Multicenter phase II study of capecitabine plus oxaliplatin as a first-line therapy in Chinese patients with advanced gastric cancer

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The efficacy of chemotherapy for advanced gastric cancer with palliative intent compared with supportive care alone is now widely accepted. However, the survival advantage is small, and no internationally accepted standard regimen has emerged. This study is performed to evaluate the response rate, time to progression, and safety of the combination of capecitabine (1000 mg/m^2 twice daily, days 1–14) plus oxaliplatin (130 mg/m^2 as a 2-h intravenous infusion on day 1) every 3 weeks, in previously untreated Chinese patients with advanced gastric cancer. Sixty-five (95.6%) of the 68 patients were assessable for response. Three cases of complete response and 34 cases of partial response were confirmed, giving an overall response rate of 54.4% [95% confidence interval (CI), 42.6–66.2%]. The median time to progression and overall survival for all patients were 5.7 months (95% CI, 2.0–8.8 months) and 10.5 months (95% CI, 5.0–15.1 months). The most severe hematologic adverse event was neutropenia, which occurred with grade 3 intensity in three (4.6%) patients and grade 4 in one (1.5%) patient. Thrombocytopenia and leukopenia occurred with grade 3 intensity in five (7.7%) and three (4.6%) patients, respectively. However, no grade 4 thrombocytopenia and leukopenia were observed. Grade 1/2 nausea/vomiting and diarrhea were observed in 33 (50.8%), 17 (26.2%), 26 (40%), 44 (67.7%), and 13 (20%) patients, respectively, and grade 3 nausea/vomiting and diarrhea were observed in one (1.5%) and four (6.2%) patients. Yet, no grade 4 nonhematologic toxicity was observed. Capecitabine/oxaliplatin combination chemotherapy is active in Chinese patients with previously untreated advanced gastric cancer. ***Anti-Cancer Drugs*** **19:825–831 © 2008 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Introduction

Although the incidence of gastric carcinoma has fallen in most Western countries, it remains a significant problem in terms of global health and is the second most common cause of cancer mortality worldwide [1]. Gastric cancer is often diagnosed at a very advanced stage, with approximately half of all patients presenting with unresectable, locally advanced, or metastatic disease. Four randomized studies comparing best supportive care with best supportive care plus chemotherapy for advanced gastric cancer (AGC) have shown that chemotherapy can improve survival and quality of life [2–5]. There is no single, global standard regimen for the first-line treatment of advanced disease. 5-fluorouracil (5-FU) and/or cisplatin (CDDP)-based combination chemotherapy continues to be widely used [6,7]. However, continuous infusion of 5-FU requires chronic venous access, which is inconvenient, cumbersome, and associated with venous thrombosis and sepsis. Patients with cancer generally prefer oral alternatives to intravenous chemotherapy, provided that efficacy is maintained [8–10].

Capecitabine (N4-pentoxycarbonyl-5′-deoxy-5-fluorocytidine; Xeloda; Hoffmann–La Roche Ltd, Basel, Switzerland) is a 5-FU prodrug developed to reduce the toxicity and enhance the intratumor concentrations of 5-FU. Capecitabine is absorbed as an intact molecule from the small bowel mucosa and converted sequentially to 5-FU in a multistep enzymatic process [11,12]. In the first step, capecitabine is metabolized by hepatic carboxyl esterase to 5′-deoxy-5-fluorocytidine (5′-DFCR). This intermediate is metabolized by cytidine deaminase to doxifluridine (5′-DFUR) in hepatic and extrahepatic tissues, including malignant tumors. Finally, 5′-DFUR is converted to 5-FU by the pyrimidine nucleoside phosphorylase thymidine phosphorylase (dThdPase), a potent tumor-associated angiogenesis factor preferentially expressed in malignant cells [13]. In preclinical xenograft models, capecitabine was highly active against several tumors, including breast, colorectal, gastric, and cervical tumors [14,15], and against both 5-FU-sensitive and 5-FU-resistant tumors [16]. Intermittent capecitabine (1250 mg/m^2 daily dose for 14 days, followed by a 7-day

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rest period) was shown to be active as a single agent in previously untreated AGC patients, with a response rate of 28.2% in 39 patients [17]. Moreover, the combination of capecitabine with other drugs, such as cisplatin, oxaliplatin, epirubicin, and docetaxel, had an objective response rate of 40–68% as first-line treatment in patients with AGC [18–21].

Oxaliplatin is an alkylating agent that inhibits DNA replication by forming adducts between two adjacent guanines or guanine and adenine molecules. However, the adducts of oxaliplatin appear to be more effective than cisplatin adducts with regard to the inhibition of DNA synthesis [22–24]. Oxaliplatin has a more favorable safety profile compared with cisplatin; benefits of oxaliplatin include no ototoxicity or renal toxicity and its dose-limiting toxicity is a cumulative sensory peripheral neuropathy [25]. In contrast to cisplatin, oxaliplatin has demonstrated efficacy alone and in combination with 5-FU in metastatic colorectal cancer (MCRC). Oxaliplatin is active in both MCRC and as adjuvant treatment for early colon cancer, with superior efficacy over 5-FU/LV alone [26,27]. Many studies are ongoing to test the combination of 5-FU and oxaliplatin in noncolorectal gastrointestinal tumors and other malignancies [28].

The combination of oxaliplatin and capecitabine has been tested in several phase II studies in patients with MCRC [8,29]. Grade 3/4 diarrhea was seen in 33–50% of the patients treated with capecitabine 1250 mg/m^2 twice daily and oxaliplatin 130 mg/m^2 in the study performed by Borner *et al.* [8]. Cassidy *et al.* [29] reported grade 3/4 diarrhea in 16% of the patients treated with oxaliplatin 130 mg/m^2 and capecitabine 1000 mg/m^2 twice daily. The response rate was comparable, 49 and 55%, respectively. Therefore, a capecitabine dose of 1000 mg/m^2 twice daily on days 1–14 in combination with oxaliplatin 130 mg/m^2 on day 1 in a 21-day treatment cycle is the recommended dose.

Based on these favorable results of oxaliplatin combined with capecitabine in gastrointestinal malignancies, we conducted the present phase II study to evaluate the safety and efficacy of the combination of oxaliplatin and capecitabine in previously untreated Chinese patients with AGC.

Patients and methods

Eligibility criteria

All the patients involved in the current study had histologically confirmed metastatic or recurrent gastric adenocarcinoma with at least one unidimensionally measurable lesion (i.e. a diameter ≥ 1 cm, as assessed by spiral computed tomography). The patients were 18–75 years of age with a performance status of 0–2 on the Eastern Cooperative Oncology Group (ECOG) scale. Plus, adequate hematological (absolute neutrophil count $\geq 1.5 \times 10^9$/l, platelet count $\geq 100 \times 10^9$/l, hemoglobin ≥ 9 g/dl), renal (serum creatinine ≤ 1.5 mg/dl and creatinine clearance ≥ 50 ml/min), and hepatic (total bilirubin ≤ 2.0 mg/dl and serum transaminase level ≤ 3 times the upper limit of the normal range) levels were also required.

Exclusion criteria were a contraindication to any drug contained in the chemotherapy regimen; evidence of central nervous system metastases; previous adjuvant treatment with capecitabine or platinum completed less than 6 months before the study; evidence of serious gastrointestinal bleeding; and history of another malignancy within the past 5 years. The institutional review board of each author's institution approved the protocol, and written informed consent was obtained from all patients before enrollment.

Study treatment

Patients received capecitabine (1000 mg/m^2 twice daily, days 1–14) plus oxaliplatin (130 mg/m^2 as a 2-h intravenous infusion on day 1) every 3 weeks. Capecitabine was administered on days 1–14, followed by a 1-week rest period. Treatment continued until disease progression, intolerable toxicity, or eight cycles being reached. If the disease progressed, it could be treated with other chemotherapy provided it did not include either capecitabine or oxaliplatin. If patients could not tolerate oxaliplatin, then they could continue to receive capecitabine monotherapy until disease progression or intolerable toxicity.

Dose modification

Capecitabine or oxaliplatin treatment interruption or dose reduction was not indicated for the first occurrence of grade 1 toxicity (National Cancer Institute Common Toxicity Criteria for Adverse Events, version 2.0). For hematological toxicity, treatment was interrupted in cases of grade 3 or 4 events. The next treatment cycle could only start in case of recovery with grade 1 or 0 toxicity.

For nonhematological toxicities, capecitabine and oxaliplatin doses were reduced by 25% for patients who experienced the first occurrence of a grade 3 event, and a second occurrence of a given grade 3 event. Treatment was stopped permanently if grade 4 nonhematological toxicities occurred. For nonhematological toxicities more severe than grade 2, capecitabine treatment was interrupted and could not be continued unless toxicities resolved to grade 1 or less. For grade 3 nonhematological toxicities, oxaliplatin was suspended for a maximum of 3 weeks from the scheduled date of reinfusion until toxicity was resolved. After recovery from grade 3 toxicity to grade 2 or less, a dose reduction of oxaliplatin to 100 mg/m^2 in subsequent cycles was made.

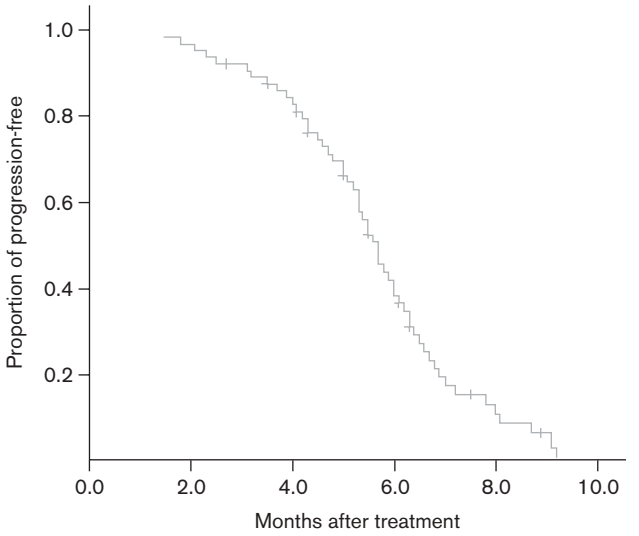
Response to treatment and adverse effects

Before entering the study, all patients underwent a physical examination, and full blood count and serum chemistry analyses. Chest radiograph, ECG, upper gastrointestinal endoscopies, abdominal computer tomographic (CT) scans, and other appropriate procedures were also performed. Patients were given a physical examination, a subjective/objective symptom evaluation, and routine blood tests twice weekly. Every 4 weeks, a biochemistry blood examination was added to this basal evaluation. After every two cycles of treatment, the response was evaluated using RECIST criteria. Of the lesions observed before treatment, a maximum of five measurable lesions from each metastasized organ up to a total of 10 lesions were selected as target lesions. In cases of partial or complete response (CR), a confirmative CT scan was performed 4 weeks later and this was followed by a CT scan after every two treatment cycles. Toxicity was reported using a National Cancer Institute-Common Toxicity Criteria (NCI-CTC) version 2.0 toxicity scale.

Statistical analysis

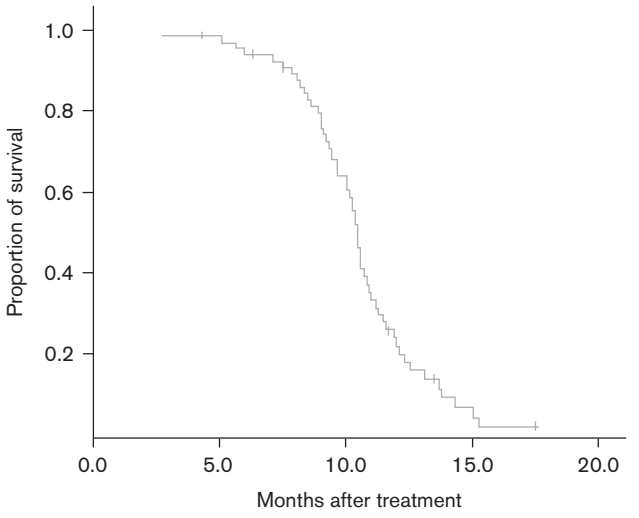
The current trial used a two-stage optimal design, as proposed by Simon, with a 90% power to accept the hypothesis and 5% significance to reject the hypothesis [30]. Plus, the current trial was designed to detect a response rate of 40% as compared with a minimal, clinically meaningful response rate of 20%. Allowing for a follow-up loss rate of 10%, the total sample size was 60 patients with a measurable disease. All enrolled patients were included in the intention-to-treat analysis of efficacy. The duration of response, time to progression (TTP), and survival analyses were all estimated using the Kaplan–Meier method. The duration of response was defined as the interval from the onset of a CR or partial response until evidence of disease progression was found. Meanwhile, the TTP was calculated from the initiation of chemotherapy to the date of disease progression, whereas overall survival was measured from the initiation of chemotherapy to the date of the last follow-up or death. The statistical data were obtained using an SPSS software package (SPSS 11.5 Inc., Chicago, Illinois, USA) (Figs 1 and 2).

Fig. 1



Time to disease progression for all patients.

Fig. 2



Overall survival for all patients.

Results

Patient characteristics

From July 2004 to July 2006, a total of 68 patients were enrolled in the current study from four centers. The characteristics of the patients are summarized in Table 1. The median age was 58 (range, 26–72) years, with 38 males and 30 females. Most of the patients (94.1%) had a good performance status (ECOG 0 or 1). Forty-four (64.7%) patients had a metastatic disease, whereas 24 patients had a recurrent disease after surgical resection (total or subtotal gastrectomy) of the primary tumor. Distal lymph nodes, liver, and peritoneum were the most common sites of the metastases. No patients had received prior chemotherapy or radiotherapy.

Efficacy and survival

Sixty-five (95.6%) of the 68 patients were assessable for response, of the three patients not assessable, two were lost to follow-up after the first cycle of the treatment, and the other died after the first cycle of unknown cause, although brain metastasis was suspected. All efficacy data are reported using the intent-to-treat patient population.

Table 1 Patient characteristics

Characteristics	Number of patients $n=68$ (%)
Age (years)	
Median (range)	58 (26–72)
Male/female	38/30
ECOG performance status	
0	11 (16.2)
1	53 (77.9)
2	4 (5.9)
Disease status	
Metastatic	44 (64.7)
Recurrent	24 (35.3)
Location of primary tumor	
Upper	9 (13.2)
Middle and lower	59 (86.8)
Histology	
Adenocarcinoma	61 (89.7)
Signet ring cell carcinoma	7 (10.3)
Metastatic sites	
Lymph node	44 (64.7)
Liver	18 (26.5)
Peritoneum	17 (25.0)
Ovary	5 (7.4)
Others (bone, kidney, pancreas)	4 (5.9)
Number of metastases	
1	26 (38.2)
2	17 (25.0)
≥ 3	25 (36.8)

ECOG, Eastern Cooperative Oncology Group.

Table 2 Tumor response (intention-to-treat analysis, $n=68$)

Response	*n* (%)
Overall response rate	37 (54.4)[a]
Complete response (CR)	3 (4.4)
Partial response (PR)	34 (50.0)
Stable disease (SD)	16 (23.5)
Progressive disease (PD)	12 (17.6)
CR + PR + SD	53 (77.9)
Not assessable	3 (4.4)

[a]95% confidential interval (CI) = 42.6–66.2%.

Three cases of CR and 34 cases of partial response were confirmed, giving an overall response rate of 54.4% [95% confidence interval (CI), 42.6–66.2%). Of 37 responses, six (16.2%) were observed after three cycles, 24 (64.9%) after four cycles, five (20.8%) after six cycles, and two (5.4%) after eight cycles of chemotherapy. (Table 2). The median follow-up period was 12.5 months. The median TTP for all patients was 5.7 months (95% CI, 2.0–8.8 months). Forty-four patients had died at the time of the present evaluation. The estimated median overall survival was 10.5 months (95% CI, 5.0–15.1 months).

Toxicity

A total of 305 cycles were administered in 65 patients assessable for toxicity, with a median of six cycles per patient (range 1–8 cycles). The occurrence and the incidence of the hematologic and nonhematologic toxicities are shown in Table 3. The most severe hematologic adverse event was neutropenia, which occurred with grade 3 intensity in three (4.6%) patients and grade 4 in one (1.5%) patient. Thrombocytopenia and leukopenia occurred with grade 3 intensity in five (7.7%) and three (4.6%) patients, respectively. However, no grade 4 thrombocytopenia and leukopenia were observed.

Table 3 Adverse reactions (by patients, $n=65$)

	Grade[a] *n* (%)			
	1	2	3	4
Hematologic				
Anemia	41 (63.1)	4 (6.2)	0	0
Leukopenia	20 (30.8)	7 (10.8)	3 (4.6)	0
Neutropenia	18 (27.7)	7 (10.8)	3 (4.6)	1 (1.5)
Thrombocytopenia	5 (7.7)	9 (13.8)	5 (7.7)	0
Nonhematologic				
Nausea/vomiting	26 (40.0)	7 (10.8)	1 (1.5)	0
Stomatitis	7 (10.8)	6 (9.2)	0	0
Alopecia	2 (3.1)	1 (1.5)	0	0
Diarrhea	10 (15.4)	7 (10.8)	4 (6.2)	0
Constipation	2 (3.1)	0	0	0
HFS[b]	17 (26.2)	9 (13.8)	0	0
Neuropathy	40 (61.5)	4 (6.2)	0	0
Elevated transaminase	3 (4.6)	1 (1.5)	0	0
Elevated creatinine	1 (1.5)	0	0	0
Hyperbilirubinemia	2 (3.1)	0	0	0

[a]National Cancer Institute-Common Toxicity Criteria (NCI-CTC) version 2.0.
[b]Hand–foot syndrome.

Nausea/vomiting, diarrhea, hand–foot syndrome (HFS), neuropathy, and stomatitis were the most common nonhematological toxicities. Grade 1/2 nausea/vomiting and diarrhea were observed in 33 (50.8%), 17 (26.2%), 26 (40%), 44 (67.7%), and 13 (20%) patients, respectively, and grade 3 nausea/vomiting and diarrhea were observed in one (1.5%) and four (6.2%) patients. Yet, no grade 4 nonhematologic toxicity was observed.

Six patients (8.8%) were hospitalized because of treatment toxicities (five due to infections and one due to general weakness). However, there were no treatment-related deaths during this study. Overall, the treatment was delayed or the dose reduced in 85 (27.9%) and 41 (13.4%) cycles, respectively. Most of the treatment delays (68/85; 80.0%) and dose reductions (28/41; 68.3%) were because of hematologic toxicities (leukopenia and thrombocytopenia). The other reasons for dose modification were HFS and neurotoxicity.

Treatment delays or dose reductions were necessary in 65 of 305 (21.3%) cycles. Doses were reduced in 36 cycles (11.8%) as a result of neutropenia and thrombocytopenia. Treatment was delayed in 29 cycles (9.5%). The median dose intensities of both drugs exceeded 90%.

Discussion

Unresectable advanced or metastatic gastric cancer still has a poor prognosis, with a median survival of just 7–10 months. Several combinations regimens of chemotherapy have been developed, but the survival advantage appears

to be marginal, and no worldwide standard regimens have as yet been established. A recent meta-analysis has been carried out to assess the efficacy and tolerability of chemotherapy in patients with AGC. Analysis of chemotherapy versus best supportive care [hazard ratio (HR) = 0.39, CI 95% 0.28–0.52] and combination versus single agent, mainly 5-FU, (HR = 0.83, 95% CI 0.74–0.93) demonstrated significant overall survival results in favor of chemotherapy and combination chemotherapy [31]. However, there is no single, global standard regimen for the first-line treatment of advanced disease.

This phase II study demonstrated that capecitabine 1000 mg/m^2 orally twice daily plus oxaliplatin [capecitabine/oxaliplatin (XELOX) regimen] was active and well-tolerated as first-line therapy in patients with AGC. The overall response rate was 54.4% and, after a median follow-up of 12.5 months, median TTP was 5.7 months and median overall survival was 10.5 months. These findings compare favorably with two phase II studies (using similar patient populations) investigating the efficacy of cisplatin in combination with capecitabine as first-line therapy in patients with AGC, which reported overall response rates of 54.8 and 46%, respectively, (using capecitabine doses of 1250 and 1000 mg/m^2 twice daily, respectively) [18,32], and two other phase II studies investigating the efficacy of oxaliplatin plus capecitabine as first-line therapy in patients with AGC, which reported overall response rates of 65 and 63%, respectively [21,33]. The objective response rate was higher than two phase II studies by Kang *et al.* (54.4 vs. 28%) and Qian *et al.* (54.4 vs. 29.2%) [34,35]. It is logical that the same chemotherapeutic regimen should have a lower response rate in patients who have previously received fluoropyrimidine-based adjuvant therapy than those who have not. The median TTP and overall survival of this study are similar to previous studies by Kim *et al.* [18], Kang *et al.* [33], and Park *et al.* [34] (listed in Table 4).

However, considering the high response rate, TTP is relatively short. Further research to overcome this point should be followed. In effect, utilizing this combination of oxaliplatin and capecitabine as a so-called 'backbone' regimen, adding a newer biologic agent, and testing this three-drug regimen against any one of several other commonly used regimens appears to be a reasonable trajectory of future development [36–38]. Recently developed new agents, such as camptothecins, taxanes, platinum analog, and oral fluopyrimidines, have been investigated in clinical trials. Contrary to the recent advances in colorectal cancer, no confirmation of improved results with newer-generation regimens as compared with older-generation regimens have yet been achieved. Molecular targeting agents are another new topic in the field of cancer therapy, and may provide a significant impact also in gastric cancer treatment, as successful results have been observed in colorectal cancer [39,40] and gastric or gastrooesophageal junction cancer [41–44].

A recent randomized phase III trial in 316 patients with AGC reported that capecitabine plus cisplatin combination chemotherapy showed highly significant

Table 4 Phase II trial of capecitabine ± cisplatin (or oxaliplatine) chemotherapy in patients with AGC or AOC

Method	Study	Treatment	Cancer	No. of patients	RR (%)	TTP	OS
Capecitabine	Koizumi *et al.* 2003 [36]	Capecitabine: 828 mg/m^2 (b.i.d., days 1–21); q4w	AGC	32	19.4	85.0 days	247.5 days
	Hong *et al.* 2004 [17]	Capecitabine: 1250 mg/m^2 (b.i.d., days 1–14); q3w	AGC	44	34	3.2 months	9.5 months
	Sakamoto *et al.* 2006 [37]	Capecitabine: 828 mg/m^2 (b.i.d., days 1–21); q4w	AGC	60	23	3.4 months	10.0 months
Capecitabine + cisplatin	Kim *et al.* 2002 [18]	Capecitabine: 1250 mg/m^2 (b.i.d., days 1–14); cisplatin: 60 mg/m^2 (1 h infusion day 1); q3w	AGC	42	54.8	6.3 months	10.1 months
	Kang *et al.* 2004 [34][a]	Capecitabine: 1250 mg/m^2 (b.i.d., days 1–14); cisplatin: 60 mg/m^2 (1 h infusion day 1); q3w	AGC	32	28	5.8 months	11.2 months
	Jin *et al.* 2006 [32]	Capecitabine: 1000 mg/m^2 (b.i.d., days 1–14); cisplatin: 20 mg/m^2 (1 h infusion day 1); q3w	AGC	130	45	–	–
Capecitabine + oxaliplatin	Park *et al.* 2006 [21]	Capecitabine: 1000 mg/m^2 (b.i.d., days 1–14); oxaliplatin: 130 mg/m^2 (2 h infusion day 1); q3w	AGC	20	65	7.5 months	–
	Meerten *et al.* 2007	Capecitabine: 1000 mg/m^2 (b.i.d., days 1–14); oxaliplatin: 130 mg/m^2 (2 h infusion day 1); q3w	AOC	51	39	–	8 months
	Park *et al.* 2008 [33]	Capecitabine: 1000 mg/m^2 (b.i.d., days 1–14); oxaliplatin: 130 mg/m^2 (2 h infusion day 1); q3w	AGC	54	63	5.8 months	11.9 months
	Qian *et al.* 2004 [35]	Capecitabine: 1250 mg/m^2 (b.i.d., days 1–14); oxaliplatin: 85 mg/m^2 (2 h infusion day 1, 15); q4w	AGC	24	29.2	5 months	–
	Jatoi *et al.* 2006 [38]	Capecitabine: 1000 mg/m^2 (b.i.d., days 1–14)[b]; oxaliplatin: 130 mg/m^2 (2 h infusion day 1); q3w	AOC, AGOC[c]	43	35	4 months	6.4 months
	This study	Capecitabine: 1000 mg/m^2 (b.i.d., days 1–14); oxaliplatin: 130 mg/m^2 (2 h infusion day 1); q3w	AGC	68	54.4	5.7 months	10.5 months

AGC, advanced gastric cancer; AGOC, advanced gastrooesophageal cancer; AOC, advanced oesophageal cancer; b.i.d., twice daily; OS, median overall survival; RR, response rate; TTP, median time to progression.
[a]This is the randomized phase III trial.
[b]Four treatment-related deaths in the first 24 patients led to a reduction in capecitabine to 850 mg/m^2 orally twice a day, days 1–14, for the remainder of the cohort.
[c]Patients with metastatic adenocarcinoma of the oesophagus, gastrooesophageal junction, and gastric cardia.

noninferiority for progression-free survival and significant superiority for overall response rate versus 5-FU/cisplatin (median overall survival capecitabine/cisplatin: 10.5 months; 5-FU/cisplatin: 9.3 months) with similar safety [34]. This trial suggests that capecitabine should become the fluoropyrimidine of choice for AGC, given the efficacy, reduced hospitalization time, and simplified treatment regimen. Furthermore, a separate large randomized phase III trial (REAL 2) involving 1002 patients has shown that capecitabine can replace 5-FU and oxaliplatin can replace cisplatin in triplet combinations used for the treatment of advanced oesophagogastric cancer [45]. The best arm of the REAL2 study was the epirubicin, oxaliplatin, capecitabine (EOX) arm, which led to a median overall survival of 11.2 months. However, the use of anthracyclines in gastric cancer has never been widely adopted on a global scale. Therefore, the current study reinforces the rationale for a capecitabine plus oxaliplatin (XELOX) regimen as a new effective and well-tolerated drug combination in AGC.

An important finding from our phase II multicenter study was that XELOX had a good safety profile. In our study, no patient stopped treatment because of treatment-related adverse events. The most severe hematologic adverse event was neutropenia, which occurred with grade 3/4 intensity in four (6.2%) patients. Thrombocytopenia and leukopenia occurred with grade 3 intensity in five (7.7%) and three (4.6%) patients, respectively. However, no grade 4 thrombocytopenia and leukopenia were observed. Considering the exceptionally poor prognosis of AGC and the importance of good feasibility for AGC, the safety profile reported with XELOX in our trial compares favorably with that of capecitabine/cisplatin, as previously reported [18,32,34], and capecitabine/oxaliplatin [21,24,33–35,38]. For example, there were similar rates of grade 3/4 thrombocytopenia reported here and in the studies by Kim *et al.* [18]. However, the rate of grade 3/4 neutropenia was considerably lower here (6 vs. 33% of patients). It is also noteworthy that the rates and severities of stomatitis and HFS reported in this study were lower than those reported by Kim *et al.* [18] and this might be the result of the lower dose of capecitabine used here (1000 mg/m^2). Indeed, in the phase III study using the same dose of capecitabine (1000 mg/m^2 orally twice daily) and cisplatin 80 mg/m^2 intravenously [34], the rate of grade 3/4 neutropenia was 13%, which is higher than that reported here (6%).

When comparing oxaliplatin with cisplatin, oxaliplatin has a more favorable safety profile as it has no renal toxicity. In addition, oxaliplatin does not require hydration, unlike cisplatin, making it more convenient to use. Hence, if oxaliplatin and cisplatin are equivalent in terms of efficacy and tolerability, oxaliplatin would be the preferred agent in terms of convenience. An important phase III trial of FLP (5-FU, leucovorin and cisplatin) versus FLO (5-FU, leucovorin and oxaliplatin) for 220 AGC patients has been reported by a German group [46]. They showed that FLO reduced toxicity and improved efficacy as compared with FLP. This result also supported that oxaliplatin can replace cisplatin.

In conclusion, capecitabine/oxaliplatin (XELOX) combination chemotherapy is effective in Chinese patients with previously untreated AGC. This promising combination regimen overcomes the issues of poor tolerability and inconvenience associated with other regimens currently used in AGC. On the basis of these results, and the recently presented phase III data, XELOX can be a good therapeutic option for the treatment of AGC, particularly with the addition of new biological agents such as bevacizumab, cetuximab, or others.

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