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Update on capecitabine alone and in combination regimens in colorectal cancer patients

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SUMMARY

Capecitabine is an orally administered fluoropyrimidine carbamate which has been developed as a prodrug of 5-FU with the goal to improve its tolerability and intratumoral drug concentration. The review aims to provide an evidence-based update of clinical trials investigating the clinical efficacy, adverse-event profile, dosage and administration of this drug, alone or in combination with conventional chemotherapeutics and/or new target-oriented drugs, in the management of colorectal cancer patients.

Introduction

5-fluorouracil (5-FU) has been the cornerstone of chemotherapy for the past 50 years in the treatment of metastatic colorectal carcinoma (mCRC). We know from several studies and meta-analyses that its combination with leucovorin (LV) improves outcome in terms of response rate (RR) and survival.[1] It has also been demonstrated that continuous-infusion 5-FU/LV is better than bolus intravenous injection of 5-FU.[2] Even with the recent introduction of new cytotoxic agents (eg, irinotecan and oxaliplatin) and targeted therapies such as bevacizumab, cetuximab, and panitumumab, 5-FU remains a key component of most recommended chemotherapy regimens. One potential drawback of 5-FU is its poor oral absorption, which requires a permanent venous access and a portable pump and might cause complications.

Capecitabine is an orally administered prodrug of 5-FU that is absorbed readily by the gastrointestinal tract with a bioavailability of almost 100%. The maximum plasma concentration (Cmax) and area under the plasma concentration-time curve are linearly proportional to the oral dosage. In fact, after a standard single dose of capecitabine (1250 mg/m^2), the Cmax is achieved in 1.5–2 hours. Capecitabine is metabolized by the liver, where it is converted initially to 5′-deoxy-5-fluorocytidine and subsequently, to 5′-deoxy-5-fluorouridine (5′-DFUR). Finally, 5′-DFUR is converted to 5-FU by thymidine phosphorylase (TP), which is present in amounts 3- to 10-fold higher in neoplastic tissue compared with the normal adjacent tissue (Fig. 1). The higher concentration of TP in tumor tissues leads to a final concentration of 5-FU that is 3-fold higher than in normal tissues.[3]

Capecitabine as single agent in mCRC

Phase I–II trials conducted in mCRC patients defined the recommended daily dose of capecitabine, which is 1250 mg/m^2 bis in die (bid) for two consecutive weeks, and one week rest, repeating this treatment every 3 weeks.[4] Two phase III randomized

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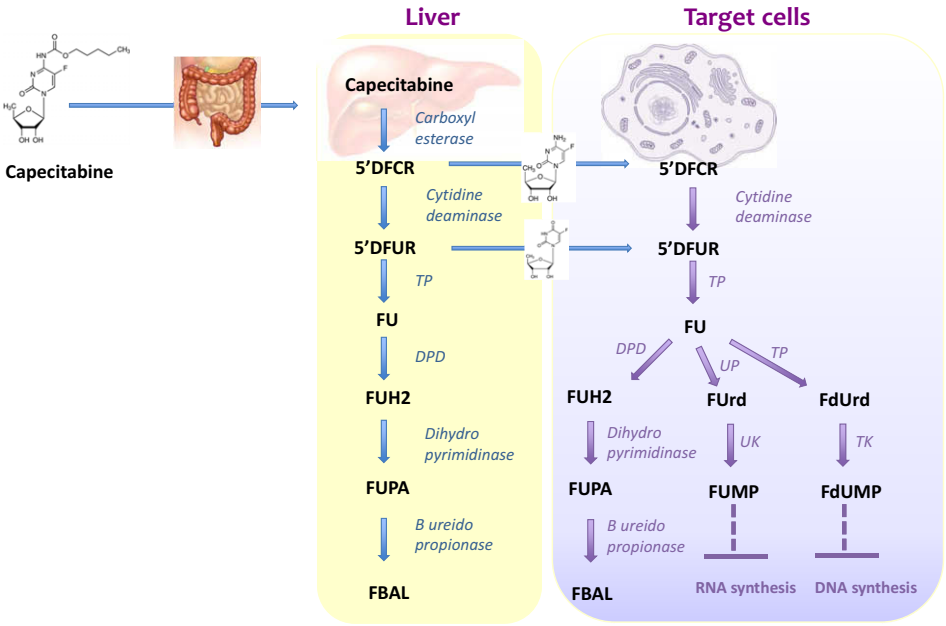

Fig. 1. Stages in the metabolism of capecitabine.

Table 1
Randomized phase III trials comparing capecitabine with 5-FU/LV (Mayo Clinic) in mCRC

Author	Regimen	No. of patients	ORR (%)	median TTP (months)	median OS (months)	G3–4 toxicity
Hoff et al.[5]	Capecitabine versus	302	25.8 $p < 0.05$	4.3	12.5	HFS: 18%; Stomatitis: 3%
	5-FU/LV	303	11.6	4.7	13.3	HFS: 1%; Stomatitis: 16%
Van Cutsem et al.[6]	Capecitabine versus	301	18.9	5.2	13.2	HFS: 16.2%; Stomatitis: 1.3%
	5-FU/LV	301	15	4.7	12.1	HFS: 0.3%; Stomatitis: 13.3%

trials compared capecitabine with the Mayo Clinic regimen in this subset of patients (Table 1).[5,6] Both studies met their primary end point, which was to demonstrate at least statistical equivalence between the 2 regimens, while objective response rates (ORRs) were significantly improved for capecitabine, and significant differences in toxicity were noted. In particular, in a pooled comparison of safety parameters from these 2 phase III trials, the safety profile of capecitabine was superior to that of 5-FU/LV, with significantly ($p < 0.001$) less diarrhea, stomatitis, nausea, alopecia, and grade 3/4 neutropenia.[7] In contrast, capecitabine was associated with a higher incidence of hand and foot syndrome (HFS) (53.5% versus 6.2%) and hyperbilirubinemia (G3: 18.3% versus 3.3%), which was typically unconiugated bilirubin. Most patients required no dose reductions, moreover, a dose modification scheme reduced the incidence of several toxicities without compromising the efficacy. Given its good toxicity profile, capecitabine has been assessed in a phase II trial for the treatment of elderly (aged ≥70 years) mCRC patients.[8] Authors observed an ORR of 24% with a median time to progression (TTP) and overall survival (OS) of 7 months and 11 months, respectively. Capecitabine was extremely well tolerated with grade ≥3 adverse events occurring in only 12% of patients.

Capecitabine in combination regimens in mCRC

Given the activity of single-agent capecitabine versus 5-FU/LV for mCRC, multiple studies have evaluated capecitabine in combination with other agents in this subset of patients.

Capecitabine plus oxaliplatin

Two different schedules compare capecitabine and oxaliplatin. The XELOX regimens include oxaliplatin 130 mg/m^2 on day 1 every 3 weeks, whereas CAPOX regimens split the oxaliplatin dose to 70 mg/m^2 on days 1 and 8. Capecitabine 1000 mg/m^2 bid is given for 2 consecutive weeks with 1 week rest. Early phase II trials considering XELOX and CAPOX regimens achieved promising ORRs of 37–55%, median TTP of 6–8 months, and median OS of 16–20 months (Table 2) with feasible and safe toxicity profiles.[9–13] Recently, Maiello et al. reported preliminary results of a phase II trial considering an innovative schedule considering a biweekly administration of oxaliplatin and capecitabine (XELOX-2).[14] Preliminary results showed that this combination is active and well tolerated with only one patient presented G4 toxicity (diarrhea).

On the basis of this background, some randomized studies were conducted in order to show at least non inferiority and allowing for the substitution of capecitabine for continuous-infusion 5-FU/LV (Table 3). One of the first trials to compare capecitabine/oxaliplatin was the TREE (*Three Regimens of Eloxatin Evaluation*)-1 trial.[15] This study was initially designed to investigate the role of oxaliplatin in the first-line treatment for mCRC patients with three different fluoropyrimidine regimens: modified FOLFOX6, bFOL, or XELOX. ORR was 43%, 22% and 35% respectively, while median TTP was 8.7, 6.9 and 5.9 months, and median OS was 19.2, 17.9 and 17.2 months. The investigators observed that XELOX caused an inacceptable occurrence of severe dehydration (27%) in comparison with FOLFOX6 (8%) or bFOL (12%). The worse tolerability of capecitabine in US patients, as opposed to patients treated in other

Table 2
Capecitabine plus oxaliplatin in the first line setting of mCRC: results from phase II studies

Author	No. of patients	Regimen	ORR (%)	median TTP (months)	median OS (months)
Borner et al.[9]	43	XELOX	49	5.9	17.1
Cassidy et al.[10]	96	XELOX	55	7.7	19.5
Grothey et al.[11]	71	CAPOX	49	6.6	15.8
Shields et al.[12]	35	XELOX	37	6.9	NA
Zeuli et al.[13]	43	XELOX	44	8.2	20
Fedele et al.[14] (GOIM 2503)	51	XELOX-2	51	5+	NA

NA: not available
XELOX: oxaliplatin 130 mg/m^2 on day 1 and capecitabine 1000 mg/m^2 bid on days 1 → 14 q 3 w
CAPOX: oxaliplatin 70 mg/m^2 on days 1 and 8 and capecitabine 1000 mg/m^2 on days 1 → 14 q 3 w
XELOX-2: oxaliplatin 100 mg/m^2 on day 1 and capecitabine 1000 mg/m^2 bid on days 1 → 7 q 2 w

Table 3
Oxaliplatin plus capecitabine versus oxaliplatin plus 5-FU/LV: results of phase III studies

Author	Regimen	Line of therapy	No. of patients	ORR (%)	medianTTP (month)	medianOS (month)	G3–4 toxicity
Hochster et al.[15] (TREE-1 trial)	mFOLFOX6 versus	I	49	41	8.7	19.2	Less neutropenia (15%) but more dehydration (27%) with XELOX
	bFOL versus		50	20	6.9	17.9	
	XELOX		48	27	5.9	17.2	
Cassidy et al.[16] (NO16966 trial)	XELOX versus	I	317	37	7.3	NA	More diarrhea (20%) and HFS (6%) with XELOX
	FOLFOX4		317	39	7.7	NA	
Porschen et al.[17]	CAPOX versus	I	241	48	7.1	16.8	More HFS (10%) with CAPOX
	FUFOX		233	54	8	18.8	
Díaz-Rubio et al.[18]	XELOX versus	I	171	37	8.9	18.1	Less diarrhea (14%) with XELOX
	FUOX		171	46	9.5	20.8	
Rothenberg et al.[19]	XELOX versus	II	627	20	4.8	11.9	Lower neutropenia (5%) but more diarrhea (20%) and HFS (3.5%) with XELOX
	FOLFOX4			18	4.7	12.6	

bFOL: oxaliplatin 85 mg/m^2 on day 1 and 5-FU 500 mg/m^2 plus LV 20 mg/m^2 on days 1 and 8 q 2 w
CAPOX: capecitabine 1000 mg/m^2 bid on days 1 → 14 and oxaliplatin 70 mg/m^2 on days 1 and 8 q 3 w
XELOX: capecitabine 1000 mg/m^2 bid on days 1 → 14 and oxaliplatin 130 mg/m^2 on day 1 q 3 w
FUFOX: oxaliplatin 50 mg/m^2, LV 500 mg/m^2 and 5-FU 2000 mg/m^2 over 24 hours weekly for 4 weeks and 2 weeks of rest
FUOX: continuous infusion 5-FU 2250 mg/m^2 over 48 hours weekly for 6 weeks plus oxaliplatin 85 mg/m^2 every other week
mFOLFOX6: oxaliplatin 85 mg/m^2 plus LV 300 mg/m^2, 5-FU 500 mg/m^2 bolus and 5-FU 2400 46-hour infusion on day 1 q 2 w
FOLFOX4: oxaliplatin 85 mg/m^2 on day 1, LV 200 mg/m^2, 5-FU 400 mg/m^2 bolus and 5-FU 600 mg/m^2 over 22 hours on days 1 and 2 q w 2

countries, has been attributed to the difference in dietary intake of folic acid due to the vitamin enrichment of fruit in North America.[20] After 150 patients had been enrolled, data regarding bevacizumab efficacy became available. At that point trial was amended, and 213 more patients were randomized to the same arms plus bevacizumab (2.5 mg/kg/week). Indeed, dosage of capecitabine in the XELOX regimen was decreased to 1750 mg/m^2 for 2 weeks. In comparison with the TREE-1 study, addition of bevacizumab was reported to improve the efficacy in all arms. In fact, ORR, mPFS and mOS were 53%, 9.9 months, and 26 months on FOLFOX plus bevacizumab; 41%, 8.3 months, and 20.7 months on bFOL plus bevacizumab arm; 48%, 10.3 months, and 27 months on XELOX plus bevacizumab arm. The second and largest reported randomized phase III trial (NO16966) compared FOLFOX4 with XELOX.[16] This study accrued 634 patients and was then amended with the addition of bevacizumab when it became registered for first-line therapy. Actually, the non inferiority of the XELOX versus FOLFOX4 regimen was demonstrated, because the TTP was 8 months versus 8.5 months. Additionally, XELOX reduced the incidence of grade ≥3 neutropenia (7% versus 44%), but produced more severe diarrhea (20% versus 11%) than the FOLFOX regimen. Bevacizumab did not increase the ORR of either XELOX or FOLFOX4, but significantly prolonged the median TTP in comparison with placebo (8 months versus 9.4 months; $p = 0.0023$).[21] Porschen et al. compared the FOLFOX regimen with the CAPOX regimen.[17] No significant differences in ORR, median TTP or median OS were reported for the two arms of the study. Tolerance profiles again showed that both regimens had an acceptable toxicity rate, with a higher incidence of HFS in the CAPOX arm. Diaz-Rubio et al. compared FUOX with XELOX.[18] Although patients treated with the XELOX regimen had a lower ORR, the median TTP and OS were not significantly different. Capecitabine treatment was associated with more HFS (10%). A pooled of six trials comparing oxaliplatin-capecitabine versus oxaliplatin-5-FU as first line therapy of mCRC, including 3,494 patients, showed that the ORR was significantly higher for 5-FU based regimens, but this did not affect TTP and OS, which were similar in both treatment arms.[22] The toxicity analysis showed the characteristic toxicity of each of the different 5-FU schedules, with thrombocytopenia and HFS consistently more prominent in the capecitabine regimens.

Table 4
Capecitabine plus irinotecan in first-line treatment of mCRC: results of phase II/III studies

Author	Phase	No. of patients	Regimen	ORR (%)	Median TTP (months)	Median OS (months)	G3–4 toxicity
Cartwright et al.[24]	II	49	XELIRI (irinotecan 240 mg/m^2 on day 1 and capecitabine 1000 mg/m^2 bid on days 1 → 14 q 3 w)	45	6.2	13.4	Diarrhea: 20% Neutropenia: 12% Dehydration: 10%
Patt et al.[25]	II	52	CAPIRI (irinotecan 250 mg/m^2 on day 1 and capecitabine 1000 mg/m^2 bid on days 1 → 14 q 3 w)[a]	46	7.1	15.6	Neutropenia: 25% Diarrhea: 20% Dehydration: 10%
Rea et al.[26]	I/II	57	XELIRI (irinotecan 250 mg/m^2 on day 1 and capecitabine 1000 mg/m^2 bid on days 1 → 14 q 3 w)	42	8.3	–	Diarrhea was the most common serious toxicity
Bajetta et al.[27]	II randomized	68	CAPIRI (irinotecan 150 → 120 mg/m^2 on days 1 and 8 and capecitabine 1250 → 1000 mg/m^2 bid on days 2 → 15 q 3 w) versus	44	7.6	–	Diarrhea: 16% → 37%
		66	XELIRI (irinotecan 300 → 240 mg/m^2 on day 1 and capecitabine 1250 → 1000 mg/m^2 bid on days 2 → 15 q 3 w)	47	8.3		Diarrhea: 35% → 25%
Borner et al.[28]	II randomized	37	CAPIRI (irinotecan 70 mg/m^2 on days 1, 8, 15, 22, 29 and capecitabine 1000 mg/m^2 bid on days 1 → 14 q 3 w) versus	34	6.9	17.4	Diarrhea: 34% Neutropenia: 5%
		38	XELIRI (irinotecan 300 → 240 mg/m^2 on day 1 and capecitabine 1000 mg/m^2 on days 1 → 14 q 3 w)	25	9.2	24.7	Diarrhea: 19% Neutropenia: 19%
Colucci et al.[29] (GOIM 2405)	II randomized	95	FOLFIRI (irinotecan 180 mg/m^2 on day 1, leucovorin 100 mg/m^2 and 5-FU bolus 400 mg/m^2 on days 1 and 2, 5-FU 600 mg/m^2 continuous infusion on days 1 and 2 q 2 w) versus	32	6.5	24.6	Neutropenia: 16% Diarrhea: 3%
			XELIRI (irinotecan 250 mg/m^2 on day 1 and capecitabine 1000 mg/m^2 bid on days 1 → 14 q 3 w)[a]	48	8.7	26.5	Neutropenia: 17% Diarrhea: 12%
Kohne et al.[30] (EORTC 40015)	III (suspended)	43	XELIRI (irinotecan 250 mg/m^2 on day 1 and capecitabine 1000 mg/m^2 bid on days 1 → 14 q 3 w) +/– CELECOXIB (800 mg/die)	22–48	5.9	14.8	Six deaths with XELIRI and 2 with FOLFIRI
Fuchs et al.[31] (BICC-C)	III	145	XELIRI (irinotecan 250 mg/m^2 on day 1 and capecitabine 1000 mg/m^2 bid on days 1 → 14 q 3 w)	38	5.5	18.9	Diarrhea: 47% Neutropenia: 32%
Koopman et al.[32] (CAIRO)	III	398	XELIRI (irinotecan 250 mg/m^2 on day 1 and capecitabine 1000 mg/m^2 bid on days 1 → 14 q 3 w)	41	7.8	17.4	Diarrhea: 26% Neutropenia: 7%

[a] Patients ≥65 years of age and those qith impaired renal function or with a history of prior radiotherapy received lower doses of both agents (200 mg/m^2 and 750 mg/m^2 bid, respectively).

A phase III trial was conducted to demonstrate the non-inferiority of the XELOX versus the FOLFOX4 regimen in 627 patients who had received a prior treatment with irinotecan.[19] The non-inferiority of the XELOX in terms of TTP and OS was proven even if it was associated with a greater incidence of severe diarrhea and HFS.

In amulticenter, randomized, phase III study Tabernero et al. evaluated the efficacy and tolerability of 6 cycles of bevacizumab (7.5 mg/kg) plus XELOX (capecitabine 1000 mg/m^2 on days 1 → 14 and oxaliplatin 130 mg/m^2 on day 1 every 3 weeks) followed by XELOX/bevacizumab (arm A) or single-agent bevacizumab (arm B).[23] After a follow up of 16 months, there were not statistically differences in ORR, TTP, and OS between the 2 arms. Preliminary analysis of safety showed that tolerability was acceptable in the 2 arms, with G3–4 diarrhea in 11% and 13%, HFS in 12% and 6%, and neuropathy in 24% and 7% in arms A and B, respectively.

Capecitabine plus irinotecan

Different schedules combining capecitabine and irinotecan were evaluated in phase II trials. Administration of irinotecan 100–150 mg/m^2 on days 1 and 8 or weekly irinotecan 70 mg/m^2 (CAPIRI) was compared with the application of irinotecan at higher doses only at day 1 every 3 weeks (XELIRI) (Table 4).[24–28] In particular, Bajetta et al. allocated 140 patients to receive capecitabine plus irinotecan either on day 1 (arm A) or on days 1 and 8 (arm B), every 3 weeks.[27] After a reduction of dosages of irinotecan and capecitabine, diarrhea was registred in 26% of patients in arm A, and in 38% of patients in arm B; ORR and TTP were comparable. Similarly, two dosages of irinotecan (weekly or every 3 weeks) in combination with capecitabine were evaluated by Borner et al..[28] ORR was comparable with the 2 regimens even if mTTP and mOS were both in favor of the arm with irinotecan every 3 weeks, which also caused less ≥3 diarrhea.

In summary, data of these trials were encouraging with ORR of XELIRI or CAPIRI of 34–47%, TTP of 6–9 months, and OS of 13–25 months, respectively. Nevertheless, irinotecan and capecitabine displayed partly overlapping adverse events, particularly with respect to gastrointestinal toxicity. In fact, up to 36% of patients in these studies developed ≥ grade 3 gastrointestinal toxicity, and many patients required dose modification.[33]

Definitive results of a phase II randomized trial of Gruppo Oncologico dell'Italia Meridionale (GOIM)

From July 2005 to August 2008 a multicenter randomized phase II study was conducted by GOIM (protocol n.2405) to evaluate both efficacy and tolerability of FOLFIRI and XELIRI in chemo-naïve patients with mCRC.[29] Arm A (FOLFIRI) regimen consisted of irinotecan 180 mg/m^2 on day 1 with LV 100 mg/m^2 administered as a 2-hours infusion before 5-FU 400 mg/m^2 administered as an

Table 5
Recommended dose modifications with capecitabine monotherapy

Toxicity NCIC grade	During a course of therapy	Dose adjustment for the next treatment
Grade 1	Maintain dose level	Maintain dose level
Grade 2		
First appearance	Interruption until G0–1	100% of starting dose
Second appearance	Interruption until G0–1	75% of starting dose
Third appearance	Interruption until G0–1	50% of starting dose
Fourth appearance	Permanent interruption	–
Grade 3		
First appearance	Interruption until G0–1	75% of starting dose
Second appearance	Interruption until G0–1	50% of starting dose
Third appearance	Permanent interruption	–
Grade 4		
First appearance	Permanent interruption, or if patient's best interest is to continue, interruption until G0–1	Eventually 50% of starting dose

intravenous bolus injection; 5-FU 600 mg/m^2 was administered as a 22-hours infusion immediately after 5-FU bolus injection. LV and 5-FU were repeated on days 1 and 2 every 2 weeks. Arm B (XELIRI) consisted of irinotecan 250 mg/m^2 (200 mg/m^2 for patients ≥70 years) only on day 1, with capecitabine 1000 mg/m^2 bid (750 mg(m^2 bid for patients >70 years) on days 1–14 every 3 weeks. A total of 95 consecutive patients were assessable for response. ORR in arms A and B were 32.2% and 48.4% respectively. By adding up ORR plus stable disease, the tumor growth control rate was 80.6% and 85.9%, respectively. Median TTP was 6.5 months and 8.7 months in arms A and B, respectively. Overall, the majority of adverse events in both arms were mild or moderate and gastrointestinal or myeloid in nature. In particular, the most common grade 3 or 4 treatment-related events were leuko/neutropenia (3.2/16.1% versus 7.8/17.2% in arms A and B, respectively) and diarrhea 3.2% versus 12.5% in arms A and B, respectively). Only one case of G3 HFS was reported in the XELIRI arm. Dose reduction due to adverse events was required in 15% of patients in the FOLFIRI arm and 21% of patients in the XELIRI arm. There were no treatment-related deaths during the study.

Phase III trials

The EORTC 40015 study was the first phase III trial aiming to randomize 692 patients in a 2×2 factorial design to receive XELIRI versus FOLFIRI with or without the cyclooxygenase-2 inhibitor celecoxib.[30] This trial had to be suspended after the accrual of 85 patients (n = 43 for XELIRI) because of 8 fatal events unrelated to disease progression (6 in XELIRI arm and 2 in the FOLFIRI arm). In addition, 61% of patients starting the XELIRI treatment required dose reduction as opposed to only 7% in the FOLFIRI arm. Due to the small sample size following early termination, no definitive conclusions can be drawn in relation to the non inferiority of XELIRI compared with FOLFIRI. A second randomized phase III trial (BICC-C) evaluated FOLFIRI versus modified IFL versus XELIRI with or without celecoxib and randomized 145 patients into the XELIRI arm.[31] There was a trend toward higher ORR and improved OS for FOLFIRI compared with the mIFL and XELIRI arms. The addition of celecoxib did not affected activity and toxicity of each regimen. However, XELIRI regimen produced an unacceptably higher occurrence of severe diarrhea and dehydration (48% and 19%) than either FOLFIRI (13% and 6%) or mIFL (19% and 7%). This observation led to the closure of this arm in the trial. Today, the largest cohort of patients (n = 398) with XELIRI first-line treatment for mCRC was the CAIRO (CApecitabine, IRinotecan, Oxaliplatin) trial investigating sequential versus combination chemotherapy in a phase III setting (arm A: capecitabine → irinotecan → XELOX; arm B: XELIRI → XELOX).[32] In arm B, ORR (41% versus 20%, p = 0.0001) and TTP (7.8 versus 5.8 months, p = 0.0002) were significantly improved, but the difference in OS was not significant (17.4 versus 16.3 months). The following grade ≥3 toxicity were reported with XELIRI: 26% diarrhea, 10% nausea, 7% febrile neutropenia, and 6% HFS. The investigators observed that the overall incidence of ischemic and thromboembolic events were comparable and low in both arms.[34] As a consequence, the negative results of the EORTC 40015 and the BICC-C trials were not confirmed in this much larger cohort of patients receiving XELIRI.

A phase III randomized study compared XELIRI plus bevaciuzmab versus FOLFIRI plus bevacizumab as first line treatment in mCRC patients.[35] After a median follow up of 28.7 months, the trial did not show significant differences in efficacy between the two arms. Most frequent G3–4 toxicities were neutropenia (12% versus 22%) and diarrhea (18% versus 11%).

Special considerations with XELIRI

Patients receiving XELIRI regimen need to be informed in details about the possibility of delayed diarrhea and measures to be taken, including the potential consequences of not communicating these events with the physician and nursing staff. Indeed, doses of irinotecan and capecitabine need to be adjusted in case of liver or renal dysfunction, and doses have to be reduced in presence of ≥ grade 3 gastrointestinal toxicity.[36] In particular, guidelines for capecitabine dose modification/interruption have been developed, and they should be used when trying to optimize oral fluoropyrimidine therapy for patients with mCRC (Table 5).

Capecitabine in the adjuvant treatment of CRC

Oral chemotherapies may be advantageous in the adjuvant setting because of their easy administration and patient preference.[37] Based of its successful use in patients with metastatic disease, capecitabine was also studied in the adjuvant setting.

The Capecitabine Adjuvant Chemotherapy for Colon Cancer Trial (X-ACT) was conducted to assess the equivalence for disease-free survival (DFS) between 5-FU/LV therapy (Mayo Clinic) and oral capecitabine (1250 mg/m^2 twice daily, from day 1 to 14, every 3 weeks), both for 6 months in patients with resected stage III CRC.[38] At 3 years disease free survival (DFS) was significantly superior (p = 0.0407), and OS rates showed also a trend toward superiority in favour of capecitabine (71.4% versus 68.4%, HR = 0.84,

Table 6
Single agent capecitabine in the neoadjuvant treatment of rectal cancer

Author	Phase (No. of patients)	Treatment		Disease response	G3–4 toxicity
		Chemotherapy	Total RT dose		
Dunst et al.[46]	I (36)	Capecitabine 250–1000 mg/m^2 bid (MTD: 825 mg/m^2 bid)	50.4 Gy	10% ypCR	Diarrhea: 3%
Ngan et al.[47]	I (28)	Capecitabine 425–100 mg/m^2 bid 5 days qw (MTD: 900 mg/m^2 bid)	50.4 Gy	56% tumor downstaging 19% ypCR	Diarrhea: 4%
Kim et al.[48]	II (45)	Capecitabine 825 mg/m^2 bid on days 1–14 q3w × 2 cycles and Leucovorin 20 mg/m^2/die on days 1–14 q3w × 2 cycles	50.4 Gy	84% tumor downstaging 31% ypCR	HFS: 7% Diarrhea: 4% Fatigue: 4%
De Paoli et al.[49]	II (54)	Capecitabine 825 mg/m^2 bid with RT followed by resection followed by Capecitabine 1250 mg/m^2 bid on days 1–14 q3w × 4 cycles	52.5 Gy (last 5 fractions bid)	59% tumor downstaging 18% ypCR	Diarrhea: 2% Proctitis: 4%
Krishnan et al.[50]	II (54)	Capecitabine 825 mg/m^2 bid followed by resection followed by Capecitabine 1250 mg/m^2 bid on days 1–14 q3w × 4 cycles	52.2 Gy	59% tumor downstaging 18% ypCR	Diarrhea: 2% Proctitis: 4%
Chan et al.[51]	Retrospective analysis (34 versus 68)	Capecitabine 825 mg/m^2 bid 5 days qw versus 5-FU 20 mg/kg/die, LV 200 mg/m^2 on days 1–4 and Mytomicin C 8 mg/m^2 on day 1	50 Gy	59% tumor downstaging in both groups; 21% versus 18% ypCR	Diarrhea: 3% versus 1%

p = 0.0706). The incidence of diarrhea, nausea/vomiting, stomatitis, neutropenia, and alopecia was significantly less in the capecitabibe group, whereas HFS occurred more frequently in the arm receiving capecitabine. This drug has, however, never been tested against continuous-infusion 5-FU, which is known to provide better RRs and improved tolerances compared with bolus 5-FU/LV. Recently, Dimovski et al. evaluated the predictive value of TS promoter, MTHFR C667T, MSI and/or 18qLOH markers on efficacy/toxicity of adjuvant capecitabine monotherapy in 142 CRC patients.[39] The authors observed that MSI+ and MTHFR677TT genotype are predictive of mid-term relapse-free survival of colon cancer patients treated with this drug.

XELOX as adjuvant therapy for stage III CRC has been tested by comparing 5-FU/LV (either Mayo Clinic or Rosweel Park regimens). The planned safety analysis comprised 1.864 patients, of whom 938 received XELOX and 926 received 5-FU/LV. Occurrence of grade ≥3 toxicity was in favour of the XELOX regimen for febrile neutropenia (0.2% versus 3.8%) and severe stomatitis (0.6% versus 7.9%); nevertheless, the XELOX produced more skin (3.6% versus 0.2%) and neurosensory (8.1% versus 0%) toxicity.[40] With a median follow up of 57 months, patients treated with XELOX had a 3-year DFS significantly higher than patients treated with 5-FU/LV (71% versus 67%, p = 0.0045).[41] Additionally, efficacy benefits seemed to be maintained in patients ≥70 years.[42]

Capecitabine in the neoadjuvant treatment of rectal cancer

Preoperative chemoradiotherapy (CRT) has become the standard of care for patients with T3–4 rectal cancers after a randomized trial by the German Rectal Cancer Study Group comparing preoperative with postoperative CRT and using conventional fractionation and continuous infusion 5-FU at weeks 1 and 5 along with 4 months of adjuvant 5-FU chemotherapy.[43] The results of this study provided a similar OS rate but a lower rate of local recurrence and toxicity for patients with locally advanced rectal cancer.

Capecitabine can be given on a daily basis to approximate infusional administration and it potentially achieves the described benefits of 5-FU infusion in conjunction with RT.[44] Indeed, preclinical studies suggest that capecitabine may offer greater synergy with radiotherapy, as shown by the enhanced TP expression in human colorectal tumor cell line xenografts treated with RT in preclinical studies.[45]

Single agent capecitabine

Two phase I dose-finding studies investigated the feasibility of using concurrent RT and capecitabine and defined the maximum tolerated dose (MTD).[46,47] In both studies the MTD of the drug was found to be 1000 mg/m^2 bid. As a result, the recommended dose of capecitabine with RT is 825 mg/m^2 bid administered from the first to the last day of standard pelvic RT.

Several phase II studies have evaluated the combination of capecitabine 825 mg/m^2 bid with preoperative RT in this subset of patients (Table 6). Kim et al. administered two cycles of capecitabine and LV (20 mg/m^2/daily) for 14 days, followed by a 7-day rest, during pelvic RT; they reported a tumor downstaging in 63% and a ypCR in 31% of patients.[48] No grade ≥3 hematologic toxicity was registered, while severe diarrhea affected 4% of patients. In another study capecitabine given continuously during pelvic RT achieved a ypCR in 24% of patients with only 6 (11%) patients suffering from grade 3 toxicity.[49] Krishnan et al. delivered the same combination of capecitabine and pelvic RT and achieved 9 (24%) ypCR with 12 (24%) patients showing microscopic residual disease.[50] Diarrhea occurred in 2% of patients. Chan et al. compared in a retrospective case-matching study preoperative RT with capecitabine versus preoperative RT with intermittent 5-FU infusion, LV, and mytomicin C and observed a comparable pathologic tumor response between the two arms of treatment.[51] Hofhneinz et al. reported preliminary results of a phase III trial comparing capecitabine with 5-FU as neoadjuvant or adjuvant chemotherapy associated with RT.[52] Authors observed, in the neoadjuvant setting, that capecitabine achieved a non-significant higher rate of tumor-downstaging (52% versus 39%) and N0 (71% versus 56%) than 5-FU. Furthermore, a lower incidence of leucopenia (25% versus 35%) but more HFS (31% versus 2%) were reported in the arm with capecitabine.

In summary, the results of these studies suggest that the response rates with capecitabine CRT are similar or better than those achieved with intravenous 5-FU.

Capecitabine in combination regimens

Irinotecan has radiosensitizing effects[53] but, unlike oxaliplatin, it has not been shown to improve DFS in the adjuvant treatment of colon cancer when added to 5-FU. Capecitabine and weekly irinotecan during pelvic RT were assessed by Klautke et al. in a phase I/II trial with a ypCR in 19% of patients.[54] Grade 3 diarrhea was the most common toxicity, reported in 37% of patients. In a

Table 7
Capecitabine in combination regimens in the neoadjuvant treatment of rectal cancer

Author	Phase (No. of patients)	Treatment		Disease response	G3–4 toxicity
		Chemotherapy	Total RT dose		
Irinotecan					
Klautke et al.[54]	I/II (28)	Capecitabine 500–25 mg/m^2 bid (MTD: 750 mg/m^2) and Irinotecan 40 mg/m^2 qw × 6	50.4 Gy	64% tumor downstaging 36% ypCR	Diarhhea: 39%
Willeke et al.[55]	II (36)	Capecitabine 500 mg/m^2 bid and Irinotecan 50 mg/m^2 qw	50.4 Gy	55% tumor downstaging 57% ypCR	Diarrhea: 4% Leukopenia: 19%
Oxaliplatin					
Rödel et al.[58]	I/II (32)	Capecitabine 825 mg/m^2 bid days 1–14 and 22–35 and Oxaliplatin 50–60 mg/m^2 days 1, 8, 22, and 29 (MTD: 50 mg/m^2)	50.4 Gy	55% tumor downstaging 19% ypCR	Diarrhea: 32%
Glynne-Jones et al.[59]	I (18)	Capecitabine 500–825 mg/m^2 bid (MTD: 725 mg/m^2) and Oxaliplatin 130 mg/m^2 days 1 and 29	50.4 Gy	72% tumor downstaging 28% ypCR	Diarrhea: 11%
Machiels et al.[60]	II (40)	Capecitabine 825 mg/m^2 bid 5 days a week and Oxaliplatin 50 mg/m^2 qw × 5	45 Gy	53% tumor downstaging 14% ypCR	Diarrhea: 30%
Chua et al.[61]	II (105)	Capecitabine 1000 mg/m^2 bid on days 1–14 q3w × 3 and Oxaliplatin 130 mg/m^2 q3w × 3 followed by Capecitabine 825 mg/m^2 bid with RT followed by resection followed by Capecitabine 1250 mg/m^2 bid on days 1–14 q3w × 4	54 Gy	89% tumor downstaging 24% ypCR	Diarrhea: 3%
Rödel et al.[62]	II (104)	Capecitabine 825 mg/m^2 bid days 1–14 and 22–35 and Oxaliplatin 50 mg/m^2 days 1, 8, 22, and 29 with RT followed by resection followed by Capecitabine 1000 mg/m^2 bid days 1–14 q3w and Oxaliplatin 130 mg/m^2 day 1 q3w × 4 cycles	50.4 Gy	16% ypCR	Diarrhea: 12% Leukopenia: 4%
Gerard et al.[63]	III (598)	Capecitabine 800 mg/m^2 bid 5 days a week with RT versus Capecitabine 800 mg/m^2 bid 5 days a week and Oxaliplatin 50 mg/m^2 weekly	45 Gy versus 50 Gy	ypCR 13.9% versus 19.2%	Diarrhea: 3.2% versus 12.6%
Target therapies					
Czito et al.[64]	I (11)	Capecitabine 625–825 mg/m^2 bid 5 days qw and Bevacizumab 15 mg/kg day 1 and 10 mg/kg days 8 and 22 and Oxaliplatin 50 mg/m^2	50.4	82% tumor downstaging 18% ypCR	Diarrhea: 27% Dehydration: 18%
Velenik et al.[65]	II (39)	Bevacizumab 5 mg/kg q2w before neoadjuvant CRT followed by Bevacizumab 5 mg/kg on weeks 3, 5, and 7 and Capecitabine 825 mg/m^2 bid during RT	50.4	32% tumor downstaging 16% ypCR	Diarrhea: 3.8% Proteinuria: 7.7%
Machiels et al.[66]	I/II (40)	Capecitabine 650–825 mg/m^2 daily days 1–33 (MTD: 825 mg/m^2) and Cetuximab 400 mg/m^2 7 days before initiation of RT, 250 mg/m^2 qw × 5	45 Gy	38% tumor downstaging 5% ypCR	Diarrhea: 15% Dermatitis: 8%
Hofheinz et al.[67]	I (20)	Capecitabine 400–500 mg/m^2 bid days 1–38 and Irinotecan 40–50 mg/m^2 weekly × 5 and Cetuximab 400 mg/m^2 day 1 and 250 mg/m^2 days 8, 15, 22, and 29 (MTD: Capecitabine 500 mg/m^2 bid, Irinotecan 40 mg/m^2)	50.4 Gy	42% tumor downstaging 25% ypCR	Diarrhea: 20%
Rödel et al.[68]	I/II (60)	Capecitabine 500–825 mg/m^2 bid days 1–24 and 22–35 (MTD: 825 mg/m^2) and Oxaliplatin 50 mg/m^2 days 1, 8, 22, and 29 and Cetuximab 400 mg/m^2 7 days before initiation of RT, 250 mg/m^2 qw × 6	50.4	47% tumor downstaging 9% ypCR	Diarrhea: 19% Leukopenia: 4%

subsequent phase II study Willeke et al. administered a lower dose of capecitabine and reported a ypCR in 14% of patients with 11% of grade 3 diarrhea.[55]

The concurrent administration of oxaliplatin with concurrent capecitabine and RT has been most widely studied to date. In part, this is a consequence of oxaliplatin radiosensitizing effect[56] and its demonstrated benefit in terms of DFS in conjunction with adjuvant 5-FU for resected, locally advanced colon cancer.[57] Phase I studies have found the MTD of oxaliplatin to be 50 mg/m^2 weekly[58] or 130 mg/m^2 every 3 weeks,[59] when administered with capecitabine (725–825 mg/m^2 bid) and 50.4 Gy of RT. Indeed, oral capecitabine in combination with oxaliplatin and pelvic RT has been shown to be effective and well tolerated in several phase II studies, resulting in pCR in 10–28% of patients (Table 7)[60–62] even if the administration of oxaliplatin was associated with a lightly higher risk of toxicity, including diarrhea and neurotoxicity. It should be observed that the unpredictable rate of toxic deaths (5%) observed by Chua et al.[55] prompted authors to modify the eligibility criteria with the exclusion of patients with coronary disease or arhytmia, even when controlled with medications. Following the protocol amendment for cardiovascular safety, only one further thromboembolic event was reported. The authors concluded that intensification of systemic therapy with neoadjuvant CRT before standard treatment is feasible in poor-risk potentially operable rectal cancer, with acceptable safety and promising long-term outcomes. Disappointing results have been reported by in a phase III trial by Gerard et al..[63] Authors

randomly assigned 598 patients to receive 5 weeks of treatment with RT with concurrent capecitabine or RT with capecitabine and oxaliplatin. The oxaliplatin arm was shown to significantly increase (25% versus 11%) the occurrence of grade ≥3 toxicity of the preoperative treatment, and produced a non-significant greater ypCR (19.2% versus 13.9%), thus suggesting that this drug should not be used with concurrent RT.

Capecitabine and target therapies

Target therapy against vascular endothelial growth factor receptor (bevacizumab)[64,65] and epidermal growth factor (cetuximab)[66–69] have been studied more recently. In particular, in a phase I study 11 patients received capecitabine, oxaliplatin and bevacizumab concurrently with RT.[64] Dose level 2 was associated with unacceptable toxicity (primarly diarrhea). The recommended phase II dose was bevacizumab 15 mg/kg day 1 + 10 mg/kg days 8 and 22, oxaliplatin 50 mg/m^2 weekly, and capecitabine 625 mg/m^2 bid during radiation days. Interim results of a phase II trial evaluating the combination of capecitabine, RT and bevacizumab have been recently reported.[65] Authors observed that this schedule is safe and feasible with a promising (16%) ypCR.

More trials evaluated the role of cetuximab in this subset of patients. In fact, the overexpression of EGFR has been reported to be associated with tumor resistance to local RT.[69] These data represent a strong rationale for combining cetuximab with preoperative RT for rectal cancer. A phase I–II study showed that the addition of weekly cetuximab to capecitabine given during pelvic RT was feasible, with a grade 3 diarrhea occurring in 15% of patients, even if the ypCR rate (5%) was disappointing.[67] Other authors reported on the feasibility of weekly cetuximab with capecitabine and irinotecan[66] or oxaliplatin.[68] However, these studies provided a surprising low rate of ypCR when compared to those previously reported with the same regimens without cetuximab. In summary, the addition of cetuximab to fluoropyrimidine-based CRT schedules suggest an overall pooled ypCR of 9.1%, compared with an overall ypCR rate of 13.5% seen with fluoropyrimidine-based chemoradiation schedules.[70] Cetuximab, if delivered concurrently with RT, could potentially abolish additive effects of 5-FU, by inhibiting proliferation. Preclinical data suggests that the sequencing of chemoradiotherapy, EGFR inhibition and RT may be clinically significant.[71] In addition, the proportion of patients with rectal cancer with mutant K-RAS varies between 30% and 40%.[72] In a preoperative chemoradiation study using cetuximab, K-RAS mutant type was found in 9/39 patients (23%).[73] Only one (11%) of these patients demonstrated a good pathologic regression compared with 11/30 (37%) patients with K-RAS wild type. As a consequence, more rationally designed preclinical and translational studies (with recognised negative predictive factors) might therefore help select out inappropriate patients.

Conclusions

The introduction of capecitabine in the treatment of CRC patients represents an important step toward offering patients an easier application of therapy requiring fewer admissions to hospital and leading to higher quality of life for many patients. The combination of capecitabine with oxaliplatin has proven to be non inferior in several phase III clinical trials and could be a substitute for continuous-infusion 5-FU/LV/oxaliplatin. The addition of bevacizumab to the XELOX regimen is safe and effective in mCRC. Indeed, capecitabine could replace bolus or continuous-infusion 5-FU as the standard combination partner for RT in the neoadjuvant treatment of rectal cancer. XELIRI regimen achieves promising efficacy data even if, owing to the partly overlapping gastrointestinal toxicity of capecitabine and irinotecan, patients must be aware of measures to be taken if delayed diarrhea occurs. Furthermore, known risk factors, such as age and the degree of renal impairment, if present, should be taken into consideration when selecting the starting dose of capecitabine. Lastly, from an economic perspective, cost-effectiveness analyses suggested that, despite higher acquisition costs, capecitabine is more cost-effective than standard i.v. treatment.[74]

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Conflict of interests

All authors declare the absence of conflicts of interest.

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