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REVIEW

Capecitabine versus 5-fluorouracil in colorectal cancer: where are we now?

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Abstract Fluorouracil (5-FU) remains the most widely used agent for colorectal cancer. Capecitabine is a rationally designed 5-FU pro-drug developed to mimic the continuous infusion of 5-FU while avoiding complications and inconvenience of intravenous administration. Capecitabine is absorbed intact from the gastrointestinal tract, converted enzymatically to active 5-FU, and released directly into the tumor. Capecitabine's efficacy and safety are shown in multiple phase III trials across different disease stages and therapy lines. Three randomized phase III trials demonstrated the equivalence of capecitabine plus oxaliplatin (XELOX) versus 5-FU/leucovorin (LV)/oxaliplatin (FOLFOX). The safety of capecitabine compared with 5-FU depends on the regimen of 5-FU used. The adverse event rate with oxaliplatin in combination with infusional 5-FU is similar to that of capecitabine plus oxaliplatin but is associated with more neutropenia and venous thrombotic events; capecitabine plus oxaliplatin-based regimens tend to be associated with more grade 3 diarrhea and hand-foot skin reaction. Combination therapy with capecitabine and irinotecan (CapeIRI) versus 5-FU/LV and irinotecan (FOLFIRI) had more variable results; some former schedules resulted in excessive treatment-related toxicity. More recent data show that lower capecitabine and irinotecan doses, different schedules, and combination with targeted agents (e.g, bevacizumab) have resulted in more favorable outcomes.

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Introduction

The most widely used agent in the treatment of colorectal cancer (CRC) is fluorouracil (5-FU), which was developed more than 50 years ago by Heidelberger et al. [1]. 5-FU enters a complex anabolic process that interferes with normal DNA and RNA functions and accounts for cytotoxicity at the cellular level. Because of poor oral absorption and intra-patient variability, 5-FU is most often administered intravenously (IV) as a rapid bolus injection; it is rapidly distributed, with triphasic elimination [2]. Preclinical studies suggested that 5-FU is a time-dependent drug, and that cytotoxicity increases with prolonged exposure [2–4]. Therefore, clinical trials were initiated with 5-FU administered for extended periods [5, 6]. Response rates in CRC increased with continuous infusion compared with bolus administration, with a more acceptable toxicity profile [7, 8]. Nevertheless, the inconvenience of protracted IV administration provided a strong impetus for the development of oral fluoropyrimidines that could be taken conveniently on a schedule that simulates continuous infusion [9].

Capecitabine is an example of a rationally designed 5-FU pro-drug intended to mimic the continuous infusion of 5-FU while avoiding the complications and inconvenience associated with IV drug administration. It is a fluoropyrimidine carbamate that is converted to the active 5-FU by the action of three enzymes: an esterase, a deaminase, and a phosphorylase [9]. In the third step, the enzyme thymidine phosphorylase (TP) converts 5′-deoxy-5-fluorouridine to 5-FU, which is released directly into

tumor tissue [10]. The enzyme TP has higher concentrations in many tumor types compared with matched normal tissue and is particularly higher in excised human colon cancer [11]. This suggests that higher tumor concentrations of 5-FU might be expected, due to a higher production of active drug in the tumor tissue, thereby providing a favorable target-to-non-target ratio for toxicity. Tumor selectivity and conversion of capecitabine to active 5-FU within the tumor tissue have been confirmed in human samples that show a 3.2-fold higher concentration of 5-FU in tumor compared with normal tissue and a 21-fold higher tumor-to-plasma ratio. In comparison, when IV 5-FU is administered, either by bolus or continuous infusion, the concentration of active drug in tumor is not higher than that in normal tissue [11]. The greater levels of the TP enzyme in tumor tissue allow for targeted intra-tumoral release of 5-FU and subsequently less systemic toxicity compared with infusions of 5-FU [12].

This review provides an up-to-date literature review and overview of how capecitabine compares with 5-FU as a single agent as well as in combination with oxaliplatin or irinotecan, and in combination with targeted therapy, in the treatment of CRC. We review the available phase I, II, and III clinical trials conducted in patients with CRC that document the metabolic activation of this compound and support its use in patients with advanced CRC and how the drug may be incorporated into the standard care of patients with CRC.

Clinical efficacy and tolerability

Various schedules of single-agent capecitabine were tested in three phase I trials (Table 1). These trials revealed that intermittent dosing allowed for higher doses of capecitabine but at the expense of increased hand-foot syndrome (HFS). Diarrhea was the dose-limiting toxicity in all treatment schedules [13–15]. A randomized phase II trial was performed to further define activity and the optimum schedule to carry forward into phase III trials. In this study, metastatic CRC (mCRC) patients were randomized between the three leading schedules of capecitabine [continuous, intermittent, or intermittent with leucovorin (LV)]. No difference in overall survival (OS) was noted between the arms; however, significant improvement in disease progression was observed for the single-agent intermittent schedule. The intermittent schedule without LV was recommended for phase III study based on its improved progression-free survival (PFS), the high dose intensity, and better therapeutic index [16].

Capecitabine as a single agent

Two multicenter, randomized, phase III studies were conducted (1 in North America, 1 in Europe) comparing capecitabine with IV 5-FU/LV as first-line therapy in metastatic CRC patients. The trials were identical with respect to study design, inclusion and exclusion criteria, primary end point of overall response rate (RR), and secondary end points such as median time to disease progression, median time to treatment failure, and OS times, in order that subsequent pooling of results could be performed (Table 2) [17–19].

Patients were randomly assigned to either capecitabine in an intermittent regimen of 3-week cycles or 5-FU/LV, administered according to the Mayo Clinic regimen (5-FU 425 mg/m^2 plus LV 20 mg/m^2 administered IV for 5 days every 28 days). The Mayo Clinic regimen was chosen as a control arm for both studies, as it was the standard of care for front-line therapy of mCRC at the time of trial design [17, 18].

Table 1 Capecitabine in phase I trials

References	Patients enrolled (*N*)	Regimen	Response	Safety, tolerability
Budman et al. [13]	33	110–1,675 mg/m^2/day continuously in two equally divided doses; 1,331 mg/m^2 established as phase II dose	One patient with a mixed response; one with SD after 18 months of therapy	Diarrhea and HFS were the most common dose-limiting toxicities
Mackean et al. [14]	34	502–3,414 mg/m^2/day in two equally divided doses for 14 days followed by 7 days' rest; 2,510 mg/m^2/day recommended as phase II dose	Objective tumor response in five patients at 2,510 mg/m^2; one CR and three PRs	HFS at higher doses for extended times
Cassidy et al. [15]	31	1,004–2,510 mg/m^2 + LV 60 mg bid for 14 days followed by 7 days' rest; 1,650 mg/m^2/day C + 60 mg LV recommended as phase II dose	Two PRs	Dose-limiting AEs at 2,000 mg/m^2/day included nausea, diarrhea, vomiting, and HFS

AEs adverse events, *bid* twice a day, *C* capecitabine, *CR* complete response, *HFS* hand-foot syndrome, *LV* leucovorin, *PRs* partial responses, *SD* stable disease

Table 2 Capecitabine as a single agent in phase III trials

References	Patients enrolled (*N*)	Regimen	Response rate	Median time to disease progression	Median overall survival	Safety, tolerability
Hoff et al. [12]	605	1,250 mg/m^2 bid for 14 days followed by 7 days' rest or 5-FU/LV (Mayo Clinic)	24.8% (C) vs. 15.5% (5-FU) ($P = 0.005$)	4.3 (C) vs. 4.7 months (5-FU)	12.5 (C) vs. 13.3 months (5-FU); $P = 0.974$	Lower rate of diarrhea, stomatitis, nausea, and alopecia with C vs. 5-FU; higher rate of HFS and hyperbilirubinemia with C vs. 5-FU
Van Cutsem et al. [18]	602	1,250 mg/m^2 bid for 14 days followed by 7 days' rest or 5-FU/LV (Mayo Clinic)	18.9% (C) vs. 15.% (5-FU)	5.2 (C) vs. 4.7 months (5-FU)	13.2 (C) vs. 12.1 months (5-FU); $P = 0.33$	Lower rate of diarrhea, stomatitis, nausea, and alopecia with C vs. 5-FU; higher rate of HFS and hyperbilirubinemia with C vs. 5-FU

Bid twice a day, *C* capecitabine, *5-FU* fluorouracil, *HFS* hand-foot syndrome, *LV* leucovorin

In both studies, RRs were higher for capecitabine compared with 5-FU/LV: 25.8 versus 11.6% ($P = 0.005$) and 18.9 versus 15%, respectively. Although capecitabine demonstrated higher RRs, median time to disease progression and median OS did not differ significantly between the arms in both studies. Compared with the 5-FU/LV group, patients in the capecitabine group experienced a significantly lower incidence of any grade diarrhea, stomatitis, nausea, and alopecia, but a higher incidence of HFS and hyperbilirubinemia [19]. These trials demonstrated that capecitabine monotherapy is a reasonable alternative for patients with mCRC.

Capecitabine in combination with oxaliplatin or irinotecan

The combination of the cytotoxic agents oxaliplatin and irinotecan, and targeted agents such as cetuximab, panitumumab, and bevacizumab with 5-FU, have significantly improved survival rates for patients with mCRC and are now the standard of care. Therefore, based on similar efficacy and reduced toxicity compared with bolus 5-FU regimens, capecitabine was tested in combination with the cytotoxic agents oxaliplatin and irinotecan.

Preclinical models have demonstrated that the combination of capecitabine and oxaliplatin is a rational combination therapy for the treatment of CRC. In a human tumor xenograft model, the combination of capecitabine and oxaliplatin inhibited the in vivo growth of CXF280 human CRC more effectively than either agent alone [20].

A phase I study in patients with metastatic solid tumors demonstrated that the combination of capecitabine with oxaliplatin is feasible and established the recommended dose regimen as IV oxaliplatin 130 mg/m^2 on day 1, with oral capecitabine 1,000 mg/m^2 twice daily on days 1–14 in a 3-week cycle [21]. When this regimen was evaluated in a phase II study in patients with mCRC, the RRs ranged between 45 and 55%, with sensory neuropathy (17%), diarrhea (16%), and nausea and vomiting (13%) as the most common treatment-related adverse events (AEs) [22].

Three randomized phase III studies, one of which was published only in abstract form, demonstrated the equivalence of capecitabine with oxaliplatin (XELOX) in comparison with 5-FU/LV/oxaliplatin (FOLFOX) as first- and second-line therapy of mCRC (Table 3) [23–25]. Patients were randomly assigned to a regimen of XELOX or FOLFOX-4.[1] These trials demonstrated that XELOX is equivalent to FOLFOX with respect to PFS when used as first- or second-line therapy in patients with mCRC. Treatment-related grade 3/4 AEs such as neutropenia/granulocytopenia (35 vs. 5%) and febrile neutropenia (4 vs. <1%) were more frequent with FOLFOX-4 than with XELOX, though grade 3 diarrhea (19 vs. 5%) and HFS (4 vs. <1%) were higher for the XELOX regimen [23–25].

A pooled analysis of six randomized phase II/III trials evaluating the role of oxaliplatin in combination with capecitabine or infusional 5-FU included 3,494 patients with mCRC and demonstrated similar PFS and OS in patients treated with the two regimens. However, patients treated with XELOX had lower RRs. In this review, FOLFOX demonstrated a statistically significant RR of 41–52% as compared to XELOX, with an RR of 27–48% ($P = 0.02$) [26]. Thus, the use of XELOX is a valid alternative regimen for patients with mCRC.

Capecitabine in combination with irinotecan was extensively studied in a wide range of schedules in

[1] FOLFOX-4 = oxaliplatin 85 mg/m^2 on day 1 only given as a 2-hour infusion concurrent with LV at 200 mg/m^2/d followed by bolus 5-FU 400 mg/m^2/d and a 22-hour infusion of 5-FU 600 mg/m^2/d, repeated for 2 consecutive days every 2 weeks.

Table 3 Capecitabine and oxaliplatin

References	Study phase, patients enrolled	Regimen	Response rate (%)	Median progression-free survival	Median overall survival	Safety, tolerability
Rothenberg et al. [24]	Phase III, $N = 627$	XELOX (2-h IV infusion Ox 130 mg/m^2 on day 1 + C 1,000 mg/m^2 bid on days 1–15 of a 3-week cycle) or FOLFOX-4 (Ox 85 mg/m^2 on day 1 as a 2-h infusion concurrent with LV 200 mg/m^2/day followed by bolus 5-FU 400 mg/m^2/day + 22-h infusion of 5-FU 600 mg/m^2/day) repeated for two consecutive days every 2 weeks	ORR: 20 (XELOX) vs. 18% (FOLFOX-4)	4.7 (XELOX) vs. 4.8 months (FOLFOX4) (ITT); XELOX noninferior to FOLFOX-4	11.9 (XELOX) vs. 12.5 months (FOLFOX-4) (ITT)	Grade 3/4 AEs: 65 vs. 50%; grade 4 AEs: 18 vs. 3%; febrile neutropenia: 4 vs. <1%; grade 3 diarrhea: 5 vs. 19%, FOLFOX-4 vs. XELOX, respectively
Cassidy et al. [23]	Phase III, $N = 2,034$	XELOX OR FOLFOX-4 B at 7.5 mg/kg or PBO added to XELOX every third week and B at 5 mg/kg or PBO added to FOLFOX-4 every third week	ORR: 47 (XELOX) vs. 48% (FOLFOX-4)	8.0 (pooled XELOX arms) vs. 8.5 months (FOLFOX-4)	19.8 (pooled XELOX arms) vs. 19.6 months (pooled FOLFOX-4 arms)	Rates of grade 3/4 AEs similar in both arms; grade 4 AEs more common with FOLFOX-4 due to grade 4 neutropenia. XELOX associated with more grade 3 diarrhea and HFS
Ducreux et al. [25]	Phase III; $N = 306$ (ITT); $N = 284$ (PP)	XELOX OR FOLFOX-6 (Ox 100 mg/m^2 day, LV 400 mg/m^2 2-h infusion, then 5-FU 400 mg/m^2 IV bolus, then 2,400–3,000 mg/m^2 46 h infusion) every 2 weeks for 6 months	RR (PP): 42 vs. 46% (XELOX vs. FOLFOX-6)	PP: 9.3 vs. 9.7 months (XELOX vs. FOLFOX-6)	PP: 19.9 vs. 18.4 months (XELOX vs. FOLFOX-6)	Grade 3/4 HFS: 3 vs. 0%; thrombocytopenia: 12 vs. 5%; diarrhea: 12 vs. 7%; grade 3/4 neutropenia: 0 vs. 6%; neuropathy: 8 vs. 19% (XELOX vs. FOLFOX-6)

AEs adverse events, *B* bevacizumab, *bid* twice a day, *C* capecitabine, *5-FU* fluorouracil, *FOLFOX* fluorouracil/leucovorin/oxaliplatin, *HFS* hand-foot syndrome, *ITT* intent-to-treat, *IV* intravenous, *LV* leucovorin, *Ox* oxaliplatin, *ORR* overall response rate, *PBO* placebo, *PP* per protocol, *XELOX* capecitabine plus oxaliplatin

different regimens (i.e., 2-weekly, 3-weekly, 4-weekly, 6-weekly, and 7-weekly) [27–30]. Reports of excessive and overlapping toxicities, specifically of gastrointestinal origin, prompted alterations in the dose and administration schedule. Promising results were demonstrated from a phase II trial evaluating capecitabine in combination with irinotecan administered every 2 weeks. This trial demonstrated a median time to progression of 8.4 months, a median duration of response of 7.3 months, and an OS of 19.3 months (Table 4) [30].

The BICC-C (Bolus, Infusional, or Capecitabine with Camptosar-Celecoxib), a randomized phase III trial explored three combinations of irinotecan-based regimens. In this study, 430 previously untreated mCRC patients randomized to FOLFIRI (irinotecan plus infusional 5-FU/LV), mIFL (irinotecan plus bolus 5-FU/LV), or CapeIRI (irinotecan plus capecitabine), all in combination with celecoxib (Table 4) [27]. The CapeIRI arm was discontinued early in the trial because of unacceptable toxicity. In addition, the trial was amended to add bevacizumab to the FOLFIRI and mIFL arms. Adding bevacizumab improved PFS for both FOLFIRI and mIFL, from 7.6 to 11.2 months and from 5.9 to 8.3 months, respectively. The OS for the FOLFIRI and bevacizumab arm was 23.1 months. Inferior efficacy results for CapeIRI might reflect early treatment discontinuation as a result of toxicity, or an interaction with celecoxib [27].

EORTC 40015 compared FOLFIRI and CapeIRI in 85 patients in the second line setting for mCRC. There was sub-randomization to celecoxib versus placebo, and median PFS and OS times were shorter for CapeIRI versus FOLFIRI and for celecoxib versus placebo. The trial was closed early following 8 deaths in the 85 patients enrolled, mostly related to gastrointestinal or thromboembolic events, but not related to disease progression. Given the small number of patients and early closure of the study, it is hard to draw meaningful conclusions [28]. Another phase III trial evaluating sequential chemotherapy versus initial combination chemotherapy with CapeIRI demonstrated a longer PFS for the combination regimen at the expense of

Table 4 Capecitabine and irinotecan

Study	Study phase, patients enrolled	Regimen	Response rate (%)	Median progression-free survival	Median overall survival	Safety, tolerability
Fuchs et al. [27]	Phase III, $N = 430$	Irinotecan + infusional 5-FU/LV (FOLFIRI) (± B) or irinotecan + bolus 5-FU/LV (mIFL) (± B) or irinotecan + C (CapeIRI)	ORR: 47.2 (FOLFIRI), 43.3 (mIFL), 38.6% (CapeIRI), ($P = NS$); CR: 5.6 (FOLFIRI), 4.3 (mIFL), 2.8% (CapeIRI)	7.6 (FOLFIRI) vs. 5.9 (mIFL) vs. 5.8 months (CapeIRI)	23.1 (FOLFIRI) vs. 17.6 (mIFL) vs. 18.9 months (CapeIRI) ($P = NS$)	Higher rates of grade 3 vomiting, diarrhea, HFS, and dehydration (CapeIRI vs. FOLFIRI)
Köhne et al. [28]	Phase III, $N = 85$	FOLFIRI OR CapeIRI ± PBO or celecoxib	OS: 14.8 vs. 19.9 months (CAPIRI vs. FOLFIRI); OS: 18.3 vs. 19.9 months (celecoxcib vs. PBO)	PFS: 5.9 vs. 9.6 (CAPIRI vs. FOLFIRI) PFS: 6.9 vs. 7.8 (celecoxib vs. PBO)	14.75 vs. 19.9 months (CapeIRI vs. FOLFIRI)	8 deaths unrelated to disease progression; grade 3/4 AEs: 74 vs. 49%.(CapeIRI vs. FOLFIRI)
Koopman et al. [29]	Phase III, $N = 803$	Sequential therapy: first-line C followed by second-line irinotecan followed by third-line C + Ox or CapeIRI followed by C + Ox second-line	OS: NS between arms	PFS in first-line treatment was significantly longer in combination vs. sequential arm ($P = 0.0002$)	Median survival: 16.3 vs. 17.4 months (sequential vs. combination); $P = NS$	Grade 3/4 toxicity greater in combination than sequential arm; diarrhea: 26 vs. 11%; grade 3/4 HFS: 12 vs. 6% (combination vs. sequential arm)
Garcia Alfonso et al. [30]	Phase II, $N = 35$	Irinotecan 175 mg/m^2 on day 1 + C 1,000 mg/m^2 bid on days 2–8, repeated every 14 days	CR: 7.5%; PR: 32%; SD: 36%; PD: 19%; ORR: 40%	Median TTP: 8.4 months; median duration of relapse: 7.3 months	19.3 months	Manageable

AEs adverse events, *B* bevacizumab, *C* capecitabine, *CapeIRI* capecitabine and irinotecan, *CR* complete response, *FOLFIRI* fluorouracil/leucovorin/irinotecan, *5-FU* fluorouracil, *HFS* hand-foot syndrome, *LV* leucovorin, *mIFL* irinotecan plus bolus fluorouracil/leucovorin, *NS* not significant, *ORR* overall response rate, *OS* overall survival, *Ox* oxaliplatin, *PBO* placebo, *PD* progressive disease, *PFS* progression-free survival, *PR* partial response, *SD* stable disease, *TTP* time to progression

greater toxicity [29]. Capecitabine and irinotecan combinations have similar activity as 5-FU and irinotecan regimens, but greater toxicity. Further studies to determine the most appropriate dose of capecitabine in combination with irinotecan and in other combination regimens for particular geographic and/or ethnic patient groups may be warranted.

Combination chemotherapy with targeted agents such as bevacizumab or cetuximab

Targeted therapies with vascular endothelial growth factor (VEGF) inhibitors such as bevacizumab, and epidermal growth factor receptor (EGFR) inhibitors such as cetuximab or panitumumab, have become a significant part of the management of mCRC.

VEGF is the central regulator of angiogenesis. In recent years, considerable interest has developed regarding the importance of angiogenesis in tumor growth and progression [31]. Increased expression of VEGF in patients with colorectal carcinoma has been associated with early recurrence and poor prognosis [32]. In randomized phase III clinical trials in patients with mCRC, bevacizumab improved RRs, OS, and PFS when combined with standard chemotherapies such as infusional 5-FU/LV plus irinotecan and FOLFOX [33, 34].

Given the improvement seen with addition of bevacizumab to 5-FU-containing regimens, new studies were designed to evaluate the combination of bevacizumab- and capecitabine-containing regimens. Results of the Three Regimens of Eloxatin Evaluation (TREE)-2 trial provided further evidence of increased efficacy when bevacizumab was added to oxaliplatin-based chemotherapeutic agents [35]. The TREE-1 and TREE-2 trials were sequentially conducted, randomized, phase II trials that initially tested three different oxaliplatin–fluoropyrimidine combination regimens. These included FOLFOX, oxaliplatin plus bolus 5-FU/LV (bFOL), or capecitabine plus oxaliplatin (CapeOx) as first-line treatment of advanced CRC. After bevacizumab was approved in 2004, the trial was amended to include bevacizumab in all arms. The addition of

Table 5 Capecitabine with bevacizumab

References	Study phase, patients enrolled	Regimen	Response rate (%)	Median progression-free survival	Median overall survival	Safety, tolerability
Giantonio et al. [34]	Phase III; $N = 829$	FOLFOX-4 with B; FOLFOX-4; B alone	ORR: 22.7, 8.6, 3.3% (FOLFOX-4 with B, FOLFOX-4, B alone)	7.3, 4.7, 2.7 months (FOLFOX-4 with B, FOLFOX-4, B alone)	Median survival duration: 12.9, 10.8, 10.2 months (FOLFOX-4 with B, FOLFOX-4, B alone)	Grade 3/4 toxicities increased 14% with FOLFOX-4 + B; grade 3/4 bleeding associated with B
Hochster et al. [35]	Sequentially randomized phase II, TREE-1, $N = 150$; TREE-2, $N = 223$; Primary end point = grade 3/4 AEs	TREE 1: modified FOLFOX-6 (Ox 85 mg/m^2 IV + LV 350 mg IV over 2 h + 5-FU 400 mg/m^2 IV bolus + 2,400 mg/m^2 infusion over 46 h) every 2 weeks or bFOL (Ox 85 mg/m^2 IV on days 1 and 15 + LV 20 mg/m^2 IV over 10–20 min followed by 5-FU 500 mg/m^2 IV push on days 1, 8, and 15 every 4 weeks) or CapeOx (Ox 130 mg/m^2 IV on day 1 and C 1,000 mg/m^2 orally bid on days 1–15 every 3 weeks TREE-2: same 3 arms + B before CT at 5 mg/kg IV every 2 weeks (FOLFOX and bFOL regimens) or 7.5 mg/kg IV every 3 weeks (CapeOx); C dose reduced to 1,700 mg/m^2/day	TREE-1: ORR: 41, 20, 27% (modified FOLFOX-6, bFOL, CapeOx) TREE-2: 52, 39, 46% (modified FOLFOX-6, bFOL, CapeOx)		TREE-1: 19.2, 17.9, 17.2 months (modified FOLFOX-6, bFOL, CapeOx) TREE-2: 26.1, 20.4, 24.6 months (modified FOLFOX-6, bFOL, CapeOx)	TREE-1: Grade 3/4 AEs during first 12 weeks: 59, 36, 67% (modified FOLFOX-6, bFOL, CapeOx); CapeOx toxicity in TREE-1 included grade 3/4 diarrhea (31%) and dehydration (27%) TREE-2: 59, 51, 56% (modified FOLFOX-6, bFOL, CapeOx)

FOLFOX-4 = oxaliplatin 85 mg/m^2 on day 1 only given as a 2-h infusion concurrent with LV at 200 mg/m^2/day followed by bolus 5-FU 400 mg/m^2/day and a 22-h infusion of 5-FU 600 mg/m^2/day, repeated for two consecutive days every 2 weeks; FOLFOX-6 = oxaliplatin 100 mg/m^2 on day 1, LV 400 mg/m^2 2-h infusion, then 5-FU 400 mg/m^2 IV bolus, then 2,400–3,000 mg/m^2 46-h infusion, every 2 weeks

AEs adverse events, *B* bevacizumab, *bFOL* oxaliplatin plus bolus 5-FU/LV, *C* capecitabine, *CapeOx* capecitabine plus oxaliplatin, *CT* chemotherapy, *FOLFOX* fluorouracil/leucovorin/oxaliplatin, *IV* intravenous, *LV* leucovorin, *ORR* overall response rate, *Ox* oxaliplatin, *TREE* Three Regimens of Eloxatin Evaluation

bevacizumab lengthened OS in the three different regimens, as seen in TREE-2 compared with TREE-1 (Table 5). In the final toxicity analysis of TREE-2, bFOL appeared to have the greater toxicity: efficacy ratio, with a 30% incidence of grade 3/4 diarrhea; for FOLFOX, the incidence was 11% and for CapeOx, 17%.

Similarly, as previously discussed, the BICC-C trial also has demonstrated benefit with the addition of bevacizumab to chemotherapy [27]. In another phase III trial, addition of bevacizumab to an oxaliplatin-based regimen such as XELOX or FOLFOX-4 demonstrated improvement in PFS (9.4 vs. 8 months; $P = 0.0023$) with no difference in RRs and OS [36]. ACCORD is a prospective, non-comparative phase II study randomizing 145 patients to XELIRI (capecitabine/irinotecan), or FOLFIRI plus bevacizumab. The study demonstrated a 6-month objective RR of 54% in the XELIRI arm and 59% in the FOLFIRI arm. Median PFS was 9.3 and 9.0 months, respectively, and median OS was 23.0 and 23.4 months, respectively, in the XELIRI and FOLFIRI arms. Clinical AEs generally were similar, acceptable, and manageable in both treatment arms. This randomized, non-comparative trial demonstrated that bevacizumab plus XELIRI and bevacizumab plus FOLFIRI are active and similarly effective treatment options for patients with mCRC [37].

Although adding bevacizumab therapy appears to improve multiple efficacy points compared with cytotoxic therapy alone, it is important to remember that the use of bevacizumab with capecitabine combinations is based on retrospective, cross-trial comparisons and phase II trial data, but should be validated further in randomized phase III trials.

EGFR gene is upregulated in 60–80% of CRC patients, and over expression of the gene is associated with poor survival. EGFR signaling pathways play a major role in cell differentiation, proliferation, migration, angiogenesis, and apoptosis. Two EGFR-directed antibodies have been approved for the treatment of patients with advanced colorectal carcinoma: cetuximab, a chimeric antibody, and panitumumab, a fully humanized monoclonal antibody [38, 39]. Phase III, CRYSTAL trial (Cetuximab Combined with Irinotecan in First-Line Therapy for Metastatic Colorectal Cancer) demonstrated improvement in PFS (8.9 vs. 8 months) and RR (46.9 vs. 38.7%) with addition of cetuximab to irinotecan in front-line setting [40]. Only improvement in RRs (22.9 vs. 10.8%) were noted in the second-line setting based on phase III data by Cunningham et al. [38]. Similarly, improvement in RR (45.6 vs. 35.7%) was noted with the addition of cetuximab to FOLFOX in a phase II OPUS (Oxaliplatin and Cetuximab in First-Line Treatment of mCRC) trial [41].

Borner et al. conducted a multicenter, randomized, phase II study comparing XELOX with the combination of XELOX plus cetuximab. This trial demonstrated an increase in RRs without a significant increase in toxicity, except for an increased frequency of skin toxicity in the arm with cetuximab. Treatment was continued up to a maximum of six cycles or until disease progression (Table 6) [42].

To date, there are limited published data on the XELIRI/cetuximab regimen. Preliminary results from two phase II trials of combinations of cetuximab with irinotecan plus capecitabine demonstrate that this combination has promising clinical activity. Heinemann et al. have demonstrated an overall RR of 42%, with an overall disease control rate of 91% (Table 6) [43, 44]. Cartwright et al. [45] have demonstrated in 53 evaluable patients that 5.7% had complete responses, 37.7% had partial responses, and 43.4% had stable disease with median survival of 20.5 months, with 45.7% of patients remaining alive at the time of the report (Table 6).

Although we are optimistic that cetuximab with a XELOX or XELIRI combination will prove to be beneficial, we await the results of ongoing phase III trials before routinely applying these phase II results.

Table 6 Capecitabine with EGFR inhibitors

References	Study phase, patients enrolled	Regimen	Response rate (%)	Median progression-free survival	Median overall survival	Safety, tolerability
Borner et al. [42]	Phase II, $N = 74$	Ox 130 mg/m^2/day + C 1,000 mg/m^2 bid days 1–14 every 3 weeks alone (XELOX) or XELOX + C 400 mg/m^2 followed by weekly infusions of 250 mg/m^2	Partial RRs: 14, 41% (XELOX vs. C); SD: 62, 35% (XELOX vs. C)	Median: 5.8 vs. 7.2 months (XELOX vs. C)	Median: 16.5 vs. 20.5 months (XELOX vs. C)	C led to skin rash in 65%
Heinemann et al. [43, 44]	Phase II, $N = 92$	C 800 mg/m^2 bid on days 1–14 + irinotecan 200 mg/m^2 on day 1 (XELIRI) or C 1,000 mg/m^2 bid days 1–14 + Ox 130 mg/m^2 on day 1 (XELOX)	ORR: 42 vs. 66%; DCR (ORR + SD): 91 vs. 93% (XELIRI vs. XELOX)			Most common grade 3/4 toxicities: diarrhea: 20.9 vs. 19.5%; skin toxicity: 16.3 vs. 26.8%; neurotoxicity: 2.3 vs. 17.1%; leucopenia: 9.3 vs. 4.9% (XELIRI vs. XELOX)
Cartwright et al. [45]	Phase II, $N = 70$; 53 evaluable	C 850 mg/m^2 bid on days 1–14 for 3 weeks + irinotecan 200 mg/m^2 IV on day 1 every 3 weeks or C 850 mg/m^2 bid on days 1–14 for 3 weeks + irinotecan 200 mg/m^2 IV on day 1 every 3 weeks + C (initially 400 mg/m^2 IV, subsequently 250 mg/m^2	CR: 5.7%; PR: 37.7%; ORR: 43.4% (PP), 34% (ITT) DCR: 86.8% (PP), 69% (ITT)	TTP: 8.1 months TTR: 1.6 months	Median: 20.5 months	Most common grade 3/4 toxicities: diarrhea, neutropenia, and nausea/vomiting

C capecitabine, *CR* complete response, *DCR* disease control rate, *EGFR* epidermal growth factor receptor, *ITT* intent-to-treat, *IV* intravenous, *ORR* overall response rate, *Ox* oxaliplatin, *PP* per protocol, *PR* partial response, *RR* response rate, *SD* stable disease, *TTP* time to progression, *TTR* time to response, *XELOX* capecitabine plus oxaliplatin

Capecitabine in the adjuvant setting

The benefits of 5-FU-based adjuvant chemotherapy in reducing the risk of relapse and prolonging survival in patients with surgically resected CRC are well established, particularly in stage III disease [46–54]. In a phase III trial [Xeloda in Adjuvant Colon Cancer Therapy (X-ACT)], capecitabine was compared to Mayo Clinic 5-FU/LV regimen as surgical adjuvant treatment in stage III CRC (Table 7) [55]. Initially, there was a trend toward superior disease-free survival (DFS) noted for the capecitabine arm compared to 5-FU/LV ($P = 0.05$). However, the difference did not hold true at the 3-year follow-up with loss of statistical difference between the arms (64.2 vs. 60.6%; $P = 0.12$). Relapse-free survival was longer for the capecitabine arm as compared to 5-FU/LV ($P = 0.04$), though OS did not differ significantly ($P = 0.07$). Overall, there was a significantly lower incidence of neutropenia and stomatitis and lower rates of nausea, vomiting, alopecia, and diarrhea in the setting of adjuvant treatment with capecitabine. However, the incidence of grade 3 HFS was significantly higher with capecitabine than with 5-FU/LV. This trial demonstrates that capecitabine is at least equivalent to the Mayo Clinic regimen of 5-FU/LV in the surgical adjuvant treatment of CRC [55].

The success of multiagent combination therapy in the treatment of mCRC has provided a compelling basis for testing such regimens in the adjuvant setting. Two large trials have demonstrated that the addition of oxaliplatin to 5-FU/LV has been shown to prolong DFS significantly in patients with stage II/III CRC, with a reduction in the risk of recurrence of 23% in the group given 5-FU/LV plus oxaliplatin compared with 5-FU/LV alone [56, 57].

These developments led to an international, randomized, phase III trial (XELOXA) in which 1,886 patients were randomized to adjuvant treatment with either XELOX or IV bolus 5-FU/LV given by 1 of 2 regimens (Mayo Clinic or Roswell Park). Bolus 5-FU/LV was chosen for comparison as it was standard at the time of study initiation. Both safety and efficacy were assessed in this study, though efficacy data were reported only in an abstract form indicating a benefit in DFS for XELOX [58].

Most treatment-related AEs occurred at similar rates in both treatment arms. However, patients receiving capecitabine plus oxaliplatin experienced less all-grade diarrhea and alopecia, and more neurosensory toxicity, vomiting, and HFS than with 5-FU/LV. Compared with the Mayo regimen, capecitabine plus oxaliplatin demonstrated fewer grade 3/4 hematologic AEs and more grade 3/4 gastrointestinal AEs. Compared with the Roswell Park regimen,

Table 7 Capecitabine in the adjuvant setting

References	Patients enrolled (*N*)	Regimen	Disease-free survival	Median survival	Safety, tolerability
Twelves et al. [54] (X-ACT)	$N = 1{,}987$ with resected stage III CRC	C 1,250 mg/m^2 bid on days 1–14 every 21 days or six cycles of rapid IV infusion of LV 20 mg/m^2 followed immediately by IV bolus of 5-FU 425 mg/m^2 on days 1–5 every 28 days	C group ≥5-FU group; relapse-free survival (3-year rate): 65.5 vs. 61.9% (C vs. 5-FU/LV)	OS (3 years) 81.3 vs. 77.6% (C vs. 5-FU/LV)	Less neutropenia, stomatitis, nausea, vomiting, alopecia, and diarrhea, but more HFS with C vs. 5-FU/LV
Schmoll et al. [58]	$N = 1{,}864$ (safety population) who have undergone surgery for stage III colon carcinoma	XELOX (IV Ox + C, 3-week cycle for 8 cycles) or IV bolus 5-FU/LV administered as Mayo Clinic or RP			Similar rates in both arms; XELOX patients had less diarrhea and alopecia; more neurosensory toxicity, vomiting, and HFS; compared with Mayo, XELOX associated with fewer grade 3/4 heme AEs and more grade 3/4 GI AEs; compared with RP, XELOX associated with fewer grade 3/4 GI AEs and more grade 3/4 hematologic AEs; higher rate of grade 3/4 neurosensory toxicity and grade 3 HFS with XELOX; treatment-related mortality at 28 days from last study dose: 0.6% in both the groups

AEs adverse events, *B* bevacizumab, *bid* twice a day, *C* capecitabine, *CRC* colorectal cancer, *HFS* hand foot syndrome, *5-FU* fluorouracil, *GI* gastrointestinal, *HFS* hand-foot syndrome, *IV* intravenous, *LV* leucovorin, *Ox* oxaliplatin, *OS* overall survival, *RP* Roswell Park regimen, *X-ACT* Xeloda in Adjuvant Colon Cancer Therapy, *XELOX* capecitabine plus oxaliplatin

capecitabine plus oxaliplatin demonstrated fewer grade 3/4 gastrointestinal AEs and more grade 3/4 hematologic AEs. As expected, grade 3/4 neurosensory toxicity and grade 3 HFS were higher with capecitabine plus oxaliplatin. It was concluded that capecitabine plus oxaliplatin has a manageable tolerability profile in the adjuvant setting [58]. The 3-year DFS, as reported at the 2009 European Cancer Conference, demonstrated 71% 3-year DFS for patients on the XELOX arm, compared with 67% for the 5-FU/LV arm (hazard ratio = 0.80; $P = 0.0045$) [59]. In addition, an update presented at the 2010 Gastrointestinal Cancers Symposium demonstrated that these differences in DFS demonstrated similar advantage for XELOX over 5-FU/LV for both patients >70 years and <70 years of age [60]. It is too early to detect a survival difference, and further follow-up is needed. These data demonstrate that XELOX can be considered as an acceptable alternative for patients with resectable stage III CRC in the adjuvant setting. There are no comparative studies between XELOX, infusional 5-FU, and oxaliplatin available at this date.

Pharmacoeconomics and patient considerations

Cost comparisons of capecitabine monotherapy versus bolus 5-FU/LV (Mayo Clinic regimen) show that the higher acquisition cost of capecitabine is partially or completely offset by costs associated with treating toxicity and the higher administration costs of IV 5-FU/LV in both the metastatic [61, 62] and adjuvant [63–66] settings.

Cost analyses of XELOX (± bevacizumab) versus FOLFOX (± bevacizumab) show the same trends. A comparison of the expected costs of XELOX and FOLFOX-4 from the United States third-party payer and societal perspectives during the study period of the randomized NO16966 phase III trial showed that patients receiving FOLFOX-4 required approximately 15–20 more office visits for drug administration and spent more hours in office and clinic visits than patients treated with XELOX (22–27 vs. 7–9 visits). The total direct medical costs were comparable between XELOX and FOLFOX-4 [67, 68].

A cost-minimization analysis found that the average cost of chemotherapy per cycle per patient was significantly lower with capecitabine plus oxaliplatin than with FOLFOX-6. In addition, the analysis determined that overall clinic/hospital resource consumption was markedly reduced compared with FOLFOX-6 [69]. Finally, a retrospective database analysis reported a substantial savings associated with capecitabine plus oxaliplatin compared with 5-FU/LV/oxaliplatin chemotherapy [70]. Together, these prospective pharmacoeconomic and cost analyses, along with the retrospective claims database analysis, provide a consistent view that capecitabine-based therapy is associated with a favorable cost comparison versus infusional 5-FU-based therapy in patients with CRC.

Available quality-of-life data suggest that there are no differences between capecitabine and 5-FU-based regimens [71, 72]. A study by Liu et al. [73] suggests that patients prefer oral chemotherapy, provided that efficacy is not compromised. Formal patient preference studies suggest that oral capecitabine is preferred over IV 5-FU regimens and that patient preference is influenced by tolerability as well as route of administration [74, 75]. Even though oral chemotherapy comes with advantages such as reduced frequency of clinic visits, flexibility of taking it at home and increased control/participation in care, it does come with disadvantages such as compliance, need for extensive patient education and awareness of bioavailability and drug interactions [76].

Patients find oral chemotherapy more convenient than IV therapy [77]. In terms of convenience, XELOX requires fewer planned office visits than FOLFOX-4 or FOLFOX-6, because oxaliplatin is administered every 3 weeks and capecitabine is taken orally. Medical resource use data from the NO16966 trial demonstrated that the need for drug administration visits and central venous access are reduced with XELOX versus FOLFOX-4 despite the addition of IV agents, e.g., oxaliplatin and bevacizumab [70]. Functional Assessment of Chronic Illness Therapy Chemotherapy Convenience and Satisfaction Questionnaire data from the ML16987 trial showed that patients treated with capecitabine plus oxaliplatin waste less of their free time and are more likely to be satisfied with treatment [71].

Future directions

Another common use of capecitabine is with radiation therapy in the preoperative management of rectal cancer. There are several phase II trials supporting its role in this setting [78, 79]. We await the results of a phase III study of preoperative chemo radiotherapy comprising radiation and either capecitabine or 5-FU with or without oxaliplatin in patients with resectable rectal cancer. This trial has recently completed accrual, and results should help to define capecitabine's role in this setting [80].

Conclusions

The evolution of fluorpyrimidine regimens and the introduction of new cytotoxic and targeted agents have led to important changes in how CRC is treated. Single-agent capecitabine, an oral pro-drug of 5-FU, has been shown to be equivalent to IV 5-FU in mCRC as well as

in the adjuvant setting. Capecitabine combined with oxaliplatin also has proven to be as effective as oxaliplatin 5-FU-containing combinations in the treatment of mCRC. The primary distinction between the two regimens is related to differences in toxicity and ease of administration. Capecitabine plus irinotecan combinations in this setting have produced more variable results, with some dose regimens resulting in excessive toxicity. At this time, combination treatment with irinotecan and capecitabine generally is not recommended, though there are recent data (without celecoxib) that have been more promising.

In addition, based on recent positive phase III data, capecitabine in combination with oxaliplatin appears to be an acceptable treatment option for patients in the surgical adjuvant setting. These data were recently presented at two international meetings and approval is expected later in the year [58, 59]. The use of capecitabine in conjunction with radiation therapy for the treatment of rectal cancer awaits the results of a definitive phase III trial to further define its role in this setting.

The choice of capecitabine over IV 5-FU primarily is based on differences in toxicity and ease of administration. In general, there is less stomatitis and neutropenia with capecitabine-containing regimens, with the trade-off of more HFS reactions and diarrhea. Using capecitabine in combination therapy avoids the use of long-term indwelling catheters, infusion pumps, and their complications, and requires fewer patient visits to the clinic. In terms of direct costs, capecitabine plus oxaliplatin appears to be cost-neutral compared with 5-FU/LV/oxaliplatin. However, capecitabine plus oxaliplatin is associated with improved indirect costs and patient convenience, which may improve patient compliance and satisfaction with treatment. Capecitabine is an acceptable alternative to IV 5-FU in the treatment of CRC in most settings. The primary exceptions would be in combination with irinotecan, in which case less toxicity is observed with infusion of 5-FU as opposed to capectiabine. The other exception would be in the case of patients on long-term anticoagulation with warfarin—the intermittent schedule utilized with capecitabine and its interaction with warfarin can cause difficulty with maintaining safe and effective anticoagulation.

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