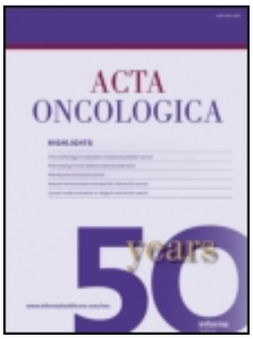

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LETTER TO THE EDITOR

Capecitabine and oxaliplatin (XELOX) is safe and effective in patients with advanced gastric cancer

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To the Editor

Gastric cancer is a leading cause of cancer-related deaths worldwide. The majority of cases are diagnosed in the advanced stages and prognosis is poor, with 5-year survival rates in the range of 5 to 15% [1]. Clinical trials have consistently supported the role of chemotherapy over best supportive care in the setting of advanced gastric cancer (AGC) [2,3].

In prospective randomised trials, combination chemotherapy with epirubicin, cisplatin and infusional 5-fluorouracil (ECF) has been shown to be superior to 5-fluorouracil, doxorubicin, and methotrexate (FAMTX) [4], improving median survival from 5.7 to 8.9 months. And more recently, Moiseyenko and colleagues [5] have demonstrated superior response rates and improved survival of docetaxel, cisplatin and 5-fluorouracil (DCF) over cisplatin and 5-fluorouracil (CF). However both ECF and DCF are toxic, associated with high rates of neutropenia, thus do not provide ideal palliation to patients with AGC.

Oxaliplatin appears to be more effective than cisplatin with regards to DNA inhibition [6] and has a more favourable toxicity profile. In combination with 5-fluorouracil, response rates of 43% and 44.9%, with median survival of 9.6 months and 8.6 months respectively, were achieved in studies by Al-Batran and Louvet [7,8]. Capecitabine is a novel oral fluoropyrimidine carbamate that generates 5-FU selectively in tumor tissue. Preliminary data from the REAL-2 study suggests that in patients with AGC, substitution of capecitabine for 5-fluorouracil does not compromise outcomes when used in combination with an anthracycline and platinum [9].

Therefore it is conceivable that the combination capcitabine-oxaliplatin (XELOX) given 3-weekly, may be efficacious in AGC. This regimen is attractive, as it is well tolerated, does not require a central venous catheter (CVC), and convenient, only requiring a short duration intravenous treatment every 3 weeks. Thus we undertook a retrospective study of all patients with AGC treated with XELOX regimen in our centre from June 2003 to March 2006. The objectives were to study the response rates and overall survival of patients and safety of this regimen.

Thirty-five patients with metastatic gastric cancer who received XELOX regimen were identified. Tumor lesions were measured using the Response Evaluation Criteria in Solid Tumors criteria. Adverse events were graded according to National Cancer Institute common toxicity criteria. Peripheral sensory neuropathy was graded according to the oxaliplatin-specific scale previously described [10]. Overall survival (OS) was calculated from time of diagnosis to time of death.

Median age at diagnosis was 58 years with 20% aged $\geq$70 years. One third of patients have an ECOG performance status of 2–4 (Table I). The median starting doses of capecitabine and oxaliplatin were 1 700 mg/m^2/day (days 1–14) and 130 mg/m^2 (day 1) respectively. The median number of cycles of chemotherapy was 5. Sixty-nine percent and 23% of patients were treated with XELOX in the first and second line setting respectively.

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Table I. Patients characteristics.

	No. of Patients (n = 35)	%
Age, years		
Median	58	
Range	38–80	
≥70 years	28	80
<70 years	7	20
Sex		
Male	18	51
Female	17	49
ECOG		
0–1	25	71
2–4	10	29
Prior Adjuvant Therapy		
Yes	6	17
No	29	83
Dose of Capecitabine (mg/m^2)		
Median	1700	
Range	1200–2500	
Dose of Oxaliplatin (mg/m^2)		
Median	130	
Range	80–130	
No. of Cycles		
Median	5	
Range	1–8	
XELOX as		
1st line chemotherapy	24	69
2nd line chemotherapy	8	23
3rd line and beyond	3	9
Measurable disease	32	91
Evaluated radiologically	29	
Evaluated non-radiologically	3*	
Non-Measurable disease	3†	9

*One patient died of non-neutropenic cholangitis, with a biliary sent-in-situ before his first evaluation scan, while two patients had good tumor marker response and declined further radiological imagings.
†One patient each had ascites, bony and peritoneal metastasis as the only site of metastatic disease.

All 35 patients were assessable for safety and survival analysis, while 29 were assessable for response. Thirty-two patients (91%) had measurable disease; one patient each had malignant ascites, bony and peritoneal metastasis as the only site of disease. Of this 32 patients, 29 were followed up radiologically, one patient died of non-neutropenic cholangitis, with a biliary sent-in-situ before his first evaluation scan, while two patients had good tumour marker response and declined subsequent radiological imagings.

The overall response rate for the 29 patients who had evaluable disease was 52%. Two patients (7%) attained a complete response (CR) and 13 (45%) attained a partial response (PR), while 10 (35%) progressed (PD) and 4 (14%) achieved stable disease (SD). Patients treated with XELOX in the first and second line setting had much better response rates than those who had two or more prior lines of chemotherapy, 61% vs. 50% vs. nil respectively (Table II). For three patients with non-measurable disease, one had clinical improvement of ascites, one had >50% reduction in levels of tumor markers associated with reversal of her paraneoplastic disseminated intra-vascular coagulation, and the third patient reported stability of clinical symptoms.

After a median follow-up of 10.1 months, 23 patients have died, 22 from disease progression. Of the 12 patients who are still alive at time of analysis, 11 patients had progressive disease. The median overall survival for the entire cohort was 7.6 months.

Toxicities were generally mild. Of a total of 161 cycles of XELOX administered, only 17% of patients had sensory neuropathy, all grade 1–2. There were five episodes of grade 3–4 toxicities, predominantly haematological (3 cases), with one patient each having fatigue and diarrhoea.

Discussion

In the current study, XELOX demonstrated good clinical activity in AGC, with an overall objective response rate of 52% and a median OS of 7.6 months. This compares favorably to the response rates of 21–45% and median OS of less than 9 months achieved with other combination chemotherapy, reported in published studies [4,5]. Notably our results were obtained in a cohort of older patients, with compromised ECOG performance status, in whom 32% had received ≥1 prior line of palliative chemotherapy.

XELOX was safe and well tolerated. Although peripheral neuropathy, hand-foot syndrome and diarrhoea were major concerns with the use of XELOX in previous studies on gastrointestinal malignancies [11], they were infrequent in our current study. All were grade 1–2 toxicities except for one patient (3%) who had a grade 3 diarrhoea.

At the time of writing 23 patients have died, one was attributed to a non-cancer death. In contrast, Jatoi and colleagues reported four treatment related deaths in their phase 2 study of 43 patients with metastatic gastro-esophageal cancers treated with first-line capecitabine and oxaliplatin [12]. This difference in toxicity profile, despite a larger proportion of patients having better performance status, could be explained in part by the higher doses of capecitabine used, median of 2000 mg/m^2/day vs. 1700 mg/m^2/day in our current study. Indeed, two of the four patients in the latter study died from myocardial infarctions, which is a known adverse effect of capecitabine [13]. The poor tolerability of XELOX at this dosing was also highlighted in Cassidy's study where 50% of patients required

Table II. Best radiological response in those with measurable disease who were evaluated radiologically (n = 29).

	Overall		Line of XELOX treatment (n = 29)					
			1st		2nd		>2nd	
	n = 29	%	n = 18	%	n = 8	%	n = 3	%
CR+PR	**15**	**52**	**11**	**61**	**4**	**50**	**0**	**0**
CR	2	7	2	11	0	0	0	0
PR	13	45	9	50	4	50	0	0
SD	4	14	3	17	1	13	0	0
PD	10	35	4	22	3	38	3	100

dose reductions [11]. As gastric cancer is inherently a chemosensitive disease, it is therefore arguable to administer XELOX at a lower dose, with capecitabine at 1700 mg/m^2/day and oxaliplatin at 130 mg/m^2, in a bid to reduce toxicity without compromising on efficacy. Another major advantage of XELOX regimen is the avoidance of a CVC and its related complications.

In conclusion, the 3-weekly XELOX, is safe, active and well tolerated in patients with AGC. Its safety profile and tolerability makes it an attractive treatment option especially for elderly patients with poor performance status.

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