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ORIGINAL ARTICLE

Capecitabine and doxorubicin combination chemotherapy as salvage therapy in pretreated advanced gastric cancer

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Abstract
Purpose The aim of this study was to evaluate the activity and the safety of a combination regimen of capecitabine and doxorubicin as salvage chemotherapy in advanced gastric cancer patients who had undergone one or two prior chemotherapy regimens.
Methods Patients received capecitabine, 2,500 mg/m^2/day PO for 14 days (D1–14) and doxorubicin, 30 mg/m^2 IV on day 1 every 3 weeks until disease progression. The response was evaluated according to RECIST criteria, and the toxicity was evaluated by NCI-CTC (version 2.0).
Results Forty-five patients were enrolled. Twenty-six patients were treated as second-line chemotherapy and the remaining patients as third-line chemotherapy. A total of 152 cycles of chemotherapy (median 2, range 1–12) were administered. Median dose intensities of capecitabine and doxorubicin were 11,326 and 9.6 mg/m^2/week, respectively. The overall response rate was 6.7% (95% CI, 4.1–12.5%) and the disease control rate was 46.7% (95% CI, 28.6–87.1%) according to an intent-to-treat analysis. The median progression-free survival was 11.3 weeks (95% CI, 5.6–16.7 weeks). The median overall survival was 29.1 weeks (95% CI, 18.3–39.9 weeks) with one-year survival rate of 24%. Severe (grade III/IV) hematologic and non-hematologic toxicity was uncommon and included nausea/vomiting in five (11.1%), neutropenia in two (4.4%), anemia in one (2.2%), and hand-foot syndrome in one patient (2.2%).
Conclusions The combination of capecitabine and doxorubicin is a feasible salvage regimen in advanced pretreated gastric cancer.

Keywords Stomach cancer · Capecitabine · Doxorubicin · Salvage regimen · *MDR1* gene · Polymorphism

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Introduction

Despite the recent decline of mortality of gastric cancer, it ranks second in global cancer mortality behind lung cancer [1] because gastric cancers are either diagnosed at an advanced stage or recur after apparently curative surgery. Apart from supportive measures, systemic chemotherapy is the only treatment option available in this situation [2].

When patients receiving chemotherapy eventually develop progressive disease, 20% of them move on to salvage chemotherapy. However, prognosis of these patients is generally poor. Despite this being a common clinical scenario, there is no effective salvage chemotherapy against refractory advanced gastric cancer. Wilson et al. [3] reported that there are four options in selecting the second-line chemotherapy. These are platinum, taxane, 5-FU/anthracycline, and irinotecan-based regimens. However, such drugs (taxanes, irinotecan, oxaliplatin) are being primarily tested for first-line treatment of gastric cancer.

Doxorubicin produced overall responses in 17% of patients with gastric cancer when given as monotherapy [4]. A combination with 5-FU and doxorubicin showed a response rate of 36%, a rate three times higher than the 13% attributed to 5-FU alone in a small-randomized trial [5]. Capecitabine demonstrated activity in first-line treatment as a

single agent [6], and has been reported to yield a promising response rate in combination treatment [7]. Because the selective production of 5-FU in tumor tissue after capecitabine administration reduces the exposure of healthy body tissue to systemic 5-FU, this regimen could potentially improve the therapeutic index and could thus be safer and more effective than intravenous infusion of 5-FU [8].

In addition, the P-gp encoded by the *MDR1* gene plays an important role in multidrug resistance by impairing the intracellular retention of anticancer drugs including anthracycline [9]. There have been several studies showing that chemotherapy response is related to the polymorphisms of the *MDR1* gene in esophageal cancer, small cell lung cancer, breast cancer and ovarian cancer [10–13]. The SNPs 2677 G > T/A and 3435 C > T have been considered most interesting because they have been shown to correlate with the P-gp expression and cancer therapy [11, 13].

Considering the anti-tumor activity, toxicity and convenience of capecitabine and doxorubicin, we have decided to investigate the efficacy and tolerability of an XA regimen in patients with advanced gastric cancer, who have received one or two prior chemotherapy regimens. Furthermore, we conducted correlative study to evaluate the effect of the *MDR1* gene 2677 G > T/A and 3435 C > T on clinical outcomes to XA treatment in advanced gastric cancer.

Patients and methods

Eligibility criteria

The patients were entered into the trial based on the following inclusion and exclusion criteria. The patients needed to be histologically confirmed gastric adenocarcinoma that had progressed during or after prior one or two chemotherapy regimens. Patients had to be ≥18 years of age, have an Eastern Cooperative Oncology Group (ECOG) performance status ≤2 and a life expectancy >3 months. Laboratory criteria included an absolute granulocyte count ≥1,500 cells/mm^3, platelets ≥100,000 cells/mm^3, hemoglobin ≥9 g/dl, serum creatinine ≤2 mg/dl, bilirubin ≤1.5 mg/dl and transaminases ≤3 times the upper limit of normal. Patients were excluded from the study if they had concurrent cancer, known history of heart problems (e.g., uncontrolled or symptomatic angina, arrhythmia or congestive heart failure), previous use of anthracycline related to the present gastric cancer, brain metastasis or an uncontrolled significant comorbid condition. An institutional review board approved the trial protocol and the clinical trial was carried out in accordance with the Good Clinical Practice guidelines. All patients had to give their written informed consent in order to participate in the study.

Treatment plan

All treatments were administered on an outpatient basis, using standard premedication. Capecitabine was administered at the dosage of 2,500 mg/m^2/day for days 1–14 of a 21-day cycle. Doxorubicin was given as an intravenous bolus at a dose of 30 mg/m^2 once every 3 weeks. All patients received prophylactic antiemetic therapy prior to administration of doxorubicin. Granulocyte colony stimulating factor (G-CSF) was not planned as a prophylactic aim. However, if hematological toxicity occurred (grade ≥ 3), the next cycle was delayed weekly with G-CSF support until neutrophil counts >1,500/μl and platelet counts >100,000/μl were reached. The dose of capecitabine and doxorubicin was reduced by 20% in cases of febrile neutropenia, grade 4 hematologic toxicity, or grade 3 or 4 non-hamatologic toxicity. In addition, the dose of capecitabine for Hand–Foot Syndrome (HFS) was adjusted as follows: a 20% reduction for grade 2 and a 40% reduction for grade 3 HFS. Once a dose reduction had been made, this continued for all subsequent cycles. Any patient who required more than 3 weeks to recover from adverse reactions except alopecia was taken out of the study. Toxicity and adverse events were reported according to NCI-CTC (version 2.0) after each cycle.

Response evaluation

For each patient, baseline evaluations included a complete medical history with physical examination, complete blood count, serum chemistries, tumor markers, urine analysis, and electrocardiography. A computed tomography (CT) scan of the measurable lesions was done within 4 weeks prior to the treatment. Fiberoptic gastroduodenoscopy was planned for examination of cases of complete remission (CR) of all measurable lesions.

During treatment, patients were evaluated by a weekly complete blood count. Physical examination, performance status, tumor markers and serum chemistries were recorded prior to each subsequent cycle. Imaging studies were repeated every two cycles. Treatment response was evaluated according to the guidelines of the Response Evaluation Criteria in Solid Tumors (RECIST) Committee. Patients were considered to be assessable for response if they had evidence of early disease progression clinically or radiologically within two cycles, or if they had received a minimum of two cycles of treatment with at least one tumor measurement. A measurable lesion was defined as one that could be accurately measured in at least one dimension with the longest diameter ≥20 mm using conventional techniques or ≥10 mm using spiral CT scan. Patients with small lesions below the limitations for measurable disease (i.e., longest diameter <20 mm with conventional techniques or <10 mm

with spiral CT) were categorized as evaluable but with a non-measurable disease. Patients who had a primary gastric lesion as the only non-evaluable lesion were excluded. We recorded tumor markers (CEA, CA 19-9) at the point of response evaluation and compared them to the radiological tumor response.

The primary efficacy endpoint of this study was the overall response rate. The secondary treatment endpoints were progression-free survival (from the onset of the treatment to the date of disease progression or death), overall survival (from the start of treatment until death) and toxicity.

Correlative study

Peripheral blood mononuclear cells (PBMCs) were isolated from blood using Ficoll-Paque (Pharmacia, Uppsals, Sweden) following the manufacturer's instructions. Genomic DNA (gDNA) from lymphocytes was extracted with the LaboPass™ Blood kit (Genotein Biotech. Korea). gDNA from each cell line was extracted with a phenol/chloroform method. Extracted gDNA amplified by PCR using an Eppendorf Mastercycler Gradient (Brinkmann Instruments, Inc. USA). PCR reactions were performed in a total volume of 50 µl containing 0.2 µg gDNA, 4 µl 2.5 mM dNTP mix, 5 µl 10× reaction buffer with 15 mM $MgCl_2$, 1 µl DNA *Taq* polymerase (5U, Super-Bio Co, Ltd. Korea), and 2 µl 20 pmol/µl forward and reverse primers. PCR cycling was done with an initial denaturation at 95°C for 2 min followed by 30 cycles of denaturation at 94°C for 30 s, annealing at 57°C for 20 s, and extension at 72°C for 30 s. After 30 cycles, a final extension was carried out at 72°C for 2 min. Forward (F) and reverse (R) primers were designed on the basis of target genes sequence obtained from the GenBank. *MDR*1 2677 G > T/A: 5′-ATTGCAA TAGCAGGAGTTGT-3′ (F), 5′-CTGGCTTTGCTACT TTCTGT-3′ (R); 3435 C > T: 5′-ACAATTATGACCTT GTTGGG-3′ (F), 5′-TTCTCTTCACTTCTGGGAGA-3′ (R). PCR products were purified using the PCR Clean-Up Kit (GENEMED, Inc., Korea).

Sequencing of PCR products was performed according to the manufacturer's instruction using the CEQ 8000 Dye Terminator Kit (CEQ™ 8000 Beckman Coulter, Inc., USA). For dye-terminator cycle sequencing, a total of 2.0 µl of PCR product was used as the sequencing template. One microliter of 100 pmol sequencing primer (same as PCR primer) and 9.1 µl DTCS premix (1.5 µl 10× sequencing reaction buffer, 0.75 µl dNTP mix, 1.5 µl each ddUTP, ddGTP, ddCTP, ddATP Dye Terminator, and 0.85 µl DNA polymerase enzyme) were added to the template, and finally, distilled water was added to adjust the total reaction volume to 15 µl. Sequencing reactions were subjected to 30 cycles of 96°C for 20 s, 53 or 51°C for 20 s, and 60°C for 4 min. DTCS premix was removed by ethanol precipitation, and then ethanol was completely eliminated by vacuum. The final products were dissolved in 40 µl Sample Loading Solution (CEQ™ Dye Terminator cycle sequencing kit, Beckman Coulter, Inc., USA). The samples were transferred to a polypropylene sample plate and covered with mineral oil, which was then loaded on the CEQ™ 8000 genetic analysis system for fluorescence detection. Sequence data were analyzed and compared using GeneDoc system (http://www.psc.edu/biomed/genedoc).

Statistical analysis

Statistics were performed using the SPSS 11.5 program (SPSS, Chicago, IL, USA). Based on the most conservative assumption of a 10% response rate (null-hypothesis) in historic controls with advanced gastric cancer, an increase to 25% or more (alternative hypothesis) could be shown with a power of 80% by investigating a sample size of at least 40 patients ($\alpha = 0.05$, Fleming's single step procedure for phase II trials). Forty-five patients were actually analyzed with a drop rate of 10%. Descriptive methods were used for the analysis of all the study variables. Survival curves were estimated using the Kaplan–Meier method and the differences in survival between the groups were assessed by a log-rank test. Univariate and multivariate analyses were performed using a Cox regression analysis model to identify prognostic factors and the risks associated with them.

The Hardy–Weinberg equilibrium of alleles at individual loci was tested with a goodness-of-fit χ^2 test with 1 *df* to compare the observed genotype frequencies with the expected genotype frequencies among the subjects. Haplotypes and their frequencies were estimated based on the Bayesian algorithm using the Phase program, which is available at http://www.stat.washington.edu/stephens/phase.html.

Results

Patient characteristics

From October 2003 to April 2006, a total of 45 patients were enrolled, and 43 patients were evaluable for tumor response. Two patients were excluded from the response evaluation because of follow-up loss after the first cycle. Patient characteristics are summarized in Table 1. The median age of 32 (71%) men and 13 (29%) women was 50 years (range 33–70 years), and the median ECOG performance status was 2 (range 1–2). Seventeen patients (38%) had received prior gastrectomy; 6 of them were treated with radical resection and the remaining 11 patients received palliative surgery due to distant metastasis. Nineteen patients had received two prior chemotherapies. The median number of cycles for the

Table 1 Patients' characteristics

Characteristic	No. of patients	Percentage
Number of enrolled patients	45	
Number of evaluable patients	43	
Number of patients with measurable lesion	39	
Sex		
Male	32	71
Female	13	29
Age (median), years	50 (33–70)	
ECOG		
0–1	18	40
2	27	60
Histology		
Well to moderately differentiated	15	33
Poorly differentiated	18	40
Signet ring cell	12	27
Previous chemotherapy		
1	26	58
2	19	42
Previous operation		
Unresectable	28	62
Radical	6	13
Palliative	11	25
Number of metastatic sites		
1	24	53
2	18	40
3	2	5
4	1	2
Disease site		
Lymph nodes	29	64
Peritoneum	11	24
Liver	15	33
Lung	3	7
Bone	1	2
Ovary	5	11

ECOG Eastern Cooperative Oncology Group

prior first-line chemotherapy was 5 (range 1–12) with a median dose intensity of 0.94 (Table 2). The median number of cycles for prior second-line chemotherapy was 4 (range 1–9) with a median dose intensity of 1. Most patients had received paclitaxel and docetaxel as components of combination chemotherapy and the others adopted a CPT-11, S-1, 5-FU based regimen as the first or second-line chemotherapy.

All patients had more than one metastatic lesion. The median number of metastatic sites per patient was 1 (range 1–4), and the main metastatic sites included the abdominal lymph node ($n = 29$), liver ($n = 15$) and peritoneum ($n = 11$).

Table 2 Summary of prior chemotherapy

Treatment group	No. of enrolled patients	Median cycle (range)	Median RDI (range)
First line	45		
Paclitaxel	15	6 (2–12)	0.94 (0.73–1)
Docetaxel	15	6 (2–12)	0.92 (0.6–1)
Others[a]	15	5 (1–12)	0.96 (0.6–1)
Second line	19		
Paclitaxel	11	4 (1–9)	1 (0.88–1)
Docetaxel	1	6	1
Others[b]	7	4 (2–4)	0.87 (0.7–1)

[a] Others: CPT-11/Cisplatin, Intraperitonial 5-FU/Cisplatin, S-1

[b] Others: CPT-11/Cisplatin, S-1

Treatment summary and dose intensity

A total of 156 cycles administered to 45 patients were assessable for toxicity (median 3, range 1–11 cycles). Total delayed weeks were 41 weeks (8.9%) and the median delay in week per cycle was 0 (range 0–0.5). In addition, dose modification for capecitabine and doxorubicin was required in 22 cycles. The cumulative percentage of patients who received chemotherapy is shown in Fig. 1. The percentage of patients declined rapidly after two cycles because of disease progress. Median dose intensities of capecitabine and doxorubicin were 11,326 mg/m^2/week (range 7,088–11,667 mg/m^2/week) and 9.6 mg/m^2/week (range 7.5–10 mg/m^2/week), respectively. The median relative dose intensities (RDI) of capecitabine and doxorubicin were 0.97 (0.61–1) and 0.96 (0.75–1), respectively. The median dose intensities and median RDI of capecitabine and doxorubicin were higher in second-line treatment than in third-line treatment due to performance status of patients (Table 3).

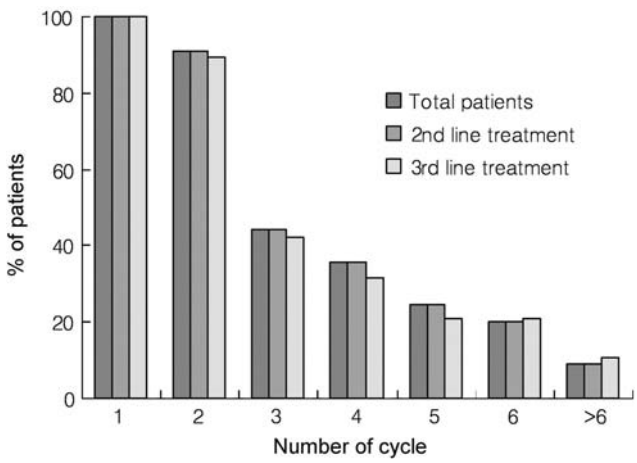

Fig. 1 Number of treated patients in each cycle

Table 3 Treatment summary and dose intensity

Treatment group		Total Patients (n = 45)	Second line (n = 26)	Third line (n = 19)
Treatment cycle	Median (range)	2 (1–11)	2 (1–9)	2 (1–11)
Treatment delay	Total cycle	156	91	65
	Delayed cycle	35	12	23
	Median delayed week	1 (1–3)	1 (1–2)	1 (1–3)
Number of dose modification (cycle)		22	9	13
Median dose intensity (range) mg/m^2/week	Capecitabine	11,326 (7,088–11,667)	11,667 (7,088–11,667)	10,816 (8,750–11,667)
	Doxorubicin	9.6 (7.5–10)	10 (7.6–10)	9.2 (7.5–10)
Median relative dose intensity (range)	Capecitabine	0.97 (0.61–1)	1 (0.61–1)	0.93 (0.75–1)
	Doxorubicin	0.96 (0.75–1)	1 (0.76–1)	0.92 (0.75–1)

Efficacy

A total of 42 patients were evaluable for response (26 in the second-line treatment group and 18 in the third-line treatment group). The overall response rates are summarized in Table 4. The median time to response was 5.4 weeks (range 4.9–11), and the median response duration was 12 weeks (range 4.1–12). Among the 26 second-line treatment patients, 24 patients had measurable lesions and three patients showed a PR. The ORR was 11.5% and disease control rate (DCR) was 42.3%. Of the 19 third-line treatment patients, 15 patients showed measurable lesions but there was no objective response. When the response rate was analyzed according to the metastatic sites, abdominal lymph nodes showed a relatively better overall response rate of 6.9% (Table 5).

Ten patients (22.2%) (six from the second-line treatment group, four from the third-line treatment group) received oxaliplatin-based treatment as a salvage regimen after disease progression occurred. The concordance rate between tumor response and tumor markers was only 44.4% for CEA, 48.9% for CA 19-9 and 57.7% for either, suggesting that these tumor markers were not good indicators of chemotherapeutic response with this regimen.

Table 4 Response evaluation (intent-to-treat analysis)

Response	Treatment group					
	No. of total patients (n = 45)		Second line treatment (n = 26)		Third line treatment (n = 19)	
	Measurable (39)	Non-measurable (6)	Measurable (24)	Non-measurable (2)	Measurable (15)	Non-measurable (4)
CR	0	0	0	0	0	0
PR	4	–	4	–	0	–
SD	15	3	8	2	7	1
PD	18	3	11	0	7	3
NA	2	0	1	0	1	0
ORR (%)	8.9%		16.7%		0%	
DCR (%)	48.9%		50.0%		36.8%	

ORR overall response rate, *DCR* disease control rate, *NA* not available

Table 5 Response evaluation by metastatic sites

Metastatic sites	No. of total sites	No. of evaluable sites	CR	PR	SD	PD	ORR (%)	DCR (%)
Lymph nodes	29	25	0	2	11	12	6.9	44.8
Peritoneum	11	11	0	0	7	4	0	63.6
Liver	15	15	0	1	6	8	6.7	46.7
Lung	3	3	0	0	1	2	0	33.3
Bone	1	1	0	0	0	1	0	0
Ovary	5	5	0	0	3	2	0	60

ORR overall response rate, *DCR* disease control rate

Survival

With a median follow-up duration of 21.7 weeks (95% CI, 13.0–30.3), 38 patients had disease progression, and 23 patients (60.5%) died. The median PFS for all patients was 11.3 weeks (95% CI, 5.6–16.7) (Fig. 2a); 12.1 weeks (95% CI, 5.5–18.7) for second-line treatment and 8.4 weeks (95% CI, 2.7–14.1) for third-line treatment.

The median OS for all patients was 29.1 weeks (95% CI, 18.3–39.9) (Fig. 2b); the OS was 35.1 weeks (95% CI, 19.6–50.6) for second-line treatment patients and 24.6 weeks (95% CI, 19.6–50.6) for third-line treatment. One-year survival rate of all patients was 24.0%; the survival rates for second and third-line treatments were 43.3 and 19.9%, respectively.

When we compared the survival profile according to clinical parameters, only ECOG performance status was found to be significant for progression-free survival and overall survival ($P = 0.032$ and $P = 0.025$, respectively) (Table 6).

Toxicity

The hematologic and non-hematologic toxicities are summarized in Table 7. Most adverse events were mild to moderate in scale and were managed through either dose interruption or reduction with optimal supportive care. No grade IV adverse events occurred in any of the patients. Only two patients experienced grade III neutropenia, and there were no febrile neutropenia and treatment-related deaths. Severe (grade III) non-hematologic toxicity was also rare and included nausea/vomiting, in five patients (11.1%), mucositis in three patients (6.7%), elevation of aminotransferase in two patients (4.4%) and HFS in one patient (2.2%).

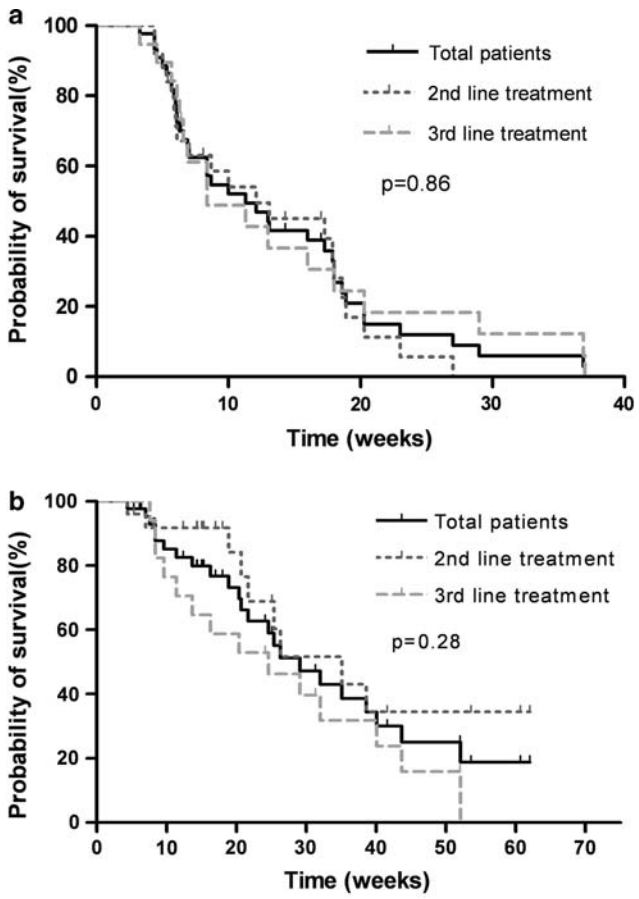

Fig. 2 Comparison of survival: progression-free survival (**a**) and overall survival (**b**)

Table 6 Prognostic factors influencing progression-free survival and overall survival

	Progression free survival	Overall survival
	Multivariate *P*-value	Multivariate *P*-value
Sex (male vs. female)	0.712	0.658
Age (<50 vs. ≥50)	0.658	0.145
ECOG (0, 1 vs. 2)	0.032	0.025
Histology (well and moderate vs. poorly and signet ring cell)	0.960	0.615
Previous chemotherapy (1 vs. 2)	0.845	0.286
CEA (<5 vs. ≥5)	0.085	0.145
CA19-9 (<30 vs. ≥30)	0.681	0.640
Relative dose intensity (<0.97 vs. ≥0.97)	0.872	0.625

Correlative study

The correlative study was conducted in 40 patients among 45 patients enrolled. The frequencies of the *MDR1* 2677 GG, GT/A, and TT, TA and AA among 40 patients were 45.0, 40.0 and 15.0%, respectively. The frequencies of the *MDR1* 3435 CC, CT and TT were 55.0, 32.5 and 12.5%, respectively. The genotype prevalence of the *MDR1* 2677 G > T/A and 3435 C > T polymorphisms among patients were in Hardy–Weinberg equilibrium. The response rate, PFS and OS according to the distributions of the *MDR1* 2677 G > T/A and 3435 C > T genotype are shown in Table 8. The relationship between 2677 G > T/A and 3435 C > T and response to chemotherapy, PFS and OS except OS in 2677 G > T/A polymorphism was not statistically significant. However, overall survival stratified by the *MDR1* 2677 GG, GT/A and TT, TA and AA was 7.4, 8.9, and 3.8 months and showed statistical significance ($P = 0.006$). There was no significant difference in the rate of hematologic and non-hematologic toxicities (grade III and IV) according to the distributions of the *MDR1* 2677 G > T/A and 3435 C > T genotype (data not shown).

The frequencies of the six haplotypes (G-C, G-T, T-C, T-T, A-C and A-T) were 48.9, 16.1, 15.6, 6.9, 6.8 and

Table 7 Toxicity profiles per patient according to NCI-CTC grade

	Grade I	Grade II	Grade III	Grade IV	Grade III/IV (%)
Hematologic toxicity					
Anemia	10 (22.2)	1 (2.2)	1 (2.2)	0 (0.0)	2.2
Neutropenia	7 (15.6)	2 (4.4)	2 (4.4)	0 (0.0)	4.4
Thrombocytopenia	1 (2.2)	2 (4.4)	0 (0.0)	0 (0.0)	0.0
Non-hematologic toxicity					
Diarrhea	5 (11.1)	2 (4.4)	1 (2.2)	0 (0.0)	2.2
Anorexia	15 (33.3)	4 (8.9)	0 (0.0)	0 (0.0)	0.0
Nausea	13 (28.9)	6 (13.3)	3 (6.7)	0 (0.0)	6.7
Vomiting	11 (24.4)	8 (17.8)	2 (4.4)	0 (0.0)	4.4
Mucositis	8 (17.8)	2 (4.4)	3 (6.7)	0 (0.0)	6.7
Constipation	6 (13.3)	3 (6.7)	0 (0.0)	0 (0.0)	0.0
Skin rash	9 (20.0)	2 (4.4)	0 (0.0)	0 (0.0)	0.0
Elevated creatinine	3 (6.7)	2 (4.4)	0 (0.0)	0 (0.0)	0.0
Elevated aminotransferase	6 (13.3)	2 (4.4)	2 (4.4)	0 (0.0)	4.4
Hyperbilirubinemia	3 (6.7)	4 (8.9)	1 (2.2)	0 (0.0)	2.2
HFS	4 (8.9)	5 (11.1)	1 (2.2)	0 (0.0)	2.2

HFS hand-foot syndrome

Table 8 MDR1 2677 G > T/A and 3435 C > T genotypes and clinical outcomes

	No. (%)	Response to chemotherapy			*P*-Value	PFS (months)	*P*-value	OS (months)	*P*-value
		PR (%)	SD (%)	PD (%)					
2677 G > T/A	40				0.528	2.6	0.601	6.7	0.006
GG	18 (45.0)	1 (5.6)	9 (50.0)	8 (44.4)		2.3		7.4	
GT/A	16 (40.0)	3 (18.8)	6 (37.5)	7 (43.8)		2.8		8.9	
TT, TA, AA	6 (15.0)	0 (0.0)	2 (33.3)	4 (66.7)		1.6		3.8	
3435 C > T	40				0.818	2.6	0.641	6.7	0.648
CC	22 (55.0)	3 (13.6)	8 (36.4)	11 (50.0)		1.9		9.3	
CT	13 (32.5)	1 (7.7)	6 (46.2)	3 (60.0)		4.0		5.7	
TT	5 (12.5)	0 (0.0)	3 (60.0)	2 (40.0)		2.8		8.1	

PR partial response, *SD* stable disease, *PD* progressive disease, *PFS* progression free survival, *OS* overall survival

5.7%, respectively. The response rate, PFS and OS according to the haplotype distribution was not significantly different (data not shown).

Discussion

Gastric cancer is considered to be moderately responsive to combination chemotherapy with response rates ranging between 30 and 70%. However, patients who respond to initial chemotherapy eventually develop progressive disease. The duration of response rarely exceeds 9 months and the median overall survival rarely exceeds 15 months.

Studies on salvage chemotherapy have not yet been established and also demonstrate divergent results, partly due to the variability in the responsiveness to the first-line chemotherapy and the nature of present chemotherapy. Indeed, various reviews on the effectiveness of chemotherapy in second-line chemotherapy revealed objective response rates in the range of 0–36%, and the responses were usually partial, of short duration, and with significant toxicity to the patients. Two previous studies using cisplatin monotherapy [14] and combination therapy with 5-FU [15] showed a response rate of 10 and 30%, respectively. The toxicity consisted of nausea and vomiting; grade III/IV hematologic toxicitywas over 20%, and reversible renal failure of 28%. In taxane-based regimens, single agent paclitaxel [16] showed a partial response rate of 22%. However, second-line docetaxel [17] showed not only inconsistent results with a response rate in the range of 4.8%, but grade II asthenia was also reported in 90% of patients. When combined with cisplatin [18], the response rate was 16.7% and toxicity was acceptable (20% grade 3 neutropenia). Weekly single-agent irinotecan [19] has shown response rates of 22% in advanced gastric cancer after previous chemotherapy. A phase II study has employed the combination

of irinotecan and cisplatin [20] with a response rate of 20%, and with 57% of grade 4 neutropenia, 20% of grade 4 diarrhea. Other studies of irinotecan in combination with mitomycin-C [21] or 5-FU/LV [22] have shown response rates in the range of 20–36%, with corresponding time to progression of 4–4.5 months and overall survival of 6.4–9 months as a second-line treatment.

To the best of our knowledge, this is the first reported experience with XA in gastric cancer patients as a salvage regimen. With little overlap of main side effects between capecitabine and doxorubicin, we used the standard, intermittent capecitabine regimen 2,500 mg/m^2 for 14 days followed by a 7-day rest period with doxorubicin 40 mg/m^2 administered on day 1 every 21 days. Doxorubicin was administered at a relatively lower dose intensity compared with many previously reported regimens so as not to decrease the compliance with capecitabine. Our XA regimen showed an overall response rate of 8.9% with DCR of 48.9%, PFS of 11.3 weeks and OS of 29.1 weeks. Interestingly, the DCR in second-line chemotherapy and third-line chemotherapy groups were 50.0 and 36.8%, respectively. One possible explanation for the high DCR, even for patients who had previously been treated with 5-FU, is that capecitabine produces higher tumor 5-FU concentrations than can be achieved with maximally tolerated doses of 5-FU itself. Additionally, twice-daily oral administration enables chronic dosing system like infusion of 5-FU, and therefore our regimen was active in patients who have previously progressed on 5-FU containing combinations.

In our study, 89% of patients were pretreated with taxane-based regimens (median dose intensity of taxanes, 0.97) and about 42 and 24% had previously received cisplatin and irinotecan, respectively. Generally, patients often have substantial cumulative toxicities from previous chemotherapy, and were of relatively poorer performance status (ECOG 2 in 60%) than those eligible for the first-line therapy. However, additional toxicity from doxorubicin was no greater than that reported when capecitabine monotherapy was used as first-line therapy [6]. No episodes of grade IV toxicity and treatment-related mortality were observed. The acceptable toxicity profile is reinforced by the observation that ten patients were fit enough to subsequently move on to the next therapy. Grade III/IV toxicities were rare considering the high doses of capecitabine (2,500 mg/m^2). This low toxicity could be explained by the following: (1) two cycles of median treatment allowed insufficient time to gain HFS and other toxicities, (2) no previous exposure to anthracycline and overlapping toxicities between capecitabine and doxorubicin, (3) optimal dose modification with supportive care, (4) administration of the relatively low-dose doxorubicin compared with many previously reported regimens.

Although it has been reported that the 2677 G > T/A and 3435 C > T polymorphism is related to response to chemotherapy, we did not have sufficient statistical power to analyze the effect of each polymorphism on treatment response and toxicity because of the limited number of responders and lower rates of grade III or IV toxicities for individual treatments. Also, it might be difficult to give a meaning to the difference of overall survival among patients according to the 2677 G > T/A polymorphism because only four patients who have TT, TA and AA genotype showed statistical significance with poor survival. In addition, it is necessary to carefully interpret the impact of genetic polymorphisms on clinical outcomes with any one gene and SNP because we enrolled heterogeneous study population that received the second and third line treatment. Therefore, this suggests that SNP association study needs to be performed with multigene-based approach, and a combination of several SNPs on one chromosome in homogeneous study population and large studies.

In conclusion, based on PFS and OS comparable to other second-line regimens, XA regimen has a feasibility as a salvage regimen in patients with multiple previous chemotherapies.

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