

Triweekly Oxaliplatin Plus Oral Capecitabine as First-Line Chemotherapy in Elderly Patients With Advanced Gastric Cancer

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Objectives: To investigate the efficacy and safety of oxaliplatin plus oral capecitabine (XELOX) as first-line chemotherapy in elderly patients with advanced gastric cancer (AGC).

Patients and Methods: Forty-four previously untreated patients with AGC aged 70 or older participated in the study. They received oxaliplatin 130 mg/m² as 2-hour intravenous infusion on day 1 and oral capecitabine 1000 mg/m² twice daily on days 1 to 14 every 3 weeks XELOX.

Results: All patients were assessable for toxicity and 41 patients for response. Median age was 75 years (range, 70–83). In total, 215 cycles of XELOX were delivered. The response rate according to Response Evaluation Criteria in Solid Tumors was 51.2% (95% confidence interval [CI]: 35.9%–66.5%), with 2 complete responses, 19 partial responses, 11 stable diseases, and 9 progressions. At 9.5 months median follow-up, median time to progression and overall survival were 5.6 (95% CI: 4.6–6.6) and 9.8 months (95% CI: 7.4–12.2), respectively. Toxicities were generally mild. Grades 3 to 4 adverse events included: neutropenia (6 patients, 13.6%), diarrhea (6 patients, 13.6%), thrombocytopenia (5 patients, 11.4%), hand-foot syndrome (4 patients, 9.1%), nausea and vomiting (2 patients, 4.5%), and anemia (1 patient, 2.3%). Neutropenic fever occurred in 2 patients. There was no treatment-related death.

Conclusions: XELOX is active and well tolerated as first-line chemotherapy for elderly patients with AGC. Given its ease of administration, it represents a good therapeutic option in the elderly.

Key Words: oxaliplatin, capecitabine, chemotherapy, advanced gastric cancer, elderly

(*Am J Clin Oncol* 2009;32: 559–563)

Despite a decline in its incidence, gastric cancer remains the fourth most commonly diagnosed cancer and is, after lung cancer, the second leading cause of cancer-related death worldwide, with about 700,000 deaths annually. Almost two-thirds of the cases occur in developing countries and 42% in China alone.¹ The incidence of gastric cancer increases with age.² Because of a progressively ageing population, it can be expected that the number of elderly with gastric cancer will increase significantly in the coming decades.

Despite recent advances achieved in the diagnosis and treatment of gastric cancer, many patients present with advanced disease. It carries a poor prognosis, amplifying the importance of palliative chemotherapy. Recently combination chemotherapy yields a significant positive development in the treatment options for patients with advanced gastric cancer (AGC).^{3–6} However, chemotherapy is used

less frequently in the elderly than in other age groups. Factors that influence the reluctance to use chemotherapy in the elderly include: a general lack of studies in this age group; the fear that the gradual degeneration of various organs with ageing might increase the susceptibility of the elderly to adverse effects and comorbidity which makes it difficult or impossible to use chemotherapy. Therefore, the search for a safe and effective chemotherapy regimen for elderly patients with AGC remains an urgent task.

Up to now there is no single, global standard regimen for the first-line chemotherapy of AGC. “Classic” chemotherapy regimens, mainly cisplatin and infusional 5-fluorouracil and cisplatin plus infusional 5-fluorouracil plus epirubicin achieve response in 20% to 40% of the patients.⁷ Nevertheless, duration of these responses is short with very few complete responses (CR). Median time to tumor progression with these regimens is only about 4 to 5 months and median survival does not exceed 7 to 10 months.⁷ Treatment with 5-fluorouracil infusion requires the use of a central venous access device which harbors potential complications such as infections⁸ or thromboembolism,⁹ and cisplatin treatment is frequently associated with moderate to severe emesis and peripheral neuropathy. Thus, more convenient but less toxic chemotherapeutic regimens need to be developed for the treatment of patients with AGC. Oxaliplatin seems to be more effective than cisplatin with regard to DNA inhibition and has a more favorable toxicity profile.¹⁰ Capecitabine is a novel oral fluoropyrimidine carbamate that generates 5-fluorouracil preferentially in tumors through exploitation of the significantly high levels of thymidine phosphorylase in tumor tissue compared with healthy tissue.¹¹ The response rate of capecitabine as a single drug was reported to be 19.3% as a first-line therapy for gastric cancer.¹² REAL-2 study indicated that cisplatin and infused 5-fluorouracil can be replaced by oxaliplatin and capecitabine in the treatment of advanced oesophagogastric cancer.¹³

Oxaliplatin plus oral capecitabine (XELOX) regimen has already been shown to be active in first- and second-line treatment for AGC.^{14–17} But there are few reports whether XELOX regimen is active and tolerable for elderly patients with AGC. So we conducted a phase II study to investigate the efficacy and safety of XELOX regimen in elderly patients with AGC.

PATIENTS AND METHODS

Selection of Patients

To be eligible for this study, patients must have histologically confirmed AGC (at least 1 measurable lesion), aged 70 or older, an Eastern Cooperative Oncology Group performance status of 0 to 2, chemo-naïve status, normal hepatic, renal and bone marrow functions, life expectancy ≥ 3 months, no central nervous system metastases, no serious or uncontrolled concurrent medical illness, and no history of other malignancies. All patients who participated in the study had filled an informed consent form, which was conducted according to the Good Clinical Practice guidelines and the principles described in the Declaration of Helsinki.

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ISSN: 0277-3732/09/3206-0559

DOI: 10.1097/COC.0b013e3181967db3

TABLE 1. Patients' Baseline Characteristics (n = 44)

Characteristics	Number (%)
Age (yr)	
Median	75
Range	70–83
Sex	
Male	33 (75.0)
Female	11 (25.0)
ECOG performance status	
0	5 (11.4)
1	37 (84.1)
2	2 (4.5)
Locally advanced disease	10 (22.7)
Metastatic disease	34 (77.3)
Sites of metastases	
Liver	26 (59.1)
Lung	5 (11.4)
Abdominal lymph nodes	32 (72.7)
Peritoneum	10 (22.7)
Other*	11 (25.0)
Differentiation	
Well differentiated	4 (9.1)
Moderately differentiated	14 (31.8)
Poorly differentiated	26 (59.1)
No. metastatic sites	
1	11 (25.0)
2	25 (56.8)
≥3	8 (18.2)
Previous surgery	
Gastrojejunostomy	1 (2.4)
Subtotal gastrectomy	2 (4.9)

*Ovary, bone, pancreas, cervical lymph node.

TABLE 2. Response Rates of Patients According to RECIST Criteria (n = 41)

Response	Number (%)
Complete response	2 (4.9)
Partial response	19 (46.3)
Stable disease	11 (26.8)
Progressive disease	9 (22.0)
Overall response rate	21 (51.2)
Overall tumor control rate	32 (78.0)

Treatment Plan

This was a single institute, nonrandomized, prospective phase II study. Oxaliplatin 130 mg/m² was administered as a 2-hour intravenous infusion in 500 mL of 5% glucose on the first day of each 3 weeks cycle. Capecitabine was administered orally at a dosage of 1000 mg/m² twice daily according to the standard intermittent schedule (from the evening of day 1 until the morning of day 15 followed by a 7-day rest period). The 2 daily doses of capecitabine were administered 12 ± 2 hours apart, 30 minutes after meals (breakfast and evening meal). All patients received 5-HT₃ antagonist for emesis prophylaxis before each oxaliplatin dose. Patients were scheduled to receive a maximum of 8 cycles, and chemotherapy was stopped in case of disease progression, patient refusal, or unaccept-

able toxicity. If the disease progressed, it could be treated with other chemotherapy regimens provided they did not include either capecitabine or oxaliplatin.

Assessment of Activity and Toxicity

Tumor responses were evaluated by physical examination and necessary imaging studies. All the measurable lesions were evaluated at base line by spiral computer tomography scans and were repeated every 2 cycles to document CR, partial response (PR), stable disease, or progressive disease according to the Response Evaluation Criteria in Solid Tumors criteria.¹⁸ All the objective responses were confirmed after 4 weeks by CT scan and clinical CR was confirmed as pathologic CR by gastroscopic biopsy.

Adverse events were classified according to National Cancer Institute Common Toxicity Criteria version 2.0. Hand-foot syndrome was graded as follows on the basis of appearance, distribution, and symptoms: grade 1 = dyesthesia/paresthesia, tingling in the hands and feet; grade 2 = discomfort in holding objects and upon walking, painless swelling, or erythema; grade 3 = painful erythema and swelling of palms and soles, periungual erythema, and swelling; and grade 4 = desquamation, ulceration, blistering, and severe pain.¹⁹

Complete blood cell counts with differential counts analyses were repeated twice a week. When neutropenia, thrombocytopenia, or anemia grade ≥2 developed, the use of recombinant human granulocyte colony-stimulating factor (G-CSF), thrombopoietin or interleukin-11 (IL-11), or erythropoietin was permitted. Prophylactic administrations of pyridoxine or G-CSF were not performed.

Dose Modification for Adverse Events

Capecitabine treatment interruption or dose reduction was not indicated for grade 1 toxicity or for events unlikely to become serious or life threatening. Treatment was interrupted in cases of grade 2 or higher events (with the exception of alopecia, nausea or vomiting, and anemia) and was not resumed until the adverse event resolved or improved to grades 1 or 0. Capecitabine dose reduction was not required at the first occurrence of a grade 2 event. Capecitabine dose was reduced by 25% to 750 mg m⁻² twice daily for patients who experienced a second occurrence of a given grade 2 event or any grade 3 event. Capecitabine dose was reduced by 50% to 500 mg m⁻² twice daily for patients who experienced a third occurrence of a given grade 2 event, a second occurrence of a given grade 3 event, or any grade 4 event. Treatment was discontinued if, despite dose reduction, a given adverse event occurred for a fourth time at grade 2, a third time at grade 3, or a second time at grade 4. If an adverse event did not improve to grade 1 or less after 3 weeks, the affected patient was withdrawn from the study.

Oxaliplatin treatment interruption or dose reduction was not indicated for grade 1 toxicity. Treatment was interrupted in cases of grade 2 or higher adverse events and was not resumed until the toxicity resolved or improved to grades 1 or 0. Treatment was discontinued in cases of grades 3 to 4 neuropathy. If paresthesiae with pain or with persistent functional impairment were the only toxicities present at the time of the next planned administration of oxaliplatin, oxaliplatin was delayed and capecitabine continued as monotherapy. If the neurologic toxicity was still present at the time of the next planned treatment cycle, oxaliplatin was discontinued permanently. In these circumstances, capecitabine was continued as monotherapy at the discretion of the investigator.

Statistical Analysis

The primary end point of the study was to determine the response rate and toxicity of XELOX regimen as first-line chemotherapy for elderly patients with AGC. The secondary end point was to measure the time to disease progression (TTP) and overall

survival time (OS). The expected number of patients for this study was calculated according to a Simon optimal 2-stage design with predetermined 1-sided (α) = 0.05, power $1-(\beta)$ = 0.80. The null hypothesis was that the response rate was $\leq 30\%$ versus the alternative that it was at least 40%, and then 41 assessable patients were to be enrolled. Follow-up controls were performed monthly thereafter.

TTP was measured from the date therapy was initiated to the date of documented disease progression. OS was measured from the date therapy was initiated to the date of death or final follow-up. All data were analyzed by SPSS software (version 10.0). TTP and OS were calculated via the Kaplan-Meier method.

RESULTS

Patients' Characteristics

From January 2002 to January 2006, a total of 44 patients with AGC aged 70 or older in Shandong Tumor Hospital and Institute were enrolled in this study. All relevant patient characteristics were listed in Table 1. All the 44 patients were evaluable for toxicity and 41 patients for response. One patient could not be evaluated for response because of follow-up loss after the second cycle of chemotherapy, and 2 patients refused further chemotherapy after the first cycle because of treatment-related diarrhea and vomiting, respectively. These 41 patients who finished more than 2 chemotherapy cycles were analyzed for both the short-term and long-term efficacy.

Efficacy

A total of 215 treatment cycles (median 5, range 1–8 cycles) were administered. Forty-one patients could be evaluated for efficacy. Two patients (4.9%) achieved a CR confirmed by gastroscopic biopsy, and 19 patients (46.3%) attained a PR, with an overall objective response rate of 51.2% (95% confidence interval [CI]: 35.9%–66.5%). Eleven patients (26.8%) had disease stabilization, and 9 patients (22.0%) progressed while on treatment (Table 2).

In the whole group, the median follow-up duration was 9.5 months (range, 2.1–22.0 months). The median TTP was 5.6 months (95% CI: 4.6–6.6 months) and median OS was 9.8 months (95% CI: 7.4–12.2 months). TTP and OS are shown in Figures 1, 2.

Toxicity and Safety

All patients could be evaluated for toxicity. Treatment was well tolerated and every grade of hematologic and nonhematologic toxicities per patient was reported in Table 3. The majority of adverse events were grades 1 to 2. Grades 3 to 4 adverse events were rare. There was no treatment-related mortality.

Eleven patients received G-CSF for grade ≥ 2 neutropenia. Among them 5 patients received G-CSF for 1 cycle, 4 patients for 2 cycles, and 2 patients for 3 cycles. Febrile neutropenia occurred in 2 patients, but both patients were treated with antibiotics and G-CSF without further complications. Five patients received IL-11 for grade ≥ 3 thrombocytopenia. Four patients received IL-11 for 1 cycle, and 1 patient for 2 cycles. No patients received erythropoietin and none of the patients received blood transfusion. Nonhematologic toxicities were manageable. Common nonhematologic toxicities were diarrhea, hand-foot syndrome, nausea/vomiting, and peripheral neuropathy, each of which affected nearly half of the total patient group.

A total of 18 patients experienced treatment delays during the study for causes unrelated to the treatment (2 patients, 11.1%), neutropenia (9 patients, 50.0%), thrombocytopenia (4 patients, 22.2%), and hand-foot syndrome (3 patients, 16.7%). All patients received full dose of oxaliplatin through the study and capecitabine dose was reduced to 75% of the starting dose in 5 patients, for neutropenia in 3 patients, and hand-foot syndrome in 2 patients. There were no patients who required a second dose reduction.

Salvage Chemotherapy on Disease Progression

Twenty-nine of 41 patients who failed XELOX treatment (70.7%) received second-line chemotherapy. Most (72.4%) of these second-line chemotherapy regimens contained docetaxel; 4 of 17 patients who received docetaxel/cisplatin achieved PR (response rate, 23.5%; 95% CI: 3.3%–43.7%). Further chemotherapy was given to 11 patients who failed second-line chemotherapy.

DISCUSSION

Age is a risk factor for cancer because of a longer time of exposition to carcinogens, the vulnerability of aging tissues to environmental carcinogens, and other bodily changes that favor the development and growth of cancer. Gastric cancer is more frequent

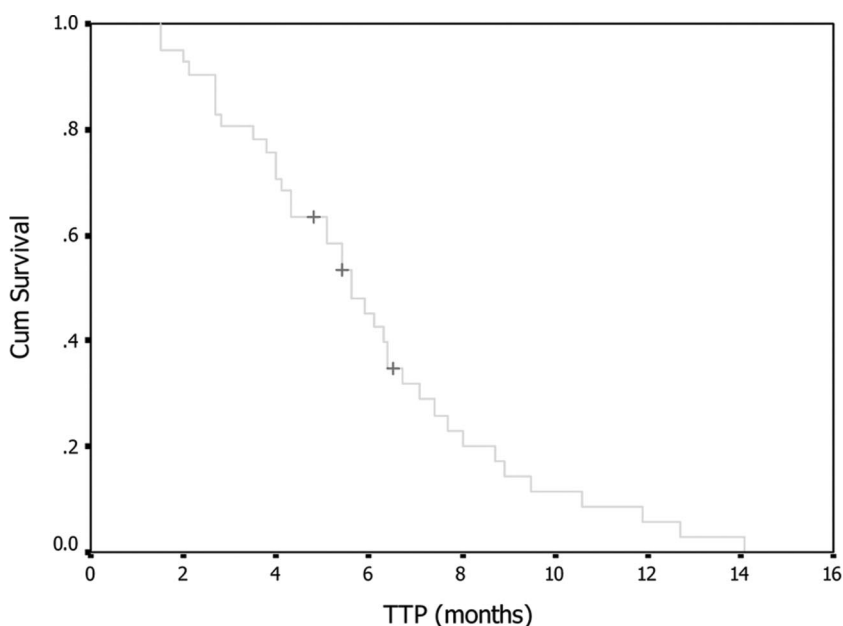


FIGURE 1. Time to progression (n = 41).

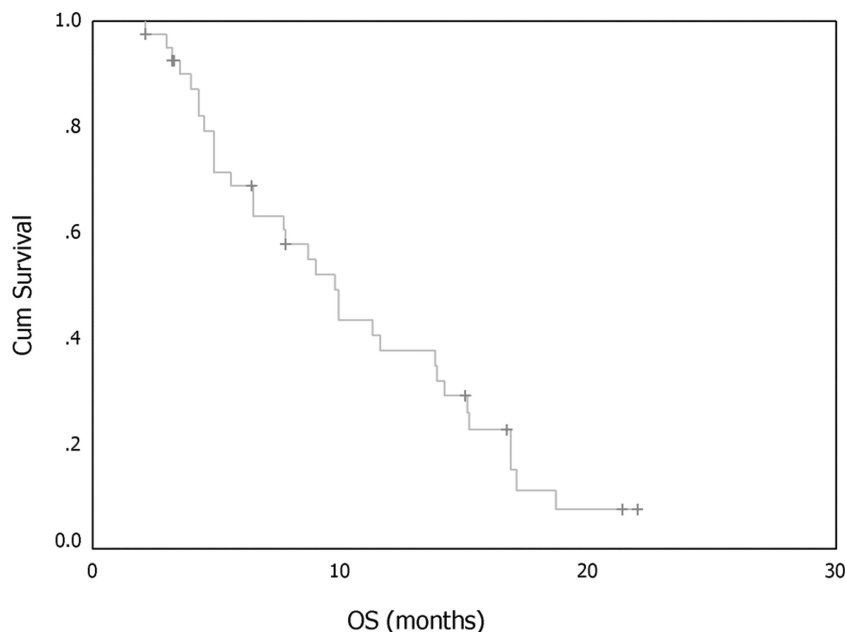


FIGURE 2. Overall survival (n = 41).

TABLE 3. Incidence of Adverse Events According to NCI-CTC Grade (n = 44)

Adverse Events	Incidence			
	Grade 1, n (%)	Grade 2, n (%)	Grade 3, n (%)	Grade 4, n (%)
Hematologic				
Anemia	22 (50.0)	2 (4.5)	1 (2.3)	0
Leucopenia	13 (29.5)	5 (11.4)	2 (4.5)	1 (2.3)
Neutropenia	11 (25.0)	5 (11.4)	4 (9.1)	2 (4.5)
Thrombocytopenia	5 (11.4)	7 (15.9)	3 (6.8)	2 (4.5)
Nonhematologic				
Diarrhea	13 (29.5)	10 (22.7)	6 (13.6)	0
Hand-foot syndrome	12 (27.3)	6 (13.6)	4 (9.1)	0
Nausea/vomiting	14 (31.8)	5 (11.4)	2 (4.5)	0
Peripheral neuropathy	17 (38.6)	2 (4.5)	0	0
Stomatitis	6 (13.6)	4 (9.1)	0	0
Abnormal liver function	3 (6.8)	2 (4.5)	0	0

in the elderly population with the mean age at diagnosis being 70 to 73 years. Notwithstanding this situation, elderly patients have been excluded from or are underrepresented in clinical trials.²⁰ Consequently, the role of palliative chemotherapy is not well defined. Advanced age is often associated with increased health problems such as declining organ function, decreasing cognitive abilities, socioeconomic precariousness, and comorbidities. These factors may possibly reduce the capacity for the elderly patient to tolerate the adverse effects of chemotherapy. As AGC is an incurable disease, treatment must be aimed at prolonging survival, relieving symptoms, and improving or at least maintaining the patient's quality of life. It is necessary to choose chemotherapeutic agents that are less toxic and easier to administer.

In our study, XELOX regimen showed promising activity, with the overall response rate and overall tumor control rate 51.2% and 78.0%, respectively. It is comparable with the activity of other oxaliplatin- or capecitabine-containing regimens.²¹⁻²⁷ XELOX regi-

men had a good safety profile. Common nonhematologic adverse events included diarrhea, hand-foot syndrome, nausea/vomiting, and peripheral neuropathy. Stomatitis and abnormal liver function could also be observed. It was reported that older patients were more susceptible to diarrhea.²⁸ Our study also confirmed this conclusion, with 65.9% in our study versus 33% by Park et al, whose study population was 70 or younger.¹⁶ Neurotoxicity occurred in 43.2% of the patients, which was especially low compared with 70% reported by Park et al.¹⁶ However, given that neurotoxicity depends on the total accumulated dose of oxaliplatin received during treatment, the low toxicity in our study can possibly be attributed to the reduced number of treatment cycles received by our patients compared with the series of Park et al¹⁶ (median 5 vs. 7 cycles, respectively). Hematologic adverse events were also well tolerated. Grades 3 to 4 hematologic toxicities were rare. Anemia was the most common hematologic adverse event and it affected 25 patients (56.8%). Incidence rate of grade 1, grade 2, grade 3, and grade 4 neutropenia was 25.0%, 11.4%, 9.1%, and 4.5%, respectively. In this study, no treatment-related deaths were observed across all chemotherapy cycles, no dose adjustments for oxaliplatin were required whereas 5 patients required a 25% reduction in the starting dose of capecitabine. The low incidence of grades 3 to 4 toxicities was very important for the setting of elderly patients.

In addition to the potential efficacy and safety advantages of XELOX regimen, it is important to consider the ease of oral administration, which avoids the possible complications and inconveniences associated with the use of infusion apparatus.

In conclusion, XELOX regimen is active and well tolerated as first-line chemotherapy for elderly patients with AGC. It overcomes issues of poor tolerability and inconvenience associated with other regimens currently used in this cancer type. Its safety profile and tolerability make it a good therapeutic option for elderly patients with AGC.

ACKNOWLEDGMENTS

The authors thank Dr. Xianrang Song for his assistance with this article.

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