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ORIGINAL ARTICLE

Capecitabine in combination with Oxaliplatin (XELOX) as a first-line therapy for advanced gastric cancer

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Abstract
Purpose We evaluated efficacy and safety of XELOX in previously untreated patients with AGC.
Patients and methods Patients received intravenous oxaliplatin 130 mg/m^2 over 2 h on day 1 plus oral capecitabine 1,000 mg/m^2 twice daily on days 1–14, every 3 weeks (XELOX). Treatment was continued until disease progression, intolerable toxicities or eight cycles reached. All tumour evaluations were reviewed and confirmed centrally. Design was according to Ensign's three-stage method.
Results Fifty-four patients (37 men) were enrolled; median age 57 years (range 29–70). In total, 311 cycles of XELOX were delivered. Overall response rate was 63% (95% CI, 50–76%), with 3 complete and 31 partial responses. At 13 months' median follow-up, median progression-free and overall survival were 5.8 (95% CI, 4.4–7.2) and 11.9 months (95% CI, 8.8–15.1), respectively. The most common haematological adverse event was anaemia (70% of patients). Grade 3–4 neutropenia was observed in four patients, with neutropenic fever in only one patient. Most common non-haematological toxicities were neuropathy (70%), vomiting (50%), diarrhoea (33%), and hand-foot syndrome (HFS) (39%). Grade 3–4 toxicities were rare. Treatment was delayed or the dose reduced in 30 and 15% of cycles, respectively. There was one treatment-related death associated with grade 4 neutropenic sepsis.
Conclusion XELOX was active and well tolerated as a first-line therapy for AGC.

Keywords Advanced gastric cancer · Capecitabine · First-line · Oxaliplatin · Phase II

Introduction

Gastric cancer remains one of the most common malignancies worldwide [1], and is the second highest cause of cancer-related deaths in Korea [2]. Once the disease becomes inoperable, the prognosis for gastric cancer is exceptionally poor. Most cases of inoperable or recurrent advanced

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gastric carcinoma (AGC) remain incurable with a median survival of only 6–12 months even in patients receiving chemotherapy [3–6]. For this reason, it is necessary to improve the effect of palliative chemotherapy, which is the mainstay treatment for AGC.

The combination of infusional 5-FU and cisplatin is used worldwide for the treatment of AGC [7, 8]. However, continuous infusion of 5-FU requires chronic venous access, which is inconvenient, cumbersome and associated with venous thrombosis and sepsis. The oral fluoropyrimidine capecitabine (Xeloda®) was designed to generate 5-FU preferentially in tumour tissue and to mimic continuous infusions of 5-FU with the advantage of oral administration [9, 10]. Capecitabine has been shown to be effective in the treatment of gastrointestinal malignancies, including its use in combination with cisplatin [4, 6, 11]. 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 [12–14]. Oxaliplatin has a more favourable 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 [15]. In contrast to cisplatin, oxaliplatin has demonstrated efficacy alone and in combination with 5-FU in metastatic colorectal cancer (MCRC). Many studies are ongoing to test the combination of 5-FU and oxaliplatin in non-colorectal gastrointestinal tumours and other malignancies [16]. Oxaliplatin is active in both MCRC and as adjuvant treatment for early colon cancer, with superior efficacy over 5-FU/LV alone [17, 18]. There is clear, preclinical synergy with capecitabine and oxaliplatin in MCRC [19] with no overlap in key toxicities. Recently, oxaliplatin plus 5-FU/LV combination chemotherapy also showed promising results in patients with AGC [20, 21].

The results of a pilot study on the efficacy and safety of the XELOX regimen for older patients with AGC have been published and it was found that XELOX produced a very good response rate and PFS [22]. Hence, the primary objective of this multicentre phase II study was to further evaluate the anti-tumor efficacy (response rate) of XELOX in previously untreated patients with AGC. Secondary objectives were to evaluate the PFS, overall survival and safety of this regimen.

Materials and methods

Overall study design

This was an open-label, single-arm, multicentre phase II study, which was conducted to further evaluate the efficacy and safety profiles of this regimen in previously untreated patients with AGC.

Inclusion and exclusion criteria

Inclusion criteria were: histologically confirmed non-resectable AGC, initially diagnosed or recurrent; one or more unidimensionally measurable tumour lesions with a diameter $\geq$20 mm using conventional CT scan or MRI, or $\geq$10 mm using spiral CT scans; age 18–75; estimated life expectancy of $\geq$3 months; Eastern Cooperative Oncology Group (ECOG) performance status $\leq$2; adequate organ function as defined by: serum creatinine $\leq$1.5 mg/dl or calculated creatinine clearance $\geq$60 ml/min; serum transaminases $<3 \times$ upper normal limit; serum bilirubin $<$2 mg/dl; neutrophil count $\geq$1,500/mm^3, haemoglobin level $\geq$8 g/dl, and platelets $\geq$75,000/mm^3. Patients had to be willing and able to comply with the protocol for the duration of the study, and to provide written informed consent prior to study-specific screening procedures, with the understanding that the patient has the right to withdraw from the study at any time, without prejudice.

Exclusion criteria were: contraindication to any drug contained in the chemotherapy regimen; tumour type other than adenocarcinoma; evidence of CNS metastases; previous adjuvant treatment with capecitabine or platinum completed less than 6 months before the study; evidence of serious gastrointestinal bleeding; history of another malignancy within the past 5 years. The protocol was approved by the institutional review boards of the four participating institutes.

Treatment schedule

Patients received capecitabine (1,000 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 day 1–14, followed by a 1-week rest period. Treatment continued until disease progression, intolerable toxicity or eight cycles 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 for adverse events

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 3.0). For haematological 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 non-haematological 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. Ttreatment was stopped permanently if grade 4 non-haematological toxicities occurred.

For non-haematological 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 non-haematological toxicities, oxaliplatin was suspended for a maximum of 3 weeks from the scheduled date of re-infusion 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.

Evaluation criteria

A physical examination, including neurological examination and complete blood counts, was performed before the first treatment cycle. Complete blood cell counts with differential and serum biochemistry analyses were repeated at each treatment cycle. Response was assessed radiologically every two cycles or when progression was suspected. Evaluations were performed by physical examination, chest X-ray and abdominal-pelvic CT scan. Complete response, partial response, stable disease and progressive disease were defined according to RECIST criteria [23]. All the objective responses were confirmed after 4 weeks and clinical complete responses were confirmed as pathological complete responses by gastroendoscopy biopsy.

Statistical analysis

All enrolled patients were included in an intent-to-treat analysis of efficacy. The null hypothesis (H0) was that the overall response rate was ≤40%. The alternative hypothesis (H1) was that the overall response rate was ≥60%. The Ensign's [24] three-stage design approach provided 80% power and a 0.05 level of significance overall, to distinguish between the null and alternative hypotheses. Ensign's three-stage design approach was used to define early stopping rules for this study. Assuming a true response rate of ≥60%, 43 patients were to be included. Taking into account the drop-out rate, the number of patients enrolled was 51. Overall response rate [with 95% confidence intervals (CI)] was calculated for all patients according to an intention-to-treat analysis. PFS was calculated from the first day of chemotherapy until the date of disease progression. Overall survival was calculated from the start of study treatment until death. PFS and overall survival curves were generated using the Kaplan–Meier method. Response duration was calculated from the date of response confirmation to the date of disease progression.

Results

Patient demographics

Overall 54 patients were enrolled (37 men, 17 women); 2 patients were dropped-out after 4 cycles of chemotherapy. Fifty-four patients were evaluated for treatment response, safety and overall survival calculations. Baseline patient characteristics are shown in Table 1. This was a typical first-line trial population, with patients having a median age of 57 years and the majority (89%) having a good performance status (ECOG 1). Median follow-up duration was 13 months (range 9–15.5).

Antitumour activity

The overall response rate was 63% (95% CI, 56–70%), with a complete response (CR) in three patients and a partial response (PR) in 31 patients (Table 2). All responses were confirmed (the three CRs were confirmed by pathological examination). Only 9% of patients (5/54) progressed while on XELOX. Stable disease (SD) was demonstrated in 13 patients (24%). Among 33 patients who showed responses, the median duration of response is 4.8 months. The median PFS was 5.8 months (95% CI, 4.4−7.2 months) (Fig. 1). The median overall survival was 11.9 months (95% CI, 8.8–15.1 months) (Fig. 2).

Table 1 Baseline patient characteristics (n = 54)

Characteristic	No. of patients	%
Median age, years (range)	57 (29–70)	
Male/female	37/17	69/31
Newly diagnosed AGC/recurrent AGC	50/4	93/7
ECOG performance status, number (%)		
1	48	89
2	6	11
Metastatic sites		
Liver	37	67
Lung	5	9
Abdominal lymph node (LN only)	27 (5)	50 (9)
Soft tissue	3	6
Peritoneal dissemination	5	9
Number of metastatic sites		
1	14	26
2 (median)	25	46
≥3	15	28

Table 2 Treatment response ($n = 54$)

Response	Number of patients	% (95% CI)
Overall response rate	34	63 (44–84)
Complete response (CR)	3	6 (5–7)
Partial response (PR)	31	57 (36–78)
Stable disease (SD)	13	24 (13–35)
Progressive disease (PD)	5	9 (7–11)
CR + PR + SD	47	87 (83–91)

CI confidence intervals

Safety

A total of 311 treatment cycles (median 6, range 1–10 cycles) were administered. Treatment was delayed or the dose reduced in 30 and 15% of cycles, respectively. Most of the treatment delay (81/93; 87%) and dose reduction (36/47; 79%) were due to haematologic toxicities (leukopenia and thrombocytopenia). The other reasons for dose modification were hand-foot syndrome (HFS) and neurotoxicity. The majority of adverse events were grade 1 or 2 in severity (Tables 3, 4). Grade 3 or 4 adverse events were rare. No patients stopped treatment because of treatment-related adverse events. The most common reason for treatment discontinuation is treatment completion (29/54, 54%). The other reasons are disease progression (23/54, 43%), and drop-out (2/54, 3%). The most common non-haematological adverse events were neuropathy (70%; Grade 1 or 2), vomiting (50%; 2% in grade 3, 48% in grade 1 or 2), diarrhoea (33%; 7% in grade 3, 26% in grade 1 or 2), and HFS (39%; 13% in grade 2, 26% in grade1) (Table 3, Fig. 3). The most common haematological adverse event was anaemia (70%; 7% in grade 2, 63% in grade1) (Table 3, Fig. 3). Neutropenia was observed in 48% of the patients. Grade 3 neutropenia was observed in three patients and grade 4 in one patient. One patient experienced neutropenic fever. Four patients experienced grade 3 thrombocytopenia, which was accompanied in one patient by grade 3 gastrointestinal bleeding. There was one treatment-related death, which was associated with grade 4 neutropenic sepsis (the same patient who experienced neutropenic fever).

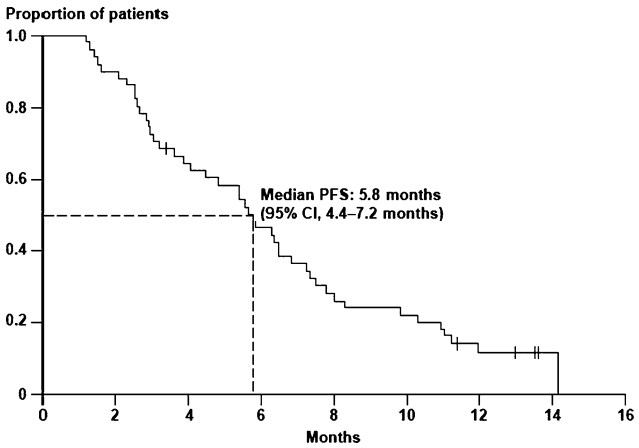

Fig. 1 Progression-free survival ($n = 54$)

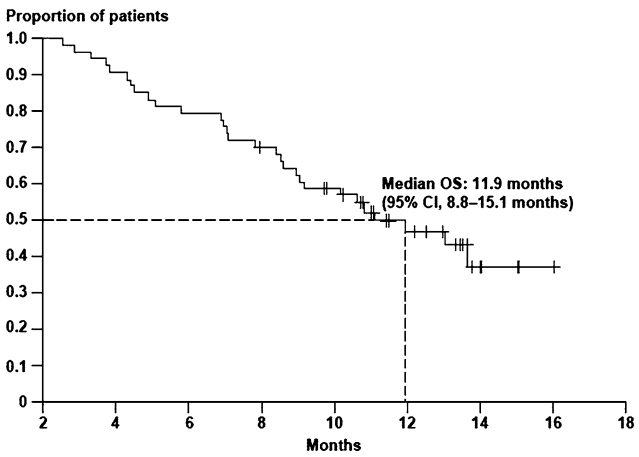

Fig. 2 Overall survival ($n = 54$)

Discussion

This phase II study demonstrated that capecitabine 1,000 mg/m^2 orally twice daily plus oxaliplatin (XELOX regimen) was active and well-tolerated as first-line therapy in patients with AGC. The overall response rate was 63% and, after a median follow-up of 13 months, median PFS was 5.8 months and median overall survival was 11.9 months. These findings compare favourably with two

Table 3 Most common adverse events ($n = 54$)

Adverse event	Grade (% of patients)			
	1	2	3	4
Non-haematological adverse events				
Neuropathy	63	7	0	0
Vomiting	41	7	2	0
Diarrhoea	15	11	7	0
Hand-foot syndrome	26	13	0	0
Stomatitis	11	9	0	0
Bleeding	0	2	7	0
Haematological adverse events				
Anaemia	63	7	0	0
Leukopenia	31	11	6	0
Neutropenia	29	11	6	2
Thrombocytopenia	9	15	9	2

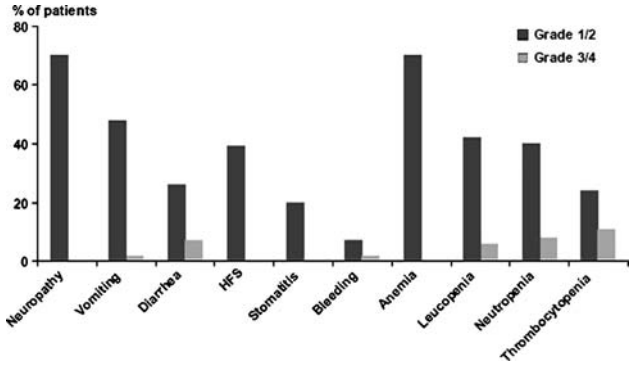

Fig. 3 Most common treatment-related adverse events (all grades, $n = 54$)

recent 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 46 and 55%, respectively (using capecitabine doses of 1,250 and 1,000 mg/m^2 twice daily, respectively) [11, 25]. The results of our previous pilot study on the efficacy and safety of the XELOX combination regimen for older patients with AGC have been published and it was found that XELOX produced a very good response rate and PFS in patients with AGC [22]. These findings are also supported by results of large phase III studies recently presented at ASCO 2006. However, considering high response rate, PFS is relatively short. This might be due to short response duration (median 4.8 months). Further research to overcome this point should be followed. Triple combination chemotherapy including other agents [26], and addition of new targeted therapy can be considered.

A recent randomized phase III trial in 316 patients with AGC reported that capecitabine plus cisplatin combination chemotherapy showed highly significant non-inferiority for PFS 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 [27]. 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 1,002 patients has shown that capecitabine can replace 5-FU and oxaliplatin can replace cisplatin in triplet combinations used for the treatment of advanced esophagogastric cancer [28]. 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 multicentre study was that XELOX had a good safety profile. In our study, no patient stopped treatment because of treatment-related adverse events. Among 47 patients (87%) who showed responses and stable disease, 28 patients (60%) had completed the maximum number of treatment cycles, and 19 patients (40%) had stopped before disease progression. 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 favourably with that of capecitabine/cisplatin as reported by Kim et al. [11]; while there were similar rates of grade 3/4 thrombocytopenia reported here and in the study by Kim et al. [11], the rate of grade 3/4 neutropenia was considerably lower here (8% 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. [11], and this might be the result of the lower dose of capecitabine used here (1,000 mg/m^2). Indeed, in the phase III study using the same dose of capecitabine (1,000 mg/m^2 orally twice daily) and cisplatin 80 mg/m^2 i.v. [27], the rate of grade 3/4 neutropenia was 13%, which is higher than that reported here. The rate of neuropathy (70%) is higher than that reported in other studies using this combination or capecitabine/cisplatin, but no grade 3 or 4 toxicities were reported. Our study showed relatively low incidence of diarrhoea and neurotoxicity when compared with those of the CRC trials [17–19]. Further research should be followed to explain these results; however, ethnic difference should also be considered.

When comparing oxaliplatin with cisplatin, oxaliplatin has a more favourable safety profile as it has no ototixicity or 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 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 [29]. They showed FLO reduced toxicity and improved efficacy as compared to FLP. This result also supported that oxaliplatin can replace cisplatin.

Given the efficacy and safety of the XELOX combination, it is feasible that it may also be effective in the adjuvant treatment of early gastric cancer. A study of XELOX versus observation has just started enrolling patients in Asia and should finish accrual by the middle of 2007. Promising results reported with adjuvant chemotherapy should encourage research with novel regimens such as XELOX.

In conclusion, capecitabine/oxaliplatin (XELOX) combination chemotherapy is active in patients with previously untreated AGC. This promising combination regimen

overcomes the issues of poor tolerability and inconvenience associated with other regimens currently used in this type of cancer. 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.

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