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EDITORIAL

Capecitabine for locally advanced and metastatic colorectal cancer: A review

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Abstract

Capecitabine (Xeloda®) is an oral fluoropyrimidine which is produced as a pro-drug of fluorouracil, and shows improved tolerability and intratumor drug concentrations following its tumor-specific conversion to the active drug. We have searched the Pubmed and Cochrane databases from 1980 to 2009 with the purpose of reviewing all available information on Capecitabine, focusing on its clinical effectiveness against colorectal cancer. Special attention has been paid to 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 on metastatic colorectal cancer, either alone or in various combinations with other active drugs such as Irinotecan and Oxaliplatin was also assessed. Finally, neoadjuvant therapy consisting of Capecitabine plus radiation therapy, for locally advanced rectal cancer was analysed. This combination of chemotherapy and radiotherapy has a special role in tumor down staging and in sphincter preservation for lower rectal tumors. Comparative trials have shown that Capecitabine is at least equivalent to the standard LV-5-FU combination in relation to progression-free and overall survival whilst showing a better tolerability profile with a much lower incidence of stomatitis. It is now known that Capecitabine can be combined with other active drugs such as Irinotecan and Oxaliplatin. The combination of Oxaliplatin with Capecitabine represents a new standard of care for metastatic colorectal cancer. Combinating the Capecitabine-Oxaliplatin regimen with promising new biological drugs such as Bevacizumab seems to give a realistic prospect of further improvement in time to progression of metastatic disease. Moreover, preoperative chemo-radiation using oral capecitabine is better tolerated than bolus 5-FU and is more effective in the promotion of both down-staging and sphincter preservation in patients with locally advanced rectal cancer. Finally, the outcomes of recently published trials suggest that capecitabine seems to be more cost effective than other standard treatments for the management of patients with colorectal cancer.

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Key words: Chemo-radiotherapy; Colorectal cancer; Capecitabine; Oxaliplatin; Xeloda

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INTRODUCTION

5-Fluorouracil (5-FU) a fluorinated analog of uracil has been commercially known since 1957. It is a member of the antimetabolite family and has substantial activity as a chemotherapeutic agent over a variety of malignant tumors including colorectal cancer (CRC). Several trials have shown improved local control and survival rates when 5-FU is combined with radiation therapy in a variety of malignancies when compared to radiation therapy alone[1].

5-FU's molecular activity is quite complex, showing interference with DNA synthesis and mRNA translation. 5-FU is transformed to 5-fluorodeoxyuridine (5FdUrd) by the action of thymidine phosphorylase[2]. 5FdUrd then binds to thymidylate synthase and to tetrahydrofolate, forming a stable complex which prevents the formation of thymidine from thymine. Finally DNA synthesis is blocked, leading to cell death.

In addition, interfering with the enzymatic path of thymidine kinase, the 5FdUrd is metabolized into fluorouridinemono- and triphosphate (FdUMP and FdUTP), which are directly inserted into the DNA, leading to pathological DNA structures. The FdUTP can also be used by mRNA polymerase for mRNA formation, resulting in blockage of mRNA translation.

Because of its unpredictable gastrointestinal absorption and degradation 5-FU 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[3]. Protracted infusion of 5 to 28 d in CRC patients has been found to increase the response rate (RR) from the 14%, achieved with bolus infusions, to 22%[4].

However, the drawbacks of continuous 5-FU infusions are hospital and/or home health costs, infection risk from intravenous devices and overall patient burden[5]. To overcome these disadvantages whilst preserving the benefits of continuous-infusion, oral pro-drugs of FU were developed.

Ftorafur (Tegafur), developed in 1967, was the first oral 5-FU prodrug and showed palliative benefits in a phase I study in patients with gastrointestinal carcinomas. However, further improvement of that product in the United States was restricted due to neurological toxicities[1]. UFT which is a combination of Tegafur with Uracil, an inhibitor of the primary enzyme responsible for FU degradation to central nervous system active metabolites, is currently being evaluated[1]. S-1 (ftorafur plus 5-chloro-2,4-dihydroxypyridine plus potassium oxonate) is an oral 5-FU pro-drug which is also a dihydropyrimidine dehydrogenase inhibitor. It was developed in 1996 by Japanese workers. Based on the good results from trials in patients with gastric cancer, S-1 was given a manufacturing approval from the Ministry of Health and Welfare of Japan in January 1999, with indications for advanced and recurrent gastric cancers[6].

Doxifluridine (5'-FdUrd; 5'-deoxy-5-fluorouridine), another oral pro drug, takes advantage of a different metabolic pathway to form 5-FU. The conversion of this pro drug to its active form is 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 indicated by diarrhea[7,8].

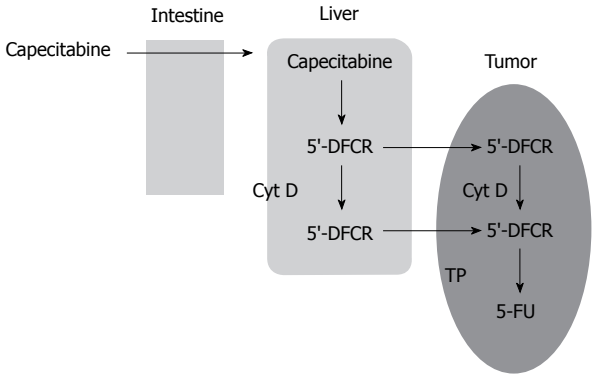

Figure 1 Metabolic conversion of capecitabine to fluorouracil in three consecutive steps. 5'-DFCR: 5'-deoxy-S-fluorocytidine; Cyt D: Cytidine deaminase; 5-FU: 5-Fluorouracil; TP: Thymidine phosphorylase.

Capecitabine is a carbonate derivative of 5'-DFUR that is absorbed through the intestine in pro-drug form. Three activation steps are necessary to metabolize capecitabine to its active form, FU (Figure 1). Capecitabine is absorbed through the intestine and converted in the liver to 5'-deoxy-S-fluorocytidine (5'-DFCR) by carboxylesterase and then to 5'-deoxy-S-fluorouridine (5'-DFUR) by cytidine deaminase (Cyt D). Finally, thymidine phosphorylase (TP) converts 5'-DFUR to the active drug, FU. This reaction occurs in both tumor and normal tissues. However, thymidine phosphorylase is found at higher concentrations in most tumor tissue than in normal healthy tissue. This theoretically allows a selective activation of the drug and low systemic toxicity[9,10].

This article reviews the available information on Capecitabine with respect to its effectiveness on locally advanced and metastatic CRC, as a first line treatment in combination with other active drugs. The efficacy of combined Capecitabine with radiation therapy in locally advanced colorectal cancer as presurgical approach is also evaluated.

IDENTIFICATION OF ELIGIBLE STUDIES

We searched MEDLINE and the Cochrane Central Register of Controlled Trials (last search on December 2009) using combinations of terms, such as: Capecitabine, Xeloda and CRC treatment. We also checked the abstracts from the major International Cancer Meetings such as the American Society of Clinical Oncology (ASCO) and Gastro-Intestinal Cancer Symposium during the last decade. We considered as eligible all, English written, meta-analyses or randomized controlled trials, providing information about the effectiveness of Capecitabine on colorectal cancer treatment, and future directions of ongoing research. Given the large volume of experience accumulated during the last few years on the use of Capecitabine for treating patients with CRC, we believe it is of the interest include a review and summary of the results of the most relevant

Table 1 Randomized controlled trials comparing capecitabine with standard 5-fluorouracil/leucovorin in patients with metastatic colorectal cancer

Author	Treatment arms	OS (mo)	RR (%)	PFS (mo)	FFS (mo)	Major toxicity
Hoff *et al*[12]	ARM1: LV 20 mg/m^2 iv + 5-FU 425 mg/m^2/per day iv, days 1-5 every 4 wk	13.3	11.6	4.7	3.1	More stomatitis with 5-FU/LV (16% *vs* 3%)
	ARM2: Capecitabine 2500 mg/m^2 per day, for 14 d every 21 d 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*[13]	ARM1: LV 20 mg/m^2 iv + 5-FU 425 mg/m^2 per day iv, days 1-5 every 4 wk	12.1	15	4.7	4.0	More stomatitis with 5-FU/LV (13.3% *vs* 1.3%)
	ARM2: Capecitabine 2500 mg/m^{2}per day, for 14 d every 21 d per os	13.2	18.9	5.2	4.2	More hand-foot syndrome with capecitabine (16.2% *vs* 0.3%)

OS: Overall survival; RR: Response rate; PFS: Progression-free survival; FFS: Failure-free survival; LV: Leucovorin; 5-FU: 5-fluorouracil.

clinical trials on this issue. We have incorporated those published as full papers in peer-reviewed journals as well as those reported recently at the major international cancer meetings such as ASCO end Gastro-Intestinal Cancer Symposium.

DATA EXTRACTION

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

CAPECITABINE *VS* STANDARD 5-FLUOROURACIL/LEUKOVORIN COMBINATION FOR LOCALLY ADVANCED AND METASTATIC COLORECTAL CANCER

For locally advanced or metastatic CRC the main treatment for more than four decades was based on FU either as a single agent in combination with leukovorin (LV) or in regimen with newer drugs such as irinotecan or oxaliplatin[11]. For metastatic CRC, Capecitabine as a single agent is compared with standard FU/LV regimen for first line therapy in two phase Ⅲ trials and but with no comparative studies with irinotecan and oxaliplatin[12-25].

The role of Capecitabine as a single agent in metastatic CRC was evaluated and compared to standard intravenous FU/LV regimen as first line treatment in two randomized non-blinded phase Ⅲ trials[12,13]. The two trials were identical regarding the study design, primary and secondary end points, patient inclusion and exclusion criteria, conduct and monitoring. Six hundred and five patients from 61 centers in the United States, Canada, Brazil and Mexico were enrolled in first study[12]. The second study included 602 patients from 59 centers in Europe, Australia, New Zealand, Taiwan and Israel[13] (Table 1). Both trials had the same primary end-point, to determine whether Capecitabine was at least as effective as 5-FU/LV in terms of objective tumor RR. The estimation was done both by investigators and by an independent review committee (IRC) which 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. A computer system was used for random allocation of patients to either Capecitabine or 5-FU/LV arm. Capecitabine (1250 mg/m^2) was taken orally within 30 min of food twice a day for 2 wk of treatment followed by 1 wk of rest.

Patients in the 5-FU/LV arm received the Mayo Clinic regimen which consisted 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; with cycles repeated every 4 wk. Depending on disease progression (or non-progression) and on toxicity (acceptable toxicity) the treatment was scheduled to be continued over a 30-wk assessment. In those patients showing response to treatment or with stable disease, treatment might be extended beyond 30 wk at the discretion of attendant physician[12,13]. 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*[12]. 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, favouring the Capecitabine arms in both cases. 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 for the 2 therapies: 4.5 mo for Capecitabine and 4.6 mo for 5-FU/LV. Median time to response was shorter in the Capecitabine patients (1.7 mo *vs* 2.4 mo, P value not reported). However, these benefits did not translate into an improvement of TTP or OS. The median TTP was 4.6 mo in the Capecitabine group and 4.7 mo for 5-FU/LV ($P = 0.95$), with no baseline characteristics demonstrating any significant differences. Median survival rates were 12.9 and 12.8 mo for the Capecitabine and FU/LV groups, respectively. As far as the toxicity profile is concerned,

Table 2 Non-comparative phase Ⅱ trials on Capecitabine with either Oxaliplatin or Irinotecan combination in patients with metastatic colorectal cancer

Author	Patients	Drugs used	Regimen	RR (%)	mTTP (mo)	MS (mo)
Cassidy *et al*[16]	96	Capecitabine Oxaliplatin	2000 mg/m^2 per day (days 1-14) 130 mg/m^2 day 1	55	7.7	19.5
Zeuli *et al*[17]	43	Capecitabine Oxaliplatin	2500 mg/m^2 per day (days 1-14) 120 mg/m^2 day 1	44	-	20
Borner *et al*[18]	43	Capecitabine Oxaliplatin	2500 mg/m^2 per day (days 1-14) 130 mg/m^2 day 1	49	5.9	17.1
Shields *et al*[19]	35	Capecitabine Oxaliplatin	1500 mg/m^2 per day (days 1-14) 30 mg/m^2 day 1	37.1	-	NR
Bajetta *et al*[20]	68	Capecitabine Irinotecan	2500 mg/m^2 per day (days 2-15) 300 mg/m^2 day 1	47	8.3	-
Bajetta *et al*[20]	66	Capecitabine Irinotecan	2500 mg/m^{2}per day (days 2-15) 150 mg/m^2 days 1and 8	44	7.6	-
Patt *et al*[21]	52	Capecitabine Irinotecan	2000 mg/m^2 per day (days 2-15) 250 mg/m^2 day 1	46	7.1	15.6
Cartwright *et al*[22]	49	Capecitabine Irinotecan	2000 mg/m^2 per day (days 2-15) 240 mg/m^2 day 1	45	5.7	13.4
Kim *et al*[23]	43	Capecitabine Irinotecan	2000 mg/m^2 per day (days 2-15) 100 mg/m^2 days 1and 8	46.6	NR	NR
Rosati *et al*[24]	46	Capecitabine Oxaliplatin	1000 mg/m^2 per day twice daily on days 1-14 every 3 wk oxaliplatin 65 mg/m^2 iv days 1 and 8	38	8	19.3
Garcia-Alfonso *et al*[25]	53	Capecitabine Irinotecan	1000 mg/m^2/d twice daily on days 2-8 every 2 wk irinotecan 175 mg/m^2 on day 1	32	9	19.2

RR: Response rate; mTTP: Median time to progression; MS: Median survival; NR: Not recorded. All capecitabine doses were divided equally and dosed twice daily. Regimens were administered every 3 wk.

results were observed which favoured 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 study by Van Cutsem *et al*[13] and in 40.5% of patients in the study by Hoff *et al*[12]. Correspondingly, 35.1% and 49.3% of the patients receiving 5-FU required dose reductions in the respective studies. Dose reduction was necessary mainly due to the hand-foot syndrome and diarrhea in the Capecitabine group, while diarrhea and stomatitis were the main causes of dose reduction in the 5-FU/LV arm[12-14].

When combining 5-FU with LV the cytotoxic effect of the active drug is prolonged through the stabilization of a tertiary complex with thymidylate synthase[1]. In order to evaluate the effect of LV with Capecitabine, a phase Ⅱ study was conducted[15]. Patients with advanced CRC were randomized to receive intermittent therapy (2 wk on treatment, 1 wk off) with either Capecitabine alone (1255 mg/m^2 twice daily, n = 34) or Capecitabine (828 mg/m^2) and LV (30 mg/d), 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 d *vs* 165 d). 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%). Combined dosing with LV did not provide added benefit in terms of RR or TTP and produced more adverse events[15].

PHASE Ⅱ TRIALS OF COMBINATIONS OF 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 CRC, and are often used as first line treatment[11]. The efficacy of combining such drugs with Capecitabine in patients with metastatic CRC has been evaluated by several non-comparative phase Ⅱ studies[16-25] (Table 2).

The fact that oxaliplatin up regulates thymidine phosphorylase can lead to synergistic activity with Capecitabine[16]. Although the two treatments were not directly compared, the Capecitabine and oxaliplatin combination gave comparable outcomes to that of FU/LV and oxaliplatin as regard the overall RR (37%-55% *vs* 34%-49% respectively) and median survival (17-20 mo *vs* 16-21 mo respectively)[12,16-19].

Furthermore, the toxicological profile was related to oxaliplatin induced sensory neuropathy, nausea and vomiting, and Capecitabine induced diarrhea[16-19]. However, although the irinotecan and Capecitabine combination was not directly compared to the 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 mo *vs* 14.8-20 mo, respectively)[12,20-25]. Diarrhea, nausea, vomiting, and neutropenia were the most frequent side effects[20-25]. Randomized,

comparative trials are needed to establish the future role of these combinations in the first line treatment of colorectal cancer.

CAPECITABINE-IRINOTECAN-DATA FROM RECENTLY PUBLISHED RANDOMIZED TRIALS

The results of the EORTC study 40015 which was terminated early due to unacceptable mortality rates, were published recently[26]. This study was designed to demonstrate the non-inferiority of Capecitabine to 5-FU/folinic acid (FA), in relation to progression-free survival (PFS) after first-line treatment of metastatic CRC and the benefit of adding celecoxib (C) to irinotecan/fluoropyrimidine regimens compared with placebo (P). Patients were randomly assigned to receive FOLFIRI: irinotecan (180 mg/m^2 iv on days 1, 15 and 22); FA (200 mg/m^2 iv on days 1, 2, 15, 16, 29 and 30); 5-FU (400 mg/m^2 iv bolus, then 22-h, 600 mg/m^2 infusion) or Capecitabine-irinotecan (CAPIRI): irinotecan (250 mg/m^2 iv infusion on days 1 and 22); Capecitabine *po* (1000 mg/m^2 bid on days 1-15 and 22-36). Additionally, patients were randomly assigned to receive either P or C (800 mg: 2 × 200 mg bid.). The trial was closed following eight deaths unrelated to disease progression in the 85 enrolled (629 planned) patients. Response rates were 22% for CAPIRI + C, 48% for CAPIRI + P, 32% for FOLFIRI + C and 46% for FOLFIRI + P. Median PFS and OS times were shorter for CAPIRI *vs* FOLFIRI (PFS 5.9 mo *vs* 9.6 mo and OS 14.8 mo *vs* 19.9 mo) and C *vs* P (PFS 6.9 mo *vs* 7.8 mo and OS 18.3 mo *vs* 19.9 mo). Dose reductions, mainly as a consequence of gastrointestinal toxicity, were more common in the CAPIRI compared with the FOLFIRI arms, with 53% *vs* 33% of patients, experiencing at least one cycle with a reduction. Thirty-four patients (41.5%) experienced treatment delays, which were more common in the FOLFIRI compared with the CAPIRI arms, with 54% and 30% of patients, respectively, experiencing at least one cycle with delay. The relative dose intensity for Capecitabine and 5-FU did not differ markedly in their P arms (82.4% *vs* 84.8%) but was lower for Capecitabine if C was also administered (66.4% *vs* 92.1% for 5-FU). Interestingly, very little difference in the irinotecan dose intensity was observed across all study arms (range 83.1%-88.4%).

The deaths were primarily linked to gastrointestinal or thromboembolic events. Sudden deaths linked to such causes have previously been noted for regimens combining irinotecan and bolus 5-FU/FA[27]. The efficacy data from this study are however consistent with those reported for the randomized, 3 × 2 factorial BICC-C trial, which assessed whether C added to FOLFIRI, CAPIRI or a modified irinotecan, bolus 5-FU and FA (m-IFL) regimen improved efficacy and/or reduced toxicity. Median time to progression and OS times in this trial were longer in the patients who received FOLFIRI compared with those who received CAPIRI or m-IFL[28]. The most common grade 3/4 adverse effect observed in this study was diarrhea, which occurred significantly more frequently in the patients receiving CAPIRI than FOLFIRI (37% *vs* 13%). The dose levels of Capecitabine and irinotecan initially selected were the same as those recommended, and found to be well tolerated by 76 patients in a recent phase I / II trial[29]. Similarly, in a large phase III study of combination chemotherapy with Capecitabine, irinotecan and oxaliplatin in 820 advanced CRC patients, CAPIRI was again found to be generally well tolerated[30]. These analyses raise the question of whether a lower Capecitabine dose may have been more effective. Further studies to determine the most appropriate dose of Capecitabine in CAPIRI and other combination regimens for particular geographic and/or ethnic patient groups may therefore be warranted. The authors have concluded that the small sample size and confounding safety issues did not allow valid conclusions to be drawn concerning the relative efficacy of CAPIRI *vs* FOLFIRI. Consistent with other studies, no benefit was seen from adding C to irinotecan/fluoropyrimidine regimens.

RANDOMIZED TRIALS COMPARING THE CAPECITABINE AND OXALIPLATINE COMBINATION TO THE FLUOROURACIL/LEUKOVORIN PLUS OXALIPLATIN REGIMEN

The literature research revealed several important randomized trials that compare Capecitabine with 5-FU (with or without FA) in combination with oxaliplatin (Table 3).

In a phase II trial, 118 patients were randomized to receive treatment with the XELOX regimen every 3 wk or with oxaliplatin (given on day 1) plus 5-FU (250 mg/m^2 daily continuous intravenous infusion for 3 wk). The RR was the same for the two treatments although the XELOX regimen produced less severe diarrhea and a substantially lower occurrence of severe stomatitis[31].

In the TREE study, the safety and efficacy of three oxaliplatin and fluoropyrimidine regimens, with or without bevacizumab, as first-line treatment for metastatic CRC were evaluated. In TREE-1 (first part of the study) 150 patients were randomly assigned to receive either (a) the mFOLFOX regimen (oxaliplatin 85 mg/m^2, FA 350 mg/m^2, 5-FU 400 mg/m^2 bolus and 2400 mg/m^2 46-h infusion on day 1) every 14 d; (b) the bFOL regimen (oxaliplatin 85 mg/m^2 on day one and 5-FU 500 mg/m^2 plus FA 20 mg/m^2 intravenously on days 1 and 8, every 14 d) or (c) the XELOX regimen every 21 d. In TREE-2, the second part of TREE study, the monoclonal antibody bevacizumab was added to the above mentioned regimens at a dosage of 5 mg/kg iv every 2 wk or 7.5 mg/kg iv every 3 wk. In this part of the trial, the Capecitabine dose which was combined with oxaliplatin was reduced to 1700 mg/m^2 per day. The results showed that the incidence of grade 3/4 treatment-related adverse events during the first 12 wk

Table 3 Randomized trials that compare oxaliplatin plus capecitabine with oxaliplatin plus 5-fluorouracil ± folinic acid in metastatic colorectal cancer

Trial	Arms	Patients No.	PFS (mo)	OS (mo)	RR (%)	Severe toxicity ⩾ grade 3
FOCA trial[31]	XELOX: (oxaliplatin 130 mg/m^2 on day 1 and capecitabine 2000 mg/m^2 per day for 14 d, repeating every 21 d)	62	7	NR	43	Less diarrhea (8 *vs* 18%) and stomatitis (19 *vs* 29 %) in XELOX arm
	pviFOX: (protracted fluorouracil intravenous infusion plus oxaliplatin)	56	9	NR	48	
US TREE-1[32]	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 day 1 and fluorouracil 500 mg/m^2 plus folinic acid 20 mg/m^2 intravenously on days 1 and 8, every 2 wk)	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 day 1)	49	8.7	17.6	41	
German trial[33]	CAPOX: (oxaliplatin 70 mg/m^2 on days 1 and 8, and capecitabine 2000 mg/m^2 per day for 2 wk, recycling every 3 wk)	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[34]	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[35]	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 2, fluorouracil 400 mg/m^2 bolus and 2400 mg/m^2 infused over 48 h)	150	9.3	20.5	46	
NO16966 trial[36]	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 day 1, 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[38]	OXXEL: (oxaliplatin 100 mg/m^2 on day 1 and capecitabine 2000 mg/m^2 per day from day 1 to day 11 every 2 wk)	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 day 1, folinic acid 250 mg/m^2 infused over 2 h on day 1, fluorouracil 850 mg/m^2 bolus on day 2)	164	6.3	17.1	33	

PFS: Progression free survival; OS: Overall survival; RR: Response rate; NR: Not recorded.

of treatment were 59%, 36% and 67% for mFOLFOX6, bFOL, and XELOX, respectively, (TREE-1) and 59%, 51% and 56% for the corresponding treatments plus bevacizumab (TREE-2; primary end point). XELOX toxicity in TREE-1 included grade 3/4 diarrhoea (31%) and dehydration (27%) whilst Capecitabine dose reduction to 1700 mg/m^2 per day in TREE-2 resulted in improved tolerance. Overall RRs were 41%, 20% and 27% (TREE-1) and 52%, 39% and 46% (TREE-2); median OS was 19.2, 17.9 and 17.2 mo (TREE-1) and 26.1, 20.4 and 24.6 mo (TREE-2). For all treated patients, median OS was 18.2 mo (95% CI: 14.5 to 21.6; TREE-1) and 23.7 mo (95% CI: 21.3 to 26.8; TREE-2). The authors concluded that the addition of bevacizumab to oxaliplatin and fluoropyrimidine regimens is well tolerated as first-line treatment of metastatic CRC and does not markedly change overall toxicity. XELOX tolerability and efficacy is improved with reduced-dose Capecitabine. First-line oxaliplatin and fluoropyrimidine-based therapy plus bevacizumab resulted in a median OS of approximately 2 years[32].

The German Colorectal Study Group compared the FUFOX regimen (5-FU 2000 mg/m^2 given 24 h in continuous infusion, FA 500 mg/m^2 and oxaliplatin 50 mg/m^2 infused over 2 h) given weekly for 4 wk with 2 wk of rest, with the CAPOX regimen (oxaliplatin 70 mg/m^2 on days 1 and 8, and Capecitabine 2000 mg/m^2 daily for 2 wk, repeating every 21 d). For the two arms of the study no significant difference, was observed regarding the RR, median PFS and median OS. However, patients treated with CAPOX regimen had a significantly greater incidence of grade 2-3 had-foot syndrome[33].

A Spanish trial set out with the aim of testing the non-inferiority of the XELOX regimen compared with a regimen including a 48-h infusion of 5-FU 2250 mg/m^2 once a week plus oxaliplatin 85 mg/m^2 given twice a week. Despite the fact that, patients treated with the XELOX regimen had a lower RR, the median PFS and OS were not substantially different. Patients treated in the XELOX

arm were observed to have significantly lower incidence of severe diarrhea and grade 1-2 mucositis. Nevertheless, Capecitabine treatment was associated with more hand-foot syndrome[34].

The RR to XELOX and FOLFOX6 (Table 3) regimens, was randomly evaluated by a French phase Ⅲ trial. The authors concluded that the XELOX regimen 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 mo in the XELOX arm *vs* 9.3 mo in the FOLFOX6 and median OS was 19.9 mo *vs* 20.5 mo. The incidence of neutropenia, febrile neutropenia and neuropathy was significantly lower in the XELOX arm[35].

The NO16966 trial was primarily designed in order to examine the equivalence in terms of PFS of the XELOX regimen in comparison to FOLFOX4 (Table 3). The initial design of this trial was a randomized, two-arm, non-inferiority, phase Ⅲ comparison of XELOX *vs* FOLFOX-4. In 2003, after patient accrual had begun the trial design was amended after bevacizumab phase Ⅲ data became available. The resulting 2 × 2 factorial design randomly assigned patients to XELOX *vs* FOLFOX-4, and then to also receive either bevacizumab or P. The results have shown that the median PFS was 8.0 mo in the pooled XELOX-containing arms *vs* 8.5 mo in the FOLFOX-4-containing arms [hazard ratio (HR) = 1.04; 97.5% CI: 0.93 to 1.16]. The median OS was 19.8 mo with XELOX *vs* 19.6 mo with FOLFOX-4 (HR = 0.99; 97.5% CI: 0.88 to 1.12). FOLFOX-4 was associated with more grade 3/4 neutropenia/granulocytopenia and febrile neutropenia than XELOX, and XELOX with more grade 3 diarrhea and grade 3 hand-foot syndrome than FOLFOX-4. The authors concluded that XELOX is not inferior to FOLFOX-4 as a first-line treatment for metastatic CRC, and may be considered as a routine treatment option for appropriate patients[36]. When bevacizumab became available for clinical use, the trial structure was modified and a total of 1401 patients entering the study were also randomized to receive either bevacizumab at a dosage of 5 mg/kg iv every 2 wk or 7.5 mg/kg iv every 3 wk or P in addition to chemotherapy. The results showed that median PFS was 9.4 mo in the bevacizumab group and 8.0 mo in the P group (HR = 0.83; 97.5% CI: 0.72 to 0.95, P = 0.0023). Median OS was 21.3 mo in the bevacizumab group and 19.9 mo in the P group (HR = 0.89; 97.5% CI: 0.76 to 1.03, P = 0.077). RRs were similar in both arms. Analysis of treatment withdrawals showed that, despite protocol allowance of treatment continuation until disease progression, only 29% and 47% of bevacizumab and P recipients, respectively, were treated until progression. The toxicity profile of bevacizumab was consistent with that documented in previous trials. The authors concluded that the addition of bevacizumab to oxaliplatin-based chemotherapy significantly improved PFS in this first-line trial in patients with metastatic CRC. OS differences did not reach statistical significance, and RR was not improved by the addition of bevacizumab. Treatment continuation until disease progression may be necessary in order to optimize the contribution of bevacizumab to therapy[37].

The Southern Italy Cooperative Oncology Group randomly assigned the OXXEL regimen (Table 3) with a combination of oxaliplatin, FA and 5-FU (OXAFAFU) (Table 3) to a total of 322 patients with metastatic CRC. The results showed that eleven complete and 42 partial responses were registered with OXXEL (RR = 34%) while six complete and 48 partial responses were obtained with OXAFAFU (RR = 33%) (P = 0.999). Severe adverse events were less frequent (32% *vs* 43%) with OXXEL, which also showed lower levels of severe neutropenia (10% *vs* 27%) and febrile neutropenia (6% *vs* 13%), but produced more gastric side effects (8% *vs* 3%) and diarrhea (13% *vs* 8%). Quality of life did not differ between the two arms. Median PFS was 6.6 mo in the OXXEL, and 6.5 mo in the OXAFAFU arm (HR = 1.12, P = 0.354). Median OS was 16.0 and 17.1 mo (HR = 1.01, P = 0.883). The authors concluded that OXXEL and OXAFAFU regimens were equally active in metastatic CRC[38].

CAPECITABINE PLUS RADIATION THERAPY AS PREOPERATIVE THERAPY IN LOCALLY ADVANCED RECTAL CANCER

The addition of chemotherapy to preoperative radiotherapy, in patients with locally advanced rectal cancer, leads to improvement of down staging and thus improves local control. Proof that the addition of chemotherapy to preoperative radiotherapy improves local control rates has lately been given by two separate trials. The EORTC 22921 trial which randomized between preoperative radiotherapy (45 Gy), and preoperative chemo-radiotherapy (45 Gy plus infusion of 5-FU/LV). The local control rates were significantly increased in the chemo-radiation arm: 91% *vs* 83 %[39,40]. In the French FFCD 9203 study similar results were found. This trial randomized patients with locally advanced rectal cancer to preoperative radiation alone (45 Gy) *vs* the same preoperative radiation therapy plus infusion of 5-FU/LV. The results showed a local recurrence rate of 16.5% for radiation therapy alone and 8% for combined treatment[41]. Several phase Ⅱ trials have been conducted in order to investigate whether orally administered Capecitabine may be more effective and less toxic than intravenous 5-FU[42-53] (Table 4). These trials concluded that preoperative chemo-radiation combined with Capecitabine achieved encouraging down-staging and sphincter preservation with a low toxicity profile.

Kim *et al*[54] conducted a phase Ⅲ trial to compare the efficacy of oral Capecitabine *vs* bolus 5-FU in preoperative radiotherapy for locally advanced rectal cancer (LARC). Between July 1993 and June 1999, 127 patients with LARC received concurrent preoperative chemo-radiation using two cycles of intravenous bolus 5-FU (500 mg/m^2 per day) and LV (20 mg/m^2 per day) for 5 d each (Group Ⅰ). Another LARC group with 97 patients received concurrent

Table 4 Phase Ⅱ trials for locally advanced rectal cancer treated with preoperative chemo-radiation therapy using orally capecitabine

Study	Patients enrolled	Treatment used	Complete response (%)	Down staging (%)	Severe toxicity
Dupuis *et al*[42]	51	RT: 45 Gy/1.8 Gy fraction/25 fractions Capecitabine: 825 mg/m^2 bid throughout RT	20	48	No grade 4 toxicity
Desai *et al*[43]	30	RT: 50.4 Gy/1.8 Gy day Capecitabine: 1330 mg/m^2 per day in 2 divided doses throughout RT	11	37	No grade 4 toxicity
Korkolis *et al*[44]	30	RT: 50.4 Gy/1.8Gy day Capecitabine: 825 mg/m^2 bid throughout RT	23	84	No grade 4 toxicity
Willeke *et al*[45]	36	RT: 50.4 Gy/1.8Gy day Capecitabine: 500 mg/m^2 bid (days 1-38) Irinotecan: 50 mg/m^2 weekly	15	41	Grade 4 leucopenia in 2 patients
Velenik *et al*[46]	57	RT: 45Gy/25 fractions/1.8 Gy Capecitabine: 1650 mg/m^2 per day in 2 divided doses throughout RT	9.1	49.1	No grade 4 toxicity
Krishnan *et al*[47]	54	RT: 52.5 Gy/30 fractions Capecitabine: 825 mg/m^2 bid throughout RT	18	52	No grade 4 toxicity
De Paoli *et al*[48]	53	RT: 50.4 Gy/1.8 Gy day Capecitabine: 825 mg/m^2 bid throughout RT	24	57	No grade 4 toxicity
Machiels *et al*[49]	40	RT: 45 Gy/25 fractions/1.8 Gy Capecitabine: 825 mg/m^2 bid throughout RT Oxaliplatin: 40 mg/m^2 weekly for 5 wk	14	32	Grade 3/4 toxicity 30%
Kim *et al*[50]	95	RT: 50 Gy/25 fractions Capecitabine: 1650 mg/m^2 per day in 2 divided doses throughout RT	12	71	No grade 4 toxicity
Carlomagno *et al*[51]	43	RT: 45 Gy/25 fractions Capecitabine: 825 mg/m^2 per day twice daily on days 1-14 every 3 wk/2 Cycles Oxaliplatin 50 mg/m2 days 1 and 8 every 3 wk	20.9	NR	No grade 4 toxicity
Fakih *et al*[52]	25	RT: 50.4 Gy/1.8 Gy day Capecitabine: 725 mg/m^2/d twice daily Monday to Friday concomitant with RT Oxaliplatin 50 mg/m^2 weekly for 5 wk	24	52	Grade 3 diarrhea, in 20% of patients
Craven *et al*[53]	70	RT: 45 Gy/1.8 Gy day Capecitabine: 900 mg/m^2 per day Monday to Friday concomitant with RT	9.2	66	No grade 4 toxicity

RT: Radiation therapy; bid: Twice daily; NR: Not recorded.

chemo-radiation using two cycles 1650 mg/m^2 per day of oral Capecitabine and 20 mg/m^2 per day of LV (Group Ⅱ). Radiation therapy was delivered to the primary tumor at 50.4 Gy in both groups. Definitive surgery was performed 6 wk after the completion of chemo-radiation. Pathologically complete remission was achieved in 11.4% of patients in Group Ⅰ and in 22.2 % of patients in Group Ⅱ ($P = 0.0042$). The down-staging rates of the primary tumor and lymph nodes were 39.0%/68.7% in Group Ⅰ and 61.1%/87.5% in Group Ⅱ ($P = 0.002/0.0005$). Sphincter-preserving surgery was possible in 42.1% of patients in Group Ⅰ and 66.7% of those in Group Ⅱ ($P = 0.021$). Grade 3 or 4 leucopenia, diarrhea, and radiation dermatitis were statistically more prevalent in Group Ⅰ than in Group Ⅱ, while the opposite was true for grade 3 hand-foot syndrome. Preoperative chemo-radiation using oral Capecitabine was better tolerated than bolus 5-FU and was more effective in the promotion of both down-staging and sphincter preservation in patients with LARC. However, larger Phase Ⅲ trials are needed to better clarify these promising results from combination preoperative chemo-radiotherapy using Capecitabine in patients with LARC.

CONCLUSION

In the Unites States, Capecitabine is currently the only oral 5-FU pro-drug approved for use. In patients with locally advanced and metastatic CRC, Capecitabine is as effective as 5-FU and has a toxicity profile that consists most commonly of gastrointestinal and dermatologic side-effects. In patients with locally advanced and metastatic CRC the effectiveness of this drug has been tested in large trials.

These showed that Capecitabine is at least equivalent to the standard LV-5-FU combination in terms of progression-free and OS whilst demonstrating a better tolerability profile with a much lower incidence of stomatitis. The clinical evidence from these trials on June 15, 2005, led the U.S. Food and Drug Administration to approve Capecitabine as a single-agent adjuvant treatment for Dukes' stage C colon cancer patients who have undergone complete resection of the primary tumor in those instances when fluoropyrimidine therapy alone would be preferred. Additionally, The committee for medicinal products for human use during its February 2005 plenary meeting, approved the use of Capecitabine for the adjuvant treatment of patients following surgery of stage Ⅲ (Dukes' stage C) colon cancer and during its December 2007 plenary meeting extended the indication to the treatment of patients with metastatic CRC. Although the combination of Capecitabine with either oxaliplatin or irinotecan, sometimes increases the occurrence of gastrointestinal adverse effects compared with the corresponding combinations including infusional 5-FU plus FA, it is a more easily delivered therapy may improve the compliance of patients. The addition of bevacizumab to the combination of Capecitabine and oxaliplatin is feasible and promising, and it is currently under evaluation in the adjuvant setting. Additionally, preoperative combination of chemotherapy and radiation therapy using oral Capecitabine is better tolerated than bolus 5-FU and is more effective in the promotion of both down-staging and sphincter preservation in patients with locally advanced rectal cancer. Finally, from a health-economic perspective, cost-effectiveness analyses demonstrate that, despite higher acquisition costs, Capecitabine appears to be more cost effective than standard treatments for the management of patients with CRC.

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