VOLUME 22 · NUMBER 11 · JUNE 1 2004

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

XELOX (Capecitabine Plus Oxaliplatin): Active First-Line Therapy for Patients With Metastatic Colorectal Cancer

Jim Cassidy, Josep Tabernero, Chris Twelves, René Brunet, Charles Butts, Thierry Conroy, Filippo Debraud, Arie Figer, Johannes Grossmann, Noriaki Sawada, Patrick Schöffski, Alberto Sobrero, Eric Van Cutsem, and Eduardo Díaz-Rubio

From the Department of Medicine and Therapeutics, Aberdeen; Beatson Oncology Centre, Glasgow; University of Leeds and Tom Connors Cancer Research Centre, Bradford, United Kingdom; Hospital Vall d'Hebrón University Hospital, Barcelona; Hospital Clínico San Carlos Servicio de Oncología, Madrid, Spain; Institut Bergonie, Bordeaux; Centre Alexis Vautrin, Nancy, France; Cross Cancer Institute, Edmonton, Canada; European Institute of Oncology, Milan; Clinica Oncologica, Udine, Italy; Sourasky Medical Center, Tel-Aviv, Israel; Universität Regensburg; Medizinische Hochschule Hannover, Germany; Chugai Pharmaceutical Company Limited, Kamakura, Japan, and University Hospital Gasthuisberg, Leuven, Belgium.

Submitted November 13, 2003; accepted March 8, 2003.

Supported by F. Hoffmann-La Roche Ltd.

Authors' disclosures of potential conflicts of interest are found at the end of this article.

Address reprint requests to Jim Cassidy, MD, CRC Department of Oncology, University of Glasgow, Garscube Estate, Bearsden, Glasgow G61 1DB, United Kingdom; e-mail: j.cassidy@beatson.gla.ac.uk..

0732-183X/04/2211-2084/$20.00

DOI: 10.1200/JCO.2004.11.069

ABSTRACT

Purpose
Capecitabine has demonstrated high efficacy as first-line treatment for metastatic colorectal cancer (MCRC). Oxaliplatin shows synergy with fluorouracil (FU), with little toxicity overlap. The XELOX regimen (capecitabine plus oxaliplatin), established in a previous dose-finding study, should improve on infused oxaliplatin with FU and leucovorin (FOLFOX) regimens. The present studies further characterize efficacy and safety of the XELOX regimen.

Patients and Methods
The antitumor activity of XELOX was investigated in a colon cancer xenograft model. Patients with MCRC received first-line XELOX in 3-week treatment cycles: intravenous oxaliplatin 130 mg/m^2 (day 1) followed by oral capecitabine 1,000 mg/m^2 twice daily (day 1, evening, to day 15, morning).

Results
A preclinical study confirmed that capecitabine has supra-additive activity with oxaliplatin. In the clinical study, 53 of 96 patients (55%) achieved an objective response, and 30 (31%) experienced disease stabilization for ≥ 3 months following treatment. After 24 months' minimum follow-up, median time to disease progression (TTP) and median overall survival were 7.7 and 19.5 months, respectively. XELOX safety was predictable and similar to the FOLFOX4 regimen, except that myelosuppression was uncommon with XELOX (grade 3 or 4 neutropenia, 7%). Most adverse events were mild to moderate, the most common being acute sensory neuropathy (85%). Sixty-day, all-cause mortality was 2%.

Conclusion
XELOX is a highly effective first-line treatment for MCRC. Response rates, TTP, and overall survival are similar to those observed with FU/leucovorin/oxaliplatin combinations. XELOX provides a more convenient regimen, likely to be preferred by both patients and healthcare providers. Capecitabine has the potential to replace FU/LV in combination with oxaliplatin for MCRC.

J Clin Oncol 22:2084-2091. © 2004 by American Society of Clinical Oncology

INTRODUCTION

Intravenous fluorouracil (FU) has been the mainstay of chemotherapy for metastatic colorectal cancer (MCRC) for many years. Prolonged infusion of FU in combination with the biomodulator leucovorin (LV) has an improved safety and efficacy profile compared with the bolus FU/LV,[1-3] but the inconvenience and morbidity associated with long-term central venous access emphasized the need for alternative regimens. Capecitabine is an oral fluoropyrimidine that was rationally designed to generate FU preferentially at the tumor site, via a three-step enzymatic process that exploits the significantly higher activity of thymidine phosphorylase (TP) in tumors, compared with healthy tissue.[4] Twice-daily dosing of oral capecitabine obviates the drawbacks of prolonged infusions of FU. A prospective, integrated analysis of two large, randomized phase III trials in MCRC demonstrated that capecitabine monotherapy achieves significantly higher tumor response rates compared with FU/LV (Mayo Clinic regimen)

(26% *v* 17%, $P < .0002$).[5-7] Capecitabine also had an improved safety profile versus FU/LV (Mayo Clinic regimen), causing significantly less diarrhea, stomatitis, nausea, alopecia, and neutropenia, leading to less neutropenic fever/sepsis and associated hospitalizations.[8] Hand-foot syndrome (HFS) occurred more frequently with capecitabine than with FU/LV, but this cutaneous side effect is never life-threatening and rarely led to hospitalization. A large phase III trial (n = 1,987) is also evaluating capecitabine as adjuvant treatment for patients with Dukes' C colon cancer. A planned safety analysis, conducted 19 months following the enrollment of the last patient, has confirmed that the improved safety profile of capecitabine versus intravenous (IV) FU/LV observed in the metastatic setting is mirrored with adjuvant treatment.[9] Capecitabine is therefore a highly active, more convenient, and better-tolerated alternative to FU/LV in colorectal cancer therapy.

Infused FU/LV in combination with oxaliplatin, a third generation platinum analog, proved more effective than FU/LV alone in the first- and second-line treatment of MCRC. Addition of oxaliplatin to FU/LV therapy significantly increased response rates and time to disease progression (TTP) compared with FU/LV in the first-line treatment of colorectal cancer in three randomized studies[10-12] and as second-line therapy versus FU/LV.[13] Recently, a large cooperative group trial (N9741) showed significant improvements in response rate, TTP, and overall survival with oxaliplatin plus infused FU/LV versus irinotecan plus bolus FU/LV.[14]

Despite the increased efficacy associated with infused FU/LV plus oxaliplatin, the administration schedules for the FU component are inconvenient for both patients and healthcare professionals. These require two bolus injections plus two 22-hour infusions every 2 weeks,[10] or 5 days of continuous infusion with chronomodulation equipment every 3 weeks,[11] or weekly 24-hour infusion.[12] Because capecitabine has already demonstrated its ability to replace FU/LV as a highly effective and more convenient treatment for colorectal cancer, there is a strong rationale for investigating the efficacy and safety of capecitabine in combination with oxaliplatin.

A phase I study showed that the combination of capecitabine with oxaliplatin (XELOX) is feasible and established the recommended dose regimen as IV oxaliplatin 130 mg/m^2 on day 1 followed by oral capecitabine 1,000 mg/m^2 twice daily, days 1 to 14, in a 3-week cycle.[15] A xenograft study has also been performed to further elucidate the preclinical rationale for the XELOX combination. In addition, the current international, phase II study was conducted to evaluate further the efficacy and safety of this regimen as first-line therapy for patients with MCRC and thus determine the potential of capecitabine to replace FU/LV as the standard combination partner for oxaliplatin.

PATIENTS AND METHODS

Evaluation of Capecitabine Plus Oxaliplatin in a Human Cancer Xenograft Model

The effect of capecitabine and oxaliplatin, alone and in combination, on tumor growth and expression of TP in a human colon cancer xenograft model was investigated. The human colon cancer xenograft model, CXF280, was provided by H.H. Fiebig (Freiburg University, Freiburg, Germany). Tumor tissue from human colon cancer CXF280 was inoculated subcutaneously into *BALB*/c nu/nu mice. Drugs were administered when tumor volume (1/2 × length × width × width) reached approximately 0.3 to 0.5 cm^3. To evaluate the antitumor effect of capecitabine and oxaliplatin, tumor size and body weight were measured twice a week. Capecitabine, dissolved in 40 mmol/L citrate buffer (pH 6.0) containing 5% gum arabic, was administered orally for 14 consecutive days. Oxaliplatin in 5% glucose solution was given intravenously on day 1. Tumor TP was measured by enzyme-linked immunosorbent assay, with monoclonal antibodies specific for human TP as described previously.[16]

Phase II Study Design

This was a large, open-label, phase II study, conducted at 13 centers in Europe, Israel, and North America. The primary end point was overall response rate as assessed by the investigator. Secondary end points included independently reviewed response rate, TTP, overall survival, 1-year survival, and safety. The study was performed in accordance with the Helsinki declaration and its amendments, and ICH-GCP guidelines.[17] All patients provided written, informed consent.

Patients

Patients aged 18 to 75 years with measurable, histologically confirmed metastatic or locally advanced colorectal cancer were eligible for the study. Patients were required to be ambulatory and have a Karnofsky performance status of $> 70\%$, with a life expectancy of ≥ 3 months. Prior chemotherapy for advanced disease was not permitted, but adjuvant or neoadjuvant chemotherapy was allowed, providing it was completed at least 6 months before start of study treatment. Exclusion criteria included prior therapy with capecitabine, oxaliplatin, or irinotecan, history of previous malignancy within 5 years, clinically significant cardiac disease, evidence of CNS metastases, radiotherapy or surgery within 4 weeks before treatment, neutropenia (< 1.5 /μL), thrombocytopenia (< 100/μL), severe renal function impairment (creatinine clearance < 30 mL/min), or abnormal liver function. Pregnant or lactating women were excluded from the study; women of childbearing potential and sexually active males were required to agree to practice appropriate and adequate contraception.

Study Assessments

Prestudy screening assessments included a full medical history, vital signs and physical measurements, and hematologic and blood chemistry tests. Tumor assessments were performed by computed tomography scan, x-ray, and/or magnetic resonance imaging during screening, after the first three cycles of treatment, then after every two cycles of treatment until disease progression or withdrawal from study medication. In patients whose disease had not progressed when stopping treatment, tumor assessments were performed every 3 months until progression. In addition to investigator assessment, tumor imagery was evaluated by an independent review committee (IRC), using x-ray, magnetic resonance imaging, or computed tomography scans. Investigators and

the IRC assessed the same scans. In addition, survival was monitored at intervals of every 3 months in each patient leaving the study. Tumor response was assessed according to WHO criteria[18] and confirmed at least 4 weeks later by the same evaluation. TTP was defined as the interval between the first dose of study treatment and the first recording of disease progression or death.

Adverse events, including neurosensory toxicity and HFS, were classified by National Cancer Institute Common Toxicity Criteria version 2.

Treatment

Treatment comprised IV oxaliplatin 130 mg/m^2 (diluted in a 5% glucose solution) day 1 then oral capecitabine 1,000 mg/m^2 twice daily from the evening of day 1 to the morning of day 15, followed by a 7-day treatment-free interval, in a 3-week cycle. Pyridoxine prophylaxis or treatment for HFS was not permitted during this study, given that pyridoxine has been reported to reduce the efficacy of cisplatin.[19] The capecitabine starting dose was reduced to 75% of the standard capecitabine starting dose in patients with moderate renal impairment (30 mL/min $\leq$ creatinine clearance $<$ 50 mL/min). The dose of capecitabine was adjusted for adverse events of grade 2 or higher intensity, according to the standard scheme, described in detail by Blum et al.[20] The dose of oxaliplatin was reduced for grade 3 vomiting, grade 3 or 4 thrombocytopenia, or grade 4 neutropenia, and for paresthesiae with pain or functional impairment $>$ 7 days, or paresthesiae with pain persistent between cycles. For paresthesiae with functional impairment persistent between cycles, oxaliplatin was discontinued.

The planned number of treatment cycles was 11, but patients maintaining a response or stable disease after this time could continue treatment at the discretion of the investigator. Patients could also continue capecitabine monotherapy after discontinuation of oxaliplatin irrespective of the number of cycles already received.

Statistical Analysis

The efficacy analyses were based on the intent-to-treat population. The primary end point was overall confirmed response rate, as assessed by the investigators. The 95% CI for response risk was calculated. According to the method of Fleming,[21] 80 assessable patients were required to demonstrate a 40% overall response rate with a power of 90%. TTP and survival were estimated by Kaplan-Meier analysis. Safety was analyzed in all patients who received at least one dose of study medication.

Clinical cutoff for the study analysis was January 15, 2003. A minimum follow-up of 24 months had been reached in all patients.

RESULTS

Capecitabine and Oxaliplatin in a Preclinical Xenograft Model

In a human tumor xenograft model, the combination of capecitabine and oxaliplatin inhibited the in vivo growth of CXF280 human colon cancer more effectively than either agent alone, administered at their maximum-tolerated doses (Fig 1). Toxicity in terms of weight loss did not appear to be additive in the capecitabine plus oxaliplatin group. Furthermore, oxaliplatin upregulated TP expression in CXF280 tumor tissue (Fig 2). The high activity observed with capecitabine and oxaliplatin may be due, therefore, to upregulation of TP. The fact that toxicity (monitored by assessing body weight loss) was not enhanced with the XELOX combination may support the hypothesis that TP upregulation is a tumor-specific phenomenon.

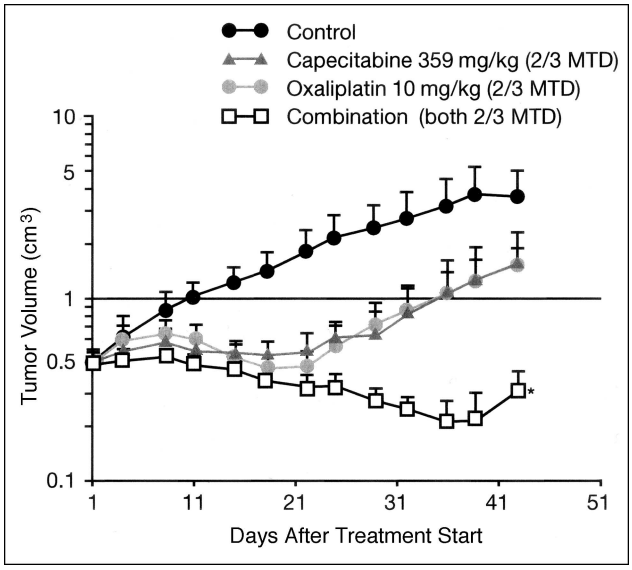

Fig 1. Inhibition of tumor growth (± standard deviation) by capecitabine, oxaliplatin, and the combination in a human colon cancer xenograft model CXF280. $P < .05$ versus both single agents. MTD, maximum tolerated dose.

Patient Demographics

A total of 96 patients were recruited between July 2000 and March 2001, from 13 centers in seven countries (Belgium, Canada, France, Germany, Israel, Italy, Spain, and the United Kingdom). The patient profile was typical of a first-line MCRC trial population: approximately half of the patients (54%) had multiple metastases, with liver, lymph nodes, and lung being the most frequent sites of metastases (Table 1). One enrolled patient initially diagnosed with a colorectal cancer liver metastasis was subsequently found to have a hemangioma, rather than metastatic disease. The median time from the primary diagnosis of colorectal can-

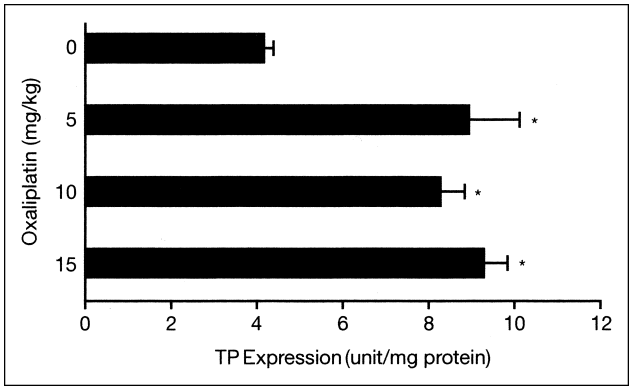

Fig 2. Oxaliplatin further upregulates thymidine phosphorylase in CXF280 human colon cancer xenografts (bars indicate standard deviation). $P < .05$ versus control (oxaliplatin). TP, thymidine phosphorylase.

Table 1. Patient Characteristics (N = 96)

	No. of Patients	%
Sex		
Male	64	
Female	36	
Age, years		
Median	64	
Range	34-79	
KPS		
Median	100	
Range	80-100	
Type of cancer		
Colon only	61	64
Rectal only	32	33
Colon and rectal	3	3
Single metastasis	43	45*
Multiple metastases	52	54
Metastatic sites		
Liver	74	77
Lymph node	36	38
Lung	31	32
Differentiation		
Well differentiated	12	13
Moderately differentiated	62	65
Poorly differentiated	14	15
Undetermined/unknown	8	8
Prior (neo)adjuvant chemotherapy	27	28
IV FU†	26	27
Oral tegafur/uracil	1	1
Prior radiotherapy	11	11

Abbreviations: KPS, Karnofsky performance status; FU, fluorouracil; IV, intravenous.
*A single lesion in one patient originally recorded as a metastatic site was subsequently found to be a hemangioma.
†With or without biomodulating agent.

cer to inclusion was 2.9 months. Of the 27 patients (28%) who had received prior adjuvant or neoadjuvant chemotherapy, 26 had received IV FU, and one had received oral tegafur/uracil. Eleven patients (11%) had received prior radiotherapy.

Treatment

A total of 39 patients (39%) completed the planned 11 cycles of either XELOX or capecitabine monotherapy, of whom 21 (22%) continued with either XELOX or capecitabine monotherapy after 11 cycles. A median of eight cycles of XELOX combination therapy (range, one to 26 cycles) were administered, and patients received a median of two cycles of capecitabine monotherapy after discontinuation of oxaliplatin (range, one to 39 cycles). Table 2 shows the numbers of patients receiving XELOX or capecitabine monotherapy at each cycle.

Efficacy

All efficacy analyses were conducted on the intent-to-treat population, which comprised all patients enrolled—that is, none of the enrolled patients withdrew before receiving treatment. All patients were followed up for a minimum of 24 months. An objective response was observed in 53 patients (55%; 95% CI ,45% to 65%; Table 3), with complete response in two patients (2%). All objective responses were confirmed at least 4 weeks after first observation. Disease stabilization was achieved in a further 30 patients (31%; 95% CI, 22% to 42%). Notably, disease stabilization lasted longer than 3 months from start of treatment in all of these patients.

Table 2. Patients Receiving XELOX or Capecitabine Monotherapy at Each Cycle

Cycle	Total No. of Patients*	No. of Patients Receiving	
		XELOX	Capecitabine Monotherapy
1	96	96	0
2	89	89	0
3	86	84	2
4	81	79	2
5	78	76	2
6	72	70	2
7	66	63	3
8	59	51	8
9	53	42	11
10	42	22	20
11	39	15	24

Abbreviation: XELOX, Capecitabine plus oxaliplatin.
*Number of patients starting each cycle.

The response rate by IRC assessment was 45% (43 patients; 95% CI, 35% to 55%). Concordance between investigator and IRC was high, with identical assessments in 63 of the 85 patients (74%) for whom an assessment by both investigator and IRC was available. The majority of discrepancies were between patients classified as showing partial response or stable disease.

Response rates were analyzed in patient subpopulations (Fig 3). XELOX achieved consistently high (> 50%) response rates in all patient subpopulations studied.

After a minimum follow-up of 24 months, the median TTP in the intent-to-treat population was 7.7 months (95% CI, 6.4% to 8.6%; Fig 4). Median overall survival was 19.5 months (95% CI, 15.3% to 21.6%; Fig 5). The survival rate was 70% at 1 year and 30% at 2 years.

Table 3. Tumor Response to Treatment (investigator-ITT Population)

	No.	%	95% CI
Objective response (CR and PR)	53	55	45 to 65
Stable disease	30	31	22 to 42
Progressive disease	6	6	2 to 13
Not assessable*	7	7	3 to 14

Abbreviations: ITT, intent-to-treat; CR, complete response; PR, partial response.
*Patients without post-baseline tumor assessment.

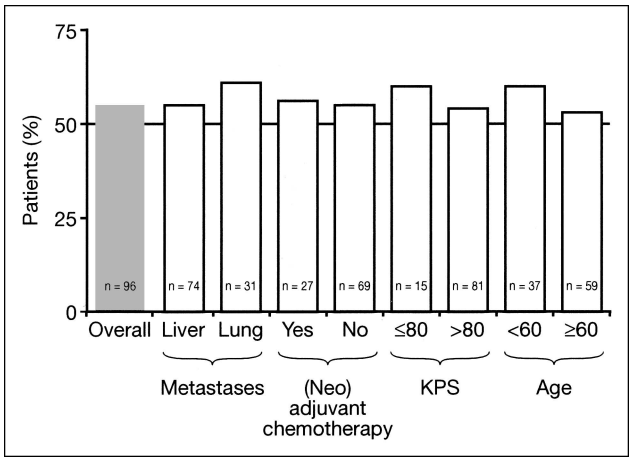

Fig 3. Response rates among patient subgroups. KPS, Karnofsky performance status.

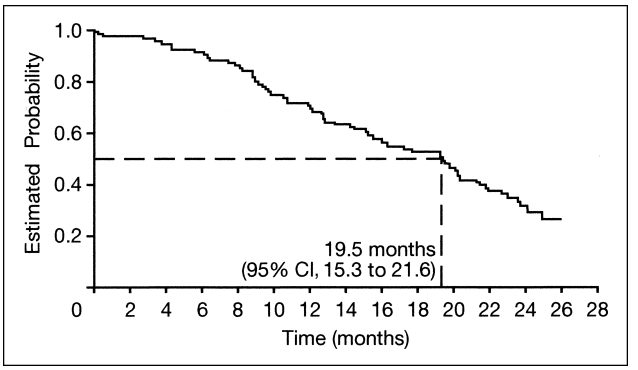

Fig 5. Overall survival (n = 96).

Poststudy Treatment

A total of 66 patients (69%) received second-line and 35 (36%) received third-line chemotherapy. The most common second-line chemotherapy was irinotecan (48 patients; 50%), either as monotherapy or in combination with FU (Table 4). Second-line capecitabine was given to 11 patients after disease progression (including four who received further XELOX). Twelve patients (13%) received palliative radiotherapy, and five underwent surgery, including four patients who underwent partial hepatic resection and one who underwent a partial liver and lung resection.

Safety

Safety was evaluated in all patients who received treatment (n = 96). Of the 59 patients withdrawing during the treatment phase (the first 11 cycles), the majority (35 patients) withdrew because of disease progression (Table 5).

The most common (> 20%) treatment-related adverse events are shown in Figure 6. Sensory neuropathy, a frequent side effect of oxaliplatin, was the most common treatment-related adverse event, occurring in 85% of patients. The majority of neuropathy was mild to moderate, with only 17% experiencing cumulative neurotoxicity (grade 3 or 4). The majority of treatment-related adverse events were mild to moderate in intensity. The most common grade 3 or 4 treatment-related adverse events were sensory neuropathy (17%), diarrhea (16%), and nausea or vomiting (13%; Fig 7). Only five patients (5%) experienced grade 4 treatment-related adverse events. HFS was experienced by 35 patients (36%), but at grade 3 intensity in only three patients (3%).

Grade 3 elevations in laboratory parameters were rare, comprising neutropenia (7%), thrombocytopenia (4%), anemia (1%), and hyperbilirubinemia (4%). Hyperbilirubinemia was an isolated laboratory abnormality and was not accompanied by grade 3 or 4 elevations in alkaline phosphatase or liver transaminases. No grade 4 elevations in laboratory abnormalities were observed.

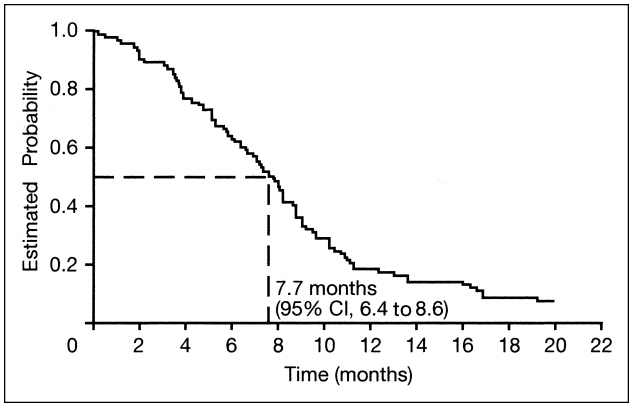

Fig 4. Time to disease progression (n = 96).

Table 4. Chemotherapy After Withdrawal From Study Treatment

Treatment	Second Line (n = 66)		Third Line (n = 35)	
	No. of Patients	%	No. of Patients	%
Irinotecan	48	50	9	9
As monotherapy	27	28	5	5
Plus FU/LV	21	22	4	4
Capecitabine	12	13	4	4
As monotherapy	7	7	3	3
As XELOX	4	4	1	1
Oxaliplatin *v* FU ± LV	—		2	2
FU ± LV	5	5	5	5
Cisplatin/mitomycin/FU ± LV	1	1	—	
Tegafur/uracil	—		4	4
Oxaliplatin/raltitrexed	—		1	1
Raltitrexed	—		1	1
Investigational treatment	1	1*	9	9†

Abbreviations: FU, fluorouracil; LV, leucovorin.
*BAY598862 (taxane).
†Cetuximab (C225, n = 2); monoclonal antibody (n = 2); not specified (n = 2); epothilone (n = 1); megestrol or placebo (n = 1); TZT 1017 (n = 1).

Table 5. Reasons for Withdrawal During the First 11 Cycles

Reason for Withdrawal	No. of Patients	%
All withdrawals	59	61
Progression of MCRC	35	36
Adverse events*	16	17
Death	3	3
Refused treatment	3	3
Other†	2	2

Abbreviation: MCRC, metastatic colorectal cancer.
*Adverse events most commonly leading to withdrawal from the study were thrombocytopenia, asthenia, and diarrhea.
†One patient had a hepatic resection, and one patient achieved maximal response and was removed from the study.

XELOX demonstrated a similar favorable safety profile among the subgroups of patients aged ≥ 65 years or younger than 65 years. Stomatitis was the only treatment-related adverse event more common in patients at least 65 years old than those younger than 65 years (34% *v* 17%, respectively), but no patients in either age group experienced grade 3 or 4 stomatitis. Overall, there was a similar incidence of grade 3 or 4 treatment-related adverse events in the two age groups (64% of patients younger than 65 years and 59% of patients 65 years or older). Among the subgroups of patients at least 65 years old or younger than 65 years, there were no significant differences in the incidences of any grade 3 or 4 treatment-related adverse events, including peripheral sensory neuropathy (15 *v* 18%, respectively), diarrhea (14 *v* 18%, respectively), nausea or vomiting (12 *v* 14%, respectively), neutropenia (6 *v* 5%), and HFS (6 *v* 0%, respectively).

Forty-eight patients (50%) received full doses of capecitabine and oxaliplatin throughout the study. Dose reduction was required for capecitabine alone in 14 patients (15%), for oxaliplatin alone in 12 patients (13%), and for both agents in 22 patients (23%). The majority of dose reductions were by one level (reduction to 75% of starting dose of capecitabine and/or 100 mg/m^2 oxaliplatin). Only seven patients (7%) required a second level dose reduction, to 50% of starting dose of capecitabine and/or 80 mg/m^2 oxaliplatin. Adverse events most commonly leading to dose reduction were myelosuppression and neurotoxicity. The incidence of dose reduction was similar in the subgroups of male and female patients and those younger than 65 years or at least 65 years (data not shown).

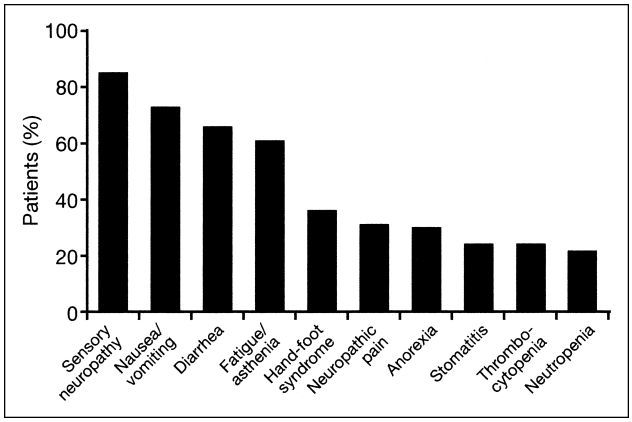

Fig 6. Most common (> 20%) treatment-related adverse events (all grades).

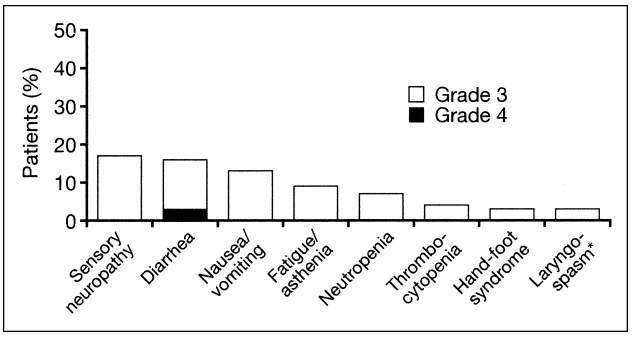

Fig 7. Most common (≥ 2%) treatment-related grade 3 or 4 adverse events.

Three deaths occurred during or within 28 days of withdrawal from study treatment during the planned 11 treatment cycles, but only one of these was considered possibly related to treatment (pulmonary fibrosis, a rare but known side effect of oxaliplatin, which occurred during cycle 8). The other two deaths were caused by colonic perforation and cardiac arrest, both during cycle 1. Sixty-day all-cause mortality was therefore 2%.

DISCUSSION

The XELOX regimen is a rational combination treatment. The addition of oxaliplatin to infused FU/LV chemotherapy results in higher response rates and TTP in both first- and second-line treatment of advanced colorectal cancer. Oral capecitabine monotherapy has previously shown superior antitumor activity to bolus FU/LV (Mayo Clinic regimen) in this setting, with higher response rates (26% *v* 17%, $P < .0002$) and at least equivalent TTP and overall survival in two large randomized studies.[5–7]

The high clinical activity of the XELOX combination may be explained in part by the preclinical data suggesting that capecitabine and oxaliplatin have supra-additive activity in combination. Our studies show that the combination of capecitabine and oxaliplatin inhibit the in vivo growth of CXF280 human colon cancer more effectively than either agent alone. Furthermore, oxaliplatin upregulates TP, the key enzyme involved in tumor-specific generation of FU with capecitabine, in CXF280 tumor tissues. Oxaliplatin-induced upregulation of TP could therefore result in supra-additive activity with XELOX that may

not occur with IV infused oxaliplatin with FU and leucovorin (FOLFOX) combinations.

This clinical study was undertaken to further evaluate the combination of XELOX as first-line therapy for MCRC. XELOX achieved a high response rate of 55%, with an additional 31% of patients maintaining stable disease for at least 3 months. Moreover, subgroup analysis showed that the response rate remained high ($>$ 50%) irrespective of patient and disease characteristics for all subgroups explored, which included those younger than 65 years or at least 65 years, and those with Karnofsky performance status $\leq$ 80 or $>$ 80, prior adjuvant therapy, and liver or lung metastases. These efficacy results compare favorably with the randomized studies of FU/LV with or without oxaliplatin,[10-12] which demonstrated significant improvements for the combination (FOLFOX4) compared with FU/LV alone. XELOX achieves similar response rates and progression-free and overall survival to all of the regimens combining protracted FU/LV infusion with oxaliplatin. Capecitabine and oxaliplatin do not have overlapping key toxicities, and the combination was well tolerated even with the long treatment duration. The safety profile of XELOX was similar to that of FU/LV plus oxaliplatin, with a lower incidence of grade 3 or 4 neutropenia. Only three patients experienced grade 3 HFS. The low incidence of grade 3 HFS with XELOX may be due to the 20% lower dose of Xeloda used in the XELOX trial compared with the monotherapy studies. However, HFS is thought to be due to chronic daily exposure, and it is also possible that oxaliplatin-induced neurotoxicity may be masking the symptoms of HFS. In addition, XELOX demonstrated a similar safety profile in patients younger than 65 years or at least 65 years. Fifty percent of patients received the full doses of capecitabine and oxaliplatin throughout the study. The median time to first dose reduction was identical for both agents (2.9 months). There was a similar incidence of dose reduction in males and females younger than 65 years or at least 65 years.

The data therefore indicate that three-times-weekly XELOX is a highly effective regimen for the first-line treatment of advanced colorectal cancer and that capecitabine has strong potential to replace FU/LV as the optimal combination partner for oxaliplatin. The XELOX dose schedule of capecitabine 1,000 mg/m^2 twice daily with oxaliplatin 130 mg/m^2 had been previously identified in a phase I dose-escalation study.[15]

Other regimens with capecitabine and oxaliplatin have been evaluated. Before completion of the dose-escalation study, another phase II trial evaluated a higher dose of capecitabine, 1,250 mg/m^2 twice daily (the recommended dose for capecitabine monotherapy), in combination with oxaliplatin 130 mg/m^2 in patients with pretreated and previously untreated MCRC.[22] While a response rate of 49% was obtained in patients receiving the combination as first-line therapy, the incidence of grade 3 or 4 diarrhea was 33% in treatment-naïve patients and 50% in pretreated patients. Although the authors recommend the full dose of both agents for treatment of patients with advanced CRC, more than 25% of the chemotherapy-naïve population required a capecitabine dose reduction after the first cycle. A randomized, phase II trial has evaluated two schedules of capecitabine plus oxaliplatin as first-line therapy in 89 patients with MCRC.[23] Patients were randomly assigned to receive a dose-intensified regimen (capecitabine 1,750 mg/m^2 twice daily on days 1 to 7 and 14 to 21 plus oxaliplatin 85 mg/m^2 on days 1 and 14, every 28 days) or XELOX as given in the present study (capecitabine 1,000 mg/m^2 twice daily days 1 to 14 plus oxaliplatin 130 mg/m^2 on day 1, every 21 days). No formal prospective comparison of efficacy in the two treatment groups was planned and the study was not powered statistically for such a comparison. Both regimens were active, achieving response rates of 55% and 42%, with median progression-free survival of 10.5 and 6.0 months, respectively. However, in the absence of data from a prospective, randomized, phase III comparison, no conclusions about the efficacy and safety of the dose-intensified regimen relative to XELOX can be drawn. Another phase II study has evaluated a lower dose of capecitabine (750 mg/m^2 twice daily) than used in the XELOX regimen.[24] This regimen achieved a response rate of only 34% in 35 patients treated. In summary, the dose of 1,000 mg/m^2 capecitabine twice daily in combination with oxaliplatin, as used in the XELOX regimen, achieves high efficacy while maintaining a good safety profile.

The XELOX regimen has demonstrated similar efficacy and safety to FOLFOX. Interestingly, the incidence of grade 3 or 4 neutropenia is lower with the XELOX regimen than with the FOLFOX4 regimen (7% *v* 42% to 47%), as is the incidence of febrile neutropenia (0% *v* 1% to 4%).[10,14] In addition, XELOX requires only one clinic visit per 3-week cycle for a 2-hour infusion of oxaliplatin. This constitutes a marked advantage over regimens combining infused FU/LV and oxaliplatin in terms of the impact on patients' daily lives and convenience for both patients and caregivers. With these regimens, FU/LV is administered in two 22-hour infusions over 3 days every 2 weeks,[10] a 5-day chronomodulated infusion every 3 weeks,[11] or a weekly 24-hour infusion.[12] In patients with MCRC, for whom treatment is essentially palliative, these protracted infusion times represent a significant portion of the patient's remaining life span. In addition, patients are exposed to the potential complications of central venous access. The simplified XELOX regimen is thus likely to have important implications for patients' well-being and autonomy.

In summary, this study shows that XELOX is a highly effective therapy for patients with MCRC. Response rates, time to progression, and overall survival compare favorably with previous studies of FU/LV/oxaliplatin, and the XELOX combination offers substantially improved convenience and is less

disruptive for patients. Capecitabine therefore could replace FU/LV as the standard combination partner for oxaliplatin in this setting. Phase III evaluation of XELOX versus FU/LV plus oxaliplatin in both the first- and second-line settings is ongoing, as is evaluation of the XELOX regimen as adjuvant treatment for Dukes' C colon carcinoma. In addition, the XELOX regimen offers a novel, well-tolerated, and active backbone for incorporation of innovative targeted agents such as the EGFR-directed drugs gefitinib, erlotinib, and cetuximab, or the antiangiogenic monoclonal antibody bevacizumab.

Acknowledgment

We thank Stuart Teller, Jan Fagerberg, Stefan Frings, Eileen Codner, Peter Stoll, Patricia Kalber, Anne DiGiacomo, and Pierre Ducournau; Sanofi-Synthelabo for providing oxaliplatin; and Dr H.H. Fiebig of Freiburg University, Germany, for the CXF280 colon cancer line.

Authors' Disclosures of Potential Conflicts of Interest

The following authors or their immediate family members have indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. Acted as a consultant within the last 2 years: Jim Cassidy, Roche; Alberto Sobrero, Sanofi; Chris Twelves, Roche; Charles Butts, Roche. Performed contract work within the last 2 years: Eric Van Cutsem, Roche, Sanofi; Patrick Schöffski, Roche. Received more than $2,000 a year from a company for either of the last 2 years: Alberto Sobrero, Sanofi; Chris Twelves, Roche.

REFERENCES

1. de Gramont A, Bosset J-F, Milan C, et al: Randomized trial comparing monthly low-dose leucovorin and fluorouracil bolus with bimonthly high-dose leucovorin and fluorouracil bolus plus continuous infusion for advanced colorectal cancer: A French intergroup study. J Clin Oncol 15:808-815, 1997
2. Köhne CH, Wils J, Lorenz M, et al: Randomized phase III study of high-dose fluorouracil given as a weekly 24-hour infusion with or without leucovorin versus bolus fluorouracil plus leucovorin in advanced colorectal cancer: European organization of Research and Treatment of Cancer Gastrointestinal Group Study 40952. J Clin Oncol 21:3721-3728, 2003
3. André T, Colin P, Louvet C, et al: Semimonthly versus monthly regimen of fluorouracil and leucovorin administered for 24 or 36 weeks as adjuvant therapy in stage II and III colon cancer: Results of a randomized trial. J Clin Oncol 21:2896-2903, 2003
4. Miwa M, Ura M, Nishida M, et al: Design of a novel oral fluoropyrimidine carbamate, capecitabine, which generates 5-fluorouracil selectively in tumours by enzymes concentrated in human liver and cancer tissue. Eur J Cancer 34:1274-1281, 1998
5. Hoff PM, Ansari R, Batist G, et al: Comparison of oral capecitabine versus intravenous fluorouracil plus leucovorin as first-line treatment in 605 patients with metastatic colorectal cancer: Results of a randomized phase III study. J Clin Oncol 19:2282-2292, 2001
6. Van Cutsem E, Twelves C, Cassidy J, et al: Oral capecitabine compared with intravenous 5-fluorouracil plus leucovorin (Mayo Clinic regimen) in patients with metastatic colorectal cancer: Results of a large phase III study. J Clin Oncol 19:4097-4106, 2001
7. Van Cutsem E, Hoff P, Harper P, et al: Oral capecitabine versus intravenous 5-fluorouracil and leucovorin: Integrated efficacy data and novel analyses from two large, randomised, phase III trials. Br J Cancer 90:1190-1197, 2004
8. Cassidy J, Twelves C, Van Cutsem E, et al: First-line oral capecitabine therapy in metastatic colorectal cancer: A favorable safety profile compared with intravenous 5-fluorouracil/leucovorin. Ann Oncol 13:566-575, 2002
9. Scheithauer W, McKendrick J, Begbie S, et al: Oral capecitabine as an alternative to i.v. 5-FU-based adjuvant therapy for colon cancer: Safety results of a randomized, phase III trial. Ann Oncol 14:1735-1743, 2003
10. de Gramont A, Figer M, Seymour M, et al: Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. J Clin Oncol 18:2938-2947, 2000
11. Giacchetti S, Perpoint B, Zidani R, et al: Phase III multicenter randomized trial of oxaliplatin added to chronomodulated fluorouracil-leucovorin as first-line treatment of metastatic colorectal cancer. J Clin Oncol 18:136-147, 2000
12. Grothey A, Deschler B, Kroening H, et al: Phase III study of bolus 5-fluorouracil (5-FU)/folinic acid (FA) (Mayo) vs weekly high-dose 24h 5-FU infusion/ FA + oxaliplatin (OXA) (FUFOX) in advanced colorectal cancer (ACRC). Proc Am Soc Clin Oncol 21:129a, 2002 (abstr 512)
13. Rothenberg ML, Oza AM, Bigelow RH, et al: Superiority of oxaliplatin and fluorouracil-leucovorin compared with either therapy alone in patients with progressive colorectal cancer after irinotecan and fluorouracil-leucovorin: Interim results of a phase III trial. J Clin Oncol 21:2059-2069, 2003
14. Goldberg RM, Sargent DJ, Morton RF, et al: A randomized controlled trial of fluorouracil plus leucovorin, irinotecan, and oxaliplatin combinations in patients with previously untreated metastatic colorectal cancer. J Clin Oncol 22:23-30, 2004
15. Díaz-Rubio E, Evans TR, Tabernero J, et al: Capecitabine (Xeloda) in combination with oxaliplatin: A phase I, dose-escalation study in patients with advanced or metastatic solid tumors. Ann Oncol 13:558-565, 2002
16. Nishida M, Hino A, Mori K, et al: Preparation of anti-human thymidine phosphorylase monoclonal antibodies useful for detecting the enzyme levels in tumor tissues. Biol Pharm Bull 19:1407-1411, 1996
17. ICH website. http://www.ich.org
18. World Health Organization Handbook for Reporting Results of Cancer Treatment. Geneva, Switzerland, World Health Organization, 1979
19. Wiernik PH, Yeap B, Vogl SE, et al: Hexamethylmelamine and low or moderate dose cisplatin with or without pyridoxine for treatment of advanced ovarian carcinoma: A study of the Eastern Cooperative Oncology Group. Cancer Invest 10:1-9, 1992
20. Blum JL, Jones SE, Buzdar AU, et al: Multicenter phase II study of capecitabine in paclitaxel-refractory metastatic breast cancer. J Clin Oncol 17:485-493, 1999
21. Fleming TR: One-sample multiple testing procedure for phase II clinical trials. Biometrics 38:143-151, 1982
22. Borner MM, Dietrich D, Stupp R, et al: Phase II study of capecitabine and oxaliplatin in first- and second-line treatment of advanced or metastatic colorectal cancer. J Clin Oncol 20:1759-1766, 2002
23. Scheithauer W, Kornek GV, Raderer M, et al: Randomized multicenter phase II trial of two different schedules of capecitabine plus oxaliplatin as first-line treatment in advanced colorectal cancer. J Clin Oncol 21:1307-1312, 2003
24. Shields AF, Zalupski MM, Marshall JL, et al: Treatment of advanced colorectal carcinoma with oxaliplatin and capecitabine: A phase II trial. Cancer 100:531-537, 2004