, USA) software. Survival analysis and curves were established according to the Kaplan-Meier method and compared by the log-rank test. Progression-free survival (PFS) was defined as the time from initiation of treatment to the progression of disease, or to the date of death or loss to follow-up. OS was described as the time from initiation of DCX chemotherapy to the date of the patient's death or loss to follow-up. The 95% confidence interval (CI) was used to quantify the relationship between survival time and each independent factor. All p values were two-sided in tests and p values less than 0.05 were considered to be statistically significant.

Results

Patient characteristics:

Sixteen patients (30%) were female and 38 (70%) were male, with a median age of 54 years (range: 24-76 years). The majority of patients were categorized as ECOG PS 1 (74%). Radical gastrectomy had been performed with curative intent in 11 (20%) patients, while 10 patients (19%) underwent palliative surgery. According to the extent of disease, 38 patients (70%) presented with metastatic disease, 11 (20%) patients were classified as recurrent disease after curative surgery, and 5 (10%) as locally advanced disease (LAD). A total of 13 patients (24%) had received adjuvant chemoradiotherapy with 5-fluorouracil 425 mg/m2 per day plus leucovorin 20 mg/m2 per day for five days, followed by 4500 cGy of radiation at 180 cGy per day, given 5 days per week for 5 weeks, with modified doses of fluorouracil and leucovorin on the first 4 and the last 3 days of radiotherapy, within 4 weeks after surgery. Nevertheless, seven patients had received only adjuvant radiotherapy. Most of the patients had liver (48%), abdominal lymph node (39%), and peritoneal metastases (37%). The patient baseline characteristics are listed in Table 1.

Treatment efficacy

Totally, 254 DCX cycles were administered with a median number of 4 cycles (range: 3-9). All patients were eligible for response evaluation. Twenty-eight (52%)

patients had a PR and 11 had a CR, resulting in an ORR of 72%. Four patients (8%) had stable disease (SD), while progressive disease (PD) was detected in 11 of 54 patients (20%). Curative surgery could be performed in four patients among the five with LAD who achieved a CR after DCX chemotherapy.

Table 2 shows the results of antitumor efficacy analysis of patients treated with the DCX regimen. At the median follow-up of 10 months (range: 3-39.5 months), the 1-year PFS rate and median PFS interval were 30.5% and 7.4 months, respectively (Figure 1). Moreover, median OS time and 1-year OS rate were 12.1 and 50.7%, respectively for the entire cohort of patients (Figure 2). Curative surgery could be performed in four patients among the five with LAD who achieved a CR after DCX treatment. Following surgery, pathological CR was obtained in only two patients who are still surviving, for a median of 34 and 11 months, without evidence of disease. However, the remaining two patients underwent radical surgery after recurrence, and were treated with second-line chemotherapy.

When survival analysis was performed according to the extent of disease, 1-year PFS and OS times for patients with LAD were better than that of patients with recurrent or metastatic disease (PFS; 100% *vs* 47.7% *vs* 29.8%; OS: 100% *vs* 57.7% *vs* 50.7%, respectively), but these differences were not significant (p=0.24 and 0.20,

Table 1. Initial Patient Characteristics

Characteristic		n (%)
Median age, years		54
Range		24-76
Gender	Female	16 (30)
	Male	38 (70)
ECOG PS	0	4 (8)
	1	40 (74)
	2	10 (18)
Tumor site	Upper	16 (30)
	Middle	19 (35)
	Lower	15 (28)
	Diffuse	4 (7)
Extent of disease	Metastatic	38 (70)
	Recurrent	11 (20)
	Locally-advanced	5 (10)
Previous surgery	Radical gastrectomy	11 (20)
	Paliative surgery	10 (19)
	No surgery	33 (61)
Adjuvant treatment	Chemotherapy	13 (24)
	Radiotherapy	20 (37)
Site of metastasis	Liver	26 (48)
	Lung	6 (11)
	Bone	2 (3.8)
	Cervical lymph node	3 (5.7)
	Abdominal lymph nodes	21 (39)
	Peritoneum	20 (37)
	Ovarium	1 (1.9)

*ECOG, Eastern Cooperative Oncology Group; PS, performance status

Table 2. Antitumor Efficacy analysis of Patients with AGC Received DCX Regimen

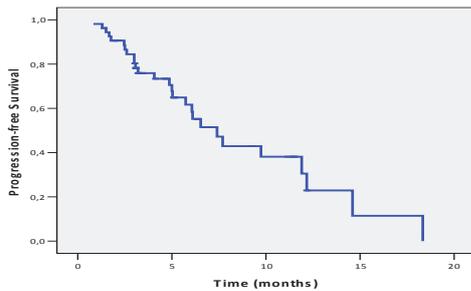|	No. of patients	%
Overall response	39	72
Partial response	28	52
Complete response	11	20
Stable disease	4	8
Progressive disease	11	20

*AGC, advanced gastric cancer

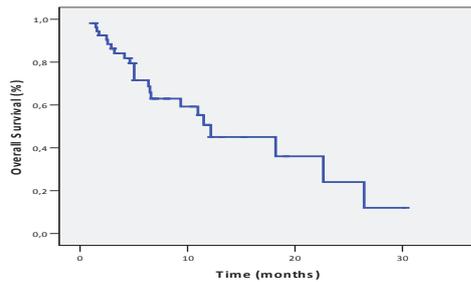**Figure 1. Progression-Free Survival Curve for Entire Cohort**

Figure 2. Overall Survival in Advanced-Gastric Cancer Patients Treated with the DCX Regimen

Table 3. Toxicity Types Associated with DCX Chemotherapy

Toxicity	Grade 1 n (%)	Grade 2 n (%)	Grade 3-4 n (%)
Non-hematologic toxicities			
Asthenia	28 (52)	18 (33)	6 (11)
Nausea/vomiting	24 (44)	14 (26)	4 (7.5)
Diarrhoea	16 (29.5)	7 (13)	-
Hand-foot syndrome	23 (42.5)	10 (18.5)	2 (4)
Stomatitis	11 (20)	10 (18.5)	4 (7.5)
Alopecia	28 (52)	22 (41)	-
Loss of appetite	26 (48)	14 (26)	5 (9)
Taste changes	38 (70)	18 (33)	-
Neuropathy	17 (31)	7 (13)	-
Nephrotoxicity	8 (15)	-	-
Skin and nail changes	30 (55.5)	14 (26)	-
Hearing impairment	2 (4)	-	-
Edema	16 (29.5)	8 (15)	2 (4)
Hematologic toxicities			
Leukopenia	20 (37)	17 (31)	10 (18.5)
Neutropenia	18 (33)	13 (24)	15 (27.7)
Febrile neutropenia	-	-	2 (4)
Anemia	25 (46)	30 (55.5)	3 (5.5)
Thrombocytopenia	10 (18.5)	9 (16.5)	2 (4)

respectively).

Toxicity evaluation:

The most commonly reported non-hematological grade 3-4 toxicity was asthenia, loss of appetite, nausea/vomiting, and stomatitis, which occurred in 11, 9, 7.5, and 7.5% of patients, respectively. Treatment-related hand-foot syndrome (HFS) was frequently observed (64.8%), but only two of the patients had grade 3-4. On the other hand, neutropenia was the most frequently detected grade 3-4 hematological toxicity. Although 27.7% of patients suffered from grade 3-4 neutropenia, only two patients (4%) experienced febrile neutropenia, which was successfully treated with i.v. antibiotics and G-CSF,

with hospitalization. No death was observed because of neutropenic fever. Secondary prophylaxis with G-CSF was undertaken for patients who experienced grade 3-4 toxicity until completion of DCX treatment. Grade 3-4 anemia and thrombocytopenia occured only in 3 (5.5%) and 2 (4%) patients, respectively. The adverse events are summarized in Table 3. Dose modification was done in 12 patients, due to toxicity in 8, and noncompliance in 4. Interruption of treatment of up to 1 week due to grade 3-4 toxicity occurred in 14 patients (26%), but discontinuation of treatment because of unacceptable grade 3-4 toxicity did not occur.

Discussion

Palliative chemotherapy with several agents or combinations including fluorouracil, cisplatin, anthracyclines, and taxanes versus best supportive care (BSC) for patients with AGC has been evaluated in several clinical trials, which showed that palliative chemotherapy improved OS compared with BSC and resulted in response rates of 25-45% and median OS of 7-9 months (Pyrhonen et al., 1995; Glimelius et al., 1997; Wagner et al., 2006). However, no palliative chemotherapy regimen has been accepted standard for patients with AGC.

In the V325 phase III trial performed by Van Cutsem et al. (Van Cutsem et al., 2006), the combination of DCF was compared against the reference CF regimen in patients with untreated AGC. The DCF arm showed an overall disease control rate of 67%, with 2% CR,35% PR, and 30% SD. Meanwhile, the median TTP and OS times in patients who received DCF were significantly better than those of patients who received CF. However, high toxicity rates were reported in the DCF arm, including a 29% rate of complicated febrile neutropeniawhich has limited its use in daily clinical practice. Modifications of this triple regimen provided promising efficacy and improved the tolerability (Lorenzen et al., 2007; Ozdemir et al., 2010; Kos et al., 2011; Alici et al., 2013). Another modification is the introduction of capecitabine into the treatment regimen to replace continuous infusion of fluorouracil (Cunningham et al., 2008; Kang et al., 2009).

In our study, the efficacy and feasibility of the modified dose DCX regimen were investigated in untreated patients with HER2-negative AGC. We found that the DCX regimen had prominent anti-tumor activity in the first-line setting for patients with HER2-negative AGC. Moreover, our results showed that the DCX regimen provided good efficacy, with an ORR of 72%, median PFS of 7.4 months, and median OS of 12.1 months. The DCX regimen provided an improvement in both the response rate and OS in our study compared with previous results on the CX doublet regimen (72 *vs* 55% and 12.1 *vs* 10.1 months, respectively) (Kang et al., 2009), indicating a contribution by docetaxel. Recently, an incremental improvement in OS has been confirmed in patients who received capecitabine-based regimens compared with patients treated with fluorouracil-based combinations by meta-analysis (Okines et al., 2009). As such, the efficacy results of the present study were superior to those of the V325 study (Van Cutsem et al., 2006) with respect to ORR

(72 *vs* 39%) and OS (12.1 *vs* 10.2 months).

Polyzos et al. reported in their phase II study that a PR in 16 patients and SD in 12 patients were obtained with a modified DCX regimen in 36 patients with metastatic gastric cancer, resulting in an overall disease control rate of 78% (Polyzos et al., 2012). However, a CR could not be achieved with the DCX regimen and the median TTP and OS were found to be 5 and 12 months, respectively.

In a phase I/II study carried out by Kang et al., the authors aimed to determine the optimal dosage of the DCX regimen and investigated its efficacy in patients with AGC. In a phase II part of study in 40 patients, 4 CR and 23 PR were detected, providing an ORR of 68%. In addition, ten patients with good response had undergone surgery and four pathological CR were found. The median OS and PFS times were found to be 14.4 and 7.6 months, respectively (Kang et al., 2011).

Efficacy results of our study are thus compatible with the literature. However, we used low dose capecitabine (1650 mg/m2, days 1-14) to reduce toxicity and improve tolerability compared with these studies (1875 and 2000 mg/m^2, respectively, days 1-14) (Kang et al., 2011; Polyzos et al., 2012). Despite the low dose of capecitabine, our patients' survival seem to be similar to those of previous trials, although it is difficult to make a comparison directly. The rate of recurrent patients who underwent curative gastrectomy was high in our study (27%). This may have influenced our patient survival.

The DCX regimen was previously investigated for patients with AGC in the neoadjuvant setting (Sym et al., 2010; Thuss-Patience et al., 2012). Sym et al. demonstrated that 34 of 49 patients underwent surgery and R0 resection could be achieved in 31 patients. R0 resection was possible in 71% of patients with unresectable LAD, 70% of patients with para-aortic lymph node metastasis, and 36% of patients with peritoneal metastasis (Sym et al., 2010).

A recent prospective phase II study assessed the feasibility and efficacy of perioperative DCX chemotherapy in 51 patients with gastric cancer or cancer of the gastro-oesophageal junction or the lower third of the esophagus (Thuss-Patience et al., 2012). Most patients (94.1%) received all three planned cycles preoperatively and 52.9% received three cycles postoperatively. The R0 resection rate was found to be 90.2% and in 13.7% of patients, pathological CR was achieved. Toxicity was acceptably tolerable without prophylactic G-CSF use. Thus, the authors concluded that DCX was a safe and feasible perioperative regimen in the treatment of gastro-oesophageal adenocarcinoma, with high efficacy in terms of R0 resection rate and pathological CR. In our study, four patients of the five with LAD who achieved CR after DCX treatment underwent curative gastrectomy. Following surgery, pathological CR was obtained in only two patients (50%). However, the remaining two patients who had undergone radical surgery experienced recurrence, but all four patients are still surviving. Our results are compatible with the literature (Sym et al., 2010; Thuss-Patience et al., 2012).

Because we included only patients with histopathologically confirmed HER2-negative disease, our study is unique compared to previous studies evaluating modified DCX regimens in AGC patients (Kang et al., 2011; Polyzos et al., 2012). In the era of targeted therapy, the number of clinical investigations associated with targeted agents has recently increased. Trastuzumab was the first targeted drug developed, and the Trastuzumab for Gastric Cancer (ToGA) trial, a pivotal randomized, prospective, multicenter, phase III clinical trial, evaluated the efficacy of anti-HER2 trastuzumab in combination with cisplatin/fluoropyrimidine-based chemotherapy in patients with HER-2-positive advanced, mostly metastatic gastric cancer (Bang et al., 2010). The ORR was significantly higher in the trastuzumab-containing arm (47% *vs* 35%) and the median OS was significantly longer in the trastuzumab-containing arm (13.8 *vs* 11.1 months). Furthermore, a pre-planned subgroup analysis showed that median OS was 16 months for patients whose tumours had high HER2 expression (IHC 2+ and FISH-positive or IHC 3+) in those assigned to trastuzumab plus chemotherapy compared with 11.8 months in those assigned to chemotherapy alone. Our ORR and OS rate are better than those of patients in both arms of the ToGA trial, even patients with high HER2 expression. In this trial, the rate of LAD and patients who had undergone previous gastrectomy were 3% *vs* 3% and 24% *vs* 21% for both arms, respectively. Although the rate of LAD in our study is similar to that of the ToGA trial, our rates of surgery (radical and palliative) are higher (39%) (Bang et al., 2010). In addition, four patients with LAD who achieved a CR had undergone curative gastrectomy. The comparable efficacy results of the present study may be related to the high rate of surgery and more tolerable DCX dosage, but our results require further confirmation in studies with a larger sample size.

In our study, the most common grade 3-4 adverse events were hematological toxicity, with neutropenia occurring in 15 patients (27.7%), but only two patients experienced febrile neutropenia. These patients were successfully treated in hospital. No toxic death was noted. Our modified DCX regimen seems to be tolerable compared with the reported high toxicity rates of V325 trial (Van Cutsem et al., 2006). Kang et al. reported that grade 3-4 neutropenia was detected in 62.5% of patients, with febrile neutropenia in 10% of patients who received the DCX regimen (Kang et al., 2011). On the other hand, in another study, grade 3-4 neutropenia and neutropenic fever were reported in 16.6% and 17% of patients, respectively with the DCX regimen (Polyzos et al., 2012). Thus, our results show much better tolerance compared with these trials. Unlike the present study, the dosage of capecitabine in these trials was 1875 and 2000 mg/m^2/day, respectively (Kang et al., 2011; Polyzos et al., 2012). This reduced myelotoxicity and risk of infection may be due to the reduced dose of capecitabine in our study.

The relative small sample size, short follow-up time and retrospective nature of this study are major limitations. These might have influenced our findings. To date, there is no study in the literature that has evaluated the efficacy and safety of a modified DCX regimen in patients with HER2-negative AGC. Although our results should be confirmed by prospective, randomized, phase III trials, we believe

that our study has made contributions to the literature because of the comparable efficacy and tolerability with previous studies (Van Cutsem et al., 2006; Kang et al., 2009; Kang et al., 2011; Polyzos et al., 2012)

In conclusion, the DCX regimen offers pronounced anti-tumor activity with low toxicity making it to be considered an effective first-line treatment, for patients with HER2-negative AGC. Furthermore, capecitabine is also an effective and well-tolerated oral alternative to the continuous infusion of 5-fluorouracil, which requires placement of a central venous access device. Our results need to be confirmed by prospective and randomized studies in a large number of subjects and with different schedules of DCX in future.

Acknowledgements

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