available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejconline.com

A randomised phase II study of combination chemotherapy with epirubicin, cisplatin and capecitabine (ECX) or cisplatin and capecitabine (CX) in advanced gastric cancer

*Jina Yun, Jeeyun Lee, Se Hoon Park *, Joon Oh Park, Young Suk Park, Ho Yeong Lim, Won Ki Kang*

Division of Hematology-Oncology, Department of Medicine, Sungkyunkwan University Samsung Medical Center, Seoul 135-710, Republic of Korea

ARTICLE INFO

Article history:
Received 14 November 2009
Received in revised form 5 December 2009
Accepted 9 December 2009
Available online 7 January 2010

Keywords:
Stomach cancer
Epirubicin
Capecitabine
Cisplatin

ABSTRACT

Background: Both cisplatin/capecitabine (CX) and epirubicin plus CX (ECX) have clearly demonstrated efficacy against advanced gastric cancer (AGC).

Methods: Chemotherapy-naïve patients with histologically confirmed, measurable AGC were randomised to receive CX (cisplatin 75 mg/m^2 iv on day 1 and capecitabine 1000 mg/m^2 bid po on days 1–14) or ECX (epirubicin 50 mg/m^2 plus CX) every 3 weeks. The primary endpoint was progression-free survival (PFS).

Results: Of the 91 registered patients, 45 patients were treated with CX and 44 with ECX. A total of 241 CX (median, 6; range, 1–12) and 201 ECX (median, 5; range, 1–11) cycles were delivered. Treatment duration was similar for both arms (4.4 for CX versus 4.2 months for ECX). There was no relevant difference in the occurrence of overall grade 3 or 4 toxicities between the CX and ECX arms (80% versus 78%, respectively; $P = 0.516$). However, none in the CX and 12% in the ECX arm discontinued treatment because of toxicity. There were no significant differences in therapeutic efficacy between CX and ECX with respect to the response rate (38% versus 37%, respectively) and PFS (6.4 versus 6.5 months).

Conclusion: Both CX and ECX appear to be active as first-line chemotherapy for AGC, and the safety profiles are acceptable. Given the comparable efficacy results, CX could be a reasonable standard chemotherapy for untreated AGC patients.

1. Introduction

Gastric cancer is the most frequently occurring malignancy in Korea, and is one of the main causes of cancer death.[1] The benefit of systemic chemotherapy for advanced gastric cancer (AGC) in the palliative setting has long been known. Several randomised trials have demonstrated that fluorouracil (FU)-based chemotherapy is superior to best supportive care in terms of survival and preservation of quality of life.[2,3] Multi-drug combination chemotherapy regimens have generally provided significantly higher response rates, but no better overall survival (OS).[4] However, combination regimens that are mostly FU-based have been widely used in most countries because FU monotherapy has only limited activity.[5]

Capecitabine (Xeloda®, F. Hoffmann La-Roche) is an oral fluoropyrimidine designed to mimic a continuous infusion of FU. Capecitabine is considered to be as effective and more tolerable than FU,[6] and has been shown to exhibit an

* *Corresponding author:* Tel.: +82 2 3410 3459; fax: +82 2 3410 1754.
E-mail address: hematoma@skku.edu (S.H. Park).
0959-8049/$ - see front matter
doi:10.1016/j.ejca.2009.12.015

anti-tumour activity against AGC both as a single agent[7] and in two- or three-drug combinations.[8,9] A randomised phase III study of cisplatin and capecitabine (CX) combination in patients with AGC showed that CX produced an overall response rate (RR) of 46% and a median progression-free survival (PFS) of 5.6 months,[9] which were significantly better than the results with FU/cisplatin (CF) regimen. However, since anthracyclines are still considered to be one of the key drugs for the treatment of AGC,[5] a combination of these three active drugs (epirubicin, cisplatin and capecitabine; ECX) seemed to be a promising strategy to treat AGC. The REAL-2 study[8] suggested that for the first-line chemotherapy of esophagogastric cancer, capecitabine could replace FU. In a meta-analysis of these two studies,[8,9] capecitabine-containing chemotherapy resulted in longer OS and RR.[10]

We previously conducted phase II studies, on chemotherapy-naïve Korean patients with AGC, and they were administered with ECF or ECX.[11,12] There was good adherence to treatment and the three-drug combinations were found to be potentially active for AGC. This randomised phase II study was conducted in patients with AGC to evaluate the safety profile and anti-tumour activity of CX and ECX chemotherapy regimens given as first-line therapy.

2. Patients and methods

We performed a randomised, open-label, single-centre phase II study. Patients were eligible for inclusion if they had a histologically confirmed, measurable AGC and aged $\leqslant$ 75 years. Other inclusion criteria included an Eastern Cooperative Oncology Group (ECOG) performance status $\leqslant$ 2, a life expectancy of at least 3 months and adequate bone marrow (neutrophil count > 1500/mm,[3] platelet count > 100,000/mm^3), hepatic (AST/ALT $\leqslant$ 2.5x ULN, bilirubin $\leqslant$ 1.5 mg/dL), cardiac (left ventricular ejection fraction $\geqslant$ 60%) and renal (creatinine clearance $\geqslant$ 60 mL/min or serum creatinine $\leqslant$ ULN) functions. No prior chemotherapy or only adjuvant chemotherapy that had been completed more than 6 months before registration and no radiotherapy within 4 weeks before study registration were allowed. Patients were excluded from the study if they had any severe comorbid illness, including cardiac dysfunction, or a known history of anaphylaxis of any origin. This study protocol was reviewed and approved by the Samsung Medical Center (Seoul, Korea) institutional review board. To obtain informed consent, the nature of the study was fully discussed with the patients before the initiation of treatment, including an explanation of the risk and possible discomfort, as well as the potential benefits.

Patients were stratified by their ECOG performance status (0–1 versus 2) and then randomly assigned to receive CX or ECX every 3 weeks. CX consisted of cisplatin 75 mg/m^2 on day 1, and oral capecitabine 1000 mg/m^2 twice daily as an intermittent regimen of 2 weeks of treatment followed by a 1-week rest. For practical reason, capecitabine doses were rounded either up or down to the nearest dose that could be administered with 500 mg and 150 mg tablets of the drug. In the ECX arm, epirubicin 50 mg/m^2 was administered on day 1. Our department policy recommends the placement of central venous catheter (CVC) for chemotherapy drug infusion. Treatment was continued until disease progression or lack of clinical benefit, withdrawal of consent, justifiable withdrawal at the investigator's discretion, or toxicity. The dosage of the subsequent cycles was adjusted according to the toxic effects that developed during the preceding cycle. All patients received standard supportive regimen consisting of hydration and antiemetics. The prophylactic use of hematopoietic growth factors was not allowed during treatment, except for the patients with febrile neutropaenia or grade 4 myelosuppression at the investigators' discretion. After this combination chemotherapy had failed, second-line chemotherapy was recommended to all the patients if their performance status was preserved.

The baseline evaluation included a complete medical history and physical examinations, blood counts, serum chemistry, 2-D echocardiography, chest X-ray and abdominopelvic computed tomography (CT) scan. Follow-up history, physical examinations and toxicity assessment were performed before each 3-week cycle of treatment. Complete blood counts, blood chemistry and a chest X-ray were obtained before the beginning of each cycle. Toxicity grading was based on the National Cancer Institute criteria (NCI-CTCAE v3). The first evaluation with imaging was done after the completion of 2 cycles of chemotherapy. Response was evaluated according to the Response Evaluation Criteria in Solid Tumours (RECIST),[13] and was assessed by abdominopelvic CT or by the same tests that were initially used to stage the tumour. Progression in the non-measurable lesions that led to the deterioration of the patient's status was classified as progressive disease, regardless of the status of the measurable lesions.

The primary end point was PFS, which was calculated from the day of randomisation to the day that a patient experienced progressive disease or to the date of death. All events of progressive disease were included, regardless of whether the patient was receiving study treatment at the time of the event or had previously discontinued chemotherapy. This study was designed to assess the chemotherapy outcome and safety of CX and ECX. To estimate the PFS for two regimens simultaneously and to minimise patient selection bias, we designed this study not as a comparative study but as a randomised phase II study. On the basis of the published data for CX[9] and ECX,[8] we hypothesised that an observed 6-month PFS of less than 40% would suggest lack of activity, and an improvement in the 6-month PFS to at least 60% was considered to be of clinical interest. It was determined that a sample size of 40 patients per arm would provide 90% power to detect the difference at a one-sided significance level of 10%. Interim analysis was not planned. Secondary endpoints were RR and safety. Exploratory investigations of efficacy were also carried out as unplanned subgroup analyses in patients stratified by prognostic factors. All treated patients were included in the evaluation of the primary endpoint.

3. Results

During 2008, a total of 91 AGC patients gave informed consent (47 patients in the CX arm and 44 in the ECX arm) and were

screened for study entry. Two CX patients did not receive protocol therapy because of the rapid clinical deterioration or consent withdrawal. The clinical characteristics for all randomised patients are listed in Table 1.

3.1. Treatment delivery

A total of 241 CX (median, 6; range, 1–12) and 201 ECX (median, 5; range, 1–11) cycles were delivered. Of the 86 patients who started treatment, the main reasons for discontinuing treatment in the CX and ECX arms were progressive disease (58% versus 54%, respectively), toxicity (0% versus 12%, respectively) and the patient's refusal or lack of clinical benefit (42% versus 34%, respectively). Dose reduction was required in 56% and 76% of patients in the CX and ECX arms, respectively. In the CX arm, 29 (64%) patients had a treatment delay of >1 week at some time during therapy. In the ECX arm, treatment delays were required in 66% patients. For the patients treated with CX, the median dose intensity of capecitabine 7747 mg/m^2/week and cisplatin 21 mg/m^2/week corresponded to 83% and 84% of the scheduled doses, and the median duration of therapy was 4.4 months (95% confidence interval [CI], 3.8–4.9 months). In the ECX arm, the median dose intensity of capecitabine and cisplatin were 8000 mg/m^2/week (86% of the scheduled dose) and 21 mg/m^2/week (85%), respectively, and the median treatment duration was 4.2 months (95% CI, 3.4–5.0 months). The median administered dose intensity for epirubicin was 13 mg/m^2/week, which corresponded to 75% of the planned dose.

3.2. Safety outcomes

Both CX and ECX were generally well tolerated. There was no relevant difference in the occurrence of overall grade 3 or 4 toxicities between the CX and ECX arms (80% versus 78%, respectively; $P = 0.516$). The haematologic and non-haematologic toxicities are presented in Table 2. Grade 3 or 4 anaemia was observed in 5 (11%) CX patients and 5 (11%) ECX patients. When grade 2 anaemia was taken into account, the incidence of grade $\geqslant 2$ anaemia was 24% in the CX arm and 26% in the

Table 2 – Maximum grade toxic effects per patient.

	CX ($n = 45$)		ECX ($n = 44$)	
	All grades	Grade 3 or 4	All grades	Grade 3 or 4
Anaemia	40	5	35	5
Thrombocytopaenia	20	1	17	3
Neutropaenia	29	15	28	18
Febrile neutropaenia		1		5
Anorexia	26	9	30	10
Nausea	24	5	31	6
Vomiting	12	4	17	5
Oral mucositis	18	3	21	6
Diarrhoea	12	2	9	2
Constipation	7	1	5	0
Fatigue	16	5	14	5
Peripheral neuropathy	15	1	13	3
Hand-foot syndrome	14	2	15	3

Table 1 – Patient characteristics.

	CX	ECX
Number of patients registered	47	44
Treated	45	44
Age, years		
Median	58	55
Range	33–75	35–71
Male gender	34	28
Prior antitumor treatment		
Curative resection	8	3
Palliative surgery	12	14
Adjuvant chemotherapy ± radiotherapy	6	2
ECOG performance status[a]		
0–1	41	40
2	4	1
Weight loss > 5% within the last 3 months	16	13
Baseline heamoglobin < 10 g/dL	11	3
Site(s) of metastatic disease[b]		
Abdominal lymph node	28	35
Peritoneum	23	26
Liver	16	10
Lung and/or malignant pleural effusion	3	2
Ovary	2	2
Bone	4	1

a ECOG denotes the Eastern Cooperative Oncology Group.
b Because patients could have metastases at multiple sites, the total numbers of metastases are greater than the number of patients.

ECX arm. All patients with grade ⩾ 2 anaemia were treated with erythropoietic growth factors and/or red blood cell transfusions. Grade 3 or 4 neutropaenia occurred in 15 (33%) CX and 18 (41%) ECX patients. One patient in the CX arm and 5 patients in the ECX arm developed febrile neutropaenia. The incidence of non-haematologic toxic effects was not differed between the two arms. Two ECX patients developed symptomatic CVC-related thromboembolism leading to anticoagulation and CVC removal. Intracranial bleeding was occurred in a patient in the ECX arm. This event was thought to be possibly related to the chemotherapy but the blood counts and chemistry profiles were within normal limits at the time of onset. No patients developed symptomatic cardiac failure. There were no treatment-related deaths.

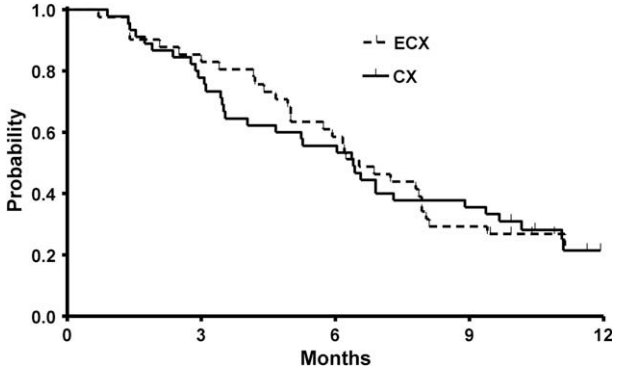


Fig. 1 – Kaplan–Meier estimates for progression-free survival by the treatment arm.

3.3. *Efficacy outcomes*

All but one ECX patient were evaluable for response. RR was 38% (95% CI, 24–52%) and 37% (95% CI, 22–52%) in the CX and ECX arms, respectively. Additionally, 20 (44%) CX and 21 (51%) ECX patients had stable disease. Disease control (response plus stable disease) was achieved in 82% and 88% ($P = 0.139$) of the patients treated with CX and ECX, respectively.

The median follow-up duration for all patients was 12.4 months (95% CI, 11.6–13.1 months). Both arms showed similar PFS (6.4 months for the CX arm versus 6.5 months for the ECX arm; $P = 0.863$; Fig. 1). The probability of remaining progression-free by 6 months was 56% (95% CI, 41–70%) and 59% (95% CI, 43–74%) for the CX and ECX arms ($P = 0.476$). Cox proportional hazards model suggested that only previous gastrectomy affected the risk of progression (Table 3). There was no evidence of any significant heterogeneity of therapy effect according to the baseline characteristics of the patients (data not shown). Although not specified in the protocol, we offered second-line chemotherapy to 42 patients after failure: 19 and 23 patients for the CX and ECX arms, respectively. One patient in the CX arm was felt to have resectable primary lesion after sixth cycle and discontinued chemotherapy for resection with a curative intent.

4. Discussion

This is the first randomised study comparing a fluoropyrimidine/platinum doublet regimen with an anthracycline-con-

Table 3 – Results of multivariate Cox model for progression-free survival.

Parameter	Group	Univariate			Multivariate		
		HR	95% CI	P	HR	95% CI	P
Gender	Male	1					
	Female	1.40	0.82–2.40	0.218			
Age	⩽45 years	1					
	>45 years	0.82	0.42–1.61	0.557			
Prior gastrectomy	No	1			1		
	Yes	0.46	0.27–0.79	0.004	0.49	0.28–0.85	0.011
Performance status	0–1	1			1		
	2	2.99	1.18–7.58	0.021	1.72	0.63–4.71	0.295
Weight loss	No	1			1		
	Yes	2.01	1.20–3.37	0.008	1.69	0.96–2.98	0.068
Baseline haemoglobin	⩽10 g/dL	1			1		
	>10 g/dL	0.49	0.26–0.91	0.024	0.54	0.28–1.01	0.055
Peritoneal seeding	No	1					
	Yes	1.17	0.71–1.93	0.546			
Liver metastasis	No	1					
	Yes	1.19	0.70–2.00	0.523			
Bone metastasis	No	1					
	Yes	1.47	0.59–3.68	0.413			
Treatment	CX	1					
	ECX	0.96	0.58–1.57	0.863			

taining triplet regimen, with each arm receiving identical doses of CX chemotherapy. The study was initiated because there is no current reference chemotherapy regimen for AGC and there is an urgent need for such therapy; further, the recent data suggested the efficacy and tolerability of capecitabine-based combinations.[8,9] The rationale for designing this study was based on the potential for improved anti-tumour activity with the addition of epirubicin to CX. As a result, both the CX and ECX combination regimens demonstrated tolerability and activity in the patients suffering with AGC. However, when compared with CX, the addition of epirubicin did not increase the RR or PFS. An identical dose regimen of cisplatin and capecitabine was used for both treatment arms. Thus, the administration of epirubicin 50 mg/m^2 in the ECX arm was the only different variable between the two treatments.

The best choice of chemotherapy regimen for patients with AGC is still a matter of controversy and requires further investigation.[4] Currently, CF combination chemotherapy is accepted as a standard regimen by many oncologists. It is presently unclear whether the addition of anthracyclines is superior to CX for patients with AGC. A meta-analysis showed a difference in OS of approximately 2 months in favour of the anthracycline-containing 3-drug combination versus CF.[5] However, this 2-months OS improvement is potentially misleading since in none of the studies that were included in the meta-analysis, including REAL-2 study,[8,14,15] there was not a statistically significant difference in OS between arms. Among other 3-drug combination regimens, docetaxel-containing chemotherapy (DCF) showed superior time-to-progression (5.6 months versus 3.7 months) and OS.[16] However, the OS benefit of DCF over CF was less than 1 month (9.2 months versus 8.6 months), and there was substantial grade 3 or 4 toxicity.

In the current study, this ECX chemotherapy was well tolerated. The overall RR of 37% and the median PFS of 6.5 months obtained with ECX chemotherapy are consistent with those reported in the REAL-2 study.[8] Another multicentre phase III study performed on chemotherapy-naïve patients with AGC showed that CX had good safety profiles and a trend towards superior PFS than CF.[9] Our study was designed as it was anticipated that a further incremental improvement in the PFS might be achieved with the addition of epirubicin. Although the data presented here is from a relatively small phase II study, and the study was not adequately powered to compare the two treatment arms, the results suggest that the addition of epirubicin did not improve efficacy over CX regimen.

The similar efficacy results reported here are rather unexpected considering the results from randomised studies,[8,9] and those from non-randomised studies in first-line setting.[12,17] One possible explanation may be that exposure to epirubicin was lower than expected. The median dose intensity rate for epirubicin was only 75%. As expected, myelosuppression, notably severe neutropaenia, was more common in ECX arm than in CX arm; five patients in the ECX arm required hospitalisation for febrile neutropaenia compared with only one in the CX arm. Dose reductions and treatment delays were significantly more frequent in the ECX arm resulting in the lower dose intensity. Another argument can be made that this study was underpowered and it represents only a small group of patients with AGC. However, several factors favour using the CX doublet as standard chemotherapy in future clinical trials. For instance, patients on randomised clinical trials may have had an inherently more favourable prognosis. Our own AGC prognostic model, originally published in 2007, identified poor performance status, no prior gastrectomy, low albumin, elevated alkaline phosphatase, bone metastasis and the presence of ascites as poor prognostic factors.[18] However, in the REAL-2 trial,[8] 20–25% of the patients had locally advanced disease, while the number of patients with metastatic disease was only 60%. In contrast, all the patients included in the present study had metastatic disease indicating a population with a generally poor prognosis. Consideration should always be given to the baseline characteristics of patients in clinical trials since results may not be applied to the general oncology population, which is often of poorer performance status.

With regard to the relatively short OS of patients with AGC and the palliative nature of therapy, the choice of chemotherapy should, at least in part, be based on a favourable toxicity profiles and convenience of the administration. More patients had a treatment delay and discontinuation due to toxicity in the ECX arm than in the CX arm. Interestingly, symptomatic thromboembolism was observed in two ECX patients. In a recently published report analysing patients treated with epirubicin-containing triplet chemotherapy,[19] the incidence of CVC-related thromboembolism was 7%, and OS was worse for patients who experienced thromboembolism. The current randomised phase II study shows no evidence that the addition of epirubicin to CX may result in better treatment outcome. CX may form the backbone of first-line chemotherapy regimens in AGC, and the current results indicate that ECX has no or minimal benefit over CX.

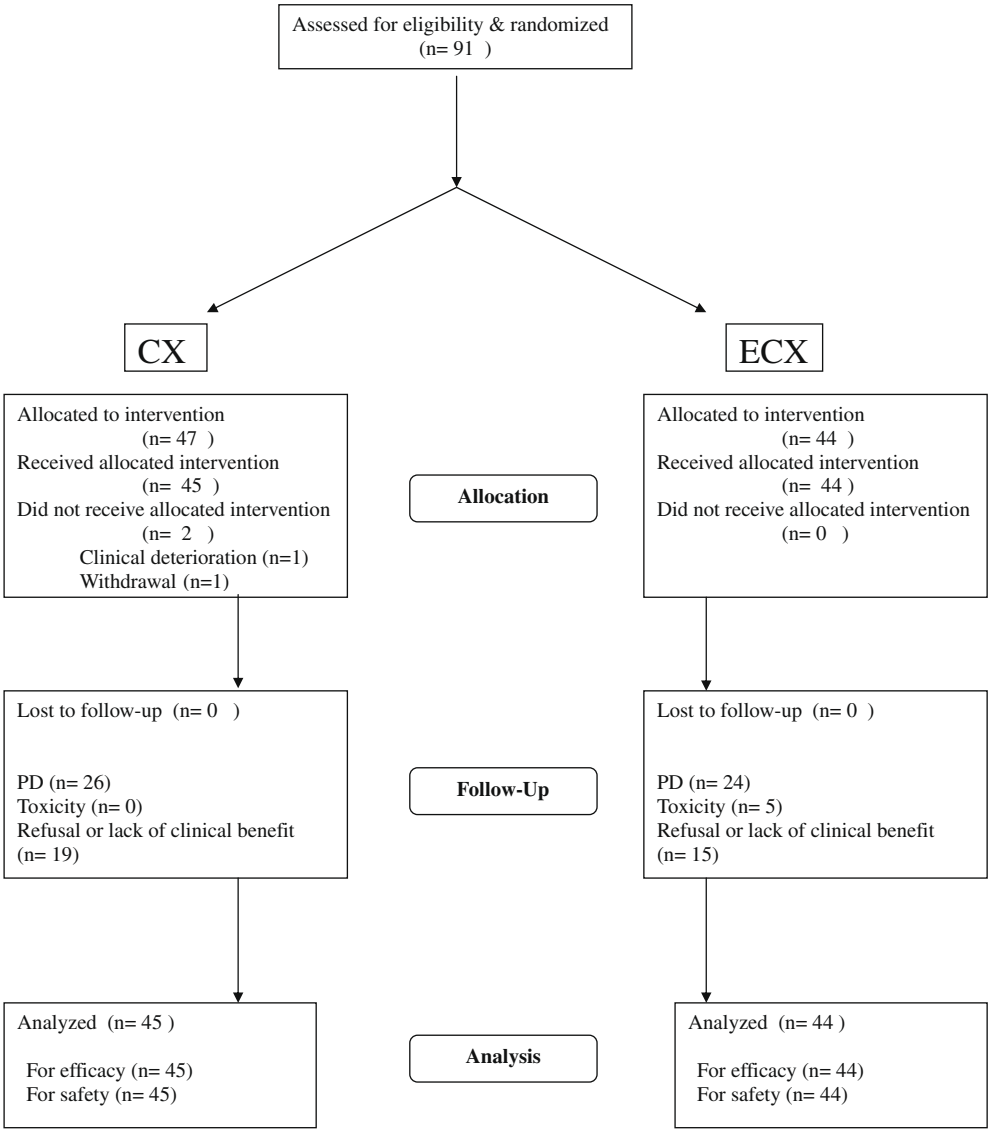
Although cisplatin is often used in combination with other agents, it is well known that cisplatin is associated with significant toxicity and usually requires a high level of clinical monitoring and supportive care including intensive intravenous hydration. Oxaliplatin-based regimens have been actively investigated to improve the efficacy and tolerability of combination chemotherapy for AGC patients.[8,20] Oxaliplatin has significant activity against some cisplatin-resistant tumours and a favourable safety profile over cisplatin.[21]

In conclusion, both CX and ECX were tolerable and effective as the first-line treatment for AGC, but ECX did not prove to be superior to CX in terms of RR or PFS. Given the comparable efficacy results, we believe that CX could be a reasonable standard chemotherapy for untreated AGC patients. It is conceivable that addition of a third drug, notably molecularly targeted agents, to CX could improve the efficacy for treating patients with AGC without compromising tolerability.

Conflict of interest statement

None declared.

Consort



Acknowledgement

This study was registered in advance to ClinicalTrials.gov (No. NCT00743964).

REFERENCES

1. Won YJ, Sung J, Jung KW, et al. Nationwide cancer incidence in Korea, 2003–2005. *Cancer Res Treat* 2009;**41**(3):122–31.
2. Pyrhonen S, Kuitunen T, Nyandoto P, Kouri M. Randomised comparison of fluorouracil, epidoxorubicin and methotrexate (FEMTX) plus supportive care with supportive care alone in patients with non-resectable gastric cancer. *Brit J Cancer* 1995;**71**(3):587–91.
3. Glimelius B, Ekstrom K, Hoffman K, et al. Randomized comparison between chemotherapy plus best supportive care with best supportive care in advanced gastric cancer. *Ann Oncol* 1997;**8**(2):163–8.
4. Ohtsu A, Yoshida S, Saijo N. Disparities in gastric cancer chemotherapy between the East and West. *J Clin Oncol* 2006;**24**(14):2188–96.
5. Wagner AD, Grothe W, Haerting J, Kleber G, Grothey A, Fleig WE. Chemotherapy in advanced gastric cancer: a systematic review and meta-analysis based on aggregate data. *J Clin Oncol* 2006;**24**(18):2903–9.
6. Twelves C. Can capecitabine replace 5-FU/leucovorin in combination with oxaliplatin for the treatment of advanced colorectal cancer? *Oncology (Williston Park)* 2002;**16**(12 Suppl no. 14):23–6.
7. Hong YS, Song SY, Lee SI, et al. A phase II trial of capecitabine in previously untreated patients with advanced and/or metastatic gastric cancer. *Ann Oncol* 2004;**15**(9):1344–7.

8. Cunningham D, Starling N, Rao S, et al. Capecitabine and oxaliplatin for advanced esophagogastric cancer. *New Engl J Med* 2008;**358**(1):36–46.
9. Kang YK, Kang WK, Shin DB, et al. Capecitabine/cisplatin versus 5-fluorouracil/cisplatin as first-line therapy in patients with advanced gastric cancer: a randomised phase III noninferiority trial. *Ann Oncol* 2009;**20**(4):666–73.
10. Okines AF, Norman AR, McCloud P, Kang YK, Cunningham D. Meta-analysis of the REAL-2 and ML17032 trials: evaluating capecitabine-based combination chemotherapy and infused 5-fluorouracil-based combination chemotherapy for the treatment of advanced oesophago-gastric cancer. *Ann Oncol* 2009;**20**(9):1529–34.
11. Cho EK, Lee WK, Lim DY, et al. Epirubicin, cisplatin, and protracted venous infusion of 5-fluorouracil for advanced gastric carcinoma. *J Korean Med Sci* 2002;**17**(3): 348–52.
12. Cho EK, Lee WK, Im SA, et al. A phase II study of epirubicin, cisplatin and capecitabine combination chemotherapy in patients with metastatic or advanced gastric cancer. *Oncology* 2005;**68**(4–6):333–40.
13. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* 2000;**92**(3):205–16.
14. Webb A, Cunningham D, Scarffe JH, et al. Randomized trial comparing epirubicin, cisplatin, and fluorouracil versus fluorouracil, doxorubicin, and methotrexate in advanced esophagogastric cancer. *J Clin Oncol* 1997;**15**(1):261–7.
15. Ross P, Nicolson M, Cunningham D, et al. Prospective randomized trial comparing mitomycin, cisplatin, and protracted venous-infusion fluorouracil (PVI 5-FU) with epirubicin, cisplatin, and PVI 5-FU in advanced esophagogastric cancer. *J Clin Oncol* 2002;**20**(8):1996–2004.
16. Van Cutsem E, Moiseyenko VM, Tjulandin S, et al. Phase III study of docetaxel and cisplatin plus fluorouracil compared with cisplatin and fluorouracil as first-line therapy for advanced gastric cancer: a report of the V325 Study Group. *J Clin Oncol* 2006;**24**(31):4991–7.
17. Kim TW, Kang YK, Ahn JH, et al. Phase II study of capecitabine plus cisplatin as first-line chemotherapy in advanced gastric cancer. *Ann Oncol* 2002;**13**(12):1893–8.
18. Lee J, Lim T, Uhm J, et al. Prognostic model to predict survival following first-line chemotherapy in patients with metastatic gastric adenocarcinoma. *Ann Oncol* 2007;**18**(5):886–91.
19. Starling N, Rao S, Cunningham D, et al. Thromboembolism in patients with advanced gastroesophageal cancer treated with anthracycline, platinum, and fluoropyrimidine combination chemotherapy: a report from the UK National Cancer Research Institute Upper Gastrointestinal Clinical Studies Group. *J Clin Oncol* 2009;**27**(23):3786–93.
20. Al-Batran SE, Hartmann JT, Probst S, et al. Phase III trial in metastatic gastroesophageal adenocarcinoma with fluorouracil, leucovorin plus either oxaliplatin or cisplatin: a study of the Arbeitsgemeinschaft Internistische Onkologie. *J Clin Oncol* 2008;**26**(9):1435–42.
21. Cvitkovic E. Ongoing and unsaid on oxaliplatin: the hope. *Brit J Cancer* 1998;**77**(Suppl 4):8–11.