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ORIGINAL ARTICLE

Capecitabine chemotherapy for metastatic colorectal cancer. Chemical structure, combinations and efficacy

G. Koukourakis[1], V. Kouloulias[2], G. Zacharias[3], M. Koukourakis[4]

[1]Saint Savvas Anticancer Institute of Athens, 2nd Department of Radiation Therapy, Athens; [2]Attikon University Hospital, Radiation Therapy Unit, Athens; [3]General Hospital of Corinth, Intense Therapy Unit, Corinth; [4]Democritus University Hospital of Thrace, Department of Radiation Therapy, Alexandroupolis, Greece

Summary

Purpose: *Capecitabine is an oral fluoropyrimidine which had been developed as a pro-drug of fluorouracil (FU), and had shown improved tolerability and intratumor drug concentrations through its tumor-specific conversion to the active drug. Our purpose was to make a comprehensive literature review regarding capecitabine's efficacy in metastatic colorectal cancer.*

Methods: *We searched the Pubmed and Cochrane databases regarding all available information on capecitabine, focusing on its clinical effectiveness against metastatic colorectal cancer. Special attention was paid on trials that compared capecitabine with standard folinic acid (leucovorin/LV)-modulated intravenous 5-fluorouracil (5-FU) bolus regimens in patients with metastatic colorectal cancer. Moreover, the efficacy of capecitabine alone or in several combinations with other active drugs such as irinotecan and oxaliplatin on metastatic colorectal cancer were also assessed.*

Results: *Comparative trials showed that capecitabine is at least equivalent to standard 5-FU/LV combination regarding progression-free and overall survival, expressing at the same time a better tolerability profile with a much lower incidence of stomatitis. Conclusion: Nowadays it is known that capecitabine can be combined with other active drugs such as irinotecan and oxaliplatin and the combination of oxaliplatin with capecitabine represents a new standard of care for metastatic colorectal cancer.*

Key words: capecitabine, colorectal cancer, oral chemotherapy, xeloda

Introduction

5-FU is a fluorinated analog of uracil which is commercially known from 1957. It belongs to the antimetabolite family and has a broad activity over a diversity of malignant tumors including colorectal cancer. An improvement in local control and survival rates when combined with radiation therapy in a variety of malignancies compared to radiation therapy alone has been shown in several trials [1].

The 5-FU molecular activity is quite complex, interfering with DNA synthesis and mRNA translation. With the action of thymidine phosphorylase 5-FU is transformed to 5-fluorodeoxyuridine (5FdUrd) which further binds to thymidylate synthase and to tetrahydrofolate and forms a stable complex which prevents the formation of thymidine from thymine. Finally, DNA synthesis is blocked leading to cell death.

Furthermore, interfering with the enzymatic path of thymidine kinase, the 5FdUrd is metabolized into fluorouridine mono- and triphosphate (FdUMP and FdUTP), which are directly inserted into the DNA, leading to abnormal DNA structures. The FdUTP can also be used from mRNA polymerase for mRNA formation leading to blockage of the mRNA translation.

Due to the fact that 5-FU has an unpredictable gastrointestinal absorption and degradation, it must be administered intravenously. The concentrations of 5-FU in plasma depend on drug dosage as well as the rate of administration because it exhibits saturable pharmacokinetics [2]. The protracted infusion of 5 to 28 days in colorectal cancer patients has been found to increase

Correspondence to: Georgios Koukourakis, MD. Saint Savvas Anticancer Institute, Second Department of Radiation Therapy, 171, Alexandra's Ave, Athens 125 34, Greece. Tel: +30 210 6409421, Fax: +30 210 6409218, E-mail: gkoyokoyrakis@yahoo.gr

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the response rate (RR) from 14%, achieved with bolus infusions, to 22% [3].

Nevertheless, the drawbacks of continuous 5-FU infusions are that they can be complicated by hospital and/or home health costs, infection risk of intravenous devices and overall patient burden [4]. To overcome these disadvantages and preserve the profits of continuous infusion, oral prodrugs of FU have been developed.

Ftorafur (Tegafur) was the first oral 5-FU prodrug developed in 1967 and a phase I study in patients with gastrointestinal carcinomas showed palliative benefits. However, further improvement of that product in the United States was restricted due to neurological toxicities [1]. UFT represents a combination of Tegafur and Uracil, an inhibitor of the primary enzyme responsible for FU degradation to central nervous system active metabolites and is currently being evaluated [1].

Doxifluridine (5'-FdUrd; 5'-deoxy-5-fluorouridine) is another oral prodrug that takes advantage of a different metabolic pathway to form 5-FU. The conversion of this prodrug to its active form is necessary through the enzyme thymidine phosphorylase. This enzyme is expressed in higher levels in tumors and the intestinal tract and is responsible for dose-limiting toxicity causing diarrhea [5,6].

Capecitabine is a carbonate derivative of 5'-DFUR that is absorbed through the intestine in prodrug form (Figure 1). Three activation steps are necessary to metabolize capecitabine to its active form, FU **(**Figure 2). Capecitabine is absorbed through the intestine and converted to 5'-deoxy-5-fluorocytidine (5'-DFCR) by carboxylesterase and then to 5'-deoxy-5-fluorouridine (5'-DFUR) by cytidine deaminase (Cyt D), both steps taking place in the liver. Finally, thymidine phosphorylase (TP) converts 5'-DFUR to the active drug, FU. This occurs in both tumor and normal tissues; however, the

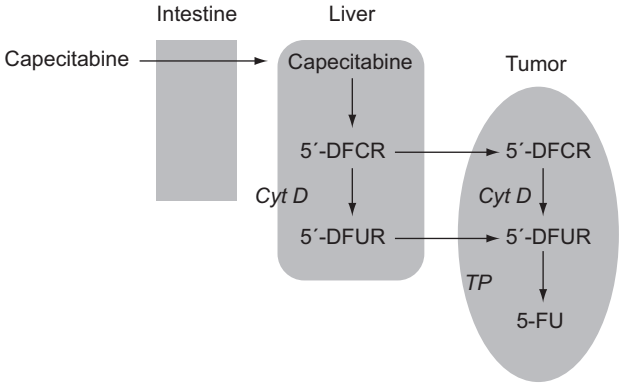

Figure 1. The three consecutive steps of metabolic conversion of capecitabine to fluorouracil (FU). 5´-DFCR: 5´ deoxy-fluorocytidine, 5´-DFUR: 5´-deoxy-5-fluorouridine, TP: thymidine phosphorylase, Cyt D: cytidine deaminase.

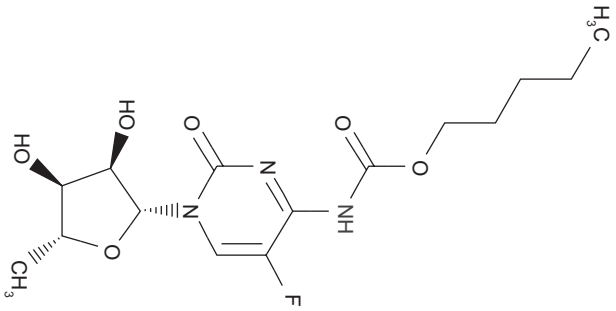

Figure 2. Chemical structure of capecitabine.

enzyme is found at higher concentrations in most tumor tissues compared with normal healthy tissue. This theoretically allows a selective activation of the drug and low systemic toxicity [7,8].

This article provides the available information on capecitabine with respect to its effectiveness as first line treatment on metastatic colorectal cancer in combination with other active drugs.

Methods

Identification of eligible studies

We searched MEDLINE and the Cochrane Central Register of Controlled Trials (last search in December 2009) using combinations of terms, such as: capecitabine, xeloda and metastatic colorectal cancer treatment. We considered all, English written, meta-analyses or randomized controlled trials, providing information about the effectiveness of capecitabine on metastatic colorectal cancer as eligible.

Data extraction

We extracted information from each eligible study. The data recorded included author's name, year of publication, number of patients included in the study, combination(s) of drugs used, doses of drugs, percent overall response, median time to progression and median survival.

Results

Capecitabine vs. standard 5-FU/LV combination in metastatic colorectal cancer

5-FU either in combination with leucovorin (LV) or in combination with newer drugs such as irinotecan or oxaliplatin has been the main treatment for locally

advanced and metastatic colorectal cancer for more than 4 decades [9]. In metastatic colorectal cancer capecitabine as a single agent was compared with standard 5-FU/LV regimen as first line therapy in two phase III trials and in no comparative studies with irinotecan and oxaliplatin [10-23].

Two randomized non-blinded phase III trials have evaluated and compared the role of capecitabine as a single agent in metastatic colorectal cancer to standard intravenous 5-FU/LV as first line treatment [10,11]. The two trials were identical regarding their design, primary and secondary end points, patients' inclusion and exclusion criteria, conduct and monitoring. The first study enrolled 605 patients from 61 centers of the United States, Canada, Brazil and Mexico [10]. The second study included 602 patients from 59 centers of Europe, Australia, New Zealand, Taiwan and Israel [11] (Table 1). The primary end point was the objective tumor response rate (RR), and it was shown that capecitabine was at least as active as 5-FU/LV in inducing tumor responses. The estimation was done both by investigators as well as by an Independent Review Committee (IRC) which was consisted of a panel of blinded radiologists who estimated tumor response based only on imaging. Secondary endpoints were time to progression (TTP), overall survival (OS), duration to response, time to treatment failure, time to first response, safety and quality of life. For the patients' randomization a computer system was used to either capecitabine or 5-FU/LV arm. Capecitabine (1,250 mg/m^2/day) was taken orally within 30 min of food intake twice a day for 2 weeks of treatment followed by 1 week of rest.

Patients in the 5-FU/LV arm received the Mayo Clinic regimen consisting of LV 20 mg/m^2 as a rapid intravenous injection followed by 5-FU 425 mg/m^2 as a bolus injection every day from day 1 to day 5; cycles were repeated every 4 weeks. Depending on disease evolution (no progression) and on toxicity (acceptable toxicity) the treatment was scheduled to be continued for 30 weeks. In responding patients or those with stable disease, treatment might be extended beyond 30 weeks, at the discretion of attendant physician [10,11]. According to the extent and site of metastatic disease as well as baseline prognostic indicators, the two arms were well balanced in both studies with the exception of a higher alkaline phosphatase concentration in the capecitabine group in the study by Hoff et al. [10]. The overall RRs were 26 vs. 17% ($p < 0.001$) when evaluated by the investigators, and 22 vs. 13% ($p < 0.001$) when assessed by the IRC, with both rates favoring the capecitabine arms. Subgroup analysis showed a higher RR for capecitabine-treated patients who had received adjuvant therapy before the trial (21.1 vs. 9.0%, $p < 0.05$), for patients with predominantly lung metastasis (33.3 vs. 10.3%, $p < 0.05$), and for those with only 1 metastatic site (37.8 vs. 21.8%, $p < 0.05$). The median duration of treatment was similar between the 2 therapies: 4.5 months for capecitabine and 4.6 months for 5-FU/LV. Median time to response was shorter in the capecitabine patients (1.7 vs. 2.4 months, p-value not reported). These benefits did not translate into an improvement of TTP or OS, however. The median TTP was 4.6 months in the capecitabine group and 4.7 months in the 5-FU/LV group ($p=0.95$), with no baseline characteristics demonstrating any significant differences. Median survival rates were 12.9 and 12.8 months for the capecitabine and FU/LV groups, respectively. As for toxicity, the following results were observed in favor of the capecitabine arm: diarrhea 47.7 vs. 58.2%, stomatitis 24.3 vs. 61.6%, alopecia 6.0 vs. 20.6%, grade 3-4 neutropenia 2.3 vs. 22.8% and neutropenic fever 0.2 vs. 3.4%. Hand-foot syndrome occurred more frequently in the capecitabine groups (53.5 vs. 6.2%). Dose reductions due to toxicity of capecitabine were necessary in 27.3% of patients in the

Table 1. Randomized clinical trials comparing capecitabine with standard 5-FU/LV in patients with metastatic colorectal cancer

Authors	*Treatment arms*	*OS (months)*	*RR (%)*	*PFS (months)*	*FFS (months)*	*Major toxicity*
Hoff et al. [10]	Arm 1: LV 20 mg/m^2 i.v. + 5-FU 425 mg/m^2/i.v./day, days 1-5 every 4 weeks.	13.3	11.6	4.7	3.1	More stomatitis with 5-FU/LV (16 vs. 3%)
	Arm 2: Capecitabine 2500 mg/m^2/day, for 14 days every 21 days per os.	12.5	25.8 ($p=0.005$)	4.3	4.1	More hand-foot syndrome with capecitabine (18 vs. 1%)
Van Cutsem et al. [11]	Arm 1: LV 20 mg/m^2 i.v. + 5-FU 425 mg/m^2/i.v./day, days 1-5 every 4 weeks.	12.1	15	4.7	4.0	More stomatitis with 5-FU/LV (13.3 vs. 1.3%)
	Arm 2: Capecitabine 2500 mg/m^2/day, for 14 days every 21 days per os.	13.2	18.9 ($p=0.013$)	5.2	4.2	More hand-foot syndrome with capecitabine (16.2 vs. 0.3%)

i.v.: intravenous, LV: leucovorin, OS: overall survival, RR: response rate, PFS: progression-free survival, FFS: failure-free survival

study by Van Cutsem et al. [11] and in 40.5% of patients in the study by Hoff et al. [10]. 35.1% and 49.3% of the patients receiving 5-FU required dose reductions in the respective studies. Dose reduction was necessary due to hand-foot syndrome and diarrhea in the group of capecitabine, while diarrhea and stomatitis were the main causes of dose reduction in the 5-FU/LV arm [10-12].

When combining 5-FU with LV the cytotoxic effect of the active drug is prolonged through the stabilization of tertiary complex with thymidylate synthase [1]. In order to evaluate the effect of LV with capecitabine a phase II study was conducted [13]. Patients with advanced colorectal cancer were randomized to receive intermittent therapy (2 weeks on treatment, 1 week off) with either capecitabine alone (1,255 mg/m^2 twice daily, n = 34) or capecitabine (828 mg/m^2) and LV 30 mg/day, both dosed twice a day, n = 35). Overall RRs were 24% in the single-agent arm and 23% in the LV arm (p-values not reported). Median TTP favored the single-agent group (230 vs. 165 days). The capecitabine/LV combination produced more diarrhea (any grade: 44 vs. 57%; grade 3 or 4: 9 vs. 20%) and hand-foot syndrome (any grade: 44 vs. 55%; grade 3: 15 vs. 23%). The authors concluded that the combined dosing with LV did not provide added benefit in terms of RR or TTP and produced more adverse events [13].

Phase II studies that combined capecitabine with oxaliplatin or irinotecan in metastatic colorectal cancer

The combinations of 5-FU/LV with the camptothecin irinotecan or the platinum analog oxaliplatin have produced encouraging RRs in patients with metastatic colorectal cancer, and are often used as first line treatment [9]. Several non-comparative phase II studies have evaluated the efficacy of combination of these drugs with capecitabine in patients with metastatic colorectal cancer [14-23] (Table 2).

Table 2. Non-comparative phase II trials of combinations of capecitabine with oxaliplatin or irinotecan in patients with metastatic colorectal cancer

Authors	*Patients, n*	*Drugs used*	*Regimen*	*RR (%)*	*mTTP (Months)*	*MS (Months)*
Cassidy et al. [14]	96	Capecitabine Oxaliplatin	2000 mg/m^2/day (days 1-14) 130 mg/m^2 i.v. day 1	55	7.7	19.5
Zeuli et al. [15]	43	Capecitabine Oxaliplatin	2500 mg/m^2/day (days 1-14) 120 mg/m^2 i.v. day 1	44	–	20
Borner et al. [16]	43	Capecitabine Oxaliplatin	2500 mg/m^2/day (days 1-14) 130 mg/m^2 i.v. day 1	49	5.9	17.1
Shields et al. [17]	35	Capecitabine Oxaliplatin	1500 mg/m^2/day (days 1-14) 30 mg/m^2 i.v. day 1	37.1	–	NR
Bajetta et al. [18]	68	Capecitabine Irinotecan	2500 mg/m^2/day (days 2-15) 300 mg/m^2 i.v. day 1	47	8.3	–
Bajetta et al. [18]	66	Capecitabine Irinotecan	2500 mg/m^2/day (days 2-15) 150 mg/m^2 i.v. days 1 and 8	44	7.6	–
Patt et al. [19]	52	Capecitabine Irinotecan	2000 mg/m^2/day (days 2-15) 250 mg/m^2 i.v. day 1	46	7.1	15.6
Cartwright et al. [20]	49	Capecitabine Irinotecan	2000 mg/m^2/day (days 2-15) 240 mg/m^2 i.v. day 1	45	5.7	13.4
Kim et al. [21]	43	Capecitabine Irinotecan	2000 mg/m^2/day (days 2-15) 100 mg/m^2 i.v. days 1 and 8	46.6	NR	NR
Rosati et al. [22]	46	Capecitabine Irinotecan	1000 mg/m^2/day twice daily on days 1-14 every 3 weeks 80 mg/m^2 i.v. days 1 and 8	36	7	14
Rosati et al. [22]	46	Capecitabine Oxaliplatin	1000 mg/m^2/day twice daily on days 1-14 every 3 weeks 65 mg/m^2 i.v. days 1 and 8	38	8	19.3
Garcia-Alfonso et al. [23]	53	Capecitabine Irinotecan	1000 mg/m^2/day twice daily on days 2-8 every 2 weeks 175 mg/m^2 i.v. on day 1	32	9	19.2

RR: response rate, mTTP: median time to progression, MS: median survival, NR: not reported, i.v.: intravenous. All capecitabine doses were divided equally and dosed twice daily. Regimens were administered every 3 weeks

Considering that oxaliplatin upregulates thymidine phosphorylase, it can lead to synergistic activity with capecitabine [14]. Although the two treatments were not directly compared, the capecitabine and oxaliplatin combination gave comparable results to that of 5-FU/LV and oxaliplatin regarding overall RR (37-55 vs. 34-49%, respectively) and median survival (17-20 vs. 16-21 months, respectively) [10, 14-17].

Additionally, the toxicological profile was related to oxaliplatin-induced sensory neuropathy, nausea and vomiting, and capecitabine-induced diarrhea [14-17]. Even though the irinotecan and capecitabine combination was not directly compared to 5-FU/LV and irinotecan regimen, the two treatments gave comparable results regarding the overall RR (44-47 vs. 39-54%, respectively) and median survival (13.4-15.6 vs. 14.8-20 months, respectively) [10,18-23]. Diarrhea, nausea, vomiting, and neutropenia were the side effects most often encountered [18-23]. Therefore, well randomized, comparative trials were needed to establish the future role of these combinations as first line treatment of colorectal cancer

Randomized trials that compare capecitabine and oxaliplatin combination to the FU/LV plus oxaliplatin regimen

The capecitabine and oxaliplatin combination was compared to 5-FU (with or without folinic acid) and oxaliplatin regimen in several randomized comparative trials. (Table 3).

In a phase II trial, 118 patients were randomized to receive treatment with the XELOX regimen every 3 weeks or with oxaliplatin given on day 1 plus 5-FU 250 mg/ m^2 daily continuous intravenous infusion for 3 weeks. The RR was the same for the two treatments; nevertheless XELOX produced less severe diarrhea and a substantially lower occurrence of severe stomatitis [24].

In the TREE-1 study the role of eloxatin (oxaliplatin) has been evaluated (Three Regimens of Eloxatin Evaluation). The patients were randomly assigned to receive either: (a) the mFOLFOX regimen (oxaliplatin 85 mg/m^2, folinic acid 350 mg/m^2, 5-FU 400 mg/m^2 intravenously bolus and 2400 mg/m^2 46-h infusion on day 1) every 14 days; (b) the bFOL regimen (oxaliplatin 85 mg/m^2 on day 1 and 5-FU 500 mg/m^2 plus folinic acid 20 mg/m^2 intravenously on days 1 and 8, every 14 days); and (c) the XELOX regimen every 21 days. The three regimens had the same effectiveness. Nevertheless, XELOX produced a significantly greater incidence of severe dehydration, whereas the occurrence of grade $\geq$ 3 neutropenia was much lower with XELOX [25]. TREE-2 was the second part of TREE-1 study in which bevacizumab monoclonal antibody at a dosage of 5 mg/kg twice weekly or 7.5 mg/kg three times a week was added to the above mentioned regimens. In this second part of the trial, the capecitabine dosage in combination with oxaliplatin was reduced to 1750 mg/m^2/day. All the efficacy parameters of TREE-2 trial compared with the TREE-1 trial were improved by the addition of bevacizumab, whereas the incidence of severe dehydration caused by the modified XELOX plus bevacizumab regimen was substantially decreased [25].

The German Colorectal Study Group compared the FUFOX regimen (5-FU 2000 mg/m^2 given in continuous 24-h infusion, folinic acid 500 mg/m^2 and oxaliplatin 50 mg/m^2 infused over 2 h) given weekly for 4 weeks with 2-week rest, with the CAPOX regimen (oxaliplatin 70 mg/m^2 on days 1 and 8, and capecitabine 2000 mg/m^2 daily for 2 weeks, repeating every 21 days). No significant difference was observed regarding the RR, median PFS and median OS between the two regimens. However, patients treated with CAPOX had a significantly greater incidence of grade 2-3 had-foot syndrome [26].

The aim of testifying the non-inferiority of XELOX compared with a regimen that contains 48-h infusion of 5-FU 2250 mg/m^2 once a week plus oxaliplatin 85 mg/m^2 given twice a week has been set in a Spanish trial. Despite the fact that patients treated with XELOX had a lower RR, the median PFS and OS were not substantially different. Patients treated with XELOX showed significantly lower incidence of severe diarrhea and grade 1-2 mucositis. Nevertheless, capecitabine treatment was associated with higher incidence of hand-foot syndrome [27].

Regarding RRs the XELOX and FOLFOX6 regimens had been evaluated by a French phase III trial (Table 3). The authors concluded that XELOX was as effective as FOLFOX6 because the 95% upper limit of the difference in RR (39 vs. 46%) was below the non-inferiority margin. Median PFS was 8.8 months in the XELOX arm vs. 9.3 months in the FOLFOX6 arm, and median OS was 19.9 vs. 20.5 months, respectively. The incidence of neutropenia, febrile neutropenia and neuropathy was significantly lower in the XELOX arm [28].

The NO16966 trial was firstly designed to demonstrate the non-inferiority in terms of PFS of XELOX in comparison with FOLFOX4 (Table 3). This endpoint has been confirmed because the PFS was 8.0 months vs. 8.5 months with a HR of 1.05 (97.5% CI 0.94-1.18). In addition, XELOX decreased the risk of severe neutropenia but generated more severe diarrhea than FOLFOX4 [29]. When bevacizumab became available for clinical use, the trial structure was modified and new patients entering the study were also randomized to re-

Table 3. Randomized trials comparing oxaliplatin plus capecitabine with oxaliplatin plus 5FU ± folinic acid in metastatic colorectal cancer

Trial/Authors	*Arms*	*Patients, n*	*PFS (months)*	*OS (months)*	*RR (%)*	*Severe toxicity (≥ grade 3)*
FOCA Martoni et al. [24]	XELOX: oxaliplatin 130 mg/m^2 on d1 and capecitabine 2000 mg/m^2/day for 14 days, every 21 days	62	7	NR	43	Less diarrhea (8 vs. 18%) and stomatitis (19 vs. 29%) in XELOX
	pviFOX: protracted fluorouracil intravenous infusion plus oxaliplatin	56	9	NR	48	
US TREE-1 Hochster et al. [25]	XELOX: as above	49	5.9	17.2	27	Less neutropenia (15%) but more dehydration (27%) with XELOX
	bFOL: oxaliplatin 85 mg/m^2 on d 1 and fluorouracil 500 mg/m^2 plus folinic acid 20 mg/m^2 intravenously on d 1 and 8, every 2 weeks	50	6.9	17.9	20	
	mFOLFOX: oxaliplatin 85 mg/m^2, folinic acid 350 mg/m^2, fluorouracil 400 mg/m^2 bolus and 2400 mg/m^2 46-h infusion on d1	49	8.7	17.6	41	
German trial Porschen et al. [26]	CAPOX: oxaliplatin 70 mg/m^2 on d 1 and 8, and capecitabine 2000 mg/m^2/day for 2 weeks, recycling every 3 weeks	241	7.1	16.8	48	More skin toxicity (10 vs. 4%) with CAPOX
	FUFOX: fluorouracil 2000 mg/m^2 infused over 24 h, folinic acid 500 mg/m^2 and oxaliplatin 50 mg/m^2 infused over 2 h	233	8.0	18.8	54	
Spanish trial Diaz-Rubio et al. [27]	XELOX: as above	171	8.9	18.1	37	Less diarrhea (14 vs. 24%) with XELOX
	FUOX: fluorouracil 2250 mg/m^2 infused over 48 h once a week plus oxaliplatin 85 mg/m^2 twice a week	171	9.5	20.8	46	
French trial Ducreux et al. [28]	XELOX: as above	156	8.8	19.9	39	Less neutropenia (5 vs. 47%), febrile neutropenia (0 vs. 6%) and neuropathy (11 vs. 25%) with XELOX
	FOLFOX6: oxaliplatin 100 mg/m^2, folinic acid 200 mg/m^2 infused over 2h, fluorouracil 400 mg/m^2 bolus and 2400 mg/m^2 infused over 48 h	150	9.3	20.5	46	
NO16966 trial Cassidy et al. [29]	XELOX: as above	317	7.3	NR	37	Less neutropenia (7 vs. 43%) but more diarrhea (20 vs. 11%) and hand foot syndrome (6 vs. 1%) with XELOX
	FOLFOX4: oxaliplatin 85 mg/m^2 on d1, folinic acid 100 mg/m^2, fluorouracil 400 mg/m^2 bolus and 600 mg/m^2 infused over 22 h	317	7.7	NR	39	
COFFEE trial Comella et al. [31]	OXXEL: oxaliplatin 100 mg/m^2 on d1 and capecitabine 2000 mg/m^2/d from d1 to d11 every 2 weeks	158	6.2	16.0	34	Less neutropenia (10 vs. 27%) and febrile neutropenia (6 vs. 13%), more gastric symptoms (8 vs. 3%) and diarrhea (13 vs. 8%) with OXXEL
	OXAFAFU: oxaliplatin 85 mg/m^2 infused over 2 h on d1, folinic acid 250 mg/m^2 infused over 2 h on d1, fluorouracil 850 mg/m^2 bolus on d2	164	6.3	17.1	33	

PFS: progression free survival, OS: overall survival, RR: response rate, NR: not reported, d: day

ceive either bevacizumab in dosage of 5 mg/kg twice weekly or 7.5 mg/kg three times a week or placebo in addition to chemotherapy. The addition of bevacizumab to either XELOX or FOLFOX4 din not increase the RR of these regimens (47 vs. 49%) but did significantly prolong the median PFS from 8.0 to 9.4 months (HR=0.83, p=0.0023). With regard to the side effects, excluding the incidence of severe hypertension, the addition of bevacizumab did not significantly increase toxicity in comparison with placebo [30].

The Southern Italy Cooperative Oncology Group assigned the OXXEL regimen (Table 3) with a combination of oxaliplatin, folinic acid and 5-FU (OXAFA-FU) (Table 3). The authors observed no difference in the two arms of the study with regard to RR, PFS and OS. Less neutropenia and febrile neutropenia but more diarrheas were reported with OXXEL [31].

Conclusions

In the USA capecitabine is currently the only oral 5-FU prodrug approved for use. In patients with metastatic colorectal cancer, capecitabine is as effective as 5-FU, having a toxicity profile that consists most commonly of gastrointestinal and dermatologic side-effects. In metastatic colorectal cancer the effectiveness of this drug has been tested in large trials. The clinical evidence of these trials led the FDA (Food and Drugs Administration) to approve its use in these patients. The combination of capecitabine with either oxaliplatin or irinotecan, although sometimes increasing the occurrence of gastrointestinal adverse effects compared with the combinations including infusional 5-FU plus folinic acid, may improve the compliance of patients providing an easily delivered therapy. The addition of bevacizumab to the combination of capecitabine and oxaliplatin if feasible and promising, and is currently under evaluation in the adjuvant setting.

References

1. Rich TA, Shepard RC, Mosley ST. Four decades of continuing innovation with fluorouracil: Current and future approaches to fluorouracil chemoradiation therapy. J Clin Oncol 2004; 22: 2214-2232.
2. Milano G, Etienne MC, Renée N et al. Relationship between fluorouracil systemic exposure and tumour response and patient survival. J Clin Oncol 1994; 12: 1291-1295.
3. Meta Analysis Group in Cancer. Efficacy of intravenous continuous infusion of fluorouracil compared with bolus administration in advanced colorectal cancer. J Clin Oncol 1998; 16: 301-308.
4. Anderson N, Lokich J. Controversial issues in 5-fluorouracil infusion use. Dose intensity, treatment duration, and cost comparisons. Cancer 1992; 70: 998-1002.
5. Bollag W, Hartmann HR. Tumor inhibitory effects of a new fluorouracil derivative: 5' Deoxy 5 fluorouridine. Eur J Cancer 1980; 16: 427-432.
6. Bajetta E, Colleoni M, Rosso R et al. Prospective randomised trial comparing fluorouracil versus doxifluridine for the treatment of advanced colorectal cancer. Eur J Cancer 1993; 29A: 1658-1663.
7. 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 1998; 34: 1274-1281.
8. Budman DR, Meropol NJ, Reigner B et al. Preliminary studies of a novel oral fluoropyrimidine carbamate: Capecitabine. J Clin Oncol 1998; 16: 1795-1802.
9. Braun AH, Achterrath W, Wilke H, Vanhoefer U, Harstrick A, Preusser P. New systemic frontline treatment for metastatic colorectal carcinoma. Cancer 2004; 100: 1558-1577.
10. 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 2001; 19: 2282-2292.
11. Van Cutsem E, Twelves C, Cassidy J et al. Xeloda Colorectal Cancer Study Group. Oral capecitabine compared with intravenous fluorouracil plus leucovorin in patients with metastatic colorectal cancer: Results of a large phase III study. J Clin Oncol 2001; 19: 4097-4106.
12. Ishikaw T, Fukase Y, Yamamoto T et al. Antitumor activities of a novel fluoropyrimidine, N4-pentyloxycarbonyl 5' deoxy S fluorocytidine (capecitabine). Bid Pharm Bull 1998; 21: 713-717.
13. Van Cutsem E, Findlay M, Osterwalder B et al. Capecitabine, an oral fluoropyrimidine carbamate with substantial activity in advanced colorectal cancer: Results of a randomized phase II study. J Clin Oncol 2000; 18: 1337-1345.
14. Cassiy J, Tabernero J, Twelves C et al. XELOX (capecitabine plus oxaliplatin): Active first-line therapy for patients with metastatic colorectal cancer. J Clin Oncol 2004; 22: 2084-2091.
15. Zeuli M, Nardoni C, Pino MS et al. Phase II study of capecitabine and oxaliplatin as first-line treatment in advanced colorectal cancer. Ann Oncol 2003; 14: 1378-1382.
16. 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 2002; 20: 1759-1766.
17. Shields AF, Zalupski MM, Marshall JL, Meropol NJ. Treatment of advanced colorectal carcinoma with oxaliplatin and capecitabine: A phase II trial. Cancer 2004; 100: 531-537.
18. Bajetta E, Di Bartolomeo M, Mariani L et al. Italian Trials in Medical Oncology (I.T.M.O.) Group. Randomized multicenter phase II trial of two different schedules of irinotecan combined with capecitabine as first-line treatment in metastatic colorectal carcinoma. Cancer 2004; 100: 279-287.
19. Patt YZ, Lin E, Liebman J. Capecitabine plus irinotecan: A highly active first line treatment for metastatic colorectal cancer. Proc Am Soc Clin Oncol 2004; 23; 228 (abstr).
20. Cartwright TH, Encarnacion C, Vukelja SJ. A phase II open label study of capecitabine in combination with irinotecan as

first-line treatment for metastatic colorectal cancer. Proc Am Soc Clin Oncol 2004; 23: 271 (abstr).
21. Kim TW, Kang WK, Park JO. Phase II study of irinotecan plus capecitabine as first-line chemotherapy in advanced colorectal cancer. Proc Am Soc Clin Oncol 2003; 22: 1278 (abstr).
22. Rosati G, Cordio S, Bordonaro R et al. Capecitabine in combination with oxaliplatin or irinotecan in elderly patients with advanced colorectal cancer: results of a randomized phase II study. Ann Oncol 2009, Aug 27 [Epub ahead of print].
23. Garcia-Alfonso P, Muñoz-Martin A, Mendez-Ureña M, Quiben-Pereira R, Gonzalez-Flores E, Perez-Manga G. Capecitabine in combination with irinotecan (XELIRI), administered as a 2-weekly schedule, as first-line chemotherapy for patients with metastatic colorectal cancer: a phase II study of the Spanish GOTI group. Br J Cancer 2009; 101: 1039-1043.
24. Martoni AA, Pinto C, Di Fabio F. Capecitabine plus oxaliplatin (XELOX) versus protracted 5-fluorouracil venous infusion plus oxaliplatin (pviFOX) as first-line treatment in advanced colorectal cancer: a GOAM phase II randomised study (FOCA trial). Eur J Cancer 2006; 42: 3161-3168.
25. Hochster HS, Hart LL, Ramanathan RK. Safety and efficacy of oxaliplatin/fluoropyrimidine regimens with or without bevacizumab as first-line treatment of metastatic colorectal cancer (mCRC): final analysis of the TREE-Study. 42nd Annu Meet Am Soc Clin Oncol. J Clin Oncol 2006; 24: 18 (abstr #3510).
26. Porschen R, Arkenau H-T, Kubicka S. Capecitabine plus oxaliplatin compared with fluorouracil and leucovorin plus oxaliplatin: a randomized comparison in metastatic colorectal cancer. A final report of the AIO Colorectal Study Group. J Clin Oncol 2007; 25: 4217-4223.
27. Diaz-Rubio E, Tabernero J, Gomez-Espana J. Phase III study of capecitabine plus oxaliplatin versus continuous infusion fluorouracil plus oxaliplatin as first-line therapy in metastatic colorectal cancer: final report of the Spanish Cooperative Group for the Treatment of Digestive Tumors Trial. J Clin Oncol 2007; 25: 4224-4230.
28. Ducreux M, Bennouna J, Hebbar M. Efficacy and safety findings from a randomised phase III study of capecitabine (X) + oxaliplatin (O) (XELOX) vs. infusional 5- FU/LV + O (FOLFOX-6) for metastatic colorectal cancer (MCRC). 43rd Annu Meet Am Soc Clin Oncol. J Clin Oncol 2007; 25 (Pt I), 18S (abstr #4029).
29. Cassidy J, Clarke S, Diaz-Rubio E. XELOX vs FOLFOX4 efficacy results from XELOX-1/NO16966, a randomized phase III trial in first-line metastatic colorectal cancer (MCRC). G.I. Cancer Symp 2007. J Clin Oncol 2007; 25: 4165 (abstr #270).
30. Saltz LB, Clarke S, Diaz-Rubio E. Bevacizumab (Bev) in combination with XELOX or FOLFOX4: efficacy results from XELOX-1/NO16966, a randomized phase III trial in the first line metastatic colorectal cancer (MCRC). G.I. Cancer Symp 2007. J Clin Oncol 2007; 25: 1539 (abstr #238).
31. Comella P, Massidda B, Filippelli G et al. Randomised trial comparing biweekly oxaliplatin plus oral capecitabine versus oxaliplatin plus i.v. bolus fluorouracil/leucovorin in metastatic colorectal cancer patients: results of the Southern Italy Cooperative Oncology Group trial 0401. J Cancer Res Clin Oncol 2009; 135: 217-226.